Mastering The Boards and Clinical Examinations In Internal Medicine

Part 1

Cardiology, Endocrinology, Gastroenterology, Hepatology and Nephrology

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This book complements

Mastering The Boards and Clinical Examinations

In Internal Medicine - Part II

Neurology, Respirology and Rheumatology

A.B.R. Thomson

Mastering The Boards and Clinical Examinations In Internal Medicine

Part 1

Cardiology, Endocrinology, Gastroenterology, Hepatology and Nephrology

A.B.R. Thomson

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THE WESTERN WAY

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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 examination. They would provide a complete and organized assessment. Participants are encouraged to identify key features, and they develop an approach to problem-solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic base provides the means for the candidate to establish an appropriate management plan based on the best available evidence 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, to ask questions in an open-ended manner, and to provide constructive, 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 are able, and then to interact with another health professional participant to move forward 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 then to share this with other small group participants through effective delegation of work. Some of the material they must access demands that they use information technology effectively 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 the answering of the questions and case discussions, the participants are required to consider the risks, benefits, and costs and impacts of 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 of 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 to give and take 360^0 feedback.

Knowledge
The basic science aspects of gastroenterology are considered in adequate detail to understand the mechanisms of disease, 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 C's 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 what is often two decades of study, sacrifice, long hours, dedication, ambition and drive, we who have chosen Internal Medicine, and possibly through this a subspecialty, have a 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, that a patient is neither a MCQ or 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, care for our patients.

The process by which we study for clinical examinations is so is different than for 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.

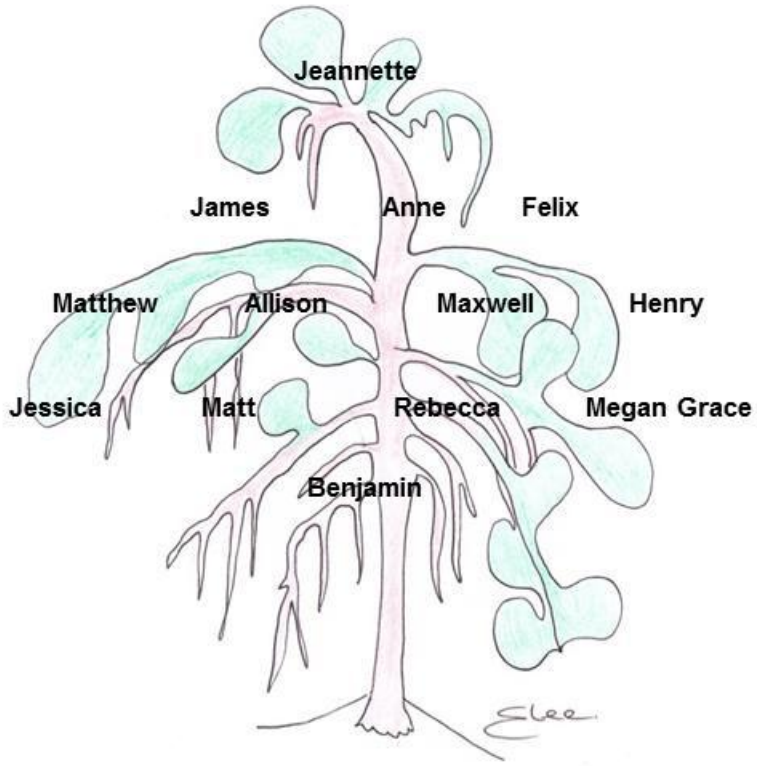
This book provides clinically relevant questions of the process of taking a history and performing a physical examination, with sections on Useful background, and where available, evidence-based performance characteristics of the rendering of our clinical skills. Just for fun are included "So you want to be a such-and-such specialist!" to remind us that one if 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 My Family



For your support, caring and love

During these challenging years

And always.

Mark 15:34

Luke 23:34

Domenichino 16:41

Corinthians 1:13

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 behaviour 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 and Felix 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 C's - competence, caring, and compassion - and to make my very private personal life dedicated to family - to you all.

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Questions

Cardiology

1. Perform a focused inspection of the patient for cardiac disease.
2. Take a directed history for disease of the cardiovascular system.
3. Perform a focused physical examination for disease of the heart and cardiovascular system.
4. Perform a focused physical examination of the cardiovascular system for 5 syndromes suggested from the inspection of a person's body appearance.
5. Perform a focused physical examination for the causes of elevated jugular venous pressure (JVP).
6. Take a directed history and perform a focused physcal examination for congestive heart failure (CHF). Perform a focused physical examination for the causes of right-sided congestive heart failure (R-CHF).
7. Perform a focused physical examination to distinguish between the presence of left-sided congestive heart failure (L-CHFand e.g. LV failure [LVF]), and right-sided congestive heart failure (R-CHF and e.g. RV failure [RVF]).
8. Give the chest X-ray changes seen in pulmonary edema.
9. Give 3 causes of a carotid bruit.
10. Give 4 circumstances, other than lack of adequate clinical skill, which make it difficult to access central venous pressure (CVP, from the right atrium).
11. Perform a direct physical examination to distinguish between the JVP and carotid waveforms.
12. Take a focused history to determine the risk factors for coronary artery disease.
13. Take a directed history for chest pain.
14. Take a focused history of clinical features increasing the likelihood of an acute coronary syndrome (ACS).
15. Take a directed focused history to establish the presence of high-risk features in patients with non-ST segment elevation acute coronary syndrome.
16. Perform a focused physical examination to determine if the person with an acute coronary syndrome more likely had disease of the LAD versus the RCA.
17. Take a directed history and perform a focused physical examination for syncope.

18. Perform a focused physical examination to determine the cause of leg pain.
19. Take a directed history to differentiate between intermittent claudication (from atherosclerosis and peripheral vascular disease) and pdeudoclaudication (from spinal stenosis)
20. Take a directed history for lower leg ulcers.
21. Take a directed history and perform a focused physical examination of the four most common types of lower leg ulcer.
22. Take a directed history for and perform a focused physical examination for peripheral vascular disease (arterial and venous insufficiency) in the lower extremities.
23. Take a focused history and perform a directed physical examination to distinguish between chronic vs acute (critical) ischemia.
24. Take a directed history and perform a focused physical examination to differentiate between arterial vs venous insufficiency
25. Take a directed history for the causes of postural hypotension.
26. Perform a directed physical examination for hypovolemia (volume depletion).
27. Take a directed history to determine the cause of lower leg edema.
28. Perform a focused physical examination to differentiate between venous edema versus lymphedema.
29. Perform a focused physical examination for causes of bilateral leg swelling.
30. Perform a focused physical examination to distinguish between causes of arterial and venous insufficiency.
31. Perform a focused physical examination to differentiate between the types of regional edema.
32. Perform a focused physical examination for causes of leg swelling:
33. Perform a focused physical examination for 5 causes of rapid ventricular contraction and low peripheral vascular resistance.
34. Perform a focused physical examination of the pulse to distinguish between the hyperkinetic pulse of AR versus MR.
35. Perform a focused physical examination for pulsus paradoxus (exaggeration of normal fall [> 20 mm Hg] in SBP with inspiration).
36. Give 5 causes of a collapsing pulse.
37. Give the differences in the signs & causes of PVD (peripheral vascular disease).
38. Give 3 common effects of diabetes on blood vessels.

39. Perform a focused physical examination for an abnormally widened pulse pressure.
40. Take a focused history and perform a directed physical examination for causes of hyperkinetic heart syndrome causing an abnormally wide pulse pressure (PP) (PP > 50% of systolic BP).
41. Perform a focused physical examination for AF.
42. Perform a focused physical examination to determine the cause of atrial fibrillation.
43. Perform a focused physical examination for risk factors for thromboembolism in non-rheumatic atrial fibrillation.
44. Take a directed history for the causes of sinus bradycadia and tachycardia.
45. Perform a focused physical examination for the causes of bradycardia/ heart block.
46. Take a directed history for palpitations.
47. Perform a focused physical examination for palpitations.
48. Give the disease processes associated with a loud, variable or soft intensity of S_1
49. Give 4 causes of wide & fixed splitting of S_1 (A_1, P_1); delay in producing P1 component of S_1).
50. Give 3 causes of reversed ("paradoxical") splitting of S_1.
51. Perform a focused physical examination for causes of fixed splitting of S_2.
52. Perform a focused physical examination of the heart sounds. Explain what underlying cardiac abnormalities may be determined from this examination.
53. Perform a focused physical examination for wide splitting of S_2.
54. Perform a directed physical examination of abnormal S_2 splitting to detect the presence of associated pathological abnormalities.
55. Perform a focused physical examination for the causes of fixed splitting of S_2 (splitting of S_2 which persists on supine $\rightarrow$ expiration).
56. Perform dynamic maneuvers which increase or decrease the intensity/ duration of three systolic cardiac murmurs
57. Perform a focused physical examination of the precordium, and from the timing of the murmur, give the differential of the lesion.
58. Take a directed history for the cause of a patient's cardiac murmur.
59. Perform a focused physical examination of the precordium for the site of optimal ausculatation of normal and abnormal heart sounds and murmurs.

60. Take a direct history and perform a focused physical examination to determine if a systolic murmur is benign (i.e. non-pathological).
61. Perform a focused physical examination of the precordium, which will help to distinguish between
62. Take a directed history and perform a focused physical examination for rheumatic fever and rheumatic heart disease (RHD).
63. Give 3 features obtained from auscullation which suggest that the murmur of MS is severe
64. Perform a focused physical examination for Marfan's Syndrome.
65. Perform a focused physical examination for AS.
66. Perform a focused physical examination to distinguish aortic sclerosis from stenosis.
67. Perform a focused physical examination to access the severity of AS.
68. Give 4 causes of ↑ P_2 which are associated with pulmonary hypertension.
69. Perform a directed physical examination to distinguish between the systolic murmur of pulmonary stenosis (PS) and aortic stenosis (AS).
70. Perform a physical focused physical examination to distinguish between the murmur of pulmonary stenosis (PS) and aortic stenosis (AS).
71. Perform a directed physical examination to distinguish between the systolic murmur of aortic sclerosis (no pressure gradient; due to stiff or dilated aortic root) and aortic stenosis (AS).
72. Perform a directed physical examination to distinguish between the systolic murmur from HOCM (hypertrophic cardiomyopathy, particularly septal component) and aortic stenosis (AS).
73. Perform a focused physical examination to distinguish hypertrophic obstructive cardiomyopathy (HOCM) from aortic stenosis (AS).
74. Perform a focused physical assessment for prosthetic heart valves.
75. Perform a focused physical examination for pulmonary stenosis.
76. Perform a focused physical examination for MR.
77. Give 10 causes of mitral regurgitation
78. Perform a focused physical examination to distinguish between the systolic murmur of mitral regurgitation due to dysfunctional papillary muscle (DPM) versus ruptured chordate tendinae (RCT).
79. Perform a physical focused physical examination to determine the severity of mitral regurgitation (MR).

80. Take a directed history and perform a focused physical examination for the causes of chronic mitral regurgitation.
81. Perform a physical focused physical examination to distinguish between the murmur of MR caused by rupture of the chordate tendinae (RCT) versus papillary muscle dysfunction (PMD).
82. Perform a focused physical examination to determine the severity of aortic regurgitation.
83. Perform a physical focused physical examination to determine the severity of mitral regurgitation (MR).
84. Perform a physical focaused physical examination to distinguish between the murmur of tricuspid regurgitation (TR) and mitral regurgitation (MR).
85. Perform a focused physical examination for TR.
86. Take a directed history and focused physical examination for TR.
87. Take a direct history and perform a focused physical examination for mitral valve prolapse.
88. Perform a focused physical examination for MVP (mitral valve prolapse). Perform a focused physical examination to distinguish between the diastolic murmurs of mitral stenosis (MS) versus tricuspid stenosis (TS).
89. Give 4 complications of MS
90. Perform a focused physical examination for the patient with aortic regurgitation (AR).
91. Perform a focused physical examination to access the severity of AR
92. Perform a focused physical examination for aortic regurgitation.
93. Take a directed history and perform a focused physical examination for aortic regurgitation.
94. Give 3 clinical features that suggest that a patient's AR is not due to the commonest cause (rheumatic fever), but rather is due to syphilis
95. Perform a physical examination to determine the severity of aortic regurgitation.
96. Perform a focused physical examination for hypertrophic cardiomyopathy (HC).
97. Perform a focused physical examination for the type and cause of cardiomyopathy.
98. Take a directed history and perform a focused physical examination for the three types of cardiomyopathy.
99. Perform a focused physical examination to determine if a patient's pericardial rub has progressed to the development of a pericardial effusion.

100. Perform a focused physical examination to determine if a patient's elevated JVP is due to SVC (superior vena caval) obstruction?
101. Perform a focused physical examination to determine if a patient's elevated JVP is not due to congestive heart failure.
102. Take a directed history for the causes of pericarditis.
103. Perform a focused physical examination for constrictive pericarditis.
104. Perform a focused physical examination for acute cardiac tamponade.
105. Perform a focused physical examination to distinguish between the jugular venous pulse and the carotid artery pulse.
106. Take a directed history and perform a focused physical examination for chronic constrictive pericarditis.
107. Perform a focused physical examination to distinguish between the presence of chronic pericarditis with constriction constructive pericarditis (CP) and cardiac tamponade (CT).
108. Perform a focused physical examination for constrictive pericarditis (CP) and cardiac tamponade (CT).
109. Perform a focused physical examination for acute cardiac tamponade.
110. Perform a focused physical examination to distinguish a chronic constrictive pericarditis (CP) from acute cardiac tamponade (CT).
111. Perform a focused physical examination for syphilitic aortitis with saccular aneurysm of aorta.
112. Take a directed history and perform a focused physical examination to distinguish between aortic dissection (AD) and valvular aortic regurgitation.
113. Perform a focused physical examination of the heart and cardiovascular system for coarctation of the aorta presenting in an adult.
114. Take a directed history and perform a focused physical examination for bacterial endocarditis (BE) (pathophysiological approach).
115. Perform a focused physical examination for bacterial endocarditis.
116. Perform a focused physical examination for subacute bacterial endocarditis (SBE).
117. Perform a focused physical examination to distinguish between dextrocardia, situs inversus, dextroversion, and levoversion.
118. Give the chest X-ray findings seen in 3 common causes of congenital heart disease.
119. Perform a focused physical examination for ASD.

120. Perform a focused physical examination to distinguish between a secundum and a primum ASD.
121. Perform a focused physical examination for VSD.
122. Perform a focused physical examination for a ventricular septal defect (VSD).
123. Perform a focused physical examination for PDA.
124. Perform a focused physical examination for PDA (patent ductus arteriosis).
125. Give the clinical findings of 5 causes of congenital heart disease associated with cyanosis.
126. Perform a focused physical examination to determine the cause of acyanotic, cyanose tardive, and cyanotic congenital cardiovascular disease.
127. Perform a focused physical examination for tetralogy for Fallot's.
128. Perform a focused physical examination for dextrocardia.
129. Perform a focused physical examination to distinguish between acquired versus congenital dextrocardia.
130. Take a directed history and perform a focused physical examination for Eisenmenger syndrome.
131. Perform a focused physical examination of the cardiovascular system for Eisenmenger syndrome (ES).
132. Take a focused history to determine the cardiac risk stratification for noncardiac surgical procedures.
133. Take a directed history and perform a focused physical examination for superior vena cava (SVC) obstruction.

Endocrinology

1. Take a directed history for diabetes mellitus.
2. Perform a focused physical examination for diabetic nephropathy.
3. Perform a focused physical examination of the diabetic foot.
4. Perform a focused physical examination to differentiate DKA from HONC.
5. Give a systematic approach to hypoglycemia.
6. Take a directed history and perform a focused physical examination in the adult to determine the causes of hypoglycemia.
7. Take a directed history for thyroid disease.

8. Perform a focused physical examination for thyroid disease.
9. Give 4 causes of a bruit in the neck.
10. Take a directed history and perform a focused physical examination to determine if a thyroid nodule is likely to be malignant.
11. Take a directed history for the factors which increase the pretest probability of a goiter being present.
12. Perform a focused physical examination to distinguish between Grave's disease (GD) and Toxic Nodular Goitre (TNG).
13. Perform a focused physical examination for Grave's disease.
14. Perform a focused physical examination for hypothyroidism.
15. Give a systematic approach to the causes of hypothyroidism.
16. Perform a focused physical examination to distinguish between Grave's disease from other causes of a diffuse enlargement of the thyroid gland and evidence of hyperthyroidism.
17. Perform a focused physical examination for hyperthyroidism.
18. Perform a focused physical examination for thyroid ophthalmopathy.
19. Perform a focused physical examination of the eye in a patient with thyrotoxicosis.
20. Take a directed history for multinodular goiter
21. Take a directed history for the causes of hypoadrenalism (Addison's disease).
22. Perform a focused physical examination for Addison's disease
23. Perform a focused physical examination for disorders associated with hyperpigmentation.
24. Give a systematic approach to the causes of Addison's disease.
25. Perform a focused physical examination for hypoadrenalism (Addison's Disease).
26. Perform a focused physical examination for pheochromocytoma (catecholamine-secreting tumor).
27. Give a systematic approach to the causes of Cushing's syndrome.
28. Perform a focused physical examination for Cushing's syndrome.
29. Take a directed history to determine the causes of secondary hyperlipidemia.
30. Take a directed history for causes of secondary hyperliperlipidemia.
31. Take a directed history for the causes of hypo- and hypercalcemia.

32. Give a systematic approach to the causes of hypercalcemia and hypercalciuria.
33. Perform a focused physical examination for prolonged hypocalcemia, including hypoparathyroidism.
34. Take a directed history to determine the cause of osteoporosis.
35. Give a systematic approach to the causes of osteoporosis and osteomalacia.
36. Take a directed history and perform a focused physical examination to determine the causes of gynecomastia.
37. Give the systematic approach to the causes of gynecomastia.
38. Take a directed history and perform a focused physical examination to determine the cause of amenorrhea.
39. Give a systematic approach to the causes of amenorrhea.
40. Perform a focused physical examination for acromegaly.
41. Perform a focused physical examination for paraneoplastic syndromes and hormone producing cancers.

Gastroenterology

1. Perform a focused examination of the mouth.
2. Perform a focused physical examination to determine the causes of stomatitis.
3. Take a directed history to determine the causes of halitosis.
4. Give 6 non-dental causes of halitosis.
5. Give 3 causes of an enlarged tongue (macroglossia).
6. Perform a focused physical examination to determine the causes of salivary gland swelling.
7. Perform a focused physical examination to determine the causes of parotid gland enlargement.
8. Take a directed history for dysphagia.
9. From the clinical history, what can you suspect to be the cause of N/V?
10. Define gastric volvulus, and give the pathogenesis based on the bisecting axis and the associated rotation.
11. Give 20 risk factors which predispose to the development of esophageal cancers (ECa), and 5 which may be protective.

12. Give the detailed molecular biology (molecular events) of Esophageal Cancers.
13. Give the therapeutic modalities available for early esophageal cancers.
14. Define HHT, state the genetics, give the diagnostic criteria, and outline the distribution of lesions.
15. Perform a directed physical examination for hypovolemia (volume depletion).
16. Take a directed history to determine the causes of RUQ pain.
17. Perform a focused physical examination to determine the causes of abdominal masses.
18. Give 10 bacterial adjuvant or host defense factors influencing the transition from bacterial contamination to infection.
19. Give 5 causes of intra-abdominal abscesses (IAA), and 7 clinical risk factors.
20. Give the abdominal diagnostic imaging findings suggestive of the presence of IAA.
21. Take a directed history and perform a focused physical examination for the cause of an abdominal bruit.
22. Prepare a patient for informed consent prior to their having possible bariatric surgery, explain potential complications.
23. Prepare a patient for informed consent for the use of non-steroidal anti-inflammatory drugs, explaining the potential adverse effects.
24. Give the differences on EUS of benign versus malignant GIST in mid-stomach
25. Give 4 treatable premalignant gastric conditions.
26. Take a directed history for bowel obstruction.
27. Give the benefits of strituroplasty in CD, besides the relief of a partial small bowel obstruction.
28. Prepare a patient for informed consent for the use of steroids (GCS, glucocorticosteroids) in a patient with IBD, explaining the adverse effects.
29. Classify small intestinal lymphomas, based on their morphology and clinical response to chemotherapy.
30. Perform a focused physical examination for carcinoid syndrome.
31. Give the management of the patient with known carcinoid syndrome to avoid carcinoid crisis.
32. Give 3 markers of NET which suggest possible poor prognosis (high-grade tumors with poor differentiation).

33. Name 3 conditions which are PAS positive, and indicate how they can be distinguished by special histological stains.
34. Give the features which distinguish IPSID (immunoproliferative small intestinal disease) from MALT lymphoma (marginal T-cell lymphoma).
35. Give 4 examples of disorders of the CNS, spinal cord, smooth muscle and enteric neurons which are associated with constipation, and for each give the mechanism (s) responsible for the development of the constipation.
36. Take a directed history for diarrhea.
37. Take a directed history to determine the cause of infertility in men with inflammatory bowel disease.
38. Name the Colonic Polyp Syndrome.
39. Take a directed history for colon cancer screening, and surveillance.
40. Take a directed history of alcohol abuse.
41. Perform a directed physical examination for alcohol withdrawal (SSH-DTs: shake, seize, hallucinate, DTs).
42. Give 15 common hepatobiliary complications of SOT /HCT.
43. Give the 10 benefits and AEs (adverse effects) of TZD (pioglitazone).
44. Give 20 GI/Hepatobiliary clinical manifestations of cystic fibrosis.
45. Perform a focused physical examination for hepatosplenomegaly.
46. Give 4 causes of a hard knobbly liver.
47. Perform a focused physical examination to determine the cause of pruritus.
48. Perform a physical examination for acute liver disease (acute hepatitis and fulminant liver failure).
49. Perform a focused physical examination for signs of chronic liver disease (portal hypertension).
50. Perform a focused physical examination for cirrhosis in patients with chronic liver disease.
51. Take a directed history and perform a focused physical examination for ascites.
52. Give the mechanism of action of vasopressin (ADH) in distal renal tubule (DRT).
53. Perform a focused physical examination for the HELLP syndrome.
54. Give 10 paraneoplastic syndromes associated with HCC.
55. Give 7 risk factors for HCC in HBV.
56. Give 7 risk factors for HCC in HCV.

57. Give 7 patient groups requiring screening for HCC
58. Perform a focused physical examination to determine the cause of pruritus.
59. List 4 possible causes for failure to achieve pain relief after biliary sphincterotomy for presumed sphincter of Oddi dysfunction (SOD).
60. Give 5 complications of hepatic granulomas in sarcoidosis.
61. Give 10 features of sarcoidosis seen on liver biopsy.
62. Give the Ranson prognostic criteria for acute pancreatitis.
63. Give a systematic approach to the causes of chronic pancreatitis.
64. Give 8 clinical, diagnostic imaging and laboratory features that distinguish pseudocysts from cystic neoplasms of the pancreas.
65. There are literally hundreds of drugs which may cause pancreatitis. Give drugs commonly seen being used in GI patients which are considered to have a moderately strong association with the development of pancreatitis.
66. Perform a directed examination of an abdominal x ray ('flat plate').
67. Give 7 causes of calcification on abdominal X – ray.
68. Give 7 causes of radiological hepatic calcification.
69. Give the most common clinical presentations of the neuroendocrine tumors, VIPoma (Verner-Morrison syndrome), glucagonoma, and somatostatinoma and insulinoma. The approximate frequencies are given in brackets.
70. Give the clinical features that suggest Zollinger-Ellison Syndrome.
71. Give features which distinguish P-NET from other GI-NET.
72. Give the clinical features of glucagonoma.
73. Give the clinical and laboratory features of VIPoma syndrome.
74. Give 15 prognostic factors associated with decreased survival in patients with various pancreatic endocrine tumors.
75. Give 3 mechanisms explaining alterations in serum vitamin levels in obesity.
76. Give 7 symptoms/ signs of protein/ calorie malnutrition (PCM) which may occur in obesity.
77. Give 5 GI/ liver complications associated with stem cell transplantation, and give examples.
78. Give 10 gastrointestinal and /or hepatobiliary manifestations.
79. GI complications occur in > 80% of persons with PSS, and may affect all parts of the GI part. Give 20 examples.

80. Chronic renal disease associated with a plethera of GI complications, especially for these patients on hemodialysis (HD) or peritoneal dialysis (PD). Give 10 GI complications of chronic renal disease.
81. Give 8 conditions associated with NRH.
82. Give 3 complications of intraoperative endoscopy.

Hematology

1. Take a directed history of thrombocytopenia
2. Take a directed history and perform a focused physical examination for mass/lymph nodes in the neck/axilla
3. Take a directed history and perform a focused physical examination of the patient with lymphadenopathy:
4. Perform a directed physical examination for lymph nodes in the neck and axilla.
5. Take a directed history and perform a focused physical examination for anemia.
6. Perform a focused physical examination for pernicious anemia.
7. Perform a focused physical examination for anemia.
8. Give a systematic approach to the causes of immunoglobulin deficiency.
9. Give a systematic approach to the causes of sclerosis (increase in bone density).
10. Given systematic approach to other causes of mottling in the skull.

Nephrology

1. Perform a directed physical examination systemic hypertension.
2. Take a directed history for the causes of systemic hypertension.
3. Take a focused history for complications of malignant hypertensive emergency.
4. Perform a focused physical examination of the heart in the patient with systemic hypertension.
5. Perform a directed physical examination of the patient with systemic hypertension.
6. Take a focused history for complications of malignant hypertensive emergency.

7. Give 4 nonpharmacologic therapies to reduce blood pressure in hypertensive patients
8. Perform a directed history for the causes of renal colic.
9. Give 20 common causes of acute interstitial nephritis.
10. Give a systematic approach to the causes of interstitial renal fibrosis.
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CARDIOLOGY

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General

Useful background: the "O to W" of any history"

O= **O**nset and duration
P = **P**rovoking and alleviation factors
Q = **Q**uality of pain (e. g. "Is the pain sharp or dull? Is it throbbing?")
R = **R**adiation of pain
S = **S**everity (on a scale from 1 to 10)
T = **T**iming and progression (e. g. Is the pain constant or intermittent?")
U = "How does it affect '**U**' in your daily life?"
V = déjà **V**u? (e.g. "Has it happened before?"
W = '**W**hat do you think is causing it?"

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 7.

Sensitivity	PID	present in disease
Specificity	NIH	negative in health

PLR = sensitivity/ 1-sensitivity
NLR = 1-sensitivity/specificity

Accuracy of the history and physical exam

- One study in general medical clinic found that 55% of patients had been assigned correct diagnosis at the end of the history, and that number rose to 73% by the end of the physical examination.

Source: Sackett DL, et al. *JAMA* 1992; 267: 2650-265; and Filate W, et *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 5.

- Perform a focused inspection of the patient for cardiac disease.

- Body appearance
  - Frightened, struggling, diaphoretic, tachypneic – pulmonary edema
  - Anasarca of congestive heart failure
  - Tall stature, long extremities, and sparse subcutaneous fat of Marfan syndrome. Patients are prone to mitral valve prolapse and aortic dilatation and dissection.
  - Tall stature and long extremities of Klinefelter syndrome. Patients may have atrial or ventricular septal defects, patent ductus arteriosus, and even tetralogy of Fallot.

- Long extremities, kyphoscoliosis, and pectus carinatum of homocystinuria. Patients often present with thrombosis of medium-sized arteries.
- Tall stature and thick extremities of acromegaly (associated with hypertension, cardiomyopathy, and conduction defects).
- Short stature, webbed neck, low hairline, small chin, wide-set nipples, and sexual infantilism of Turner syndrome (associated with coarctation of the aorta and valvular pulmonic stenosis).
- Dwarfism and polydactyly of Ellis-van Creveld syndrome (associated with atrial septal defects and common atrium).
- Morbid obesity and somnolence of obstructive sleep apnea (associated with hypoventilation, pulmonary hypertension, and cor pulmonale)
- Truncal obseity, thin extremities, moon face, and buffalo hump and hypertensive patients with Cushing syndrome.
- Mesomorphic, overweight, balding, hairy, and tense middle-aged patient prone to coronary artery disease.
- Hammer toes and pes cavus of Friedreich ataxia (associated with hypertrophic cardiomyopathy, angia, and sick sinus syndrome).
- Waddling gait, lumbar lordosis, and calf pseudohypertrophy of Duchenne muscular dystrophy (associated with hypertrophic cardiomyopathy and pseudoinfarcation pattern of EKG).
- Straight back of ankylosing spondylitis (associated with aortic regurgitation and complete heart block).
- Ataxic gait of tertiary syphilis (associated with aortic aneurysm and regurgitation).
- Preferential sqatting of patients with tetralogy of Fallot.
- Levine's sign (clenched fist over the chest of patients with acute myocardial infarcation).

- Face
  - Hypertelorism, pigmented moles, and webbed neck of Turner syndrome.
  - Premature aging of Werner syndrome and progeria (associated with premature coronary artery and systemic atherosclerotic disease).
  - Gargoylism of Hurler syndrome (associated with mitral and/or aortic disease).
  - Round and chubby face of congenital valvular pulmonic stenosis
  - Elfin face (small chin, malformed teeth, wide-set eyes, patulous lips, baggy cheeks, blunt and upturned nose) of congenital stenosis of the pulmonary arteries and supravalvular aortic stenosis (often associated with hypercalcemia and mental retardation).
  - Epicanthic fold, protruding tongue, small ears, short nose, and flat bridge of Down syndrome (associated with endocardial cushion defects)

- Saddle-shaped nose of polychondritis (associated with aortic aneurysm)
- Drooping eyelids, expressionless face, receding hairline, and cataracts of Stenierts disease (myotonia dystrophica, associated with conduction disorders and mitral valve prolapse).
- Dry and brittle hair, loss of lateral eyebrows, puffy eyelids, apathetic face, protruding tongue, and thick, sallow skin of patients with myxedema (with peridcardial and coronary artery disease).
- Tightening of skin and mouth, scattered telangiectasisias, and hyper/hypopigmentation of scleroderma (with pulmonary hypertension, pericarditis and myocarditis).
- Flushed cheeks and cyanotic lips of mitral stenosis (arcocyanosis).
- Paroxysmal facial and neck flushing of patients with carcinoid syndrome (with pulmonic stenosis and tricuspid stenosis/regurgitation).
- Deafness and cataracts of rubella syndrome (associated with patent ductus arteriosus or stenosis of the pulmonary artery).
- Short palpebral fissures, small upper lip, and hypoplastic mandible of fetal alcohol syndrome (associated with atrial or ventricular septal defects).
- Unilateral lower facial weakness of infants with cardiofacial syndrome, which is encountered in 5-10% of infants with congenital heart disease (usually ventricular septal defect) and often is noticeable only during crying.
- Pulsatility of the earlobes in patients with tricuspid regurgitation.
- Macroglossia of Down syndrome, myxedema and amyloidosis (which is associated with restrictive cardiomyopathy and congestive heart failure).

- Eyes
  - Lid lag, stare, and exophthalmos of hyperthyroidism (associated with supraventricular tachyarrhythias, angina, and high-output failure)
  - Stare and proptosis of increased central venous pressure.
  - Xanthelasmas of hyperproteinemia and coronary artery disease.
  - Blue sclerae of osteogenesis imperfecta (associated with aortic regurgitation).
  - Icteric sclerae of cardiac cirrhosis.
  - Enlarged lacrimal glands of sarcoidosis (associated with restrictive cardiomyopathy, conduction defects, and possibly, cor pulmonale).
  - Dislocated lens of Marfan syndrome.
  - Conjunctival petechiae of endocarditis.
  - Conjunctivitis of Reiter disease (associated with pericarditis, aortic regurgitation, and prolongation of the P-R interval).
  - Fissuring of the iris (coloboma) of total anomalous pulmonary venous return.

- Retinal changes of hypertension and diabetes (associated with coronary artery disease and congestive heart failure).
- Roth spots of bacterial endocarditis.

- Skin
  - Jaundice of hepatic congestion.
  - Cyanosis of right-to-left shunt.
  - Pallor of anemia and high-output failure.
  - Bronzing of hemochromatosis (associated with restrictive cardiomyopathy).
  - Telangiectasias of Rendu-Osler-Weber syndrome (at times associated with pulmonary arteriovenous fistulas).
  - Neurofibromas, café-au-lait spots, and axillary freckles (Crowe's sign) of Von Recklinghausen's disease (associated with pheochromocytomas).
  - Symmetric vitiligo (especially of distal extremities) of hyperthyroidism.
  - Butterfly rash of lupus erythematosus (associated with endo-, myo-, and pericarditis).
  - Eyelid with purplish discoloaration of dermatomyositis (associated with cariomyopathy, heart block, and pericarditis).
  - Skin nodules and macules of sarcoidosis (associated with cariomyopathy and heart black).
  - Xanthomas of dyslipidemia.
  - Hyperextensible skin and joints of Ehlers-Danlos syndrome (associated with mitral valve prolapse).
  - Coarse and sallow skin of hyperthyroidism.
  - Skin nodules 9sebaceous adenomas), shagreen patches and periungual fibromas of tuberous sclerosis (associated with rhabdomyomas of the heart and arrhythmias).

- Extremities
  - Cyanosis and clubbing of central mixing (as in right-to-left shunts, pulmonary arteriovenous fistulas, and drainage of the inferior vena cave into the left atrium).
  - Differential cyanosis and clubbing of patent ductus arteriosus with pulmonary hypertension (the reversed shunt limits cyanosis and clubbing to the feet and spares the hands).
  - Reversed differential dyanosis and clubbing of transposition (aorta originating from the right ventricle): hands are cyanotic and clubbed, but feet are normal.
  - Sudden pallor, pain, and coldness of peripheral embolization.

- Osler's nodes (swollen, tender, raised, pea-sized lesions of fingerpads, palms, and soles) and Janeway lesions (small, nontender, erythematous or hemorrhagic lesions of palms of soles) seen in bacterial endocarditis.
- Clubbing and subungual splinter hemorrhages of bacterial endocarditis.
- Tightly tapered and contracted fingers of scleroderma, with ischemic ulcers and hypoplastic nails (often associated with pulmonary hyertension, myocardial disease, pericarditis, and valvulopathy).
- Raynaud's phenomenon of scleroderma
- Arachnodactyly and hyperextensible joints of Marfan syndrome (associated with aortic disease and regurgitation).
- Hyperextensible joints of osteogenesis imperfecta (associated with aortic regurgitation).
- Simian line of Down syndrome (associated with ostium primum defects).
- Ulnar deviation of rheumatoid arthritis (associated with pericardial, valvular, or myocardial disease).
- Nicotine stains of hcain smokers (clue to underlying coronary artery disease).
- Leg edema of congestive heart failure.
- Mainline track lines of intravenous drug abuses (presenting with tricuspid regurgitation, septic embli, and endocarditis).
- Liver pals (erythema of thenar and hypothenar eminence) of chronic hepatic congestion.

➢ Thorax and Abdomen
- Thoracic bulges of venticular or atrial septal defects.
- Systolic and rarely diastolic murmurs of pectus carinatum, pectus excavatum, and straight back syndrome.
- Pectus carinatum, pectus excavatum, and kyphoscoliosis of Marfan syndrome.
- Barrel chest of emphysema (often associated with cor pulmonale).
- Loss of thoracic kyphosis or straight back syndrome (associated with mitral valve prolapse)
- Cor pulmonale of severe kyphoscoliosis
- Right upper quadrant pulsation of tricuspid regurgitation.
- Ascites of right-sided or biventricular heart failure.

Printed with permission: Mangione S. *Hanley & Belfus* 2000, pages 176 to179.

- Take a directed history for disease of the cardiovascular system.

➢ Cardiovascular symptoms
- Chest pain
- Dyspnea – exertion, paroxysmal nocturnal dyspnea (PND), orthopnea
- Cough
- Palpitations

- Ankle swelling
- Intermittent claudication

- Associated symptoms
  - Left side congestive heart failure (L-CHF)
    - Fatigue
    - SOB, SOBOE orthopnea
    - Cough, hemoptysis
    - Baseline exercise in tolerance
    - Cyanosis
    - Cool extremities
    - Palpations
    - Nausea, vomiting
  - Right side congestive heart failure (R-CHF)
    - Edema of ankles, sacrum
    - Tender hepatomegaly
    - Determine New York class of CHF
  - Syncope
  - Fatigue
  - Weight gain

- Functional status (New York Heart Association Classification, Angina/ dyspnea activity on activity and relationship to exercise)
  - Class I – intense
  - Class II – ordinary
  - Class III – less than ordinary
  - Class IV – at rest

- Associated conditions/risk factors
  - Hypertension
  - Hyperlipidemia
  - Hyperhomocysteinemia
  - Obesity
  - Diabetes
  - Physical inactivity
  - Smoking
  - Causes of L/R- CHF
  - Family history
  - Personal past history of CAD, PVD, rheumatic fever, cardiac murmur, cardiac surgery, cardiac events, medications
  - Risk factors for CAD

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; L-CHF, left side congestive heart failure; PND, paroxysmal nocturnal dysphea; PVD, peripheral vascular disease; R-CHF, right side congestive heart failure; SOB, shortness of breath; SOBOE, shortness of breath on exertion

Adapted from: Talley N.J, et al. *Maclennan & Petty Pty Limited* 2003, page 27.

- Perform a focused physical examination for disease of the heart and cardiovascular system.

➢ Inspection
  - General appearance
    - Scleral icterus
    - Mitral facies (rosy cheeks with blue tinge from pulmonary hypertension [PHT] and low cardiac output [MS])
    - Palour
    - Wasting
    - Oxygen mask
    - Marfan's syndrome (MS) (aortic and mitral regurgitation)
    - Down syndrome (DS) (congenital heart disease)
    - Turner's syndrome (TS) (coarctation of the aorta)
  - Mouth
    - High arched palate (MS)
    - Diseased teeth
    - Tongue, lips – central cyanosis, petechiae
  - Hands, feet
    - Clubbing
    - Splinter hemorrhages in nail beds
    - Osler nodes (Raised, red, tender nodules on the pulps of the fingers or toes, or on the thenar or hypothenar eminences)
    - Janeway lesions (Raised, red, non-tender nodules on the pulps of the fingers or on the palms)
    - Short, broad hands (DS)
    - Single palmar crease (DS)
    - Incurving fifth finger (DS)
    - Hyperflexible joints (DS)
      - Lymphedema (TS)
      - Short 4^{th} metacarpal bone (TS)
      - Increased carrying angle of elbow (TS)
    - Aracanydactyly (spider fingers) (MS)
    - Periocular xanthemalasma
  - Neck
    - Carotid arteries
    - Jugular venous pressure (JVP) elevated
    - Webbing, low hairline, redundant skin folds on back of neck (TS)

- Chest
  - Funnel shaped chest
  - Widely spaced nipples (TS)
- Vital signs
  - PR, BP, RR, % 0_2 saturation
  - Colour – white, blue, grey
  - Distress
  - Chest incisions, pacemakers
  - Signs of peripheral vascular disease
  - Fundic vessel abnormalities (hypertension, diabetes)
- Palpation
  - PMI (apex beat)
  - Thrills and heaves
  - Reduced peripheral pulses
- Percussion
  - Cardiomegaly (pulmonary edema)
  - Pleural effusion
- Auscultation
  - Supine and upright, 5 areas, bell and diaphragm for S1/S2
  - L. lateral decubitus bell for S3/S4
  - Base of heart, lean forward, bell for diastolic murmur
  - Auscultate carotids (axilla)

- Signs of left side congestive heart failure (L-CHF)
  - Dyspnea, cough, hemoptysis
  - Basal crepitations
  - Cyanosis
  - Hypotension
  - Cold extremities
  - Fever, sweating

- Signs of right side congestive heart failure (R-CHF)
  - ↑ JVP
  - Hepatojugular reflux
  - Tender hepatomegaly
  - Pulsatile murmur
  - Hepatic bruit

- Signs of other causes of CHF
  - Hypertension
  - Vascular disease
  - Endocarditis
  - Constrictive pericarditis
  - Arrythmia
  - Anemia
  - Hyperhtyroidism, pheochromocytoma

- Pregnancy
- Heat stroke
- Non compliance with other medications
- PE, AE-COPD, pneumonia
- High salt diet (salt shaker at bedside)
- Acute/chronic renal failure
- Nephrotic syndrome

- MAYO precipitating factors in heart failure
  - Diet (excessive sodium or fluid intake, alcohol)
  - Non-compliance with medication or inadequate dosing
  - Sodium retaining medications (NSAIDs)
  - Infection (bacterial or viral)
  - Myocardial ischemia or infarction
  - Arrhythmia (atrial fibrillation, bradycardia)
  - Breathing disorders of sleep
  - Worsening renal function
  - Anemia
  - Metabolic (hyperthyroidism, hypothyroidism)
  - Pulmonary embolus

- Signs of other causes of chest pain
  - Chest wall
    - Muscle strains
    - Myositis
    - Rib fracture or tumour
    - Infection (Coxsackie B)
  - Heart
    - Aortic aneurysm, pericarditis
  - Lung
    - PE, pleurisy, pneumonia, pneumothorax
  - GI
    - GERD, NCCP, PUD, pancreatitis, cholecystitis
  - MSK
    - Costochondritis
  - Skin
    - Herpes zoster
  - Psychological
    - Anxiety

Abbreviations: AE-COPD, Acute exacerabation of chronic pulmonary disease; BP, blood pressure; CHF, congestive heart failure; DS, Down syndrome; GERD, gastroesophageal reflux disease; GI, gastrointestinal; JVP, Jugular venous pressure; L-CHF, left side congestive heart failure; MS, Marfan's syndrome; MSK, musculoskeletal; NCCP, Non cardiac chest pain; PE, pulmonary embolis; PHT, pulmonary hypertension; PR, pulse rate; PUD, peptic ulcer disease; R-CHF, right side congestive heart failure; TS, Turner's syndrome;

Adapted from: Jugovic PJ, et al *Saunders/ Elsevier* 2004, Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.2, page 28

Curiosity: Accuracy of the history and physical exam

- A study in general medical clinic found that 55% of patients had been assigned a correct diagnosis at the end of the history, and that number rose to 73% by the end of the physical examination.

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 5.

Congestive heart failure

Useful background: The three positive waves of the jugular venous pulse (A, C, V), and the three negative wave forms (X, X_1, Y).

- Perform a focused physical examination of the cardiovascular system for 5 syndromes suggested from the inspection of a person's body appearance.

Syndromes	Cardiac abnormalities
➢ Acromegaly	o Hypertension o Cardiomegaly o Conduction defects
➢ Ankylosing spondylitis	o AR (aortic regurgitation) o CHB (complete heart block)
➢ Cushing	o Hypertension

Syndromes	Cardiac abnormalities
➢ Duchenne muscular dystrophy	○ HOCM ○ Pseudoinfarction pattern on ECG
➢ Ellis-van Creveld	○ ASD ○ Common atrium
➢ Friedreich ataxia	○ HOCM (hypertrophic obstructive cardiomyopathy ○ Angina ○ SSS (sick sinus syndrome)
➢ Homocysteinuria	○ Thrombosus, medium-sized arteries
➢ Klinefelter	○ ASD (atrial septal defect) ○ VSD (ventricular septal defect) ○ PDA (patent ductus arteriosus) ○ T of F (tetralogy of Fallot)
➢ Marfan	○ MVP (mitral valve prolapsed) ○ Aortic dilation & dissection
➢ Pickwick	○ Cor pulmonale ○ PHT (pulmonary hypertension) ○ Hypoventilation
➢ Tetralogy of Fallot	○ Preference for the squatting position
➢ Turner	○ Coarctation of aorta ○ VPS (valvular pulmonary stenosis)

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 177.

- Perform a focused physical examination for the causes of elevated jugular venous pressure (JVP).

➢ Heart
- ○ CHF
- ○ Valvular defects
  - TR (tricuspid regurgitation)
  - TS (tricuspid stenosis)
  - PS (pulmonary stenosis)
- ○ Conduction defects – complete heart block

➢ Lung
- ○ PHT (pulmonary hypertension; aka cor pulmonale)

- SVC (superior vena cava obstruction)
  - Neck
    - ↑ JVP prominent veins (neck, chest)
    - ↑ JVP with to pulsations
  - Face
    - Pink
    - Dyspneic
  - Eyes Horner's syndrome
  - Look for signs of cause
    - Lung – bronchogenic cancer
    - Chest – lymphoma
    - Neck – goiter
    - Heart – aortic aneurysm, constrictive pericarditis

- What is the pathophysiology of systolic (DS) and diastolic dysfunction (DD)? Give 3 examples of conditions leading to DD.

- SD
  - ↓ contractility
- DD
  - ↓ filling, from ↑ stiffness of heart
- Causes of DD
  - Severe LVH
    - AS (aortic stenosis)
    - HBP (systemic hypertension)
  - Cardiomyopathy
    - Hypertrophic cardiomyopathy
    - Restrictive cardiomyopathy

Abbreviation: LVH, left ventricular hypertrophy

Useful terms:

- Bigeminal pulse
  - Irregular rhythm, alternating strong and weak beats, due to premature contraction opeing aortic valve, premature contraction not opening aortic valve, 3:2 heartblock
- Buerger's test for PVD
  - Elevate legs 45˚ → pallor; lower legs 90˚ → cyanosis
- Campbell's sign
  - Trachea descends with inspiration; seen in acute respiratory distress, COPD, or other causes of severe airway obstruction

- Hamman's sign
  - Mediastional crunch, timed with systolic and diastolic components of heart beat, due to mediasintal air, such as with a pneumothorax
- Kussmaul respiration
  - ↑ Rate and depth of breathing is caused by anion-gab metabolic acidosis (MAKE UPL):
    - Methanol
    - ASA
    - Ketoacidosis
    - Ethylete glycol
    - Uremia
    - Paraldehyde
    - Lactic acidosis
- Kussmaul's sign
  - ↑ JVP on inspiration, in RV failure when JVP is ↑ (on inspiration, JVP normally falls). On inspiration, normally BP ↓, PR↑
- Pulsus alternans
  - Regular rhythm, alternative strong and weak beats
- Pulsus paradoxus
  - Systolic blood pressure > 10-12 mmHg with inspiration (common is cardiac tamponade [98% prevalence] and acute asthma [< 50% prevalence])
- Sinus arrhythmia
  - Normal ↓ PR on expiration

Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; JVP, jugular venous pressure; PR, pulse rate; PVD, peripheral vascular disease; RV, right ventricle

Source: Hauser SC, et al. *Mayo Clinic Gastroenterology and Hepatology Board Review*. 3rd Review. pages 598 and 600.

"We are inherently critical as scientists, and inherently kind as physicians."

Grandad

Useful background: Performance characteristics of findings on history and physical examination in emergency department patients

Finding	PLR	NLR
➢ Initial clinical judgment	4.4	0.45
➢ Past History		
o Heart failure	5.8	0.45
o Myocardial infarction	3.1	0.69
➢ Symptoms		
o Paroxysmal nocturnal dyspnea	2.6	0.70
o Orthopnea	2.2	0.65
o Edema	2.1	0.64
➢ Physical examination		
o Third heart sound (ventricular filling gallop)	11	0.88
o Abdominojugular reflux	6.4	0.79
o Jugular venous distention (JVP)	5.1	0.66
o Rales	2.8	0.51
o Any murmur	2.6	0.81
o Lower extremity edema	2.3	0.64
o Valsalva maneuver	2.1	0.41
o Systolic blood pressure < 100 mm Hg	2.0	0.97

Abbreviations: JVP, jugular venous pressure; PLR, positive likelihood ratio; NLR, negative likelihood ratio

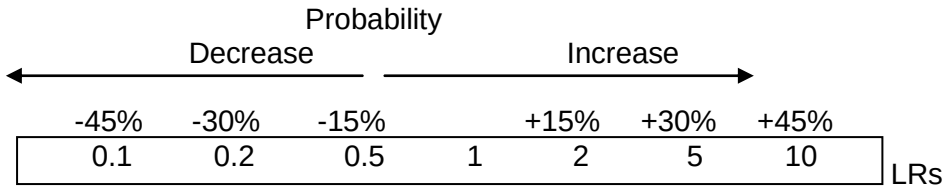
Note that many historical points, symptoms and signs on physical examination have a PLR > 2 (and are not included here)

➢ Remember the probability (%)

PLR	Increase	NLR	Decrease
2	15%	0.5	-15%
5	30%	0.2	-30%
10	45%	0.1	-45%

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

Adapted from: Simel DL, et al. *JAMA* 2009, Table 16-6.



Useful background: Causes of congestive heart failure (CHF)

- LV failure (L-CHF, systolic dysfunction)
  - Inadequate LV filling
    - Mitral stenosis
    - LV diastolic dysfunction (e.g. LVH)
    - Pericardial constriction
  - Pressure overload
    - Aortic stenosis
    - Systemic hypertension
    - Pulmonary hypertension
  - Volume overload
    - Aortic or mitral regurgitation
    - High output heart failure e.g. beri beri, thyrotoxicosis, Paget disease, AV fistula
  - LV muscle disease
    - Myocardial infarction
    - Cardiomyopathy – hypertrophic, dilated, restrictive
    - Myocarditis

- RV failure (R-CHF, diastolic dysfunction)
  - Secondary to L-CHF
  - Secondary to pulmonary hypertension ([cor pulmonate] e.g. PEs, chronic lung disease)
  - Mitral stenosis
  - Tricuspid regurgitation
  - Atrial myxoma
  - Congenital heart disease (atrial septal defect)

Abbreviation: AV, aortic valve; CHF, congestive heart failure; L-CHF, left sided congestive heart failure; LV, left ventricle; NSAIDs, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolus; R-CHF, right-sided congestive heart failure; RV, right ventricle

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-36; and Burton JL. *Churchill Livingstone*, 1971.

Useful background: The major and minor Framingham criteria for clinical diagnosis of congestive heart failure.

Major	Minor
○ PND ○ Orthopnea ○ Increased JVP ○ Rales ○ Third heart sound ○ Chest radiography - Cardiomegaly - Pulmonary edema	○ Peripheral edema ○ Night cough ○ DOE ○ Hepatomegaly ○ Pleural effusion ○ Heart rate >120 beats per minute ○ Weight loss ≥4.5 kg in 5 days with diuretic

Abbreviations: DOE, dyspnea on exertion; JVP, jugular venous pressure; PND, paroxysmal nocturnal dyspnea

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-33, page 113.

Useful background: New York heart association (NYHA) functional classification of congestive heart failure

Class	Activity evoking angina	Limits to physical activity
I	None	None
II	Ordinary physical activity	Slight
III	Walking < 2 blocks or < 1 flight of stairs	Marked
IV	Minimal or at rest	Severe

Abbreviation: NYHA, New York heart association

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 3, page 55.

"The meaning of life is to fill your three score and ten years with love, respect and compassion for others."

Grandad

Useful background: Factor that can exacerbate heart failure

- Patient-specific factors
  - Non-compliance with drug therapy or dietary restrictions
  - Anemia
  - Arrhythmias
  - Infections
  - Myocardial ischemia
  - Pulmonary embolism
  - Renal dysfunction
  - Uncontrolled hypertension
  - Valvular heart disease

- Drugs
  - Drugs that cause sodium and fluid retention:
    - NSAIDs including selective COX-2 inhibitors and high-dose salicylates
    - Corticosteroids
    - Minoxidil
    - Androgens
    - Thiazolidinediones (pioglitazone, rosiglitazone)
    - Drugs with high sodium content
    - Licorice-containing products
  - Negative inotropes:
    - Antiarrhythmic agents except amiodarone and dofetilide
    - Beta-blockers at maintenance doses
    - Calcium channel blockers: diltiazem, nifedipine, verapamil, but not amlodipine or felodipine
    - Itraconazole
  - Cardiotoxic drugs
    - Alcohol
    - Anthracyclines (doxorubicin)
    - Cocaine
    - Cyclophosphamide
    - Imatinib
    - Trastuzumab

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 527.

- Take a directed history and perform a focused physcal examination for congestive heart failure (CHF).

➢ Symptoms	o Paroxysmal nocturnal dyspnea (PND) o Orthopnea (SOB, ie shortness of breath) o Dyspnea on exertion (SOBOE, shortness of breath on exertion) o Chest pain (previous MI, CHF)
➢ Physical examination	o Jugular venous pressure (JVP) assess o Peripheral and sacral edema o S3 (ventricular filling gallop) o Rales and wheezes o Cardiac murmur
➢ Chest radiograph	o Pulmonary venous congestion o Interstitial edema o Cardiomegaly o Pleural effusion(s)
➢ Electrocardiogram findings	o Any abnormal result o Atrial fibrillation
➢ Brain natriuretic peptide	o Most useful when < 100 pg/ml for decreasing the likelihood of CHF

Abbreviations: CHF, congestive heart failure; LVH, left ventricular hypertrophy; LV, left ventricle; MI, myocardial infarction; PE, pulmonary embolus

Source: Simel DL, et al. *JAMA* 2009, Box 16-1, page 204; and Davey P. *Wiley-Blackwell*, 2006, pages156, 158,160 and 162.

Useful background: Suggested ad circumstances that prompt hospitalization in persons with congestive heart failure

- Hypotension
- Worsen renal function
- Altered mentation
- Dyspnea at rest
- Significant arrhythmias
- Disturbed electrolytes
- Lack of outpatient care/ family support

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-31, page 112.

- Low Ejection Fraction

Finding (Ref)	PLR	NLR
➢ Vital signs		
○ Heart rate >100 beats/min at rest	2.8	NS
○ Abnormal Valsalva response	7.6	0.3
➢ Heart examination		
○ Elevated neck veins	7.9	NS
○ Supine apical impulse lateral to MCL	10.1	0.6
○ S_3 gallop	3.4	0.7

Abbreviations: MCL, midclavicular line; NLR, negative likelihood ratio; PLR, positive likelihood ratio

Note: The findings of lung crackles, murmur of mitral regurgitation, hepatomegaly and peripheral edema are not shown since the valve of their PLR was < 2.

Adapted from: McGee SR. *Saunders/Elsevier* 2007, page 523.

Useful background: Performance characteristics of physical examination for congestive heart failure (CHF).

The physical examination is very useful for the diagnosis of CHF. Relating to the heart rate, tachycardia (> 10 bpm at rest) and an abnormal valsalva response yield positive likelihood ratios (PLR) of 5.5 and 7.6, respectively.

While displacement of the PMI has a PLR of 5.8 and the S_3 gallop of 5.7, the age-old JVP has considerable merit, with an ↑ JVP having a PLR of 3.9, and abdominojugular (aka hepatojugular reflex) of 8.0.

Elevated Left Heart Filling Pressures Finding	PLR
➢ Vital signs	
○ HR > 100/bpm at rest	5.5
○ Abnormal Valsalva response	7.6
➢ Lung examination	
○ Crackles	NS
➢ Heart examination	
○ Elevated jugular venous pressure	3.9
○ Positive abdominojugular test	8.0
○ Supine, apical impulse lateral to MCL	5.8
○ S_3 gallop	5.7
➢ Legs, sacrum	
○ Edema	NS

*Diagnostic standard: For elevated left heart filling pressures, *pulmonary capillary wedge pressure > 12 mmHg or > 15 mmHg, or left ventricular end diastolic pressure > 15 mmHg*

Abbreviations: CHF, congestive heart failure; HJ, hepatojugular; HR, heart rate; PLR, positive likelihood ratio; NLR, negative likelihood ratio; MCL, midclavicular line

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Table 44-1, page 522.

- Diagnosis of left ventricular dysfunction (L-CHF)

Medical inpatients, including post myocardial infarction	PLR	NLR
➢ Clinical diagnosis		
o ECG abnormal	2.0-3.1	0.41-0.62
o Outpatients	2.8	0.03
o Clinical score with a BNP > 37 pg/mL		
➢ The breathless ER patient's history		
o Patient history		
o Heart failure	5.8	0.45
o Myocardial infarction	3.1	0.69
➢ Physical examination		
o Third heart sound (S_3)	11	0.88
o Abdominojugular reflux	6.4	0.79
o Jugular venous distention	5.1	0.66
o Rales	2.8	0.51
➢ Chest radiograph		
o Pulmonary venous congestion	12	0.48
o Interstitial edema	12	0.68
o Alveolar edema	6.0	0.95
o Cardiomegaly	3.3	0.33
o Pleural effusion(s)	3.2	0.81
➢ Electrocardiogram		
o Atrial fibrillation	3.8	0.79
o New T wave changes	3.0	0.83
o Any abnormal finding	2.2	0.64
➢ Overall clinical impression		
o Initial clinical judgment that the patient is in CHF	4.4	0.45

Abbreviations: CHF, congestive heart failure; ECG, electrocardiogram; HJ, hepatojugular; JVP, jugular venous pressure; L-CHF, left side congestive heart failure; PLR positive likelihood ratio; NLR, negative likelihood ratio.

Adpated from: Simel DL, et al. *JAMA* 2009, Table 16-12, page 213.

Useful background: Distinguishing diastolic dysfunction from systolic dysfunction

Finding	LR for diastolic dysfunction	LR for systolic dysfunction (EF < 45%)
➢ Favor of normal systolic function		
o Female sex	1.6	0.62
o Systolic blood pressure ≥160 mm Hg	1.8	0.55
➢ Favor of systolic dysfunction		
o Heart rate ≥ 100/min		
o Left atrial ECG abnormality	0.42	2.4

Abbreviations: ECG, electrocardiogram; EF, ejection fraction; LR, likelihood ratio

Source: Simel DL, et al. *JAMA* 2009, Table 16-11, page 211; Hauser SC, et al. *Mayo Clinic Gastroenterology and Hepatology Board Review. 3rd Review,* Box 44-1, pages 522 and 523.

Useful background: Performance characteristics of Chest radiograph and electrocardiogram in emergency department patents in CHF

	PLR	NLR
➢ Chest radiograph		
o Pulmonary venous congestion	12	0.48
o Interstitial edema	12	0.68
o Alveolar edema	6.0	0.95
o Cardiomegaly	3.3	0.33
o Pleural effusion(s)	3.2	0.81
o Any edema	3.1	0.38
➢ ECG		
o Atrial fibrillation	3.8	0.79
o New T wave changes	3.0	0.83
o Any abnormal findings	2.2	0.64

Abbreviations: CHF, congestive heart failure; ECG, electrocardiogram; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

Note that the presence of pneumonia and hyperinflation on chest x-ray , as well as ECG evidence of either ST elevation or depression have PLRs >2, and are not included here.

Adapted from: Simel DL, et al. *JAMA* 2009, Table 16-7, page 201.

Useful background: Conditions that prompt hospitalization in heart failure

- Social
  - Lack of outpatient care
- CNS
  - Altered mentation
- Heart
  - Hypotension
  - Dyspnea at rest
  - Significant arrhythmias
- Kidney
  - Worsen renal function
  - Disturbed electrolytes

Adapted form: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-31, page 112.

- Perform a focused physical examination for the causes of right-sided congestive heart failure (R-CHF).

- Any cause of L-CHF
- Cor pulmonale
- Mitral stenosis, tricuspid incompetence
- Some forms of congenital heart disease
- Shunts
  - Heart
  - Peripheral
- Deformity of chest wall

- Perform a focused physical examination to distinguish between the presence of left-sided congestive heart failure (L-CHFand e.g. LV failure [LVF]), and right-sided congestive heart failure (R-CHF and e.g. RV failure [RVF]).

	LVF (L-CHF)	RVF (R-CHF, PHT, cor pulmonale)
➢ Inspection		
○ Nourishment	- Cachexia	
○ Breathing, RR	- ↑ - Dyspnea - Chgyne-Stokes respiration - Orthopnea	- ↑
○ Skin	- Peripheral cyanosis	- Yes – "mitral facies": rosy cheeks with blue tinge
○ Voice	-	- Hoarse (PHT: large PA compresses L. recurrent laryngeal nerve)
➢ Palpation		
○ Skin	- Cold extremities - Edema	- Cold extremities - Edema -
○ Pulse	- ↑ PR - ↓ pulse pressure - Pulsus alternans - Irregular (e.g. AF)	
○ JVP		- ↑ JVP - ↑ a, v waves - HJR - Kussmaul sign
○ Apex	- Displaced - Dyskinetic - Gallop	- RV heave - Palpable P_2
○ BP	- May be ↓ or ↑	- May be ↓ (with LVF)
○ Liver		- Tender hepatomegaly

	LVF (L-CHF)	RVF (R-CHF, PHT, cor pulmonale)
➢ Auscalation		
o Lungs	– Crackles, wheezes	- Tender hepatomegaly
o Heart sounds	– LV-S_3	- RV-S_3 - ↑ P_2 (PHT) - Systolic ejection click (PHT)
o Murmur	– Valvular disease	- PR (dilation of PA; PHT) - Systolic ejection murmur (PHT)
o Liver		- Bruit / thrill
➢ Associations		
o Anemia		
o Hyperthyroidism		
o Atherosclerosis		

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; HJR, hepatojugular reflux; JVP, jugular venous pressure; L-CHF, left side congestive heart failure; LV, left ventricle; PA, pulmonary artery; PHT, pulmonary hypertension; PR, pulse rate; PR, pulmonary regurgitation; R-CHF, right side congestive heart failure; RR, respiratory rate; RV, right ventricle; TR, tricuspid regurgitation

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 156.

"Be an advocate, seek something good for everyone:
seek justice and love"

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. In the context of wanting to pass the cardiology fellowship examination, what is “cor bovinum?”

A1. Slow and progressive left ventricular dilatation and hypertrophy in an attempt to normalize wall stress. The heart may thus become larger and heavier than in any other form of chronic heart disease – cor bovinum (bovine or ox heart)

Source: Baliga R.R. 250 Cases in Clinical Medicine. Saunders/Elsevier, Philadelphia 2007,page 15.

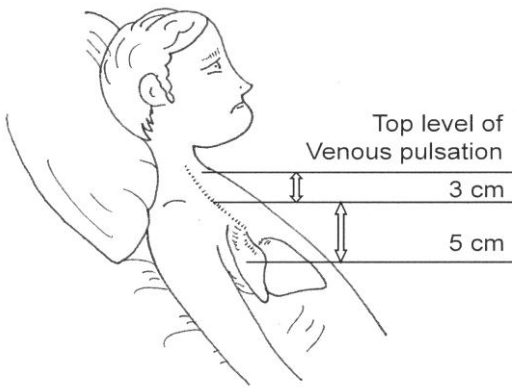
Q2. When does the person with chronic left sided (L) congestive heart failure lose their orthopnea (preferance to breathing in an upright position)?

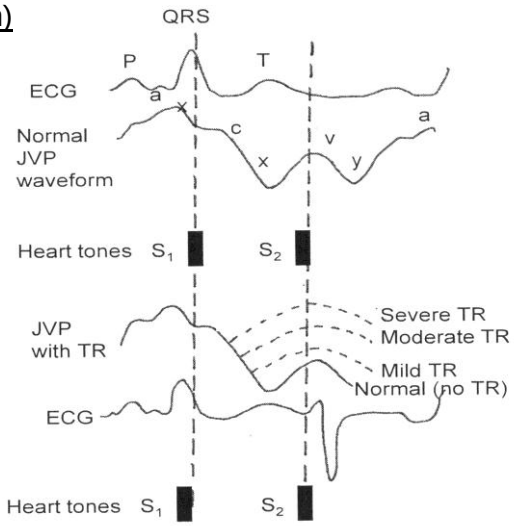
A2.Once the L-CHF causes R-CHF, the failure of the RV causes unloading of the LV, relieving the pulmonary congestion.

Q3. 95% of persons with orthopnea will have heart disease, but what pulmonary disease makes up the remaining 5%?

Evaluation of jugular venous pressure (JVP) and Central Venous Pressure (CVP)

3 cm (from sterna notch)
+ 5 cm (from right ventricle to sternal notch)
8 cm H_2O jugular venous pressure





Abbreviations: ECG, electrocardiogram; TR, tricuspid regurgitation

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Figure 3-1, page 38.

- Give the chest X-ray changes seen in pulmonary edema.
  - Costophrenic angles
    - Kerley “B” lines (septal lines)
      - Small, horizontal, parallel lines from dilated lymphotics in the inter lobar septa
    - Pleural effusions
      - Also seen in the transverse or oblique fissures
  - Hila
    - Fuzzy, homogeneous opacities radiating outwards from hila
    - Hazy hilar vessels
  - Lung fields
    - Fuzzy lower zone, or all of lung
    - Upper lobe, dilated veins

- Pulmonary edema (PE) is often associated with cardiomegaly. Give conditions in which PE is not associated with cardiomegaly.
  - CNS
    - Head injury
    - CVA
  - Lung
    - Viral pneumonia
    - Chemical pneumonitis
    - Pneumoconiosis, silicosis
  - Heart
    - Mitral stenosis
    - Constrictive pericarditis
    - Constrictive cardiomyopathy

- Give 3 causes of a carotid bruit.
  - Carotid stenosis
  - High-output states
  - AV fistula of the forearm
  - Normal finding in children (~20% of children < 15 years)

Jugular venous pressure

Mangione Pearl: “The more severe and acute the condition, the more difficult and inaccurate the bedside determination of jugular venous pulse and pressue”

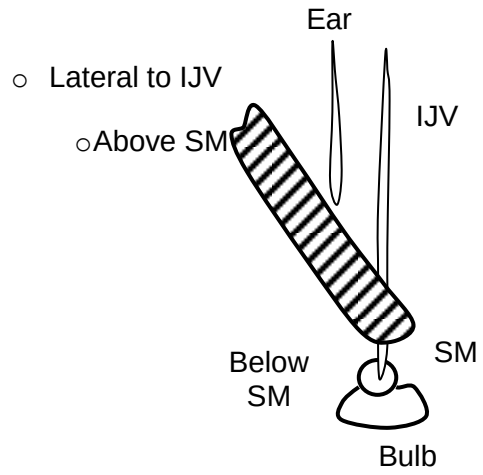
Source: Mangione S. *Hanley & Belfus* 2000, page 190.

- Give 4 circumstances, other than lack of adequate clinical skill, which make it difficult to access central venous pressure (CVP, from the right atrium).

    - ↓ CVP
    - Short, thick neck
    - Mechanical ventilation
    - Acute attack of asthma (wide respiratory swings in CVP)
    - Critically ill patients
    - Inspection of the external rather than the internal jugular vein

Useful tips to distinguish EJV (external jugular vein) from IJV (internal jugular vein)

- EJV is
    - Above SM (sternomastoids) muscle
    - Lateral to IJV
    - No bulb (bulb at junction of subclavian vein and IJV, between two heads of SM muscle



Central and jugular venous pressure

- What is a normal range for JVP?
    - Normal range is 4-5 cm above the sternal angle.

- When is the abdominojugular reflux considered abnormal?
    - Abnormality is indicated when there is a sustained rise in JVP >4cm after applying abdominal pressure for a minimum of 15-30 seconds.

- If you knew a person had a very elevated JVP but still wanted to evaluate the JVP pulsations, what could you do?
    - Use a higher elevation of the head (>30°) until pulsations are seen.

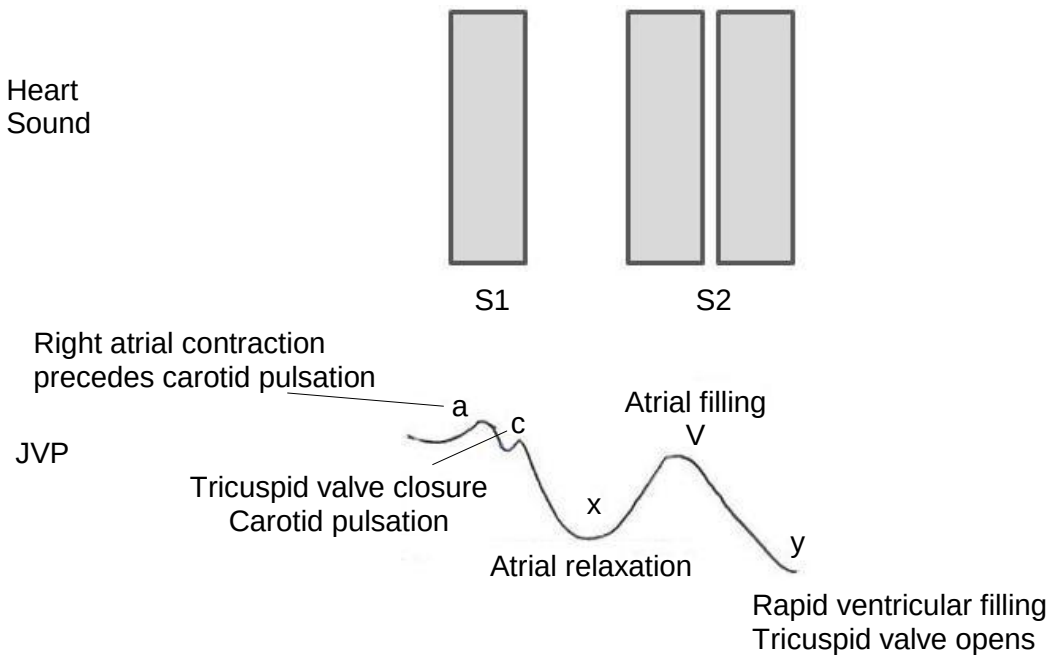
- Effect of inspiration
    - Normal inspiration - ↓JVP

- Kussmaul's sign - ↑ JVP on inspiration (opposite to normal, ie abnormal inspiratory increase in JVP). It occurs because the heart is unable to accommodate the increase in the venous return that accompanies the inspiratory fall in intrathoracic pressure.
  - R-CHF
  - SVC obstruction
  - TS
  - Constrictive pericarditis
  - Restrictive cardiomyopathy

Abbreviations: JVP, jugular venous pressure; R-CHF, right sided congestive heart failure; SVC, superior vena cava; TS, tricuspid stenosis

Adapted from: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 57.

Useful background: Jugular venous pressure, wave forms, and their relationship to the normal heart sounds



Abbreviations: CCF, congestive cardiac failure; CVP, central venous pressure; HJR, hepatojugular reflex; JVP, jugular venous pressure

Source: Talley NJ, et al *Maclennan & Petty Pty Limited* 2003, Figure 3.12, page 47.

Useful background: The physiology of JVP ascents and descents

- A wave
  - From right atrium (RA) contraction
  - S_1 and carotid upstroke
  - Coincides with S_4
  - Follows p wave on ECG
  - More permanent than V wave

- C wave
  - Poorly visible
  - from both bulging of tricuspid cusps into right atrium, as well as from transmitted carotid pulsation
  - Coincide with ventricular contraction
  - Interval between a and c wave of JVP coincides with P-R interval or RV coinciding with RV contraction
  - Occurs between S_1 and S_2
  - More prominent than Y descent

- V wave
  - At end of ventricular systole and at the early phase of ventricular diastole
  - Less prominent than A wave
- Y descent
  - At beginning of ventricular diastole
  - Caused by opening of the tricuspid valve and emptying of R. Atrium
  - Corresponds to S_3
  - Less prominent than X descent

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 193 and 194.

Useful background: Causes of Abdomino-(hepato-) jugular reflex (AJR); (Sustained ↑JVP $\geq$ 4 cm)

- R-CHF (not in L-CHF)
- Tricuspid regurgitation or stenosis
- Contructive pericarditis or pericardial tamponade
- IVC obstruction
- Hypervolemia

AJR has 66% sensitivity and 100% specificity distinguishing Tricuspid (TR) from mitral regurgitation (MR) (Note: AJR^+ in TR, AJR^- in MR).

Adapted from: McGee SR. *Saunders/Elsevier* 2007, page 381, 382; and Mangione S. *Hanley & Belfus* 2000, page 199.

Useful background: Causes of elevation of jugular venous pulse (JVP)

- SVC
  - SVC obstruction
- RA
  - RA thrombus, tumour, Bernheim effect
  - ↑ RA filling pressure
- TR
  - Tricuspid stenosis
  - Giant 'a' waves, cannon waves, tricuspid incompetence
- RV
  - ↓ RV filling
    - RV failure
    - RV infarction
    - Constrictive pericarditis
    - Cardiac tamponade
  - ↓ RV compliance
- Lung
  - Coughing, valsalva maneuvre
  - Pleural or pericardial effusion
- Circulation
  - Increased blood volume
  - Bradycardia
  - Hyperdynamic circulation

Abbreviations: RA, right atrium; RV, right ventricle; SVC, superior vena cava

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 10.

Useful background: Performance characteristics of inspection of the neck veins.

Finding	PLR
➢ Elevated venous pressure at the bedside	
○ Detecting measured CVP > 8 cm H_2O	9.0
○ Detecting measured CVP > 12 cm H_2O	10.4
○ Detecting elevated left heart diastolic pressures	3.9
○ Detecting low left ventricular ejection fraction	7.9
○ Predicting postoperative pulmonary edema	11.3
○ Predicting post-operative myocardial infarction or cardiac death	9.4
➢ Positive abdominojugular test	
○ Detecting elevated left heart diastolic pressures	8.0

Abbreviation: CVP, central venous pressure; PLR, positive likelihood ratio; NLR, negative likelihood ratio; NS, not significant

Adapted from: McGee SR. *Saunders/Elsevier*, 2007, Box 32-1, page 378.

Useful background: Abnormalities of the venous waveforms

Waveform		Cardiac Condition
➢ a waves	o Absent	- Atrial fibrillation, sinus tachycardia
	o Flutter	- Atrial flutter
	o Prominent	- First degree AV block
	o Large	- TS - Right atrial myxoma - PHT - PS
	o Cannon	- AV dissociation - Ventricular tachycardia
➢ X descent	o Absent	- TR
	o Prominent	- Conditions causing enlarged a waves
	o Large *cv* waves	- TR - Constrictive pericarditis
➢ Y descent	o Slow	- TS - Right atrial myxoma
	o Rapid	- Constrictive pericarditis - Severe R-CHF - TR - ASD
	o Absent	- Cardiac tamponade

Abbreviations: ASD, atrial septal defect; AV, atrioventricular; PHT, pulmonary hypertension; PS, pulmonic stenosis; R-CHF, right sided congestive heart failure; TR, tricuspid regurgitation, TS, tricuspid stenosis

Adapted from: Simel DL, et al. *JAMA* 2009, Table 11-1, page 126, and Mangione S. *Hanley & Belfus* 2000, pages 194 and 195.

Useful background: Kussamaul's sign

- Paradoxical increase in JVP with inspiration (normally with inspiration JVP falls)
- Causes
  - R-CHF
  - Restrictive cardiomyopathy (eg. sarcocidosis, hemochromatosis, amylodosis)
  - Tricuspid stenosis
  - SVC syndrome
  - RV infarction (33-100%)

Abbreviations: RV, right ventricle; SVC, superior vena cava

Trick Questions

Q1. Is the vessel in the neck the jugular vein (JV) or the carotid artery (CA).

A1.	JV	CA
○ Inwards x,y waves	✓	No
○ Upper level	✓	No
○ Upper level falls with inspiration	✓	No
○ Seen, better than felt	✓	No
○ Felt, better than seen	No	✓

Jugular Venous Pressure (JVP)

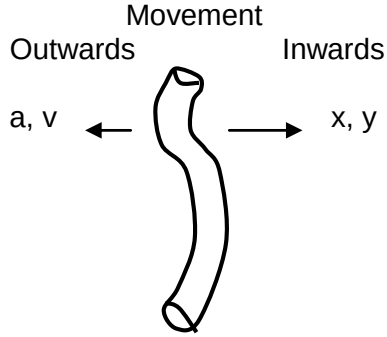
‘a’ ○ Atrial contraction
- absent in AF
- prominent in
  - PHT
  - PS
  - TS

‘x’ ○ Atrial relaxation

‘y’ ○ Tricuspid valve opens

‘c’ ○ Tricuspid valve closes

‘v’ ○ Venous blood returns to RA
○ Not due to contraction of ventricle
○ Often prominent in TR



Abbreviation: PHT, pulmonary hypertension; PS, pulmonary stenosis; TS, tricuspid stenosis; TR, tricuspid regurgitation; RA, right atrium.

Q2. In the context of the JVP, what is Kussmaul’s sign, and what are the causes of the Kussmaul sign being present?

A2.
○ Kussmaul’s sign is a reversal of the usual fall in JVP with inspiration
○ An increase in JVP with inspiration (Kussmaul’s sign) is present in
- Constrictive pericarditis
- Severe R-CHF

Q3. What are the performance characteristics of a “carotid shudder”?

A3. A palpable thrill on the slow stroke (pulsus tardis)
○ Definition of carotid shudder
○ Carotid shudder arises from the transmission of the murmurs of AS, AR, or AS plus AR to the artery.
○ “... relatively specific but insensitive sign of aortic valvular disease”

Source: Mangione S. *Hanley & Belfus* 2000, page 186.

Trick Questions!

Q1. In which side of the neck is the carotid bruit best auscultated in the person with an iatrogenic forearm AV fistula prepared for hemodialysis?

A1. Louder carotid bruit on the same side as the AV fistula.

Q2. Atherosclerotic disease is common in persons with chronic renal failure (CRF). In the CRF patient with an AV fistula for hemodialysis, what sigh if present favors the cause of the carotid bruit to be due to the fistula rather than being due to a carotid stenosis?

A2.An Associated subclavian bruit.

Q3. What is the clinical significance of auscultating a carotid bruit?

A3.
- Asymptomatic
  - Age 50, male
  - preoperative
    - 3 x ↑ annual risk of CVA, TIA, death from coronary heart disease
    - ↑ risk of postoperative dysfunction and behavior problems (but <u>not</u> predictive of ↑ post-op risk of CVA)
- Symptomatic
  - ↑ risk of 70% to 99% stenosis (“high-grade” stenosis)

Q4. How can you assess central venous pressure (CVP) from the left internal jugular vein (IJV)?

A4. The right IJV more directly reflects right atrial pressure, and CVP measured on left side is higher than on the right side.

Germs and Pearls

Under which circumstance does the patient’s pulse rate reduce the specificity of the finding of an elevated JVP to suggest CHF?

- In the presence of bradycardia

Apex Beat –PMI (point of maximum impulse)

- Perform a direct physical examination to distinguish between the JVP and carotid waveforms.

➢ JVP is defined as the pressure of the internal jugular system and is a direct assessment of the pressure in the right atrium of the heart.

➢ Characteristic	Venous Pulse	Carotid Pulse
○ Location	Low in neck and lateral	Deep in neck and medial
○ Contour	Double-peaked and diffuse	Single-peaked and sharp
○ Character	Undulant, not palpable	Force, brisk, easily felt
○ Waveform	Diffuse biphasic	Single sharp
○ Positional change	Varies with position	No variation
○ Respiratory variation	Height falls on inspiration	No variation
○ Effect of palpation	Wave nonpalpable, pressure obliterates pulse, vein fills	Pulse palpable, not compressible
○ Abdominal pressure	Displaces pulse upward	Pulse unchanged

Abbreviation: JVP, jugular venous pressure

Adapted form: Simel DL, et al. *JAMA* 2009 Table 11-2, 127; and Mangione S. *Hanley & Belfus* 2000, page 192.

- How would you modify the physical examination of the precordium to determine if there is systolic retraction of the apex beat (PMI)?
  - Have patient sit upright, and inhale

- What conditions are associated with systolic retraction of the apex beat?
  - Pericardial adhesions
  - Right ventricular hypertrophy

- What conditions give a weak apex beat?
  - Obesity
  - Emphysema
  - Pleural effusions

- Dextro cardia
- CHF (congestive heart failure)

A trick question: if the patient's apex beat is weak, and is displaced suggesting cardiomegaly from LVH (left ventricular hypertrophy), what complication of the cardiomegaly must you suspect)?

- L-CHF (left-sides congestive heart failure)

- Usually the apex beat is caused by the left ventricle. What are the findings on physical examination which suggest that the PMI is produced by an enlarged right ventricle (such as might occur in the patient with mitral stenosis)?
  - "tapping" quality of PMI
  - Parasternal heave
  - Pulsation in epigastrium

- What are the causes of a double rather than a single apex beat?
  - HOCM (hypertrophic obstructive cardiomyopathy)
  - LV aneurysm

Acute coronary syndromes

NSTEMI (non-ST segment elevation myocardial infarction) has a high longterm morbidity and mortality risk stratification is important to proceed with early angiography and revascularization.
"The TIMI (thrombolysis in myocardial infarction) Risk Score is a tool which helps to stratify patients with NSTEMI or unstable angina, using features present at the time of initial assessment in the emergency department. "One point is assigned for each feature: some of these are investigation-based, e.g.

- ↑ cardiac markers, e.g., troponin or creatine kinase-myocardial band)
- ST segment deviation ≥ 0.5 mm on ECG
- ≥ 50% coronary artery stenosis

Adapted from: Graham M, et al. Chapter 31. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 491.

Give the remaining 4 TIMI criteria which may be determined at the bedside.

A.
- Age ≥ 65 years
- ≥ 3 cardiac risk factors
  - Hypercholesterolemia
  - Diabetes
  - Hypertension
  - Current smoker
  - Family history of CHD (coronary heart disease)
- Any ASA use within 7 days
- ≥ 2 episodes of angina within the last 24 hours

Useful background: Myocardinal infarction (MI)

- Approximately 25% of patients with symptoms suggesting acute cardiac ischemia (ACI) have some other condition
- For patients with chest pain the response to nitroglycerin does not distinguish those who will prove to have an MI from those who will not.

Useful background:

- Univariate findings for acute myocardial infarction in patients with undifferentiated chest pain admitted for suspected acute coronary syndrome[a]

Clinical feature	PLR
Sign	
Chest pain radiation	
Both arms with pain	9.7
Left arm pain	2.2
Right shoulder pain	2.9
Third heart sound on auscultation (S3)	3.2
Hypotension (SBP $\leq$ 80 mm Hg)	3.1
Pulmonary crackles on auscultation	2.1
Diaphoresis	2.0
History of MI	1.5-3.0
Symptoms	
Radiation to the shoulder or to both arms	4.1
Radiation to right arm	3.8
Vomiting	3.5
Ex smoker	2.5

Abbreviation: ACI, acute cardiac ischemia; MI, myocardinal infarction; NLR, negative likelihood ratio; PLR, positive likelihood ratio; SBP, systolic blood pressure.

- Clinical features that increase the probability of a myocardial infarction (MI) in patients with acute chest pain

Note: That male gender, current smoking, radiation of pain to the left arm, and nausea/ vomiting, are not mentioned, since their PLRs were < 2.

Adapted from: Simel DL, et al. *JAMA* 2009, Table 35-11, page 473.

Useful background: Very rare coronary artery causes of MI

- Embolism (thrombus, infected vegetation)
- Thrombosis (spontaneous, prothrombotic states)
- Aneurysm (e.g. Kawasaki disease as a child)
- Spasm (drugs e.g. cocaine)
- Arteritis (SLE, PAN, Takayasu)
- Anomalous coronary artery
- Dissection, spontaneous

Abbreviations: MI, myocardinal infarction; SLE, systemic lupus erythematosis; PAN, polyarteritis nodosa.

Adapted from: Davey P. *Wiley-Blackwell* 2006, pages 150 and156.

- Take a focused history to determine the risk factors for coronary artery disease.

➢ Patient	o Demography	- Age - Male sex - Family history of premature CAD (<55 in men, <65 for primary relatives)
	o Associated disorders	- Hypertension - Diabetes - Metabolic syndrome - Stress and depression - Socioeconomic factors
	o Life style	- Smoking - Sedentary lifestyle - Obesity
➢ Laboratory	o Increased LDL: cholesterol level o Low HDL cholesterol level o Inflammatory markers (e.g. CRP,C-reactive protein) o Small, dense LDL o Lipoprotein (a) o Homocysteine o Fibrinogen	

Abbreviations: CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-23, page 92.

Useful background: Chest pain 'PQRSTU- A'

Position /location of pain

Quality: crushing (e.g. 'like someone standing on my chest'), dull, burning (suggests epigastric origin), pressing, squeezing, throbbing, knife like (sharp pain suggests chest wall/MSK pain)

Radiation (i.e. does the pain radiate? Where?

Severity: scale of 1-10 (1=mild discomfort, 10= worst pain ever had)

Timing: onset, duration and course

Uniqueness of recent symptoms (i.e. inquire if there was anything different that prompted the patient to seek help e.g. increased duration or severity) precipitating and alleviating factors

Associated symptoms: dyspnea, nausea, cough, palpitations, sweating

Abbreviation: MSK, musculoskeletal

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 123.

- Take a directed history for chest pain.

- Cardiovascular
  - Coronary artery disease (angina; acute myocardial infarction [STEMI], acute coronary syndrome [ACS; anstable angina, NSTEMI]), aortic aneurysm/ dissection, pericarditis (including constrictive pericarditis, cardiac tampnade)
- Pulmonary
  - Pneumothorax, pleurisy, pulmonary embolus, pneumonia
- Gastroinestinal
  - Esophagitis, peptic ulcer, pancreatitis, cholecystitis
- Musculoskeletal
  - Costochondrodynia, muscle spasm, nonspecific chest wall pain
- Other
  - Anxiety, herpes zoster

Abbreviation: MI, myocardial infarction;STEMI, ST elevation MI; NSTEMI, non ST elevation MI

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, page 118 to120; and Davey P. *Wiley-Blackwell* 2006, page 148.

Useful background: CCS functional classification of angina

Class	Activity evoking angina	Limits to physical activity
I	Prolonged exertion	None
II	Walking > 2 blocks or > 1 flight of stairs	Slight
III	Walking < 2 blocks or < 1 flight of stairs	Marked
IV	Minimal or at rest	Severe

Abbreviation: CCS, Canadian Cardiovascular Society

Source: Simel DL, et al. *JAMA* 2009, Table 2, page 55.

- Take a focused history of clinical features increasing the likelihood of an acute coronary syndrome (ACS).

- History
  - Profile male over 70 y
  - Pain
    - Accelerating ischemic symptoms over 48 h
    - Ongoing rest pain for > 20 min
    - Recurrent ischemic pain during observation
  - Diabetes

- Physical examination
  - S3
  - Hypotension
  - Pulmonary edema
  - Peripheral vascular disease
  - Severe arrhythmia
  - Sweating
  - Nausea/vomiting

- Investigation finding would include
  - Pathologic Q waves; abnormal ST segments; T wave inversion $\geq$0.02 mV; ST-segment depression > 0.05 mV and increased cardiac biomarkers

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-25 and Table 3-26, page 101.

- Take a directed focused history to establish the presence of high-risk features in patients with non-ST segment elevation acute coronary syndrome.

➢ History
  - Age >75 y
  - Accelerating ischemic symptoms over 48 hrs
  - Ongoing rest pain for >20 min
  - Recurrent ischemic pain during observation

➢ Physical
  - Hypotension
  - Pulmonary edema
  - Severe arrhythmia

➢ Laboratory
  - Reduced ejection fraction (<40%)
  - ST segment depression >0.5 mV
  - Increased cardiac biomarkers

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is Dressler's syndrome?

A1. Persistent pyrexia, pericarditis and pleurisy, post-myocardial infarction

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 100 and 101.

Q2. In the context of deep vein thrombosis (DVT), what is Virchow's triad?

A2.
  - Damage to the vessel wall
    - Trauma
    - Hypoxic blood
    - Drugs
    - Infection
    - Cholesterol
  - ↓ blood flow
  - ↑ blood coagulability

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 100 and 101.

- Perform a focused physical examination to determine if the person with an acute coronary syndrome more likely had disease of the LAD versus the RCA.

- LAD
  - Lung
    - Dyspnea
    - Orthopnea
    - Basal crackles
    - Cough
    - Hemoptysis
  - CNS
    - Fatigue
    - Syncope
  - Periphery
    - Hypotension
    - Cool extremities
    - Peripheral cyanosis
- RCA
  - JVP
    - Elevated JVP
    - Positive hepatojugular reflux
  - Liver
    - Hepatic tenderness
    - Hepatomegaly
    - Pulsatile liver
  - Periphery
    - Peripheral edema

Abbreviations: JVP, jugular venous pressure; LAD, left anterior descending artery; L-CHF, left side congestive heart failure; RCA, right coronary artery; R-CHF, right side congestive heart failure.

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, page 118 to120.

"Because Justice is so rare, it's such a delight."

John Irving. The last Night in Twisted River, 2009

Trivia

Q. The usual cause of ischemic heart disease (IHD) is atheroma in a coronary arteries. Give seven other causes of IHD.

A.

- Without narrowing
  - Inadequate blood supply
  - Left ventricular hypertrophy
  - ↓ blood sypply to myocardium
    - Aortic stenosis
    - Mitral stenosis (severe)
    - Pulmonary hypertension (severe)
- With narrowing
  - Embolism to coronary artery
    - Atrial thrombi
    - Air, fat emboli
    - Embolization of vegetation from infected valve in SBE
  - Congenital coronary artery fistula
  - Polyarteritis nodosa, giant cell arteritis
  - Syphilis (ostial stenosis, ie narrowing or origins of coronary artery)

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. In the context of the patient with post-myocardial infarction chest pain, what is Dressler's syndrome?

A1. Pyrexia, pericarditis, pleurisy

Source: Baliga RR. *Saunders/Elsevier*, 2007, page 101.

Q2. What is the cause and complication of Dressler syndrome?

A2.
- Chest pain, pericardial effusion and fever occureing 3 weeks to 6 months after MI
- Complications include CHF and arrhythmias

Useful background: Clinical features that increase probability of myocardial infarct (MI)

	PLR
➢ History	
o Pain in chest or left arm	2.7
o Chest pain radiating to	
- Right shoulder	2.9
- Left arm	2.3
- Left and right arm	7.1
o Chest pain most important symptom	2.0
o Previous history of MI	1.5-3.0
o Pleuritic chest pain	0.2
o Chest pain sharp or stabbing	0.3
o Positional chest pain	0.3
o Chest pain reported by palpation	0.2-0.4
o Nausea or vomiting	1.9
o Diaphoresis	2.0
➢ Physical exam	
o Third heart sound on auscultation	3.2
o Hypotension (systolic BP <80 mm Hg)	3.1
o Pulmonary crackles on auscultation	2.1
➢ ECG	
o New ST segment elevation > 1 mm	5.7-53.9
o New Q wave	5.3-24.8
o Any ST segment elevation	11.2
o New conduction deficit	6.3
o New ST segment depression	3.0-5.2
o Any Q wave	3.9
o Any ST segment depression	3.2
o T wave peaking and/or inversion >1 mm	3.1
o New T wave inversion	2.4-2.8
o Any conduction defect	2.7

Abbreviations: ECG, electrocardiography; PLR, positive likelihood ratio; MI, myocardial infarct

Adapted from: Panju AA, et al. *JAMA* 1998; 280:1256-63; Table 35.11, page 413; Simel DL, et al. *JAMA* 2009, Chapter 35, Table 35-5 and Table 35-6, page 467 and Table 35-8, page 472.

Caution: Arcus Senilis (AS)
- A sign of IHD only in men < 50 years who have had a myocardial infarction
- A tendency for hypercholesterolemia in normal men with AS
- Otherwise, a debatable sign of IHD

- Take a directed history and perform a focused physical examination for syncope.

➢ Vasovagal
- Emotional, heat, standing still
- Postural hypotension
  - Prolonged recumbency
  - Vasodilator drugs
  - Autonomic neuropathy: familial, diabetes, etc.
  - Micturition syncope
  - Swallowing syncope
- Carotid sinus hypersensitivity
- Cough syncope

➢ Cardiac
- Tachycardia
- Strokes-Adams
- Aortic stenosis, HOCM
- Atrial myxoma, ball-valve thrombus
- Constrictive pericarditis
- Cyanotic congenital heart disease

➢ Cerebral
- Anoxia
  - High altitude
  - CO poisoning
  - Anemia
  - Atheroma, embolus
  - Cervical spondylosis, strangulation
  - Subclavian steal syndrome
- Hypoglycemia
- Hypocapnai

➢ Hysterical

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 17.

Useful background: High-risk drugs at the time of hospital discharge

- Heart
  - Antiarrhythmics
  - Antihypertensives
  - Corticosteroids
  - Diuretics
  - Warfarin
- Diabetes
  - Oral hypoglycaemic agent & insulin
- Pain
  - Narcotics
- Steroids

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 13-1, page 505.

Peripheral vascular disease

PGT-BN

In the context of functionality of the valves in the leg veins, what is the difference in Trendelenburg's test and Perthe's test to assess the competence of the communicating and greater saphenous veins, as well as the deep venous system?

The competence of the valves of the peripheral veins assessed with Trendelenburg's test and with Perthe's test communicating and saphenous veins, as well as the deep venous system.

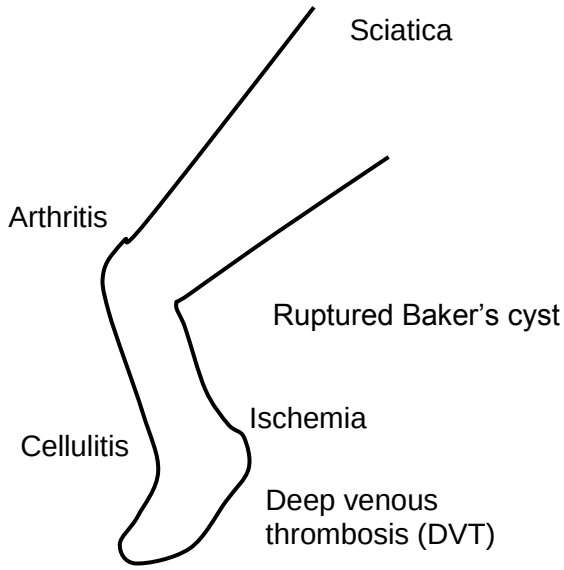
Trendelenburg's	Perthe's
➢ Raise leg from supine position to drain the veins	➢ While patient stands, apply tourniquet to mid thigh
➢ Apply tourniquet to mid thigh	➢ Instruct patient to walk for 5 minutes and watch what happens to the engorged veins while the tourniquet is in place.
➢ Have patient stand and watch the refilling of the collapsed veins with and without the tourniquet	

- Interpretation
  - Tourniquet in place, with standing the initially collapsed;
    - veins below the tourniquet become more engorged with walking (and pain develops in the leg) → the valves of the communicating veins are incompetent and the DVS is blocked;

- veins below tourniquet empty with walking → valves of communicating veins are competent, and deep venous system (DVS) is competent;
- saphenous vein (SV) refills → the valves of the communicating veins are incompetent (backfilling)

o Tourniquet removed; with standing
- Veins below the tourniquet are still engorged with walking, the valves of both the communication and the saphenous vein are incompetent; the initially collapsed SV refills → the valves of the SV are incompetent (backfilling)

- Perform a focused physical examination to determine the cause of leg pain.



Adapted from: Davey P. *Wiley-Blackwell* 2006, page 17.

- Take a directed history to differentiate between intermittent claudication (from atherosclerosis and peripheral vascular disease) and pdeudoclaudication (from spinal stenosis).

	Claudication	Pseudoclaudication
➢ Character	Cramp, ache	"Parasthetic" pins and needles
➢ Bilateral	+/-	+
➢ Onset	Walking	Walking & Standing
➢ Walking distance	Constant	Variable
➢ Relief	Standing still	Sitting down, leaning forward

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, page 1044.

- Take a directed history for lower leg ulcers.

➢ Vein
  - Stasis, with pigmentation and stasis eczema around lateral malleoli

➢ Artery
  - Large vessel: artherosclerosis, thrombangitis obliterans
  - Small vessel: vasculitis (diabetes mellitus [DM], rheumatoid arthritis [RA], sickle cell disease)
  - Nerve: Peripheral neuropathy: DM, syphilis

➢ Skin
  - Benign: Pyoderma gangrenosum, staph. aureus, TB, fungus
  - Malignant: basal cell, squamous, lymphoma, melanoma, Kaposi's sarcoma

Abbreviations: DM, diabetes mellitus; RA, rheumatoid arthritis; TB, tuberculosis

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.12, page 66 and Ghosh AK. *Mayo Clinic Scientific Press* 2008, page 1053.

- Take a directed history and perform a focused physical examination of the four most common types of lower leg ulcer.

	Type of ulcer			
	Venous	Arterial	Arteriolar	Neurotrophic
➢ History				
○ Onset	Trauma +/-	Trauma	Spontaneous	Trauma
○ Course	Chronic	Progressive	Progressive	Progressive
○ Pain	No (unless infected)	Yes	Yes	No
➢ Physical (ulcer)				
○ Location	Medial aspects of leg	Toe, heel, foot	Lateral, posterior aspect of foot	Plantar
○ Surrounding skin	Stasis changes	Atrophic	Normal	Callous
○ Ulcer edges	Shaggy	Discrete	Serpiginous	Discrete
○ Ulcer base	Healthy	Eschar, pale	Eschar, pale	Healthy or pale

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, page 1053.

- Take a directed history for and perform a focused physical examination for peripheral vascular disease (arterial and venous insufficiency) in the lower extremities.

- History

➢ Claudication
  - Leg claudication
  - Location and severity of pain at rest, on exertion, at night
  - Onset/offset
  - Distance to develop claudication
  - Aching in lower legs, especially when dependent
  - Parathesia

➢ Impotence

➢ Associated conditions/risk factors
  - Hypertension
  - Hyperlipidemia
  - Hyperhomocysteinemia
  - Obesity
  - Diabetes
  - Physical inactivity
  - Smoking
  - Causes of L/R- CHF
  - Family history
  - Personal past history of CAD, PVD, rheumatic fever, cardiac murmur, cardiac surgery, cardiac events, medications

- Physical examination

➢ Inspection

  - Pulses
    - Compare femoral, popliteal, tibial, dorsalis, pedis pulses; carotid, radial, brachial, abdominal aorta and renal arteries
    - Asymmetrical foot coolness
    - Pallor on leg elevation
    - Redness on leg dependency (positive Buerger's test)
    - Muscle atrophy
    - Bruits, thrills of abdominal aorta and femoral arteries

- Limbs
  - Size
  - Symmetry
  - Edema
  - Muscle atrophy
- Skin
  - Colour/pigmentation
  - Texture
  - Loss of hair on toes
  - Ulcers/scars
  - Gangrene
  - Nails (colour, texture)
  - Venous distribution (engorgement, varicosities)

- Palpation
  - Temperature (compares both limbs)
  - Capillary refill (compares both limbs)
  - Edema (compares both limbs)
  - Pulses (rate, rhythm, amplitude, waveform)
  - (Examined: carotid, radial, brachial, abdominal aorta; renal, femoral, popliteal, dorsalis pedis, tibial)
  - Pitting edema

- Auscultation
  - Bruits (carotid, abdominal aorta, renal, iliac, femoral)

- Special manoeuvres
  - Leg elevation for pallor
  - Dependency test for dusky rubor

- Tests of arterial insufficiency
  - Ankle/brachial index – compare palpated systolic BP values in brachial and either dorsalis pedis or posterior tibial arteries (normal A/B >1)
  - Capillary refill time
  - Venous filling time
  - Ausculatory bruit

Abbreviations: BP, blood pressure; CAD, coronary artery disease; L/R-CHF, left-/ right-sided congestive cardiac failure; PVD, peripheral vascular disease

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, page 143.

Useful background: Grading system for lower extremity arterial occlusive disease (AOD), using ankle – to – brachial systolic pressure index

Grade of AOD	Supine Resting	Post exercise
➢ Normal	1.0-1.4	No change or increase
➢ Mild disease	0.8-0.9	> 0.5
➢ Moderate disease	0.5-0.8	> 0.2
➢ Severe disease	< 0.5	< 0.2

Source: Ghosh AK. *Scientific Press*, 2008, Table 25-3, page 1044.

- Take a focused history and perform a directed physical examination to distinguish between chronic vs acute (critical) ischemia.

		Acute	Chronic
➢ Pain	o At rest	+	-
	o With exercise	-	+
	o Predictable distance	-	+
	o Relief with rest	-	+
➢ Examination	o Ulcers	+	-
	o Gangrene	+	-
	o Bruits	+	-

Adapted from Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 143 to145.

What is" the best"? The "best tests" for diagnosing PVD from physical examination are wounds or sores on foot, abnormal foot colour or coolness, absent pulses, limb bruit and venous filling time > 20 seconds.

Old age makes you redundant

So

It's OK to be redundant – if you're a gene!

Useful background: Performance characteristics of physical examination for peripheral vascular disease (PVD)

While the previously taught physical findings of atrophic skin, absent lower limb hair and capillary refill time ≥ 5 seconds all have positive likelihood ratios of < 2, other traditional signs have considerable merit.

Finding	PLR
➢ Inspection	
o Wounds or sores on foot	7.0
o Foot colour abnormally pale, red, or blue	2.8
o Atrophic skin	1.7
o Absent lower limb hair	1.7
➢ Palpation	
o Foot asymmetrically cooler	6.1
o Absent femoral pulse	6.1
o Absent posterior tibial and dorsalis pedis pulses	14.9
o At least one pedal pulse present	
➢ Auscultation	
o Limb bruit present	7.3
➢ Ancillary tests	
o Capillary refill time ≥5 seconds	1.9
o Venous filling time > 20 seconds	3.6

Abbreviations: PLR, positive likelihood ratio; NLR, negative likelihood ratio; NS, not significant; PVD, peripheral vascular disease

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 50-1, page 600.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of peripheral vascular disease, what is Buerger test?

A. Blanching" upon raising legs and "rubor" on dependency

Q. In the context of peripheral vascular disease, what is De Weese test?

A. Disappearance of palpable distal pulses after exercise

- Take a directed history and perform a focused physical examination to differentiate between arterial vs venous insufficiency.

	Arterial insufficiency	Venous insufficiency
➢ History of pain		
○ Location	- Toes, points of previous trauma, lateral malleolus	- Medial and lateral malleoli
○ Pain	- Intermittent claudication (exercise pain), rest pain	- None, or ache in lower legs on dependency
○ Paraesthesia	- Yes	- No
○ Paralysis	- Yes	- No
➢ Physical examination		
○ Skin	- Shiny, atrophic - No hair - Gangrene - Thick, ridged nails	- Brown pigment - Thick skin (scarring of skin - Skinny leg
○ Palor	- White (leg up), red (leg down)	- Normal, or blue (leg down)
○ Palor (cold)	- Yes	- No
○ Pitting edema	- Yes	- Yes
○ Pulses	- ↓	- Normal
○ Bruit	- Yes	- No

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, page 144.

Useful background: How pressure sores are graded.

- Grade I: erythema, skin intact.
- Grade II: skin loss, epidermis or dermis (abrasion, blister, shallow crater).
- Grade III: full thickness loss and damage to subcutaneous tissues.
- Grade IV: extensive destruction, tissue necrosis or damage to the underlying muscle or bone.

Source: Baliga RR. *Saunders/Elsevier* 2007, page 621.

Useful background: Interpretation of findings

	Possible pathology	Finding
➢ Arterial	o Raynaud's disease	- Sharply demarcated pallor in fingers that changes over several minutes - Normal wrist pulses
	o Arterial insufficiency	- Ulcers: ▪ Distal aspects of foot ▪ Painful ▪ Rapidly developing ▪ Often erythematous when infected
	o Chronic arterial insufficiency	- Cool, pale extremity with hair loss
	o Vasculitis	- Headache, temple soreness - Changes in skin colour and temperature - Swelling
➢ Venous	o Superficial phlebitis	- Warmth, painful to touch - Erythema due to inflammation of tissue around the vein
	o Acute DVT	- Pain secondary to inflammation in the absence of superficial changes - Swelling of distal part of the extremity
	o Venous obstruction	- Prominent veins in an edematous limb
	o Chronic venous insufficiency	- Skin: - Warm and erythematous - Thickened skin (woody) - Increased pigmentation - May have brownish ulcers around the ankles

Abbreviation: DVT, deep vein thrombosis

Permission granted: McGee SR. *Saunders/Elsevier* 2007, Table 1, page 249.

Postural orthostatic hypotension and hypovolemia

Useful background: Postural (orthostatic) hypotension

- With a change in body position
- Systolic BP decreases (>15 mmHg)
- Diastolic BP decreases (>0-10 mmHg)
- And/or heart rate increases (>20 bpm).
- Seen in conditions of autonomic dysfunction or volume depletion.

Abbreviation: BP, blood pressure

To examine a patient for orthostatic hypotension measure BP in supine patient, then have the patient sit up with the legs down or have patient stand for 2 minutes before reassessing BP.

Source: Jugovic PJ, et al. *Saunders/ Elsevier*, 2004, page 187.

- Take a directed history for the causes of postural hypotension.

- Hypovolemia
  - Bleeding, dehydration
- Drugs
  - Vasodilators, diuretics, anticholinergics (including TCAs)
- Endocrine
  - Diabetes, Addison's disease, hypopituitarism
- Autonomic neuropathy
  - Diabetes, amyloidosis, Shy-Drager syndrome
- Idiopathic

Abbreviation: TCAs, tricyclic antidepressants.

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.6, page 44.

Useful background: predicting the severity of blood loss causing hypovolemia.

Supine to standing, PR ↑ 30 bpm	Sensitivity (%)	Specificity (%)
➢ Moderate blood loss < 630 mL	22	98
➢ Severe blood loss > 630 mL)	97	-

Abbreviation: bpm, beats per minute

Source: Simel DL, et al. *JAMA* 2009, Table 24-9, page 327.

Useful background: Causes of hypovolemic shock

- Abnormal distribution
  - CNS
    - Neurogenic
  - GI
    - Hepatic failure
    - Pancreatitis
  - CVS
    - Thiamine deficiency
    - Anaphylactic
  - Infection
    - Sepsis
  - Adrenal crisis

- ↑ loses
  - GI
    - Bleeding
    - Vomiting
    - Diarrhea
  - Skin
    - Burns
    - Exudative skin lesions
  - Lung
    - Bronchorrhea
    - Allergic alveolitis
  - Kidney
    - Diuretics
    - Diabetes mellitus
    - Diabetes insipus
  - Trauma
    - Pancreatitis
    - Crush injuries
  - Malnutrition/ dehydration

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3.29, page 107, Table 4-18 and Table 4-19, page 161.

"Nothing helps more than experience."

Grandad

- Perform a directed physical examination for hypovolemia (volume depletion).
    - Tilt test: (supine or standing) – postular ↑ HR by 30 bpm (sensitivity of 97%, specificity of 96% for blood loss >630 ml)
    - Supine SBP <95 mmHg, HR > 100 bpm
    - Poor skin turgor, seen as "tenting" of skin when pinched
    - Slow capillary refill time (2 sec for children and adult males, 3 sec for adult women, 4 sec for elderly) (sensitivity for hypovolumia only 11%, but specificity of 89%)
    - Drug mucous membranes and axillae
    - Sunken eyes
    - Longitudinal tongue furrows

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 3 to 4.

Useful background: Causes of hypovolemic shock

Sources	Cause
• Hypovolemic	
➢ Trauma, postoperative	○ Bleeding
➢ Gastrointestinal tract loss	○ Bleeding, vomiting, diarrhea
➢ Renal loss	○ Diuretics, diabetes mellitus, diabetes insipus
➢ Skin	○ Burns, exudative skin lesions
➢ Respiratory	○ Bronchorrhea
➢ Third party	○ Pancreatitis, crush injuries
➢ Disable, bed bound patients	○ Lack of access to water
• Distributive shock	
○ Sepsis	
○ Adrenal crisis/hemorrhage	
○ Neurogenic	
○ Anaphylactic	
○ Hepatic failure	
○ Pancreatitis	
○ Thiamine deficiency	

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 4-18 and Table 4-19, page 161

Useful background: Performance Characteristics of Hypotension and its Prognosis

Finding	PLR
➢ Systolic blood pressure <90 mm Hg	
o Predicting mortality in intensive care unit	4.0
o Predicting mortality in patients with bacteremia	4.9
o Predicting mortality in patients with pneumonia	10.0
➢ Systolic blood pressure ≤ 80 mm Hg	
o Predicting mortality in patients with acute myocardial infarction	15.5

Source: McGee SR. *Saunders/Elsevier* 2007, Box 15.1 page 161.

Peripheral edema

Useful background: Causes of peripheral edema

- ➢ Pitting bilateral lower limb edema
  - o Cardiac
    - Congestive heartcardiac failure
    - Constrictive pericarditis
  - o Hepatic
    - Cirrhosis
  - o Renal
    - Renal failure
    - Nephrotic syndrome
  - o Gastrointestinal tract
    - Malabsorption
    - Starvation
    - Protein losing enteropathy
  - o Beri Beri (wet)
  - o Cyclical edema
  - o Drugs
    - NSAIDs
    - Calcium channel blockers
- ➢ Unilateral
  - o Deep venous thrombosis

- Compression of large veins by tumour or lymph nodes
- Lymphatic obstruction
- Venous obstruction (usually DVT; rarely, external compression)
- Venous valve incompetence from previous DVT
- Cellulitis
- Ruptured Baker's cyst
- Localized immobility (e.g. hemiparesis)

- Non-pitting lower limb edema
  - Hypothyroidism
  - Lymphedema
    - Infectious (e.g. filariasis)
    - Malignant (tumour invasion of lymphatics)
    - Congenital (lymphatic development arrest)
    - Allergy
  - Ideopathic
    - Milroy's disease (unexplained lymphedema which appears at puberty and is more common in females)

Abbreviations: DVT, deep vein thrombosis; NSAIDs, nonsteroidal anti-inflammatory drugs.

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.11, page 54; Davey P. *Wiley-Blackwell* 2006, Table 5.1, page 15.

- Take a directed history to determine the cause of lower leg edema.

➢ Heart	○ R-CCF, constrictive pericarditis, Beri beri
➢ Thyroid	○ Hypothyroidism (myxedema)
➢ GI lumen	○ Maldigestion/malabsorption, or protein-losing enteropathy
➢ Liver	○ Portal hypertension with hypoalbuminemia
➢ Lymphatic obstruction	○ Tumor, allergy, infection, idiopathic (Milroy's disease)
➢ Deep vein obstruction	

Abbreviation: GI, gastrointestinal; R-CCF, right-sided congestive cardiac failure

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.11, page 64; Davey P. *Wiley-Blackwell* 2006, page 1.

- Perform a focused physical examination to differentiate between venous edema versus lymphedema.

Useful background: Differential diagnosis of regional types of edema

Feature	Venous	Lymphedema
➢ Bilateral	+/-	+/-
➢ Foot involved	+	+
➢ Toes involved	0	+
➢ Thicken skin	0	+
➢ Stasis	+	0

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 25-7; page 1049.

- Perform a focused physical examination for causes of bilateral leg swelling:

➢ Heart	o Cardiac failure
➢ Kidney	o Renal failure
➢ Skin	o Cellulitis o Trauma
➢ Vessels	o Deep vein thrombosis o Arterial occlusion o Venous causes: varicose veins, postphlebitic limb
➢ Joints	o Arthritis
➢ Lymphatics	o Lymphoedema: Milroy's disease, filariasis (in the tropics)
➢ GI	o Hypoproteinemia
➢ Congenital	o Congenital

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 560.

- Perform a focused physical examination to distinguish between causes of arterial and venous insufficiency.

Interpretation of findings

Findings	Arterial	Venous
➢ Skin		
○ Colour	Pale, pigmented	Red
○ Thickness	↑	N
○ Ulcers	Yes (medial	Yes (lateral
○ Temperature	malleolus)	malleolus)
○ Tenderness	Cold	Warm
○ Swelling	Yes	Yes
○ Prominent veins	Yes	Yes
○ Loss of hair	No	Yes
	Yes	No

Adapted from: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto*, 2005, page 249.

- Perform a focused physical examination to differentiate between the types of regional edema.

Feature	Venous	Lymphedema	Lipedema
➢ Bilateral	Occasional	+/-	Always
➢ Foot	+	+	0
involved	0	+	0
➢ Toes	0	+	0
involved	+	0	0
➢ Thicken skin			
➢ Stasis changes			

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 25-7, page 1049.

- Perform a focused physical examination for causes of leg swelling:

➢ Bilateral
  - Cardiac failure
  - Renal failure
  - Hypoproteinemia

➢ Unilateral
  - Vein

        - Deep vein thrombosis
        - Varicose veins
        - Postphlebitic limb
    - Artery
        - Arterial occlusion
    - Tissue
        - Cellulitis
        - Trauma
        - Arthritis
        - Lymphoedema: Milroy's disease
        - Filariasis
    - Congenitial

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 560.

Useful background: Causes of peripheral edema

- Pitting bilateral lower limb edema
    - Cardiac
        - Congestive heartcardiac failure
        - Constrictive pericarditis
    - Hepatic
        - Cirrhosis
    - Renal
        - Renal failure
        - Nephrotic syndrome
    - Gastrointestinal tract
        - Malabsorption
        - Starvation
        - Protein losing enteropathy
    - Beri Beri (wet)
    - Cyclical edema
    - Drugs
        - NSAIDs
        - Calcium channel blockers

- Unilateral
    - Deep venous thrombosis
    - Compression of large veins by tumour or lymph nodes
    - Lymphatic obstruction
    - Venous obstruction (usually DVT; rarely, external compression)
    - Venous valve incompetence from previous DVT
    - Cellulitis
    - Ruptured Baker's cyst
    - Localized immobility (e.g. hemiparesis)

- Non-pitting lower limb edema
  - Hypothyroidism
  - Lymphedema
    - Infectious (e.g. filariasis)
    - Malignant (tumour invasion of lymphatics)
    - Congenital (lymphatic development arrest)
    - Allergy
  - Ideopathic
    - Milroy's disease (unexplained lymphedema which appears at puberty and is more common in females)

Abbreviations: DVT, deep vein thrombosis; NSAIDs, nonsteroidal anti-inflammatory drugs.

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.11, page 54 and Davey P. *Wiley-Blackwell* 2006, Table 5.1, page 15.

Useful background: Grading system for lower extremity arterial occlusive disease

Grade	ABI Supine Resting	ABI Post exercise
Normal	1.0-1.4	No change or increase
Mild disease	0.8-0.9	> 0.5
Moderate disease	0.5-0.8	> 0.2
Severe disease	< 0.5	< 0.2

Abbreviation: ABI, ankle to brachial systolic pressure index

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 25-3, page 1044.

Peripheral pulses

Keeping your finger on the pulse

Mangione Pearls
- "The greater amplitude of distal arteries makes them better suited for the evaluation of salable findings, such as pulsus paradoxus and pulsus alternans"
- "The analysis of the arterial pulse for the evaluation of left ventricular outflow obstruction is less reliable in older patients with hypertension or atherosclerosis"

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 180.

- Perform a focused physical examination for 5 causes of rapid ventricular contraction and low peripheral vascular resistance.

    - AV fistula
    - Thyrotoxicosis
    - Exercise
    - Anemia
    - Paget's disease
    - Beriberi
    - Pregnancy

- Pulsus paradoxus (excessive fall in SBP with inspiration, best detected with a BP cuff [sphygmomanometer]) is an alarming sign, suggestive of pericardial tamponade (almost never due to constrictive pericarditis). Give 4 other causes of pulsus paradoxus.
    - Hyperventilation
    - Valsalva maneuver
    - CHF
    - Lung disorders
        - Asthma
        - Emphysema
        - Obesity

Useful background: The arterial pulse

- The primary upstroke wave occurs in systole, and is palpable
- The percussion wave is the early part of the primary wave, which is caused by the ejection of blood from the LV into the central aorta
- The interface between the percussion wave and the tidal wave is the anacrotic notch (not palpable, only seen on tracings)
- The tidal wave is the mid – to – late systolic part of the primary wave, (forward flow) which is caused by the passage of blood from the central to the peripheral portions of the aorta (reverse flow).

Adapted from: Mangione S. *Hanley & Belfus*, 2000, page 182.

There are three types of double – peak pulses, pulsus bisferiens, bifid pulse, and dicrotic pulse.

- Bifid pulse

- The "spike and dome" double pulse is palpated at the bedside only when there is severe HOCM.
    - The initial "spike" is caused by early and rapid emptying of the LV.
    - The second "dome" wave of the bifid pulse is caused by the emptying which occurs after the HOCM-associated obstruction.

Source: Mangione S. *Hanley & Belfus*, 2000, page 185.

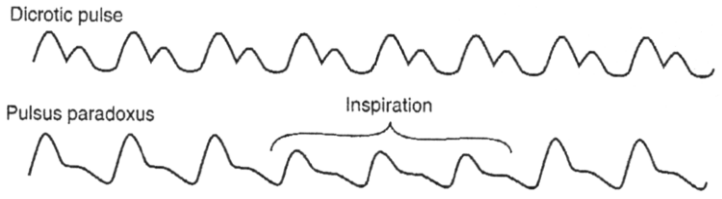
- Dicrotic pulse
  - The first peak is from emptying of the LV during systole
  - The second peak is from emptying in diastole
  - Longer interval between first and second peak than the shorter interval in the bisferiens or bifid pulse.
  - The dicrotic pulse requires elastic arteries to be palpated (not palpated in older persons)
  - Causes: low-output states
    - Pericardial tamponade (during inspiration
    - Severe congestive cardiomyopathy

- Perform a focused physical examination of the pulse to distinguish between the hyperkinetic pulse of AR versus MR.
  - Definition of hyperkinetic pulse
    - Rapid upstroke (↑ speed of contraction)
    - ↑ amplitude (↑ SV [stroke volume])
  - AR - ↑ PP (pulse pressure)
  - MR – PP is normal

Useful backgound: Pulse contours

  - Pulsus alternans is a regular pulse that has alternating strong and weak beats.

  - Pulsus bisferiens and the dicrotic pulse have two beats per cardiac cycle; in pulsus bisferiens both beats are systolic, whereas in the dicrotic pulse one is systolic and the other diastolic.



  - Pulsus paradoxus is a pulse whose systolic blood pressure falls more than 10-12 mm Hg during inspiration

- Pulsus parvus et tardus is a pulse that has a small volume and rises slowly.

- The hyperkinetic pulse is a pulse with unusually abrupt and strong force; itr may have a normal diastolic blood pressure (e.g., severe mitral insufficiency) or low diastolic blood pressure (e.g., severe aortic regurgitation).

Abnormalities of pulse contour

The normal pulse tracing (top row) is displayed with six tracings of abnormal pulse contours (bottom row).

Permission granted: McGee SR. *Saunders/Elsevier* 2007, page 125.

Useful background: Pulse contour

- Pulsus alternans
  - Regular pulse that has alternating strong and weak beats.

- Pulsus bisferiens and Dicrotic pulse
  - Have two beats per cardiac cycle: in pulsus bisferiens both beats are systolic, whereas in the dicrotic pulse one is systolic and the other diastolic

- Pulsus paradoxus
  - A pulse whose systolic blood pressure falls more than 10-12 mm Hg during inspiration

- Pulsus parvus et tardus
  - A pulse that has a small volume and rises slowly

- Hyperkinestic pulse
  - A pulse with unusually abrupt and strong force: it may have a normal diastolic blood pressure (e.g., severe mitral insufficiency) or low diastolic blood pressure, e.g., severe aortic regurgitation).

Source: McGee SR. *Saunders/Elsevier* 2007, page 125.

Useful background: Description of characteristic pulses

Pulse	Description	Causes
➢ Pulsus parvus (Hypokinetic pulse)	○ Small volume, weak pulse from ↓ LVSV	- Hypovolemia - LV failure - Shock - MI - Restrictive pericardial disease - Arrhythmia
➢ Pulsus tardus	○ Small volume, slowly rising pulse ○ Delayed with respect to heart sounds	- Aortic stenosis
➢ Hyperkinetic pulse	○ Strong, bounding pulse	○ SV - Heart block - Hyperdynamic circulation - Fever - Anemia - Exercise - Anxiety ○ Reduced peripheral resistance - Patent ductus arteriosus - Arteriovenous fistula
➢ Collapsing	○ Quick rise, quick fall	○ ↑ CO
➢ Waterhammer	○ Quick rise, full expansion, quick fall	○ AR
➢ Bisferiens	○ Double peaked pulse, mid systolic dip	○ AR, AS ○ Hypertrophic cardiomyopathy
➢ Alternans	○ Alternating amplitude of pulses (More easily detected in conjunction with blood pressure measurement)	○ CHF

Abbreviations : LVSV, left ventricular stroke volume; LV, left ventricle; MI, myocardial infarction; SV, stroke volume CHF, congestive heart failure ; CO, cardiac output ; AR, Aortic regurgitation ; AS, Aortic stenosis

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 3, page 251 and Table 4, page 252.

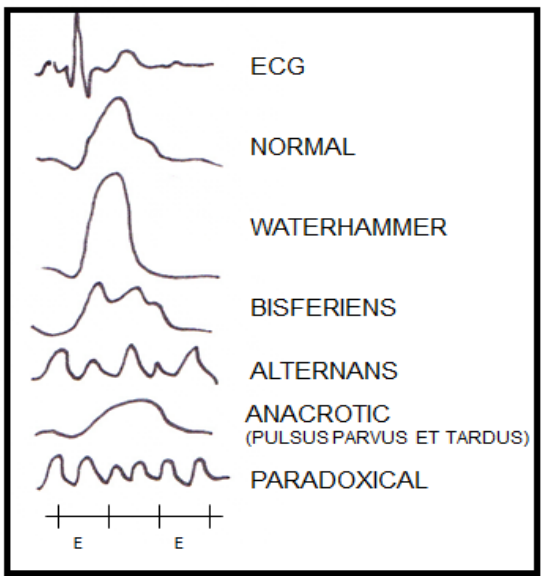
- Perform a focused physical examination for pulsus paradoxus (exaggeration of normal fall
  [> 20 mm Hg] in SBP with inspiration).

- Heart
  - L-/R- CHF
  - Pericarditis ± tamponade
  - AR
  - ASD
- Lung
  - COPD

Abbreviation CHF, congestive heart failure; AR, Aortic regurgitation; ASD, atrial septal defect

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 30-31and 63-66 .

Useful background: Abnormal arterial pulse patterns



Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 252.

Useful background: Causes of absent radial pulse

- Aberrant radial artery or congenital anomaly (check the brachials and blood pressure)
- Artery tied off at surgery or previous surgical cut-down
- Catheterization of the brachial artery with poor technique
- Following a radial artery line for monitoring of blood gases or arterial pressure
- Blalock-Taussig shunt on that side (shunt from subclavian to pulmonary artery)
- Embolism into the radial artery (usually due to atrial fibrillation)

Source: Baliga RR. *Saunders/Elsevier* 2007, page 94.

Useful background: Diagnosis of Peripheral Arterial Disease: Traditional Approach

Anatomic Segment	Location of Claudication	Femoral	Popliteal	Pedal
➢ Aortoliac	Buttock, thigh, calf	Absent	Absent	Absent
➢ Femoropopliteal	Calf	Present	Absent	Absent
➢ Peroneoribial	None or foot	Present	Present	Present

Source: McGee SR. Evidence. *Saunders/Elsevier* 2007, Table 50-1, page 598.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of increased pulse pressure in one limb (due to AV fistula), what is the area of the Branham sign? (compressing the area of suspected AV fistula causes ↓ HR).

A. Branham sign is bradycardia caused by inhibiting the ↑ RA pressure caused by the fistula, thereby inhibiting vagal and stimulating the sympathic pathway [Bainbridge reflex]).

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What is the difference between pulsus parvus plus tardis, versus hyperkinetic pulse?

A.
- Pulsus parvus plus pulsus tardis (low amplitude plus slow upstroke) usually means presence of aortic stenosis
- Hyperkinetic pulse (rapid upstroke, high amplitude): wide pulse pressure, aortic regurgitation. Normal pulse pressure, mitral regurgitation

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What is the influence of the pulse pressure (PP) on the interpretation of the palpation of a rapid arterial upstroke?

A.
- ↑ PP, rapid upstroke
  - Normal collapse
    - Mitral regurgitation
    - VSD
    - HOCM
  - Rapid collapse – aortic regurgitation
  - Hyperkinetic heart syndromes (high – output states)
- PP, rapid upstroke
  - Emptying into a low pressure area[1]
    - VSD
    - MR
  - Emptying into a high pressure area[2] - HOCM

1 rapid emptying of LV
2 LVH, delayed LV obstruction

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 184.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. Give three rechanisms for the development of pulsus parvis.

A1.
- Definition: pulsus parvis is a pulse with a low upstroke amplitude.
- Mechanisms for development of pulsus parvis
  - ↓ LV outflow, eg aortic stenosis
  - ↓ LV contraction, eg cardiomyopathy
  - ↓ LV filling, eg mitral stenosis

Q2. What is the difference in the cause of pulsus parvus by itself (↓ amplitude of upstroke, but upstroke otherwise normal), versus pulsus parvus plus pulsus tardus (slow uptake portion of arterial pulse)?

A2.
- Pulsus parvus, normal upstroke
  - ↓ LV contraction
  - ↓ LV filling
- Pulsus parvus and pulsus tardus
  - Aortic stenosis

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In which conditions may the pulse rate in one arm differ from that in the other?

A. Usually, slowing of the pulse on one side occurs distal to the aneurymal sac. Thus, an aneurysm of the transverse or descending aortic arch causes a retardation of the left radial pulse. Also, the artery feels smaller and is more easily compresses than usual An aneurysm of the ascending aorta or common carotid artery may result in similar changes in the right radial pulse.

Source: Baliga RR. *Saunders/Elsevier* 2007, page 94.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. Palpation of the peripheral arterial pulse is a time-honoured part of the physical examination. Under what circumstances should you palpate the peripheral arteries on both sides of the body, the peripheral arteries in the upper and lower portions of the body, and the carotid or brachial arteries?

A1.
- Right and left sides, considering possible asymmetry
  - Thrombosis
  - Atherosclerosis
  - Embolism
  - Dissection
  - External compression/ occlusion
- Upper and lower peripheral arteries
  - In hypertension patient who may have coarctation of the aorta, or supravalvular aortic stenosis
- Central arteries
  - When trying to characterize the form of the arterial wave

Q2. What cardiac murmur si typically associated with a slow upstroke (pulsus tardus)?

A2. Pulsus tardus is associated with aortic stenosis.

Q3. What is the mechanism causing a hyperkinetic pulse in addition to ↑ speed of contraction & ↑ SV?

A3. ↓ Arterial compliance (especially in the presence of ↑ SBP)

Abbreviation: SBP, systolic blood pressure; SV, stroke volume

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is pulsus bisferiens?

A1. Pulsus fis feriens is

- A double – peaked arterial pulse, with both peaks in systole, and both peaks usually the same height (strength)
- Characterized by
  - Rapid upstroke
  - ↑ amplitude
  - Rapid downstroke
- Caused by
  - Aortic regurgitation
  - High output states
- The pulsus bisferiens may be heard as a
  - "pistol shot" femoral bruit
  - Duroziez' double murmur

Adapted from: Mangione S.*Hanley & Belfus* 2000, page 185.

Q2. What causes a rapid arterial upstroke when input and cardiac pulse pressure are normal?

A2.
- VSD, mitrial regurgitation
- HOCM (herpertropic obstructive cardiomyopathy

A rapid arterial upstroke occurs with high output states (e.g. anemia, exercise, thyrotoxicosis, pregnancy, beriberi, Paget's disease; AV fistulas

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What is "reversed pulsus paradoxus"?

A.
- Pulsus paradoxus: inspiratory fall in systolic blood pressure (SBP) > 12 mm Hg (some authors say >10 mm Hg)
- Reversed pulsus paradoxus:
  - Expiratory fall in SBP>10 mm Hg
  - Caused by
    - HOCM
    - inspiration
    - acceleration of the sinus heart rate
    - intermittent inspiratory positive pressure breathing in L-CHF.

Source: Mangione S. *Hanley & Belfus* 2000, page 31.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is a “spike and dome bifid pulse”?

A1.
- First peak from rapid early-systolic emptying of ventricle, then an obstruction, followed by another emptying (second peak).
- Association with severe HOCM

Source: Mangione S*Hanley & Belfus* 2000, page 185.

Q2. About 98% of persons with pulsus paradoxus have cardiac tamponade. Your question: What does the remainder have?

A2.
- Atrial septal defects
- Severe left ventricular dysfunction (especially with uremic pericarditis)
- Regional tamponade (tamponade affecting only one or two heart chambers, a complication of cardiac surgery)
- Severe hypotension
- Mechanical ventilation, the amount of pulsus paradoxus, correlates with the degree of the patient's auto-positive end-expiratory pressure (auto-PEEP) (a measure of expiratory difficulty in ventilated patients).
- Aortic regurgitation - BEWARE: with AR from type A aortic dissection, the hemopericardium may eliminate the pulsus paradoxus (PP), so the lack of PP in a person with dissection does not exclude tamponade.

Source: McGee SR. *Saunders/Elsevier* 2007, page 130.

Q3. What is the difference between pulsus alternans, pulsus bisferiens, and pulsus parvus?

A3
- Pulsus alternans: strong-weak, strong-weak peripheral artery strength due to severe LV dydfunction.

- Pulsus bisferien’s are palpable peaks in systole, with fast upstroke and downstroke, with high pulse amplitude.
  - Ocurrs in severe aortic regurgitation (AR), and may be associated with concurrent aortic stenosis (AR+AS)
  - Pulsus bisforien’s once LV dydfunction occurs

- Pulsus parvus (hypokinetic pulse of the low amplitude)
  - Aortic stenosis
  - Mitral stenosis
  - Cardiomyopathy
  - ↓ LV filling or contraction

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. In the context of finding an arrhythmia, what is the “holiday heart syndrome”?

A1. Transient supraventicular arrhythmias (usually atrial fibrillation or atrial flutter) following an acute alcoholic binge in chronic alcoholics.

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 32 and 33.

Q2. In the context of the patient with an arrhythmia, what is the “holiday heart syndrome” (HHS)?

A2.
- Accentuation of the patients’ disease when their cardiologist is away on vacation!
- No!! HHS may occur when the chronic alcoholic goes on a binge of alcohol intake and develops a supraventricular arrhythmia.
- There is transient supraventicular arrhythmia (usually atrial fibrillation or atrial flutter) following an acute alcoholic binge in chronic alcoholics.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What is Friedrich’s ataxia, and what are the associated cardiac abnormalities?

A.
- Definition of Friedrich’s ataxia (FA)
  - CNS degeneration
    - Spinocerebellar tracts
    - Posterior columns
    - Pyramidal tracts
  - MSK abnormalities
    - Kyphoscoliosis
    - Pes cavis
- Cardiac abnormalities in FA
  - Cardiomegaly
  - Arrhythmias
  - Conduction defects

Useful background: Performance characteristics for Atrioventricular Dissociation and Ventricular Tachycardia

Finding	Sensitivity (%)	Specificity (%)	PLR	NLR
➢ Varying arterial pulse	63	70	NS	NS
➢ Intermittent Cannon A waves, neck, veins	96	75	3.8	0.1
➢ Changing intesitity S_1	58	98	24.4	0.4

Source: McGee SR. *Saunders/Elsevier*, 2007, Table 14-1, page 149.

Useful background: Carotid bruits in an asymptomatic patient

- Auscultated in 16% of normal adults, and 15% of children (<15 yrs)
- Increases the risk of TIAs/CVAs and the need for coronary artery bypass by 3-fold
- Seen in 10% of the surgical population
- Not predictive of perioperative CVA
- Are predictive of transient post operative dysfunction and behavioural problems

Source: Simel DL, et al. *JAMA* 2009, pages 107 to 110.

Useful background: Main diseases affecting arteries of varying sizes

Size of artery	Main lesions
➢ Large	o Arteriosclerosis o Syphilis o Embolism (due to clots, or rarely to tumour or fungus emboli) o Takayasu's disease
➢ Medium	o Polyarteritis nodosa o Monckeberg's sclerosis o Giant cell arteritis o Buerger's disease o Arteritis of severe infection and malignancy o Embolism o Arteriosclerosis
➢ Small arteries and arterioles	o Hypertension o Dermatomyositis o Scleroderma o Raynaud's phenomena o Rheumatoid arthritis o Ergotism

Source: Davey P. *Wiley-Blackwell* 2006, page 233.

Sweet Nothing:
Pulsus parvus plus pulsus tardis (low amplitude plus slow upstroke) usually indicates the presence of aortic stenosis.

- Hyperkinetic pulse (rapid upstroke, high amplitude): wide pulse pressure, aortic regurgitation.
- Normal pulse pressure, mitral regurgitation.

- What does the peripheral pulse tell you about blood pressure (BP)?
  - Systolic BP – pressure on peripheral artery needed to obliterate the pulse
  - Diastolic BP – volume of pulse

- What causes unequal radial pulses, yet equal brachial pulses?
  - Abnormal position of radial artery

- What causes unequal radial and brachial pulses?
  - Obstruction of artery: thrombus, embolus, aneurysm, mediastinal compression

- If the volume of the peripheral pulse volume seems to be abnormal, what maneuver can you undertake to establish if this is a false-positive finding?
  - Suspicion of pulse volume being
    - Large: rise arm
    - Small: lower arm

- What does the patient with systemic hypertension not develop a collapsing pulse?
  - A collapsing pulse is the result of an increase in the pulse pressure; the pulse pressure is the difference between the systolic and the diastolic blood pressures [SBP & DBP, respectively]). In systemic hypertension, there is an increase in both SBP & DBP, so the pulse pressure (SBP minus DBP) may not be sufficient to cause a collapsing pulse.

- Give 5 causes of a collapsing pulse.
  - Aortic regurgitation (AR)
  - AV shunts
  - 3rd – degree heart block
  - Fever (may be associated with “dicrotic” pulse)
  - Anemia
  - Chronic liver disease

 Aortic regurgitation (AR) increases the pulse pressure and leads to a collapsing pulse (which may be associated with marked transmitted bilateral pulsations in the neck), where as aortic stenosis (AS) leads to a low pulse pressure and a pulse volume which is small, plateau or anacrotic.

In persons with combined AR plus AS, what is the typical pulse?

- Biferiens

 What is the effect of inspiration on pulse rate and volume?

- pulse rate and volume
- When pulse rate and volume decrease on inspiration, this is called "pulses paradoxicus"
- Pulsus paradoxicus is commonly caused by
  - Reactive airway disease (asthma)
  - Constrictive pericarditis pericardial effusion
  - Obstruction of the SVC (superior vena cava)

Clinical bedside APPs "The Western Way"

 Jugular venous distention (JVP) is associated with a, c and v waves. What are the causes of

 JVP and the absence of pulsations?

- The pressure in the jugular veins is increased because of obstruction in the superior vena cava (SVC) or in the jugular veins themselves.

 Under what circumstance will the hepato-jugular reflex be absent in the person with JVP?

- JVP due to venous obstruction

- Give the differences in the signs & causes of PVD (peripheral vascular disease).
  - Obstructive
    - Claudication
    - Absent pulses
    - Colour changes
      - Leg elevation – foot blanching
      - Leg depression – slow venous filling
    - Common causes
      - Atherosclerosis
      - Thrombo- angiitis obliterans
      - Polyarteritis
      - Embolism

- Non – obstructive
  - Raynaud's phenomenon (white, blue, red)
  - Pain
  - Paresthesia
  - Coldness
  - Common causes (AT-complete)

- Give 3 common effects of diabetes on blood vessels.
  - Atheroma
  - Hypertensive arterial sclerosis
  - Small vessel disease
    - Retina
      - Microaneurysm
      - Retinitis
    - Kidney
      - Intercapillary glomerulosclerosis

- Perform a focused physical examination for an abnormally widened pulse pressure.

➢ Definition: pulse pressure > 50% of systolic blood pressure

➢ Causes
  - Hyperdynamic heart syndrome (↑SV, ↓PVR)
  - Aortic regurgitation
  - Patent ductus arteriosus (PDA)
  - Exercise
  - Anemia
  - Arteriovenous fistulas
  - Beriberi
  - Paget's disease
  - Cirrhosis
  - Pregnancy
  - Thyrotoxicosis
  - Severe exfoliative dermatitis

Abbreviations: PVR, peripheral vascular resistance; SV, stroke volume.

- Take a focused history and perform a directed physical examination for causes of hyperkinetic heart syndrome causing an abnormally wide pulse pressure (PP) (PP > 50% of systolic BP).

➢ Increased pulse pressure
  - Heart
    - Aortic regurgitation
    - Patent ductus arteriosus
    - AV fistula

- Lung
  - Hypercapnia
- Metabolic
  - Fever
  - Anemia
  - Beriberi
  - Hyperthyroidism
- Bone – Paget's disease
- Liver – cirrhosis
- Skin – severe exfoliative dermatitis
- Pregnancy

- Reduced pulse pressure (PP; PP < 25% of SBP).
  - Aortic stenois
  - Constrict percarditis
  - Cardiac tamponade
  - Tachycardia
  - Hypotension

- Differences in blood pressure between arms or between arms or between the arms and legs.
  - Occlusion or stenosis of the artery of any cuase
  - Coarctation of the aorta
  - Dissecting aortic aneurysm
  - Patent ductus arteriosus
  - Supravalvular aortic stenosis
  - Thoracic outlet syndrome

Useful background: Cause of differences in blood pressure between arms or between arms or between the arms and legs?

- Heart
  - Patent ductus arteriosus
  - Supravalvular
- Aorta
  - Coarctation of the aorta
  - Dissecting aortic aneurysm
  - Aortic stenosis
- Artery
  - Occlusion or stenosis of the artery of any cuase
  - Thoracic outlet syndrome

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 94.

Arrhythmias

Useful background: Abnormalities in the pulse rate

- Bradyarrhythmias-
  - Sinus bradycardia
  - Sick sinus syndrome
  - Junctional and ventricular escape rhythmias

- Conduction delays
  - 1°, 2°, or 3° AV nodal block
  - Fascicular block
  - Bundle branch block

- Irregular Tachyarrhythmias
  - Sinus arrhythmia
  - Atrial fibrillation
  - Multifactorial atrial tachycardia
  - Atrial flutter with variable block
  - Atrial or ventricular premature beats
  - Extrasystoles (ventricular or supra-ventricular)
  - 2º heart block
  - Ventricular fibrillation
  - Irregularity of volume also occurs in pulsus paradoxus and pulsus alternans

- Regular Tachyarrhythmias - narrow complex:
  - Supraventricular tachycardia
  - Atrial flutter
  - Wolfe-Parkinson-White syndrome
  - AV node re entry tract

- Wide complex:
  - Supraventricular tachycardia with aberrance or bundle branch block
  - Ventricular tachycardia, torsades de pointes

- Unstable arrhythmia
  - Arrhythmia plus hypotension, dyspnea, chest pain, presyncope, or syncope.

Abbreviation: AV, atrioventricular; $1^0/2^0/3^0$ – first, second or third degree heart block

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, page71 and 72; and Burton JL. *Churchill Livingstone* 1971, page 12.

Atrial fibrillation (AF)

Atrial fibrillation and flutter are supraventricular tachyarrhythmias in which there is an increased risk of thromboembolism stroke. The $CHADS_2$ score is a tool to stratify the risk of stroke in persons with non valvular atrial fibrillation or flutter, and to determine who should be treated with ASA, clopidogrel or warfarin.
Take a directed history and perform a focused physical examination to calculate the $CHADS_2$ score.

	$CHADS_2$ risk criteria	Assigned score
C	Congestive heart failure	1
H	Hypertension	1
A	Age > 75 years	1
D	Diabetes mellitus	1
S	Prior stroke or transient ischemic attack	2

Quoted from: Birnie D and Nery P. Chapter 42. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 578.

Dysrhythmias

- Definitions
  - Ventricular tachycardias (VT): "……≥ 3 consecutive ventricular complexes at a rate > 100 BPM on an ECG recording".
  - Ventricular fifibrillation (VF): "….a rapid, disorganized rhythm without recognizable QRS complexes on the ECG".

Dorian P, et al. Chapter 43. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 587.

- Perform a focused physical examination for AF.

- Pulse
  - Irregularily irregular pulse
  - Differentiate from other causes of irregularily irregular pulse
    - AF (atrila fibrillation)
    - MVE (multiple ventricular ectopics (unlike AF, MVE become less frequent with exercise)
    - Atrial flutter plus varying block
    - Complete heat block (pulse rate is slow, but irregularily irregular)

- Deficit
  - HR > PR (heart rate [HR] is greater than pulse rate [PR])
  - Pulse deficit increases when HR increases
- Exercise
  - ↑ pulse deficit
  - No effect on frequency of AF

- JVP
  - Less of 'a' waves

- Heart sounds
  - S_1 varies in intensity
  - S_2 split

- Sign of causes of AF
  - Heart
    - Mitral valve disease
    - Ischemic heart disease
    - Hypertension
    - Constrictive pericarditis
  - Thyroid - hyperthyroidism
  - Lung – chronic pulmonary disease
  - Congenital
    - ASD (atrial septal defect)
    - Ebstein's anomaly
  - "lone" atrial fibrillation

- Perform a focused physical examination to determine the cause of atrial fibrillation.

- Heart
  - Mitral valve disease
  - IHD
  - HBP
  - Constrictive pericarditis
  - Cardiomyopathy
  - ASD
  - Ebstein's anormaly
- Lung
  - Chronic pulmonary disease
- Thyroid
  - Thyrotoxicosis
- Ideopathic
  - 'Lone fibrillation'

Abbreviation: IHD, ischemic heart disease; HBP, hypertension (systemic); ASD, atrial septal defect

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, pages 32 and 33.

- Perform a focused physical examination for risk factors for thromboembolism in non-rheumatic atrial fibrillation.

Clinical Risk Factors

- Congestive heart failure
- Hypertension
- Age >75 years
- Diabetes mellitus
- Prior stroke
- Other high-risk clinical settings
  - Prosthetic heart valves
  - Thyrotoxicosis

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, page 85.

- There are many causes of sinus tachycardia (heart rate [HR]) greater than 120 bpm (beats per minute), but what are the causes of HR ≥ 140 bpm?
  - Atrial fibrillation (AF)
  - Atrial flutter
  - PAT (paroxysmal atrial fibrillation)

Using carotid massage, how can you distinguish between these 3 causes of HR > 140 bpm?
- AF – no effect on HR
- Atrial flutter – HR slowed temporarily
- PAT – stops, or no effect

From the examination of the pulse deficite (difference between heart rate and pulse rate) and the JVP, distinguish between the three major causes of an irregular pulse.

Signs	A	ES	H
o Pulse defiate	+	+	-
o Irregulate rate and rhythm	+	-	-
o Effect of exercise an irregularily	□	□	□*
o Beats followed by a compensatory pause	-	+	+

Abbreviations: AF, atrial fibrillation; ES, extrasystoles; HB, heart block; HR, heart rate

*Note: when to suspect a complete heart block
- HR of 36 – 44 bpm
- HR does not increase with exercise

- Take a directed history for the causes of sinus bradycadia and tachycardia.

➢ Sinus bradycardia
  - Physiological (conditioning)
  - Hypothyroidism
  - Jaundice
  - Increased intracerebral pressure
  - Mumps
  - Amebic abscess
  - Drugs
  - Familial
  - Congenital

➢ Causes of slow regular pulse
  - Sinus bradycardia
  - Complete heart block
  - 2:1 AV block
  - Atrial flutter with 4:1 AV block
  - Idionodal rhythm
  - Idioventricular rhythm

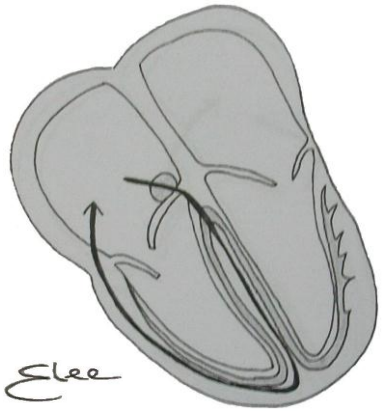
➢ Causes of a 'dropped beat'
  - Sinoatrial block
  - Blocked atrial extrasystole
  - 2nd degree heart block

➢ Tachycardia
  - Causes of sinus tachycardia
    - Exercise or emotion
    - Constitutional
    - Anemia
    - Thyrotoxicosis
    - Fever
    - Congestive heart failure
    - Constrictive pericarditis
    - Drugs (e.g adrenaline, atropine, nitrites)
    - Acute hemorrhage
  - Supraventricular (atrial or nodal) tachycardia
  - Atrial flutter
  - Atrial fibrillaton
  - Ventricular tachycardia
  - Ventricular flutter

Abbreviation: AV, atrio-ventricular

Printed with permission Burton JL. *Churchill Livingstone* 1971, pages 11 and 12.

Typical mechanism of supraventricular tachycardia in patients with Wolff-Parkinson-White syndrome (WPS syndrome)

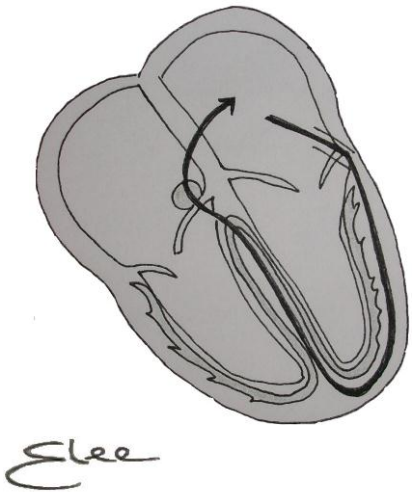


- The result WPS syndrome is a narrow QRS complex because ventricular activation is over the normal conduction system.
- WPS syndrome arises from orthodromic atrioventricular re entry.

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Figure 3-33, page 88.

Mechanism of supraventricular tachycardia in patients with

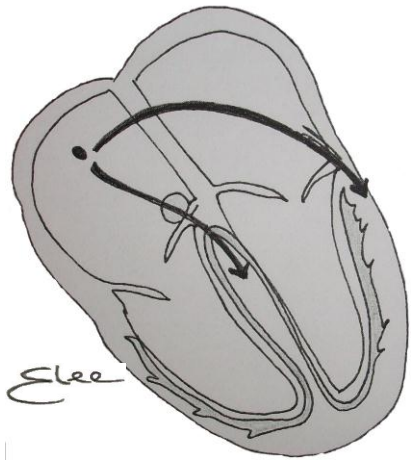
Wolff-Parkinson-White syndrome



- The result is a wide QRS complex because ventricular activation is over an accessory pathway.
- This arrhythmia is difficult to distinguish from ventricular tachycardia.

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Figure 3-34, page 88.

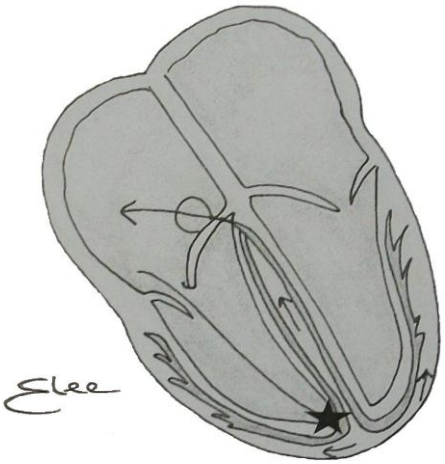
Conduction of sinus impulses in Wolff-Parkinson-White syndrome



- The ventricles are activated over the normal atrioventricular node – His-Purkinje system and accessory pathway; the result is a fusion complex (QRS and delta wave).

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Figure 3-35, page 88.

Pacemaker syndrome



- Retrograde atrial activation during ventricular pacing (star) produces simultaneous atrial and ventricular contractions.

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Figure 3-19, page 75.

Useful background: The effect of exercise and vagal stimulation on tachyarrhythmias

		Vagal stimulation	Exercise
➢ Atrial	○ flutter	↓	↑
	○ Fibrillation	-	↑
	○ PAT	↓	
	○ APC	-	↓
➢ Sinus	○ Bradycardia	-	↑
	○ Arrhythmia	-	↓
	○ 2^0 HB	-	↑
	○ 3^0 HB	-	-

Abbreviations: APC, atrial premature contraction; HR, heart rate; PAT, paroxysmal atrial tachycardia; $2^0/3^0$ HB second/third degree heart block

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.5, page 41.

- Perform a focused physical examination for the causes of bradycardia/ heart block.

➢ Classification
  - Sinoatrial block
  - AV block:
    - 1º, P.R>0.2 sec
    - 2º Mobitz (fixed PR)
    - Wenkebach (varying PR)
    - High grade (2:1, 3:1, etc)
    - 3º complete
  - Bundle branch block
  - Short PR with long QRS (Wolff-Parkinson-White)

➢ Heart
  - Athletes
  - Sleep
  - Apparent (pulse deficit [PR<HR] in AF, ventricular bigeminy)
  - Block (3˚ AV block, or type I or II 2˚ AV block)
  - Myocardial infarction (MI; ischemic heart disease)
  - Vasovagal episode
  - Cardiomyopathy
  - Sinus arrhythmia (↓PR with expiration)

➢ MSK
  - Collagen vascular disease

- Hypothermia
- Hypothyroidism
- Hepatic
  - Severe jaundice
- Head
  - Increased intracranial pressure
  - Trauma
- Drugs
  - B-blockers, digoxin, amiodarone
- Tachycardia
- Heart
  - CCF
    - Constrictive pericarditis
    - Myocardial infarction (MI)
    - Myocarditis
    - Aortic stenosis
    - Hypertension
  - Rhythm
    - Supraventricular tachycardia
    - Ventricular tachycardia – hyperthyroidism, acute hypoxia or hypercapnea, sick sinus syndrome
    - Atria flutter with 2:1 AV block, or with variable block
    - Multifocal atrial tachycardia
  - Hyperdynamic circulation
    - Exercise
    - Emotion
    - Fever
    - Hypolemia
    - Anemia
    - Hyperthyroidism
    - Pregnancy
    - AV fistula (Paget's disease)
    - Beriberi
  - Drugs
    - Anticholinergics
    - Sympathomimetics

Abbreviations: AF, arterial fibrillation; AV, atrioventricular; CCF, congestive cardiac failure; HR, heart rate; MI, myocardial infarction; PR, pulse rate; Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.5, page 41; Burton JL. *Churchill Livingstone* 1971, pages 12 and 13; and Baliga RR. *Saunders/Elsevier* 2007, page 37.

Useful background

- Causes of RBBB
  - Normal (variant)
  - RV strain (especially pulmonary embolism)
  - ASD
  - Myocardial ischemia
  - Myocarditis

- Effects of digitalis
  - Bradycardia
  - PR prolongation
  - QT shortening
  - ST depression
  - T inversion
  - Any arrhythmia

- Hyper-/ hypokalemia

	↑ K^+	↓ K^+
P	Absent	-
PR	-	Long
QRS	Wide	-
T	Tall	absent
ST	-	Depressed
U	-	Tall

- Hyper-/ hypocalcemia

	↑ Ca^{2+}	↓ Ca^{2+}
QT	Short	Long

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 21.

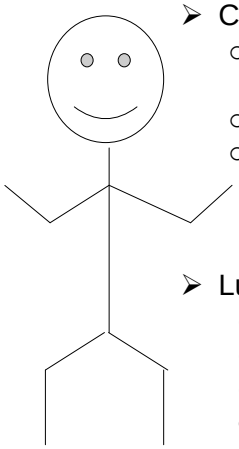
"Science, like good diagnosis, represents incremental progress of small steps taken slowly on solid ground."

Grandad

Palpitations

- Take a directed history for palpitations.

➢ Definition: sensations of a rapid or irregular heartbeat occurring in normal, healthy people during exercise and states of anxiety.



➢ General
  - Presyncope/syncope
  - Malaise/fatigue
  - Fever/chills/night sweats
  - Diaphoresis

➢ CNS
  - Numbness/paresthesia
  - Weakness
  - Visual/ speech abnormalities

➢ Heart
  - Slow vs. rapid, regular vs. irregular
  - Frequency of bouts
  - Duration
  - Nature of onset/offset

➢ Lung
  - Lung base crackles
  - Dyspnea/orthopnea/PND
  - Cough
  - Chest pain

➢ Ankles/ sacrum edema

➢ Causes
  - Heart
    - Pericardial (pericarditis)
    - Myocardial (LVH, infarction, CHF, myxoma, ASD, amyloidosis)
    - Endocardial (infarction, sick sinus, valvular- MS/MR, AS/AR
  - Lung
    - Asthma, COPD
    - Pneumonia
    - Pulmonary embolism
  - Endocrine
    - Hyperthyroid
    - Pheochromocytosis
    - Hypoglycemia
  - Drugs and Toxins
    - EtOH (binge or withdrawal)
    - CO poisoning
    - Stimulants (caffeine, theophylline, amphetamines, cocaine)
  - Metabolic – electrolyte abnormalities
  - Infection – sepsis

Abbreviations: ASD, atrial septal defect; CHF, congestive heart failure; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CVA, cerebro vascular accident; ETOH, ethanol; LVH, left ventricular hypertrophy; PND, paroxysmal nocturnal dyspnea; TIA, transient ischemic attack

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 70 and 71.

Palpations of precordium

Useful background: Palpations

- Only about 1 person in 6 with palpitations will have a cardiac arrhythmia.
- Palpitations may be present only with exercise, especially if the basal heart rate is slow.
- Causes
  - Heart disease causing
    - Tachycardia
    - Bradycardia
    - Extrasystole
  - Causes of tachycardia
    - Fever
    - Exercise
    - Hyperthyroidism
    - Pheochromocytoma
    - Hypoglycemia
  - Anxiety (da Costa's syndrome, aka cardiac neurosis)
  - Drugs

- Perform a focused physical examination for palpitations.

- Head and neck
  - ↑ JVP
  - If JVP pulsations match the heart rate, especially with tachycardia, suspect AV nodal re-entrant trachycardia
- Pulse
  - ↑ HR, ↓ HR, AF, MVE (irregular irregularity decreases with exercise)
- Heart sounds
  - S_1 varies in intensity, and S_2 may be split in AF
- Murmur
  - Any associated cardiac conditions

Going for Gold

In a patient with a history of palpitations, perform a focused physical examination of the ECG.

- P wave
  - Matched in II (AF)
  - Terminal wave > 0.04s negative (AF)
- PR interval short, with delta waves – look for WPWS (Wolff – Parkinson – White syndrome)

➢ Q wave	○ Present, suggests previous infarction, leading to possible non-sustained ventricular tachycardia ○ Deep Q waves (I, L, V4 to V6) suggesting LVH and possible HOCM
➢ QT interval long, abnormal T wave morphology	○ Possible long QT syndrome
➢ ↓ HR, HB	○ Look for long QT syndrome and torsade de pointes

Abbreviation: LVA, left ventricular hypertrophy; HOCM, hypertrophic obstructive cardiomyopathy; HB, heart block

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 35 and 36.

Useful background: Performance Characteristics of Palpation of the Precordium.

Finding	PLR	NLR
➢ Hyperkinetic apical movement		
○ Detecting associated mitral regurgitation or aortic valve disease in patients with mitral stenosis	11.2	0.3
➢ Sustained apical movement		
○ Detecting severe aortic stenosis in patients with aortic flow murmurs	4.1	0.3
○ Detecting moderate-to-severe aortic regurgitation in patients with basal early diastolic murmurs	2.4	0.1
○ Detecting right ventricular peak pressure $\geq$ 50 mm Hg	3.6	0.4
○ Palpable P_2 [1]		
- Detecting pulmonary hypertension in patients with mitral stenosis	3.6	0.05
○ Absence of palpable P2		0.05

Finding	PLR	NLR
➢ Varying intensity of S1, detecting AV dissociation in the presence of tachycardia	24.4 (probability > 50%)	0.4
➢ Palpable P2, detecting PHT	3.6 (probability ~25% ↑)	
➢ Position of apical beat - Supine apical impulse lateral to MCL		
○ Detecting cardiothoracic ratio >0.5	3.4	0.6
○ Detecting low ejection fraction	10.1	0.6
○ Detecting increased left ventricular end diastolic volume	8.0	0.7
○ Detecting pulmonary capillary wedge pressure >12 mm Hg	5.8	NS
➢ Size of apical beat - Apical beat diameter ≥4 cm in left lateral decubitus position at 45 degrees		
○ Detecting increased left ventricular end diastolic volume	4.7	NS

Note that a supine displaced apical impulse has a PLR < 2, and is not included here.

Abbreviations: AV, atrioventricular; EF, ejection fraction; PLR, positive likelihood ratio; NLR, negative likelihood ratio; MCL, midclavicular line; NS, not significant; PHT, pulmonary hypertension

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 34-2, page 404.

Useful background: Apical (pericardial) impulse (PMI, point of maximal impulse)

- Double or even triple apical impulses occur in HOCM
- Pericardial impulse in mitral stenosis represents palpable S_1 and S_2 (from P_2 components), opening snap, and diastolic thrill (patient in left lateral deculoitus position).
- Precardial impulse in tricuspid regurgitation: palpable S_2 (from P_2 component) over pulmonic area, RV parasternal, pulsatile synchrony with each cardiac systole.
- Ectopic apical impulse (superior and medially): angina/previous MI, LV aneurysm, LV dyskimesia.

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 201,202; Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, page 49 to 50; Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 7 page 58.

Useful background: Performance characteristics of size and position of palpable apical impulse.

Finding (Ref)	PLR
➢ POSITION OF APICAL BEAT	
➢ Supine apical impulse lateral to MCL	
o Detecting cardiothoracic ratio >0.5	3.4
o Detecting low ejection fraction	10.1
o Detecting increased left ventricular end-diastolic volume	8.0
o Detecting pulmonary capillary wedge pressure >12 mmHg	5.8
o Detecting increased left ventricular end-diastolic volume	4.7

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 34-1, page 402.

Heart Sounds

➢ S_1 and S_2

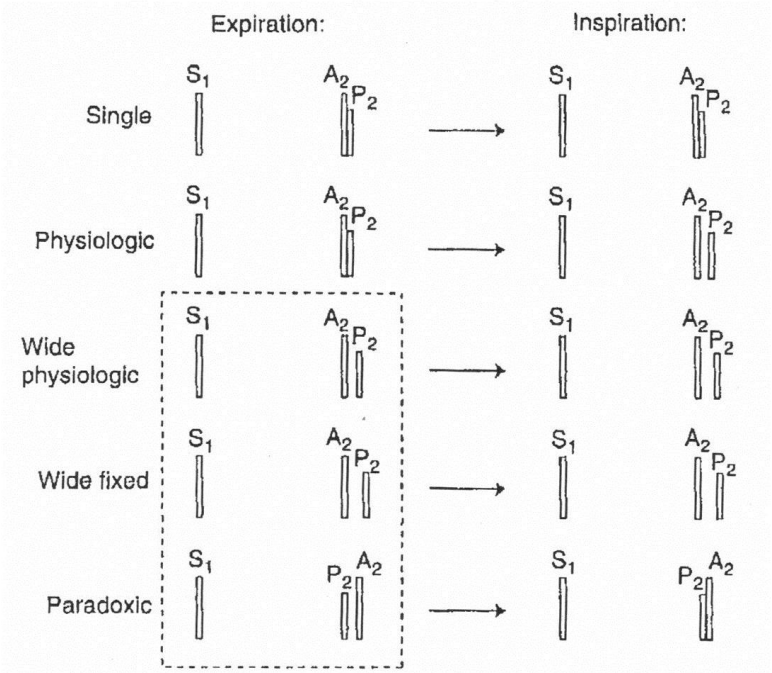
Sounds and extra sounds		Conventional teaching revisited
S1	↔	Still informative and valuable, albeit not as much as S2.
S2	↑	One of the most valuable sound, particularly in its variations of intensity and splitting.

Source: Mangione S. *Hanley & Belfus*, 2000, page 207

Useful background: Special positions and maneuvers for optimal auscultation of heart sounds

Position	Effect on heart sounds
➢ Sitting upright, leaning forward, holding exhalation	↑AS, AR, pericardial rubs
➢ Left lateral decubitus (LLD) (use bell of stethoscope)	S_3, S_4, MS

Useful background: The first (S_1) and second (S_2) heart sounds.



Adapted from: McGee SR. *Saunders/Elsevier* 2007, page 423.

Maneuver	Physiological effect	Effect on heart sounds
➢ Leg elevation	↑Venous return	↑Right sided murmurs, TR, PS
➢ Fist clenching	↑Systemic arterial resistance	↑Some left sided murmurs MR, AR, VSD; ↓ AS
➢ Squatting	↑Venous return, ↑vascular tone	↓MVP, HCM; ↑ AS
➢ Standing (opposite to squatting)		

Abbreviations: AS, aortic stenosis; AR, aortic regurgitation; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PS. Pulmonary stenosis; TR, tricuspid regurgitation; VSD, ventricular septal defect

Adapted from: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 12, page 63.

- Give the disease processes associated with a loud, variable or soft intensity of S_1.

➢ General concepts
  - Normal closure of MV and TV
  - Sequence: mitral (M_1) and then tricuspid (T_1) close, pulmonary and then aortic valves open
  - Apex high pitched
  - ↑ S_1
    - ↑ HR
    - Hyperkinetic heart (eg. AR, PDA, AV fistulas, fever, anemia, thyrotoxicosis, beriberi, Paget's disease)
    - ↑ LAP (early MS)
    - ↓ PR interval (S_1 becomes softer with AV blocks; pre-excitation syndromes such as WPW [Wolff-Parkinson-White]
    - ↓ PR interval (<160 msec)
    - ↑ Thickness of AV or TV leaflets (when leaflets later become rigid or fixed, S_1 becomes softer or absent)
    - ↑ AV pressure gradient
  - ↓ S_1
    - ↑ PR intermal (> 20 msec)
    - LV dysfunction
    - LBBB
    - 1st degree heart block
    - Calcified AV
    - Acute AI (premature closure of MV)
    - MI, TI
    - CHF
  - Variable S_1
    - AF
    - Conduction heart block
    - Progressive increase in duration of PR interval (Wenckeback phenomenon) with MS, MV prolapsed with regurgitation
    - MS
    - MV prolapsed with regurgitation
  - Split S_1: RBBB/LBBB

➢ Listen with diaphragm over apex for mitral component (M_1), and over epigastric/subxiphoid area for less important tricuspid component (T_1)

➢ S_1 should be louder than S_2 in these locations

Abbreviation: AF, Atrial fibrillation; AI, aortic insufficiency; AV, atrio-ventricular; CHF, congestive heart failure; HB, heart block; LAP, left atrial pressure; MS, mitral stenosis; MV, mitral valve; PDA, patent ductus arteriosis; TV, tricuspid valve
Adapted from: Mangione S. *Hanley & Belfus* 2000, page 207.

- Variable intensity of S1
- Variations of intensity (loudness) are what is the most useful clinically
- Second-degree heart block (type1 Wenckebach phenomenon; S_2 remains of constant intensity, S_1 progressively softens)
- Third-degree (complete) AV block (change in intensity of S_1 is random and chaotic; rhythm is slow and regular).
- Atrial fibrillation (rhythm is regularity irregular)
- Pulsus alternans
- Soft intensity of S_1
    - Calcified mitral stenosis
    - Long P-R interval
    - L-CHF
    - Severe aortic or mitral regurgitation
    - Myocardial infarction
    - LBBB
- Wide splitting of S_1
    - Best heard over left lower sternal border
    - Usually from delayed closure of tricuspid valve (T_1), such as from RBBB
    - Wide splitting of S_2 may also occur with wide splitting of S_1
- Pseudosplitting of S_1
    - Normal S_1 proceeded by S_4 (heard only at apex, low-pitched, soft heard best with bell of stethoscope)
    - S_1 may be followed by early systolic ejection click (loudest over the base, high-pitched, loud heard best with diaphragm).

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 210-216; Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, pages 54 and 55.

- Give 4 causes of wide & fixed splitting of S_1 (A_1, P_1); delay in producing P1 component of S_1).
    - RBBB
    - Pulmonary stenosis
    - R – CHF
    - ASD
    - PDA

Abbreviations: ASD, atrial septal defect; RBBB, right bundle branch block; PDA, patent ductus arteriosis; R-CHF, right-sided congestive heart failure.

Effects of inspiration

- □ flow of blood in IVC
- □ flow of blood into RV
- □ blood in RV takes longer to expel
- P valve closes after aortic valve (A-P)
- □ pulse rate and volume

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of splitting hairs, what causes splitting of the second heart sound (S2, comprised of A2 and P2)?

A.
- Physiologic
- Delayed A2 (delayed closure of Aortic valve) from
  - ASD,
  - severe MR (mitral regurgitation),
  - severe CHF,
  - severe pericardial tamponade
- Delayed A2 and P2
- Delayed P2 (delayed closure of pulmonic valve)
  - RBBB
  - Severe impedence of the emptying of RV
    - PS (pulmonary stenosis)
    - Cor pulmonale + R-CHF
    - ASD (atrial septal defect)
    - Massive PE (pulmonary embolus)

SO YOU WANT TO BE A CARDIOLOGIST!

Q. Does S2 reflect the prognosis of the underlying condition?

A. A delayed P2 will cause splitting of S2; when there is expiratory splitting of S2, there has usually been a massive pulmonary embolism leading to the development of acute cor pulmonale.

- Give 3 causes of reversed ("paradoxical") splitting of S_1.

- Definition P_1 before A_1; when LV systole is long or the LV is activated late (LBBB), the A_1 may be delayed and occur with or after P_1. If P_1 occurs with A_1 there will be only one sound during inspiration but two sounds are heard with expiration ($P_1 - A_1$)

- Cause
  - Aortic stenosis (AS)
  - Left bundle branch block (LBBB)
  - Left ventricular failure (L-VF, aKa L-CHF)

S_3
  - Mechanism : early, rapid filling of ventricles, resulting in sudden distention of walls of LV, as well as turbulent flow across the mitral valve
  - Clinical
    - Just internal to apex
    - Loudest at end of expiration
    - Patient on left side
    - Not heard when atrial fibrillation is present
  - Pathological after age 40 years
  - Caused by
    - Myocardial infarction
    - Mitral or tricuspid regurgitation
    - R-/L-CHF
    - Constrictive pericarditis
    - Ventricular septal defect

S_4
  - Due to construction of the atria at the end of diastole, but reduced filling of the ventricles.
  - Causes
    - Myocardial ischemia/ infarction
    - L-CHF
    - Finding and S_4 suggests heart disease, but does not suggest a cause

Note: When there is □ HR, the S_3 and S_4 cannot be identified separately, and the combined sound is the "summation gallop"

Useful background: Second Heart Sound, S_2 ("dub").

- General Concepts
  - Heard best with the diaphragm over base of heart in the pulmonary area (Left 2^{nd} /3^{rd} parasternal intercostals spaces).
  - Produced by the sudden slowing of blood from with closure of the aortic (A_2) and then pulmonary (P_2) valves; P_2 canbe heard normally only a few centimetres to the left of the upper sternal border
  - Splitting of S_2 and the various forms of splitting is not useful clinically; heard best (because of hearing P_2) at the 2-3 left interspace.
  - Heard best a few centimetres to the left of the sternal border.

- Loudness: a loud A_2, or a loud P_2

- Pulmonary or systemic or systemic hypertension
- Correlation of the aorta
- High-output states
- a soft A_2, or soft P_2 – aortic or pulmonary valve stenosis
- P_2 louder than A_2 – aortic or pulmonary valve stenosis
- S_2 louder than S_1 at apex – pulmonary or systemic hypertention

➢ Single splitting of S_2 (A_2 and P_2 cannot be head as distinct sounds, so merge into a single sound)
- Paradoxical (reversed) splitting (splitting in expiration)
- Pulmonary hypertension
- Emphysema (hyperinflatted lungs muffle P_2, so only A_2 is heart; P_2 is however still produced, so this is "pseudoparadoxical" splitting)

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 210 to 216 and Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, pages 54 and 55.

- Perform a focused physical examination for causes of fixed splitting of S_2.

➢ Definition
- Normal - ↑ split between A_2 and P_2 on inspiration
- Abnormal – effect of inspiration to increase the distance between A_2 and P_2 is lost.

➢ Causes
- ASD (atrial septal defect)
- VSD (ventricular septal defect)
- PR (pulmonary regurgitation)
- PS (pulmonary stenosis)
- RBBB (right bundle branch block)
- MR, VSD (mitral regurgitation)

Useful background: The performance characteristics of S_1 and S_2 findings

➢ Paradoxic splitting is of no significance in detecting aortic stenosis, and a loud P_2 is not a significant test to detect a mean pulmonary arterial pressure ≥ 50 mm Hg (pulmonary hypertension, PHT)

➢ S_1 of varying intensity has a positive likelihood ratio (PLR) of 24.4 to detect AV dissociation. S_2 with fixed wide splitting has a PLR of .6 for detecting ASD, whereas a palpable P2 has a PLR of 3.6 for detecting PHT.

Finding	PLR
➢ S_1	
○ Varying intensity, Detecting AV dissociation	24.4
➢ S_2	
○ Fixed wide splitting, detecting ASD	2.6
○ Paradoxic splitting, detecting AS (peak gradient >50 mm Hg)	NS
○ Loud P_2, detecting PHT (mean PAP $\geq$50 mm Hg)	NS
○ Palpable P_2, detecting PHT	3.6

Abbreviations; AS, aortic stenosis; ASD, atrial septal defect; AV, Atrio ventricular; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PAP, pulmonary arterial pressure; PHT, pulmonary hypertension; S1, first heart sound; S2, second heart sound

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 36.1, page 420.

- Perform a focused physical examination of the heart sounds. Explain what underlying cardiac abnormalities may be determined from this examination.

○ S_1
  - Caused by vibrations in cardiohemic system (chordae tendinae, ventricles, and blood)
  - Loudness varies beat-to-beat (strength of ventricular contraction, and position of AV leaflets at the onset of ventricular systole)
  - Loudness reflects strength of ventricular contractions
  - Mitral and tricuspid valve closure (MV before TV); synchronous with cardiac impulse beat or carotid impulse
  - Beginning of LV and RV systole
  - Loud in MS and TS, tachycardia, hypertrophy, 3˚ heart block;
  - Soft in MR, 1˚ HB, LBBB, CCF, shock; variation in intensity with any cardiac arrhythmia
  - Normally split in tricuspid area on inspiration
  - Splitting (wider on inspiration) – RBBB

➢ S_2
  - Aortic and pulmonary valve closure (AV closes before PV, but PV opens before AV) end of LV and RV systole, beginning of diastole
  - Loud A_2 in HBP, loud P_2 in PHT; soft A_2 when AV calcified or in AR
  - Normal splitting of S_2 on inspiration (A_2, AV; P_2); pathological splitting: PS, MR, RBBB, VSD, ASD

- $P_2 > A_2$ in youth; $A_2 > P_2$ in old age
- Fixed splitting of S_2 (not increasing normally on inspiration – ASD sudden opening of valve in MS or TS after S_2
- Normally split on inspiration, especially in children
- Loud narrowly split P2 in pulmonary hypertension
- Soft widely split P2 in pulmonary stenosis
- Widely split in RBBB
- Widely split fixed P2 in ASD
- Paradoxically split P2 (narrows on inspiration) in LBBB and rarely in aortic stenosis and L and R shunts

- Opening snap
  - Indicates mobile AV valve and LA pressure
  - Mitral opening snap in mitral stenosis is maximal internal to apex, louder during expiration, thereby differentiated from split P2

- LV – S_3
  - Mild diastolic gallop,
  - Louder on expiration
  - Maybe: physiological; in young persons due to rapid diastolic filing;
  - Pathological: (↓ RV compliance) LVF, AR, MR, VSD, PDA

- LV – S_4
  - Late diastole, from atrial contraction (disappears in AF)
  - AS, MR, HBP, CAD, old age
  - Causes
    - Systemic hypertension
    - Aortic stenosis
    - Cardiomyopathy
      - Ischemic
      - hypertropic

- RV – S_4
  - PHT, PS (↓ RV compliance)

- $S_3 + S_4$
  - Summation gallop (when HR > 120 bpm)

- Artificial
  - Prosthetic heart valves, pacemaker sounds

- P_2 increased in pulmonary hypertension (e.g. MS, MR, L-CHF, PE, pulmonary fibrosis)

- A_2 increased in systemic hypertension, aortic slcerosis, arteriosclerosis, syphilitic aortitis; decreased in R-CCF, hypotension, severe anemia

- Diaphragm or bell
  - Diaphragm: High pitched, high pressure gradient across a small surface (AR)
  - Bell: Low pitched, low pressure gradient across a wide surface (MS)

- Pansystolic murmurs
  - MR, TR; VSD (L-4th ICS); PDA) L-2nd ICS)

Abbreviations: A_2, aortic part of S_2; AI, aortic incompetence; AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; AV, aortic valve; CAD, coronary artery disease; CCF, congestive cardiac failure; HB, heart block; HBP, hypertension (systemic); HR, heart rate; ICS, intercostal space; LA, left atrium; LBBB, left bundle block; L-CCF, left-sided congestive cardiac failure; L-CHF, left side congestive heart failure; LV, left ventricle; LVF, left ventricular failure; MI, mitral incompetence; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; P_2, pulmonary part of P_2; PDA, patent ductus arteriosis; PE, pulmonary embolus; PHT, pulmonary hypertension; PS, pulmonary stenosis; PV, pulmonary valve; RBBB, right bundle branch block; R-CCF, right-sided congestive cardiac failure; RV, right ventricular; S_1, first heart sound; S_2, second heart sounds; TS, tricuspid stenosis; TV, tricuspid valve; VSD, ventricular septal defect

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 210-216; Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, pages 54 and 55.

- Perform a focused physical examination for wide splitting of S_2.

- Early closure of aortic valve
  - Mitral regurgitation (severe)
  - VSD
  - CHF (severe)
  - Pericardial temponade

- Late closure of pulmonary valve
  - Cor pulmonale complicated by R-CHF
  - ASD
  - Massive pulmonary embolus
  - In associated with RBBB

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, page 55 and Mangione S. *Hanley & Belfus* 2000, page 211.

Ausculatory performance physical examination for signs of pulmonary hypertension.

- Loud (even palpable) P_2 over pulmonic area
- Loud S_4, right side
- Pulmonary ejection sound
- Tricuspid regurgitation
- Inspiration widens the interval between closure of aortic and pulmonary valves
- Inspiration increases the distance between A_2 and P_2, and thus causes physiological (normal) splitting of S_2.
- Physiological splitting of S_2 is increased by lying down. Physiological splitting of S_2 occurs in about half of adults.
- Paradoxical splitting of S_2: A split S_2 in the sitting/standing patient who breaths out (expiratory) is likely to be pathological (i.e. not physiological); however wide splitting of S_2 may be normal in young adults.

- Perform a directed physical examination of abnormal S_2 splitting to detect the presence of associated pathological abnormalities.

Splitting and pathogenesis	Associations
➢ Wide physiologic	
○ P_2 late	
- Electrical delay of RV systole	RBBB LV paced or ectopic beats PS
- Prolongation of RV systole	Acute cor pulmonale Dilation of PA
- Increased hangout interval	MR
○ A_2 early	
- Shortening of LV systole	
➢ Wide and fixed	
○ Increased hangout interval or prolongation of RV systole	ASD
○ Prolongation of RV systole	R-CHF
➢ Paradoxic	
○ A_2 late	
- Electrical delay of LV systole	LBBB RV paced or ectopic beats AS IHD
- Prolonged LV systole	

Abbreviations: AS, aortic stenosis; ASD, atrial septal defect; IHD, ischemic heart disease; LBBB, left bundle branch block; L-CHF, left side congestive heart failure; LV, left ventricular; MR, mitral regurgitation; RBBB, right bundle branch block; PA, pulmonary artery; PS, pulmonary stenosis; R-CHF, right side congestive heart failure; RV, right ventricular; RV systole and LV systole refer to the duration of right and left ventricular contraction.

Printed with permission: McGee SR. *Saunders/Elsevier* 2007, Table 36-1, page 426.

- Perform a focused physical examination for the causes of fixed splitting of S_2 (splitting of S_2 which persists on supine → expiration).
  - ASD, VSD with pulmonary hypertension
  - Pulmonary stenosis
  - Pulmonary hypertension
  - Massive pulmonary embolism

Adapted from: McGee SR. *Saunders/Elsevier*, 2007, page 426, 427; Mangione S. *Hanley & Belfus*, 2000, pages 210 to 216.

THIS IS A REAL CARDIOLOGY DEAL-BREAKER!

Q1. Give the pathophysiological explanation for the cause of a widely split S_2 in the following conditions:

A1.

- ASD, VSD, PR
  - ↑ RV volume
- PS
  - ↑ RV pressure
- RBBB
  - ↓ RV conduction
- MR, VSD
  - Early LV emptying

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, pages 72 and 73.

Q2. What does the S_2 tell us in AS?

A2.

- Normal: Strong evidence against the presence of critical aortic stenosis.
- Soft S_2: Valvular stenosis (except in calcific stenosis of the elderly, where the margins of the leaflets usually maintain their mobility)
- Single: Second heart sound may be heard when there is fibrosis and fusion of the valve leaflets
- Reversed splitting of the second sound: Indicates mechanical or electrical prolongation of ventricular systole.

Source: Baliga RR. *Saunders/Elsevier* 2007, page 19.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. If there is splitting of S2 during expiration, why do you sit the patient up and listen again?

A1. Splitting of S2 in expiration which disappears on sitting is normal, where as if splitting of S2 in expiration persists on sitting, then the wide, fixed or paradoxical splitting of S2 is abnormal.

Q2. What are the causes of fixed splitting of S2 (splitting in both supine and sitting position?

A2.
- Severe CHF
- ASD
- VSD plus PHT (pulmonary hypertension)
- PS (pulmonary stenosis), PHT
- Massive PE

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 214 and 215.

Q3. When does a soft S_2 occur in As due to causes other than valvular stenosis?

A3. When the aortic valve is stenotic and is also calcified, if the leaflets remain mobile, S_2 may be soft but the stenosis is not valvular.

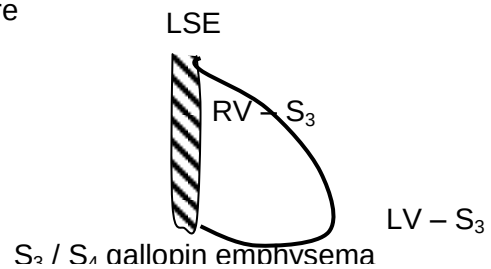
Q4. Distinguish between RBBB and LBBB, by listening to the heart sounds(!)

A4.
- RBBB: A_2-P_2 – when moving stethoscope from cardiac base to apex, the second component of S_2 dissappears; associated with wide splitting of S_2.
- LBBB: P_2-A_2 – first component of S_2 becomes softer when moving stethoscope from the base to the apex of the heart (A_2 and not P_2 is heard at the apex).

Pathological heart sounds

Gallop rhythm

- Definition
  - S_3 or S_4 plus tachycardia
- Listen
  - With bell for low pitched sound
  - "Kentucky" come before "Tennessee": S_3 before S_4
    S_3 sound like "Kentucky" S_4 sound like "Tennessee"
  - Where



S_3 / S_4 gallopin emphysema

Abbreviation: LSE, left sterna edge; RV, right ventricle; LV, left ventricle

Figuring Out S_3 and S_4

- Pathophysiology
  - S_3 – rapid filling of ventricles in early diastole
  - S_4 – rapid emptying of atria in late diastole
- Causes

	S_3	S_4
Normal	- Young persons	- Old persons
Abnormal	- CHF (L or R) - LVD (No CHF) - Murmurs ▪ MR ▪ AS ▪ TR ▪ VSD ▪ PDA	- Acute MI - Systemic hypertension - Murmurs ▪ AS ▪ PS ▪ HOCM - Not seen in CHF

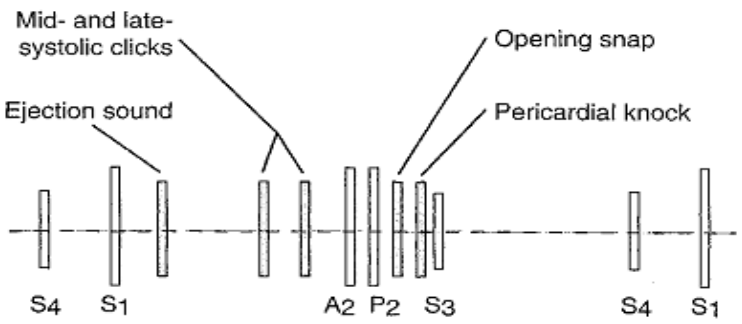
Abbreviation: AS, aortic stenosis, CHF, congestive heart failure; HOCM, hypertrophic cardiomyopathy; LVD, left ventricular dilation; MR, mitral regurgitation; PS, pulmonary stenosis; TR, tricuspid regurgitation; VSD, ventricular septal defect.

Sounds and extra sounds		Conventional teaching revisited
S3	↑	The most clinically valuable cardiac extra sound.
S4	↔	Most important for what it sounds like without being it (e.g. an S4 is important for *not* being an S3).
Pericardial friction rub	↑	One of the most valuable extra sounds (probably at the top of the list with S3)
Early systolic (ejection) click	↑	Valuable and not too much uncommon; should not be missed.
Mid-to-late systolic click	↑	As above
Open snap	↔	Important, but its prevalence is rapid fading.
Pericardial knock	↓	Neat to think of it, but it is more a canary than a sparrow.
Tumor plop	↓	As above

Source: Mangione S. *Hanley & Belfus* 2000, page 207.

- S_3 and S_4

Useful background: Miscellaneous Heart Sounds.



Adapted from: McGee S.R. *Saunders/Elsevier* 2007, Figure 38-1, page 445.

- S_3 and S_4
  - S_3/S_4 are best heard and felt at the apex (or PMI) with patient in left lateral decubitus position and accentuated by sitting, standing, exercise, leg elevation, abdominal pressure.

- Early diastolic snap of MS/TS; opening plop of myoxoma of mitral or tricuspid valve; (varies from cycle to cycle) and pericardial knock

- All about S_3
  - Caused by sudden and abnormal deceleration in left ventricular flow at the end of its rapid filling phase, reflecting early and passive LV filling.
  - May be physiologic under the age of 45, or with tachycardia, fever, excercise, anemia, hyperthyroidism, pregnancy, anxiety.
  - A pathologic S_3 "keeps bad company"
  - Ken-tu'-cky: S_3 gallops (S_3+S_1/S_2); Ten-ne-ss'es: S_4 gallop (S_4+S_1/S_2)
  - Pathological S_3 is due to diastolic overload (increased LV preload), decreased myocardial contractility, or loe ejection fraction (low-output failure)
  - An S3 (pathologic) plus an early diastolic rumble suggests sudden increased flow across the mitral valve.
  - The pressure of S_3 rules out mitral stenosis; opening sanp of MS is left sterna border, S_3 loudest at apex.
  - S3 predicts post-surgical development of CHF, predicts cardiac risk during non-cardiac surgery, and predicts response to digitalis in treatment of CHF hypertension.
  - Increased LV preload (diastolic overload): VSD, PDA (S_3 softens with the development of increased pulmonary mitral regurgitation)

Source: Mangione S. *Hanley & Belfus* 2000, pages 221 to 224.

S_3

- 40 years, may be physiologic (these persons are lean, with rapid early dibstolic filling)

- 40 years, S_3 represents ↓ejection fraction (dilated cardiomyopathy, ↓cardiac output), ↑atrial pressure

Source: McGee SR. *Saunders/Elsevier* 2007, page 436.

- All about S_4
  - Late diastolic, low-pitched extra sound due to progressive loss of compliance of ventricles, corresponding to atrial and sudden tension of the AV valve ventricle with atrial contraction and stronger atrial boost, with an increased LV diastolic pressure
  - Causes include
    - Systemic or pulmonary hypertension
    - Aortic stenosis, particularly with a high gradient
    - Coarctation of the aorta cardiomyopathy
      - Ischemic
      - Hypertrophic (almost always associated with S_4)
    - During myocardial infarction (~ 90%)

Source: Mangione S. *Hanley & Belfus* 2000, pages 223 to 225.

- Opening Snap
  - An early diastolic sound caused by opening and stretching of a stenotic mitral or tricuspid valve
  - The earlier the opening snap (OS) of mitral stenosis, the worse the stenosis; tachycardia also makes the OS earlier
  - Softening in intensity of the opening snap
    - Severe mitral stenosis (OS is present in 75-90% of MS)
    - CHF
    - Large right atrium (eg. pulmonary hypertention)
    - P_2 is loudest at the base, OS is loudest at the apex: if you think you hear an OS at the base, it's likely a P_2 (split S_2); if the sound becomes wider and louder on breathing out, you are probably hearing an OS, not a split S_2 or loud P_2 from PHT

- Mitral or Tricuspid Valve Myxoma
  - Diastolic prolapsed of a left atrial myxoma through an open valve, or a right atrial prolapsed through an open tricuspid valve
  - Vary in intensity and quality from cycle to cycle

- Ejection Sounds
  - Best hear at apex, sitting position or expiration
  - Hyperdynamic heart syndrome – fver, anemia, pregnancy, shunts, hyperthyroidism
  - Stenosis semilunar valve (valvular, not sub – or supraventricular aortic or pulmonary stenosis) or biscuspid valve
  - Sudden early ventricular systolic distention of aorta or pulmonary artery
  - Ejection sound plus an ejection murmur occurs aith stenosis of semilunar bicuspid valve with post stenosis dilation of aorta or root of pulmonary artery
  - Best heard at the apex
  - Loss of click with aortic stenosis reflects progressive fibrosis and calcification of aortic valve, with increasing gradient across aortic valve.

Source: Mangione S. *Hanley & Belfus* 2000, pages 225 to 229.

- Definition
  - Sudden opening of the mitral valve as the result of increased left atrial pressure causes a high pitched sound at the left sternal edge in persons with mitral stenosis (MS).
  - The earlier the OS in diastole, the more severe the MS
  - OS is loudest in expiration, helping to distinguish it from a split P_2

- Definition
  - High pitched, early systolic heart sound caused by vibration of cusps of stenotic aortic or pulmonary valves, or entry of blood into dilated or rigid aorta or pulmonary arteries
  - Causes
    - Stenosis at, but not below or above aortic or pulmonary valve (AS, PS)
    - Systemic hypertension
    - Atherosclerosis

Useful background: Performance characteristics of the third (S_3) and fourth (S_4) heart sounds

- S_3 has good performance characteristics in terms of its positive likelihood ratio for detecting or predicting a range of cardiac abnormalities ranging from ↑ LV filling pressures or reduced ejection fraction, to predicting a myocardial infarction or postoperative cardiac death.

  In contract, the S_4 does not have a significant use to detect ↑ LV filling pressure or aortic stenosis, but has a PLR of 3.2 for predicting 5 - year mortality in patients after a myocardial infarction.

Finding (Ref)	PLR
➢ The third heart sound – S_3	
○ Detecting ejection fraction <0.5	3.4
○ Detecting ejection fraction <0.3	4.1
○ Detecting elevated left heart filling pressures	5.7
○ Detecting elevated BNP level	10.0
○ Detecting myocardial infarction in patients with acute chest pain	3.2
○ Predicting postoperative pulmonary edema	14.6
○ Predicting postoperative myocardial infarction or cardiac death	8.0
➢ The fourth heart sound – S_4	
○ Predicting 5-year mortality in patients after myocardial infarction	3.2
○ Detecting elevated left heart filling pressures	NS
○ Detecting severe aortic stenosis	NS

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 37-1, page 438.

Useful background: Heart sounds

Sound	Location, pitch	Pathology
➢ Early ejection sound	○ Aortic: apex & base ○ Pulmonic: base (high pitched)	○ Congenital AS, bicuspid AV, congenital PS, Ao. Root or PA dilation, physiologic (flow murmur)
➢ Mid to late ejection click	○ Mitral: apex ○ Tricuspid: LLSB (high pitched)	○ MV or TV prolapse

Abbreviations: AF, arterial fibrillation; AS, aortic stenosis; AV, aortic valve; HR, heart rate; LAP, left arterial pressure; LBBB, left bundle branch block; LLSB, left lower sternal border; MS, mitral stenosis; MV, mitral valve; PA, pulmonary artery; PR, pulse rate; PS, pulmonary stenosis; RBBB, right bundle branch block; TV, tricuspid valve

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 8, pages 59 and 60.

Useful background: Systolic and diastolic normal heart sounds

Systolic		Diastolic	
Timing	Name	Timing	Name
➢ Early systolic	○ Ejection sounds (aortic or pulmonary) ○ Click (mitral or tricuspid) ○ Aortic prosthetic valve sounds	➢ Early diastolic	○ Opening snap (mitral or tricuspid) ○ Early S_3 ○ Pericardial knock ○ Tumour plop
➢ Mid-to-late systolic	○ Click (mitral or tricuspid)	➢ Mid diastolic	○ S_3 ○ Summation sound ($S_3 + S_4$)
		➢ Late diastolic (presystolic)	○ S_4 ○ Pacemaker sound

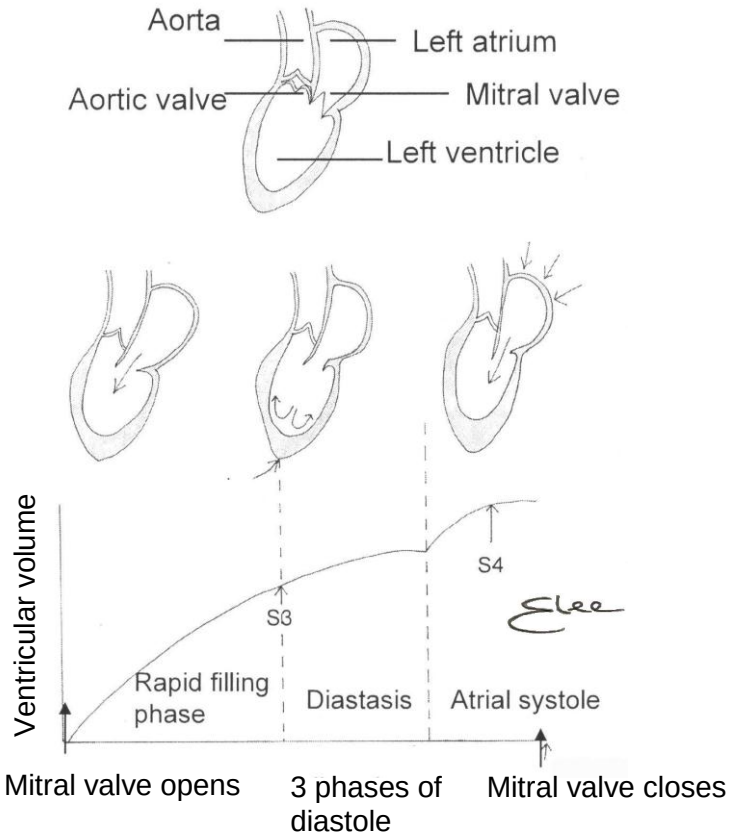
Source: Mangione S. *Hanley & Belfus* 2000, page 217.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. How do you differentiate between the fourth heart sound (S_4), a split first heart sound (S_1), and an ejection click?

A. The fourth heart sound is not heard when pressure is applied on the chest piece of the strethoscope, but pressure does not eliminate the ejection sound or the slitting of the first heart sound.

Timing and mechanism of production of third and fourth heart sounds (S_3 and S_4)



Adapted from: McGee SR. *Saunders/Elsevier* 2007, Figure 37.1, page 435.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. S_4 does not wax and wane but when may S_4 disappear?

A1. ○ When AF (atrial fibrillation), atrial flutter or L-CHF develop.

Q2. What does the fourth heart sound (S_4) indicate?

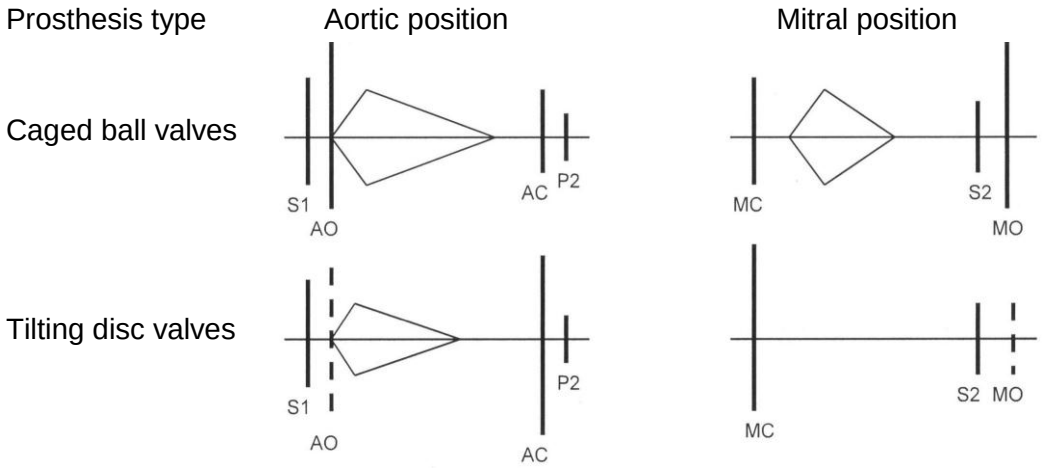
A2. ○ An audible S_4 may be physiologic, but a palpable S_4 is always pathologic

Q3. How is it possible to distinguish between a mitral opening snap (OS) and a split P_2?

A3. OS is maximal internal to the apex, and becomes louder with expiration.

Other pathological heart sounds

Prosthetic valve heart sounds



Abbreviations: AC, closure sound of aortic prosthesis; AO, opening sound of aortic prosthesis; MC, closure sound of mitral prosthesis; MO, opening sound of mitral prosthesis; P_2, pulmonary component of second heart sound; S_1, first heart sound; S_2, second heart sound

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Figure 38-2, page 449.

SO YOU WANT TO BE A CARDIOLOGY RESIDENT!

Q1. What is the relationship between the intensity of S_4 and the severity of CHF?

A1. Dah, S_4 is not associated with CHF. If an elderly person has S4 plus CHF, the S4 is a normal finding in old age.

Q2. What is the mechanism of the production of the third heart sound?

A2. Caused by rapid ventricular filling in early diastole

Source: Baliga RR. *Saunders/Elsevier* 2007, page 39.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What are the implications of the third heart sound in patients with valvular heart disease?

A1.
- In patients with mitral regurgitation, they are common but do not necessarily reflect ventricular systolic dysfunction or increase filling pressure
- In paietns with aortic stenosis, third heart sounds are uncommon but usually indicate the presence of systolic dysfunction and raised filling pressure

Q2. What are the causes of the third heart sound (S_3)?

A2.
- Physiological: in normal children and young adults
- Pathological
  - Heart failure
  - Left ventricular dilatation without failure: mitral regurgitation, ventricular septal defect, patent ductus arteriosus
  - Right ventricular S_3 in right ventricular failure, tricuspid regurgitation

Q3. Does the fourth heart sound denote heart failure, like the S_3 gallop does?

A3. No

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What are the causes of the fourth heart sound (S_4)?

A.
- Normal: in the elderly
- Pathological:
  - Acute myocardial infarction
  - Aortic stenosis (the presence of S_4 in individuals below the age of 40 indicates significant obstruction)
  - Hypertension
  - Hyper trophic cardiomyopathy
  - Pulmonary stenosis

Adapted from: McGee SR. *Saunders/Elsevier* 2007, pages 217-225 and 434-437.

SO YOU WANT TO BE A CARDIOLOGY RESIDENT!

Q. In the context of listening to the heart sounds, what is Hamman's Sign?

A.
- Crunching sound heard in time with systolic and diastolic components of heartbeat
- This "mediastinal crunch" is due to air in the mediastinum
- Seen after cardiac surgery, with a pneumothorax or aspiration of a pericardial effusion

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, page 59.

Trick Questions

Q1. An S_3 is auscultated in a patient with a systolic murmur. There are no signs of associated CHF. What prognostic value does the S_3 have in terms of ventricular systolic dysfunction or increased filling pressure?

A1. In AS, but not in MR, S_3 reflects ventricular systolic dysfunction or increased filling pressure.

Q2. What is the mechanism of the production of the S3?

A2. Caused by rapid ventricular filling in early diastole

Source: Baliga RR. *Saunders/Elsevier* 2007, page 39.

SO YOU WANT TO BE A CARDIOLOGIST

Q1. What is the difference between “a snap”, “a click”, “a knock” and “a rub”?

A1.
- “Snap” – diastole, abnormal opening of the leaflets.
- “Click” – systole, prolapse and backward ballooning of valve leaflet(s).
- “Knock” (pericardial) - Louder and higher-pitched form of S3 (caused by early ventricular filling), and sudden stretching of the LV against a thick, calcified pericardium, or also heard in constrictive pericarditis. Occur in chronic calcified or constrictive pericarditis
- “Rub” (pericardial) - High-pitched, scratchy systolic and diastolic sounds, best heard with firm pressure of diaphragm, heard best at lower (3/4 interspaces) sterna border during inspiration, due to acute pericarditis

Source: Mangione S. *Hanley & Belfus* 2000, pages 225 to 236.

Q2. What is the expression used when both the third and fourth heart sounds (S_3 and S_4) are heard with tachycardia?

A2.
- The summation gallop
- Sometimes be mistaken for a diastolic rumbling murmur

Q3. What is the expression used when both the third (S_3) and fourth (S_4) heart sounds are heard with tachycardia?

A3.
- The summation gallop
- Sometimes be mistaken for a diastolic rumbling murmur

Q. How do you differentiate between the fourth heart sound, a split first heart sound and an ejection click?

A. The S4 is not heard when pressure is applied on the chest piece of the strethoscope, but pressure does not eliminate the ejection sound or the slitting of the first heart sound.

Heart murmurs

Useful background: Likelihood ratios of the overall examination for detecting valvular disease

	LR for Valvular Disease	
	PLR	NLR
Cardiologists	38	0.31
Emergency department physicians	14	0.21
Overall	15	0.25

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

Adapted from: Simel DL, et al. *JAMA* 2009, Table 33-13, page 446.

- Effects of respiration on murmurs
  - Inspiration increases stroke volume of R ventricle, therefore increases intensity of TS, TI and PS
  - Inspiration increases vascular volume of lungs and decreases stroke volume of L ventricle, therefore decreases intensity of MS, MI, AS and AI
  - Inspiration decreases L → R shunts

- Effect of drugs on murmurs
  - Drugs increasing arteriolar resistance will decrease systolic ejection murmurs and increase regurgitant murmurs at all valves. Vasodilators have the opposite effect.

Source: Burton JL. *Churchill Livingstone* 1971, page 7.

When giving your summary of a cardiac murmur, state that the type murmur (lesion), the likely etiology, and the functional status (severity of lesion, associated dysrhythmia, CHF).

Useful background: Golden, Silver, Bronze and Tin Rules of Cardiac Murmurs

- Gold
  - Judge murmurs by the company they keep
  - A soft or absent S_2 is pathological

- Silver: Pathologic murmurs
  - All diastolic murmurs
  - All holosystolic or late systolic murmurs
  - All continuous murmurs (span the entire cardiac cycle)
- Bronze: mechanism of production of murmurs

- Abnormal size, shape, edge of the area through which flow is occurring
- Low blood viscosity
- Hyperdynamic heart syndrome

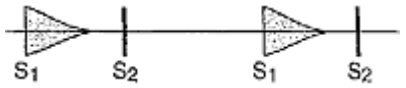
➢ Tin
- Murmur that extends into S_2 is usually pathologic; a murmur in early or mid systole is usually benign and due to ejection through semilunar aortic and pulmonary valves

Source: Mangione S. *Hanley & Belfus* 2000, page s 240 and 241.

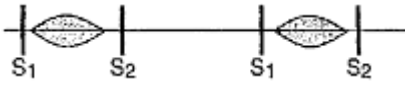
Useful background: Diagrams of various cardiac murmurs

- Normal heart tones

- Early systolic murmur



- Midsystolic murmur

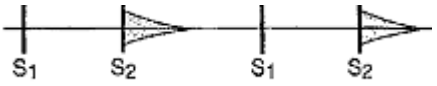


- Late systolic murmur

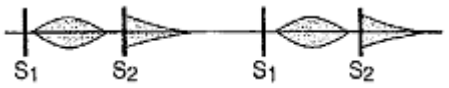
- Late systolic murmur and click © of mitral valve prolpapse

- Holosystolic murmur

- Early diastolic murmur of aortic regurgitation

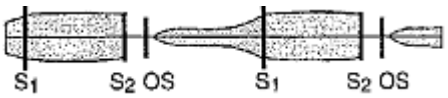


- Early diastolic murmur of aortic regurgitation and aortic flow murmur



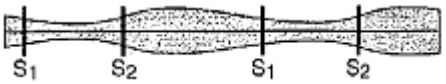
- Opening snap (OS) and diastolic rumble of mitral stenosis

- Opening snap, diastolic rumble of mitral stenosis, and mitral regurgitation



- Continuous murmur of arteriovenous fistula

- Continuous murmur of venous hum or mamary souffle



Printed with permission: McGee SR. *Saunders/Elsevier* 2007, Figure 39-1, page 457.

- Perform dynamic maneuvers which increase or decrease the intensity/ duration of three systolic cardiac murmurs.

Maneuvre	LESION			
	Hypertrophic cardiomyopathy	Mitral valve prolapse	Aortic stenosis	Mitral regurgitation
➢ Valsalva strain phase (decreases preload)	↑	↑	↓	↓
➢ Squatting or leg raise (increases preload)	↓	↓	↑	↑
➢ Hand grip (increases afterload)	↓	↓	↓	↑

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.10, page 61, and Ghosh AK. *Mayo clinic Scientific Press* 2008, Table 3-1, page 42.

Useful background: Maneuvers and Heart Murmurs

Maneuver	Technique	When to note change in murmur
➢ Normal respiration	- The patient breathes normally in & out	- During inspiration & expiration
➢ Maneuvers affecting venous return		
○ Valsalva maneuver (↓ venous return)	- The patient exhales against closed glottis for 20 seconds	- At end of the strain phase (i.e., at 20 seconds)
○ Squatting-to-standing (↓ venous return)	- The patient squats for at least 30 seconds & then rapidly stands up	- Immediately after standing
○ Standing-to-squatting (↑ venous return)	- The patient squats rapidly from the standing position, while breathing normally to avoid a Valsalva maneuver	- Immediately after squatting
○ Passive leg elevation (↑ venous return)	- The patient's legs are passively elevated to 45 degrees while the patient is supine	- 15-20 seconds after leg elevation
➢ Maneuvers affecting systemtic vascular resistance		
○ Isometric handgrip exercise (↑ afterload)	- The patient uses one hand to squeeze the examiner's index and middle fingers together tightly	- After 1 minute of maximal contraction
○ Transient arterial occlusion (↑ afterload)	- The examiner places blood pressure cuffs around both upper arms of patient and inflates them to pressures above the patient's systolic blood pressure	- 20 seconds after cuff inflation

Permission granted: McGee SR. *Saunders/Elsevier* 2007, Table 39-2 page 467.

Useful background: Performance Characteristics for Systolic Murmurs and Maneuvers (Cont'd)

Finding	PLR
➢ Louder with transient arterial occlusion	
o Detecting mitral regurgitation or ventricular septal defect	48.7
➢ Softer with amyl nitrite inhalation	
o Detecting mitral regurgitation or ventricular septal defect	10.5

Source: McGee SR. *Saunders/Elsevier*, 2007, Box 39-2, page 467.

Useful background: Likelihood ratios of individual findings for identifying systolic murmurs that are clinically significant*

Clinical Sign	PLR	NLR
➢ Systolic thrill	12	0.73
➢ Holosystolic murmur	8.7	0.19
➢ Loud murmur	6.5	0.08
➢ Plateau-shaped murmur	4.1	0.48
➢ Loudest at the apex	2.5	0.84

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

*Moderate to severe aortic stenosis or mitral regurgitation, congenital shunt, or intraventricular pressure gradient.

Note that radiation of the carotids have a PLR < 2, and is not included here.

Adapted from: Simel DL, et al. *JAMA* 2009, Table 33-14, page 96.

- ➢ Causes of Continuous Murmurs
  - o Venous hum
  - o Mitral regurgitation murmur with aortic regurgitant murmur
  - o VSD with aortic regurgitation
  - o Pulmonary arteriovenous fistula
  - o Rupture of the sinus of Valsalva
  - o Coronary arteriovenous fistula
  - o Arteriovenous anastomosis of intercostal vessels following a reactured rib

Source: Baliga RR. *Saunders/Elsevier*, 2007, page 81.

Useful background: Murmurs

- The length and intensity of a murmur do not necessarily reflect severity
- Diastolic murmurs usually represent valvular disease
- Systolic murmurs are caused by:
  - Structural valve disease
  - Dilation of heart valve (e.g., LV dilation – AR, MR), or dilation of large vessel (dilation of aorta from artherosclerosis; dilation of pulmonary artery from PHT)
  - Pressure difference
  - Rapid flow
  - Ruptured papillary muscle, or the (VSD)
  - Floating tissue – bacterial endocarditis

- Intensity
  - High pitched - large pressure difference across small orifice (e.g. AR)
  - Low pitched - small pressure difference across large orifice (e.g. MS)

Abbreviations: AR, aortic regurgitation; LV, left ventricle; MR, mitral regurgitation; MS, mitral stenosis; PHT, pulmonary hypertension; VSD, ventricular septal defect

Source: McGee SR. *Saunders/Elsevier* 2007, Box 39-2, pages 466 and 467.

Useful background: Murmur grades

Grade (out of "6")	Intensity	Thrill
1	Very faint, often not audible in all positions or by beginners	-
2	Quiet, usually audible by all listeners	-
3	Moderately loud	-
4	Loud	+
5	Very loud, audible with stethoscope partly off chest	+
6	Loudest, audible with stethoscope removed from contact with chest	+

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 9, page 61.

- Perform a focused physical examination of the precordium, and from the timing of the murmur, give the differential of the lesion.

Timing of murmur	Differential of the lesion
• Systolic	
➢ Pan	○ MR ○ TR ○ VSD ○ Aortopulmonary shunts
➢ Mid	○ AS ○ Pulmonary stenosis (PS) ○ Hypertrophic cardiomyopathy ○ ASD
➢ Late	○ Mitral valve prolapse ○ Papillary muscle dysfunction (due usually to ischemia or hypertrophic cardiomyopathy)
• Diastolic	
➢ Early	○ AR ○ Pulmonary regurgitation (PR)
➢ Mid	○ MS ○ TS ○ Atrial myxoma ○ Austin Flint murmur of AR ○ Carey Coombs† murmur of acute rheumatic fever
➢ Late (Presystolic)	○ MS ○ TS ○ Atrial myxoma
• Continuous	○ PDA ○ AS+AR ○ MS+AR ○ MS+PR ○ Venous hum ○ Aortopulmonary septal defect ○ Rupture of sinus of Valsalva into RV or RA ○ 'Mammary soufle' (in late pregnancy or early postpartum period) ○ Bronchial artery anastamosis in pulmonary atresia ○ Pericardial friction rub

NB: The combined murmurs of aortic stenosis and aortic regurgitation, or mitral stenosis and mitral regurgitation, may sound as if they fill the entire cardiac cycle, but are not continuous murmurs by definition.

Venous hum: above clavicle and down over upper sternum: ↑ by turning head, ↓ by jugular compression; distinguish from PDA (patient ductus arterious)

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; MR, mitral regurgitation; MS, mitral stenosis; PDA, patent ductus arteriosus; PR, pulmonary regurgitation; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation; TS, tricuspid stenosis; VSD, ventricular septal defect

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.9, page 58.

Useful background: Heart sounds of non-valvular origin (continuous murmurs)

Murmur	Location	Radiation	Quality	Pitch	Associated signs
➢ Pericardial friction rub	Variable, 3rd ICS	Little	Scratchy	High	3 phases: mid-systolic, mid diastolic, pre systolic
➢ Patent ductus arteriosus	2nd LICS	Left clavicle	Harsh, machinery like	Medium	Loudest in late systole fades in diastole, often silent interval in late diastole
➢ Venous hum	Above medial third of right clavicle	1st-2nd ICS	Humming, roaring	Low	Soft murmur without a silent interval, loudest in diastole

Abbreviations: ICS, intercostal space; LICS, left intercostal space

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 11, page 62.

Useful background: Heart murmurs of valvular origin

Murmur	Location	Radiation	Quality	Pitch	Associated signs
• Midsystolic murmurs 					
➢ Aortic stenosis	2nd RICS	Neck	Harsh	Medium	Ejection sound, ↓ S_2, S_4, narrow pulse pressure, slow rising and delayed pulse
➢ Pulmonic stenosis	2nd-3rd LICS	Neck, back	Harsh	Medium	Ejection sound, S_4
➢ MV prolapse	Apex	Axilla			Mid-systolic click
➢ Hypertrophic cardio-myopathy	3rd-4th LICS	LLSB → apex, base	Harsh	Medium	S_3, S_4 sustained apical impulse-two palpable components, carotid pulse rises quickly
• Pansystolic murmurs 					
➢ Mitral regurg.	Apex	L axilla	Blowing	High	↓S1; S3, S4 present, laterally displaced diffuse PMI
➢ Tricuspid regurg.	LLSB	RLSB	Blowing	High	S3, ↑JVP
➢ VSD	3rd-5th LICS	Wide	Harsh	High	Vary with severity

Murmur	Location	Radiation	Quality	Pitch	Associated signs
• Diastolic murmurs 					
➢ Aortic regurg.	2nd-4th LICS	Apex, RSB	Blowing	High	Ejection sound, S3, S4, laterally displaced PMI, wide pulse pressure, bounding pulse, midsystolic flow murmur or Austin Flint murmur
➢ Mitral stenosis	Apex	Little/ None	Rumbling	Low	↑S1, OS after S2, RV impulse, often assoc. with AV disease

Abbreviations: R/LISC, Right/left intercostals space; R/LLSB, right/left lateral sternal border; JVP, jugular venous pressure; PMI, point of maximal impulse; OS, opening snap; RV, Right ventricle; AV, Aortic valve

Printed with permission: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 10, pages 61 and 62.

- ➢ What is the difference in the diastolic murmurs of Austin Flint, and Graham Steell?
  - Austin Flint
    - Mitral diastolic murmur (MS-like) occurring with severe aortic regurgitation
    - The regurgitating blood from the AR Roughens the aortic cusp of the mitral valve, causing MS- like murmur
    - Syphilis never affects the mitral valve, so an Austin Flint murmur can be diagnosised, whereas AR from other causes (atherosclerosis; SBE; aneurysm- dissecting, or Marfan's; Aortic valve – bicuspid, ruptured cusps, surgery) may be producing true MS.
  - Graham Steell
    - Severe pulmonary hypertension causes load muumur of pulmonary incompetence

- Take a directed history for the cause of a patient's cardiac murmur.

➢ Ideopathic	○ Flow, dilation, distortion, anemia, hyperthyroidism ○ Dissecting aneurysm ○ Hypertrophic obstructive cardiomyopathy (HOCM)
➢ Inherited	○ Cyanotic, acyanotic ○ Marfan's, Turner's, Down syndrome
➢ Infection	○ Syphilis ○ Subacute bacterial endocarditis (SBE)
➢ Immune	○ Lupus (Libman Sachs murmur) ○ Ankylosing spondylitis
➢ Infiltration	○ Carcinoid ○ Tumor ○ Atrial myxoma
➢ Trauma	
➢ Inflammation	○ Rheumatic heart disease
➢ Metabolic	○ Coronary artery disease (CAD) ○ Papillary muscle rupture, ventricular septal defect (VSD)

Abbreviations: CAD, coronary artery disease; HOCM, hypertrophic obstructive cardiomyopathy; SBE, subacute bacterial endocarditis; VSD, ventricular septal defect

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 9.

"Let's see if there is mechanistic information that we can tease out."

Grandad

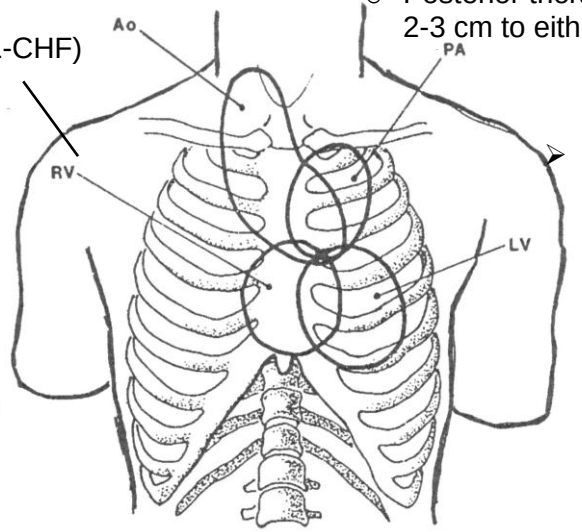
- Perform a focused physical examination of the precordium for the site of optimal ausculatation of normal and abnormal heart sounds and murmurs.

➢ Pulmonary area
  - 1-3 LICS, at manubrium, medial LIC area
  - Posterior thorax, T4,5, 2-3 cm to either side of spine

➢ Aortic area (Erb's point, 3 LICS)
  - 3 LICS, sterna edge, across manubrium to 1-3 RICS

➢ Descending thoracic area
  - Posterior thorax, T2 – T16, 2-3 cm to either side of

3-5 LICS
RVE (PHT,L-CHF)



➢ Tricuspid area (RV)
  - 3-5 LICS, 2 cm. R&L
  - RVE → extend laterally

➢ RA
  - 4-5 RICS, 2 cm. to right of sternum
  - TR

➢ Mitral area (LV)
  - 3-5 LICS, 2 cm medial & lateral to LAAL
  - LVE → extends medially
  - RVE → extends to L. axilla

➢ Aortic area	○ AS, AR ○ A2, Aortic ejection click ○ Systemic hypertension ○ Dilated aortic aneurysm
➢ Pulmonary area	○ PS, PR, flow, PDA ○ P2, pulmonary ejection click ○ PHT
➢ Mitral area	○ MS, MR, AS, AR, HSS, functional jid-diastolic rumble ○ A2, S3, S4
➢ Tricuspid area	○ TS, TR, PR, VSD ○ RV S3,S4 ○ TV opening sanp
➢ Descending thoracic area	○ Coarctation of aorta ○ Aortic aneurysms

Abbreviations: AO, aorta; AR, Aortic regurgitation; AS, aortic stenosis; ICS, intercostal space; IHSS, idiopathic hypertrophic subaortic stenosis; L-CHF, left sided congestive heart failure; LA, left atrium ; LICS, left intercostal space; LV, left ventricle; LVE, left ventricular enlargement; MR, mitral regurgitation; MS, mitral stenosis; PA, pulmonary artery; PDA, patent ductus arteriosis; PHT, pulmonary hypertension; PS, pulmonary stenosis; RA, right atrium; RICS, right intercostal space; RV, right ventricular; RVE, right ventricular enlargement; TR, Tricuspid regurgitation; TS, tricuspid stenosis; TV, tricuspid valves; VSD, ventricular septal defect

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 239 and 240; Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 7, page 58.

Useful background: Performance characteristics for physical examination for murmurs and valvular heart disease

Finding	PLR
➢ Abnormal heart examination	
o Detecting any valvular heart disease	18.3
➢ Characteristic systolic murmur	
o Detecting AS	3.3
o Detecting mild MR or worse	5.4
o Detecting moderate to severe MR	3.3
o Detecting MVP	12.1
o Detecting mild TR or worse	14.6
o Moderate to severe TR	10.1
o Detecting VSD	24.9
➢ Characteristic diastolic murmur	
o Detecting mild AR or worse	9.9
o Moderate to severe AR	4.3
o Detecting PR	17.4

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; PLR, positive likelihood ratio; MR, mitral regurgitation; MVP, mitral valve prolapse; NS, not significant; PR, pulmonary regurgitation; TR, tricuspid regurgitation; VSD, ventricular septal defect

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 39-1, page 460.

Useful background: Maneuvers to improve auscultation of heart sounds and murmurs

➢ Position		Effect
○ Leaning forward and holding breath		↑ AS, AR, pericardial rubs
○ Lying in left lateral decubitus positions; (use bell of stethoscope)		S3, S4, MS
○ Raising leg	↑venous return	↑ right sided murmur, TR, PS
○ Clenching fists	↑systemic arterial resistance	↑ some left sided murmurs MR, AR, VSD; ↓ AS
○ Standing	↓ venous return / vascular tone	↑ MVP, HCM; ↓ AS
○ Squatting	↑ venous return / vascular tone	↓ MVP, HCM; ↑ AS

Abbreviations: AS, aortic stenosis; AR, aortic regurgitation; HCM, hypertrophic cardiomyopathy; LLD, left lateral decubitus; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PS, pulmonary stenosis; TR, tricuspid regurgitation; VSD, ventricular septal defect

Adapted from: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 63.

- Take a direct history and perform a focused physical examination to determine if a systolic murmur is benign (i.e. non-pathological).

○ Pathophysiology : Due to rapid flow across the mitral or tricuspid valve or to distension of the left ventricular wall

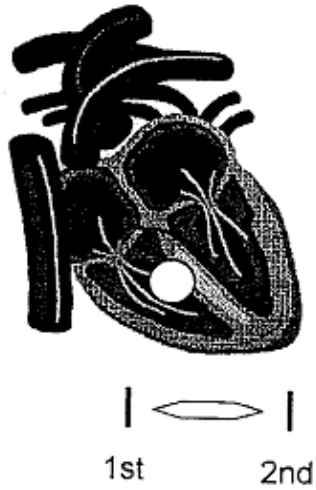
➢ History
  - ○ Family history
    - Family members with heart disease
  - ○ Past medical history
    - Ante-and perinatal history
    - Infancy and childhood
  - ○ Personal history of
    - Central cyanosis
    - Feeding difficulties
    - Poor weight gain

- Cardiovascular exam

- Characteristics of murmur
  - Short, soft (grade III/ IV, or less) diastolic murmur
  - Loudest at the apex or left sternal border
  - Follows immediately after a physiologic S3
    - Heard in normal young people
    - No supportive evidence of organic heart disease
    - Soft mid-diastolic murmur
  - Associated with Still's murmur (precordial vibratory murmur)
  - Valsalva maneuver - both pulmonary ejection and Still's murmur disappear

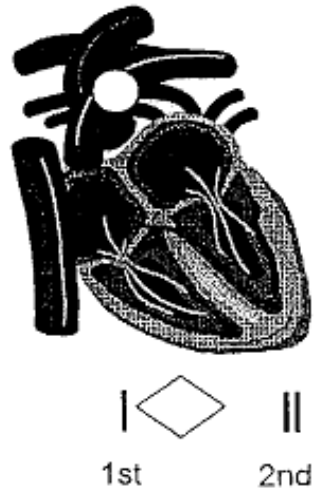
- Absence of
  - On palpitation
    - Systolic thrill, over the suprasternal area
    - Abnormal apical impulse
  - On auscultation
    - Holosystolic or diastolic murmur (a purely diastolic murmur should be considered organic until proved otherwise)
    - Presence of ejection clicks/sounds
    - Fixed splitting of S_2

- Precordial vibratory murmur (Still's murmur): Most commonly heard between the ages of 2 and 6 years



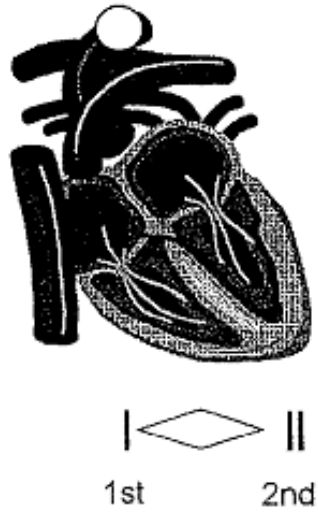
  - Short, soft (I-II/VI) mid systolic murmur
    - Low frequency, coarse, twangy
    - Starts after S_1, left lower sternal border
    - Changes with position
    - Rarely radiate to the neck (rarely)
  - Softens or disappears on standing, reappears on squatting
  - Differentiate from VSD

- Pulmonary ejection systolic murmur



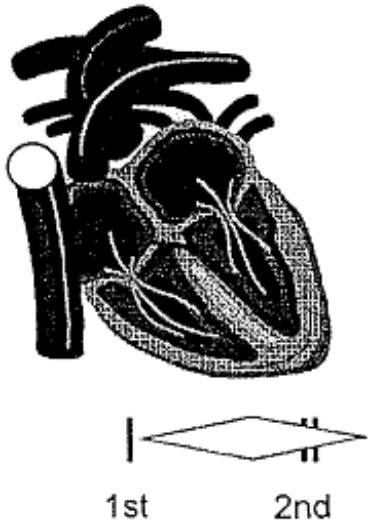
  - Location
    - Pulmonary area (2-3 L -ICS; also can be heard over the aortic area, [left sternal border], apex, or neck [left side])
    - Loudest at the second or third left interspace
  - Early systolic ejection murmur
    - Early to mid systolic
  - Short, soft, high frequency, blowing crescendo-decrescendo murmur
  - Increased in supine position
  - Normal P2, no diastolic murmur, no clicks, heaves or thrills
    - Most commonly heard in thin adolescents
  - Differentiate from ASD and PS
    - S2 normally split and of normal intensity

- Carotid arterial bruit



  - Loudest over carotid artery, at base of the heart, or right supraclavicular area (opposite to aortic stenosis, which is loudest over the second right ICS)
  - Harsh, crescendo-decrescendo, ejection systolic murmur
  - No precordial or suprasternal notch thrill
  - ↓ with
    - Hyperextension of the shoulders toward the back
    - Compression of the subclavian artery
  - Unaffected by Valsalva manoeuvre

- Venous hum



  - Maximal in early diastole
  - Continuous murmur
  - Location
    - Infraclavicular, loudest at the right supraclavicular area or upper right sternal border
  - Loudest in upright position
  - ↑ with Sudden release of the jugular veins
  - Disappears when lying down
    - ↓ in supine position
    - Compression of the jugular veins
  - Differentiate from PDA
    - Thrill palpable over the jugular veins

- Mammary soufflé
  - Usually present in late pregnancy or early lactation
    - Varies from day to day; disappears after lactation period
  - Continuous murmur related to the cardiac cycle
    - In some patients may be primarily systolic
  - Loudest at the third or fourth interspace (either side or bilateral)
  - Unaffected by Valsalva murmur

- Straight back/pecutus excavatum (due to close proximity of pulmonary artery)
  - Mid-systolic ejection murmur
  - Short, crescendo-decrescendo
    - Grade I-III/VI
  - Loudest at the left upper sternal border
  - Louder in held exhalation
  - S2 usually widely split
    - P2 (less commonly A2) can be loud
  - ASD or PS by diagnostic, but chest x-ray

Abbreviations: ASD, atrial septal defect; ICS, intercostal space; PDA, patent ductus arteriosus; PS, pulmonary stenosis; VSD, ventricular septal defect

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 246 to 250; Permission granted: McGee SR. *Saunders/Elsevier* 2007, Box 34.1, page 402.

Useful background: Characteristics of innocent functional systolic murmurs in childhood

- No other abnormality detected
- No thrill
- Usually short, of low frequency and early in systole
- Localised to apex or pulmonary area
- Intensity varies with change in posture

Source: Burton JL. *Churchill Livingstone* 1971, page 10.

Useful background: LR for a Significant Systolic Murmur vs functional systolic murmur

Clinical sign	PLR	NLR
➢ Holosystolic murmur	8.7	0.19
➢ Loud murmur	6.5	0.08
➢ Plateau-shaped murmur	4.1	0.48
➢ Loudest at the apex	2.5	0.84

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

Source: Simel DL, et al. *JAMA* 2009, Table 33-10, page 444.

Useful background: Performance characteristics of dynamic maneuvres to help determine the nature of a murmur

Finding	PLR
➢ Respiration	
○ Louder during inspiration, detecting right-sided murmurs (TR or PS)	7.8
➢ Changing venous return	
○ Louder with Valsalva strain, detecting HC	14.0
○ Louder with squatting-to-standing, detecting HC	6.0
○ Softer with standing-to-squatting, detecting cardiac myopathy	7.6
○ Softer with passive leg elevation, detecting HC	9.0
➢ Changing systemic vascular resistance (overload)	
○ Softer with isometric hand grip, detecting HC	3.6
○ Louder with isometric hand grip, detecting MR or VSD	5.8
○ Louder with transient arterial occlusion, detecting MR or VSD	48.7
○ Softer with amyl nitrite inhalation (if tachycardia induced), detecting MR or VSD	10.5

Abbreviations: HC, hypertrophic cardiomyopathy; PLR, positive likelihood ratio; NLR, negative likelihood ratio; MR, mitral regurgitation; PR, pulse rate; TR, tricuspid regurgitation; VSD, ventricular septal defect

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 39-2, page 466.

- Perform a focused physical examination of the precordium, which will help to distinguish between

- Pleural rub (vs pulmonary rales)
  - ↑ by pressure to chest wall with stethoscope
  - Present in inspiration and expiration
  - Not cleared by coughing

- Pericardial rub (vs cardiac murmur)
  - ↑ by pressure on chest wall
  - ↑ by expiration
  - ↑ by lying on L or R side
  - Sound changes from day –to- day

- Pericardial effusion (vs cardiac tamponade [restricted diastolic filling])
  - ↑ dullness of precardium
  - ↓ apex impulse
  - ↓ heart sounds
  - Pressure on adjacent structures
  - Ewart's sign (compression of lung near left scapula results in dullness, bronchial breathing, increased tactile vocal fremitus)

- Tamponade
  - ↑ JVP
  - ↓ SBP
  - Pulsus paradoxicus (shock, laboured breathing, ventiliation)
  - Absence of cardiomegaly

Abbreviations: JVP, jugular venous pressure; SBP, systolic blood pressure

Permission granted: McGee SR. *Saunders/Elsevier* 2007, Box 34-1, page 402.

Does an early ejection click (EC) occur with muscular narrowing above or below the aortic or pulmonary valves?
  - No, only with stenosis at the valve
  - So, no EC with HOCM

S_1

- A1 ↑
  - Hypertension
  - Aneurysm
  - AS/AR
  - L-CHF
  - Shock
  - MS

- P1 ↑
  - Pulmonary hypertension (associated with narrow splitting of S_2)
  - Pulmonary hypertension (PS, R-CHF)

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; PS, pulmonary stenosis.

Useful background: Select features of systolic murmurs

- In the holosystolic murmur, the murmur begins just after the first heart sound (S_1) and continues throughout the systole. In the late systolic murmur, the murmur begins at the middle of the systole or later and ends at the second heart sound (S_2). In an early peaking murmur, peak intensity is before the middle of the systole. In a mid or late peaking murmur, peak intensity is at the middle of the systole or later.

Source: Simel DL, et al. *JAMA* 2009, Figure 33-1.

"Harsh words are heavy and often fall with a big thud,
but a kind word will bounce on and on…"

Anonymous

Rheumatic fever and rheumatic heart disease

- Take a directed history and perform a focused physical examination for rheumatic fever and rheumatic heart disease (RHD).

  - Heart
    - Endocarditis
    - Pericarditis
    - Valvulitis
    - Myocarditis (MV > AV)
  - CNS
    - Chorea
  - Systemic
    - Weight loss, fever
  - Joints
    - Polyarthritis
  - Skin
    - Rheumatic nodules
    - Non-tender, painless, subcutaneous lesions along tendons and over bony prominences on back of hands, elbows, knees, spine)
    - Erythema multiforme
  - Blood
    - Anemia
  - Lung
    - Pleursy, pneumonia
  - GI
    - Peritonitis

Abbreviations: AV, aortic valve; CNS, central nervous system; GI, gastrointestinal; MV, mitral valve; RHD, rheumatic heart disease;

Adapted from: Davey P. *Wiley-Blackwell* 2006, pages 30 and 31.

Useful background: Diagnosis of initial attack of Rheumatic Fever

- Jones criteria
  - Major manifestations
    - Carditis
    - Polyarthritis
    - Chorea
    - Erythema marginatum
    - Subcutaneous nodules
  - Minor manifestations
    - Clinical findings
      - Arthralgia
      - Fever
    - Laboratory findings
      - Elevated acute phase reactants (erythrocyte sedimentation rate, C-reactive protein)
      - Prolonged PR interval

- Supporting evidence of antecedent group A streptococcal infection
  - Positive throat culture or rapid diagnostic test
  - Elevated or rising streptococcal antibody titer

- Ducket Jones diagnostic criteria for Rheumatic Fever

Rheumatic fever= 2 major or 1 major+ 2 minor + evidence of recent streptococcal infection (Group A streptococcal (throat) infection can → immune reaction → acute rheumatic fever).

Abbreviations: CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

Adapted from: Davies IJT. *Lloyd-Luke LTD* 1972, page 30, 31; Davey P. *Wiley-Blackwell* 2006, page 166; Burton JL. *Churchill Livingstone* 1971, page 9.

Major Criteria for the Diagnosis of Rheumatic Fever (Ducket Jones)

- Carditis
  - Murmurs, often mitral stenosis, may take years for the murmur to appear
  - CHF
  - Cardiomegaly
  - Pericarditis
  - Arrhythmia

- Polyarthritis
  - Large pints
  - Severity may be inversely proportional to severity of chorea

- Rheumatic nodules
  - Usually seen in children, not adults
  - Seen in severe infection
  - Usually indicates cardiac involvement
  - Attatched to tendons, ligaments (not to skin)
  - Painless
  - No inflammation

- Erythema marginatum
  - Tender red, nodules on legs, thighs
  - Distinguish from rheumatic nodules, or rash due to sweating or salicylates.

- Sydenham chorea (chorei form movement)
  - Usually face & upper limbs affected
  - Bilateral
  - □ by emotion or observation
  - □ by sleep
  - Ataxia
  - Weakness
  - Choreiform movements often inversely proportional to severity of the arthritis

Curiosity: pregnant women with rheumatic fever often develop mania.

In the patient with 2 murmurs, and using just the vital signs, determine which is likely the prominent murmur.

MS + A_2

- If there is atrial fibrillation, MS is the main murmur
- If there is □ pulse pressure, AR is the main murmur

AS + AR

- Determine which is the main murmur from the character of the pulse (collapsing □□AI, plateau □ AS)

What is the effect of the development of atrial fibrillation on the murmur of MS?

- The usual presystolic accentuation disappears.

What is “mitral facies”?

- Dilated capillaries and venules on face
- Is not pathognomonic for MS

In MS, there is right ventricular hypertrophy, without LV enlargement. In the patient with MS who has a displaced apex beat suggesting left ventricular hypertrophy, what are the explanations (murmur of MS, plus displaces apex beat)?

- A second disease valve (eg aortic regurgitation)
- Systemic hypertension
- Pericardial adhesions

Note: MS plus CHF does not by itself give a displaced apex beat.

- Give 3 features obtained from auscullation which suggest that the murmur of MS is severe.

  - Long murmur of MS
  - S_1 loud
  - Opening snap close to S_2

Caution: in the older person with onset of a diastolic murmur suggestive of MS, consider the possibility of an atrial myxoma.

What are the features seen on a chest X-ray which suggest the presence of MS?

- Enlarged hilar vessels, usually large pulmonary artery and left main branch
- Enlarged RA, but not LV

- Radiation of murmurs
  - Apical murmur to base of heart
  - Basal murmur to axilla

- What are the two diseases which are the usual causes of combined AS plus AR?
  - Atherosclerosis
  - Rheumatic heart disease
  - Rheumatic heart disease or combined AS plus MS/MR?

Systolic Murmurs

- Aortic
  - Aortic stenosis- confirmed by narrow pulse pressure and thrill (patient leaning forward in expiration)
  - Increased flow rate
  - Valve distortion without stenosis
  - Post valvar dilatation eg hypertension
  - Coarctation murmur is later in systole and may extend to 2nd sound

- Pulmonary
  - Functional, especially in young people
  - Pulmonary stenosis- may be very soft especially if associated with VSD
  - Increased flow rate ASD, VSD, TAPVD (total anomalous pulmonary venous drainage), hyperdynamic circulation
  - Post valvar dilatation, eg pulmonary hypertension

- Pansystolic murmurs
  - Continuous with the 2nd sound
  - Mitral regurgitation- propagated into axilla
  - Tricuspid regurgitation –increases with inspiration
  - VSD- 3rd or 4th LICS. Thrill in 90 per cent
  - PDA- usually in 2nd LICS. Murmur may be absent, pansystolic or continuous

Abbreviations: ASD, atrial septal defect; LICS, left intercostal space; PDA, patent ductus arteriosus; TAPVD, total anomalous pulmonary venous drainage; VSD, ventricular septal defect

Adapted from: Davies IJT. *Lloyd-Luke LTD* 1972, pages 32 to 39.

Useful background: Typical location of maximal intensity and radiation for various types of abnormal systolic murmurs

Location of maximal intensity	Radiation	Typical for
➢ Second R.ICS	○ Right carotid artery ○ Right clavicle	- AS
➢ Fifth or sixth L.ICS	○ Left anterior axillary line	- MV-P
➢ Mid left thorax	○ Left axilla	
➢ Lower L.SB	○ Lower R.SB ○ Epigastrium ○ Fifth ICS, mid left thorax	- TR
➢ Fifth L.ICS	○ Lower L.SB	- HCM

Abbreviations: HCM, hypertrophic cardiomyopathy; ICS, intercostal space; MV-P, mitral valve prolapse; SB, sternal border; TR, tricuspid regurgitation

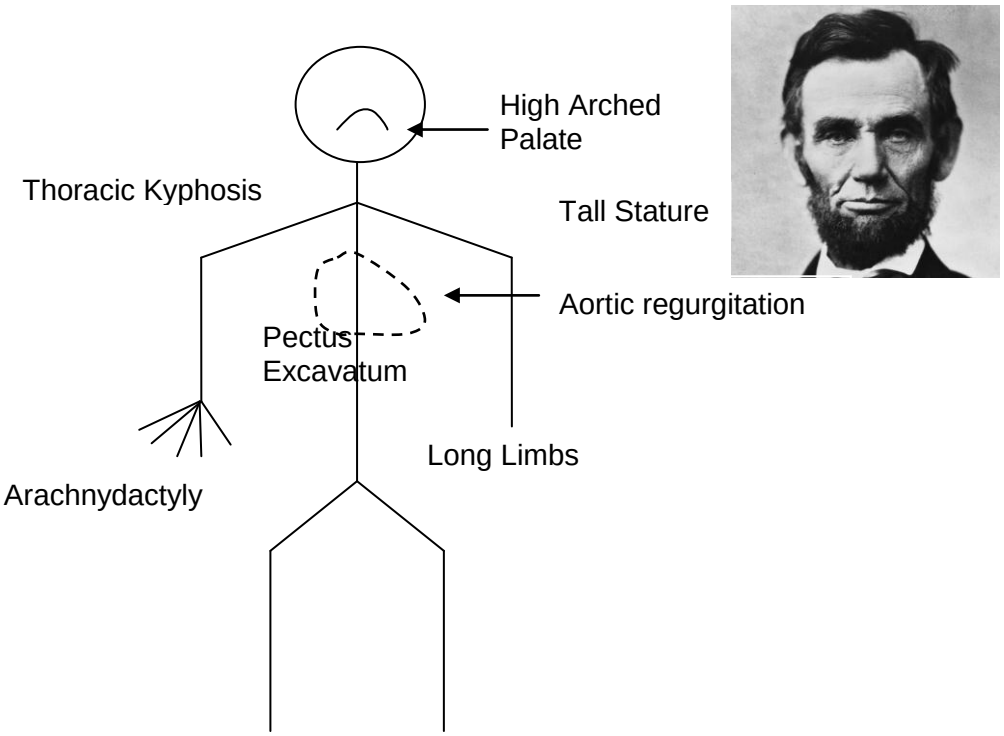
Source: Simel DL, et al. *JAMA* 2009, Table 33-2, page 435.

Be Modest-
"There is always a taller mountain."

Grandad

- Perform a focused physical examination for Marfan's Syndrome.

Marfan's Syndrome



Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 3.2, page 35.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is the way on physical examination when you find a midline mass to distinguish between a thyroid lesion and a thyroglossal cyst?

A1. Both move on swallowing, but only the thyroglossal cyst moves when the tongue is protruded.

Q2. What is the way to demonstrate a laryngocele?

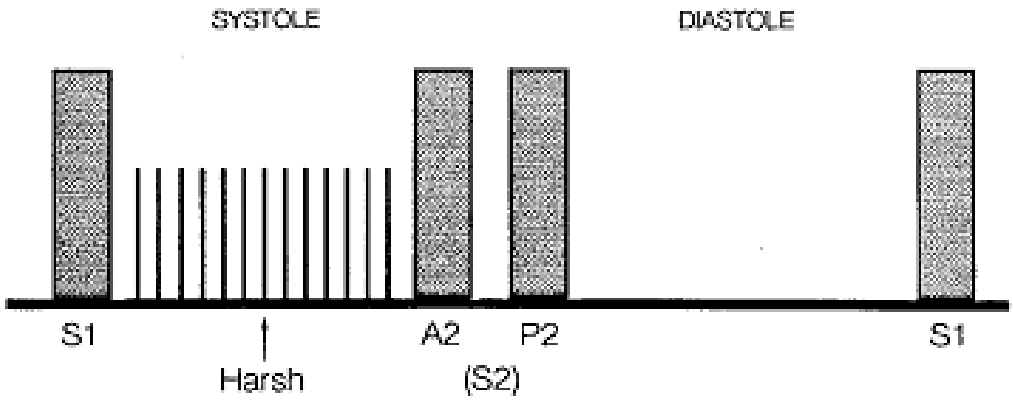
A2. A laryngocele may be demonstrated by performing the valsalva maneuver ("forced expiration against a closed glottis [bearing down], which increased intrathoracic and central nervous pressure, pushing on the diverticulum and making it more prominent in the area of the hyoid and thyroid cartilages.

Atrial Septal Defect

- Normal pulse
- Parasternal lift over pulmonary artery
- Normal jugular pulse; systolic ejection murmur in pulmonic area
- Low pitched diastolic rumble over tricuspid area (at times); persistent wide splitting of S2

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 251.

Useful background: Ventricular septal defect (VSD) (at the left sternal edge)



Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 3.33, page 83.

<u>Aortic stenosis</u>

- Perform a focused physical examination for AS.

➢ Pulse
- Normal, when gradient across the aortic valve is < 50 mm Hg
- ↓ pulse pressure (in severe AS)
- ↓ pulse volume (pulsus parvus)
  - Slow upstroke (pulsus tardis)
  - Anacrotic notch during upstroke
  - Bisferious pulse (AS plus AR)

- Heart sounds
  - Normal S_2 – mild AS
  - ↓ S_2
    - Valvular stenosis
    - More severe AS
    - Reversed splitting of S_2 (longer LV systole)
  - S_3
    - LV systolic dysfunction
    - ↑ LV filling pressure
- Apex
  - Displaced with LVD
- Aortic area
  - Thrill (may also be palpated over carotids)
  - More prominent when sitting and in expiration
- Murmur
  - Systolic
    - Crescendo – decrescendo (ejection)
    - Base of heart
    - Radiation to carotids and to right clavicle
    - Loudness does not reflect severity of AS (ie magnitude of gradient, or cross-sectional area)
  - Diastolic
    - Often associated with AR

- Perform a focused physical examination to distinguish aortic sclerosis from stenosis.
  - Aortic sclerosis
    - Pulse – normal
    - Apex beat – not displaced
    - Murmur – does not radiate

- Perform a focused physical examination to access the severity of AS.

- Heart sounds
  - ↓ S_2
  - S_2 narrow/ split
  - S_4
- Apex
  - Thrill during LV systole
  - Heave
- Pulse
  - ↓ pulse pressure
- Signs of CHF

Source: Baliga RR. *Saunders/Elsevier* 2007, page 18.

Trick Question

Q. What does S_2 indicate about the cause and severity of AS?

A.
- S_2 normal – mild AS
- S_2 splitting reversed – prolonged LV systole (electrical or mechanical prolongation)
- ↓ S_2 – valvular stenosis*
- Single S_2 (no A_2, only P_2) – valve leaflets – fused, fibrosed

SO YOU WANT TO BE A CARDIOLOGIST!

Q. The presence of aortic stenosis (AS) is decreased with any murmur radiating to the right carotid artery.

- Give 4 symptoms or signs which increase the likelihood that a systolic murmur is AS.

A.
- History
  - Effort syncope
  - Slow rate of increase of carotid pulse
- Physical
  - Reduced carotid volume
  - Slow rate of increase of carotid pulse
  - Murmur loudest at second right intercostals space
  - Apical-carotid delay, or brachioradial delay
  - Decreased or absent S_2
  - Peak murmur intensity late or mid systolic
  - Valve calcification on chest radiograph

Adapted from: Simel DL, et al. *JAMA* 2009, pages 437 and 438.

Useful background: Causes of systolic ejection murmur at base of heart

- AS
  - Valvular
  - Supravalvular
- Aortic sclerosis
- Pulmonary stenosis
- HOCM

- Causes of syncope in AS
  - Transient electro-mechanical dissociation
  - Peripheral vasodilation
  - Arrhythmia
    - Bradycardia
    - Tachycardia
    - Ventricular fibrillation

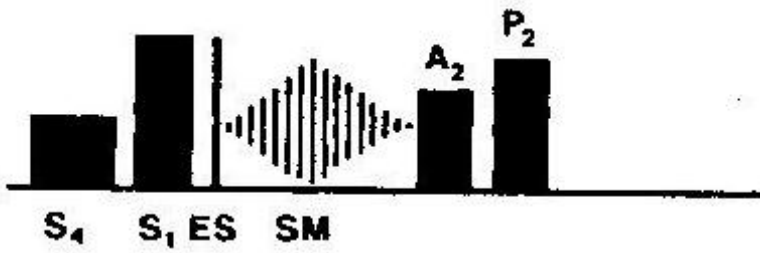
Useful background: AR plus AS (Mixed aortic lesions)

- Causes
  - < 60 years: rheumatic, congenital
  - 60 to 75 years: calcified bicuspid aortic valve, especially in men
  - > 75 years: degenerative calcification

- Importance of S_2
  - Normal S_2
    - Strong evidence against the presence of critical aortic stenosis
  - Soft S_2
    - Valvular stenosis (except in calcific stenosis of the elderly, where the margins of the leaflets usually maintain their mobility)
    - Single second heart sound
    - When there is fibrosis and fusion of the valve leaflets
  - Reversed splitting of the S_2
    - Mechanical or electrical prolongation of ventricular systole
  - Indication of more severe AS
    - Loud S_2
    - Delay of peak of crescendo-decrescendo ejection systolic murmur with increasing severity of aortic stenosis.
    - Crescendo-decrescendo murmur begins after the first heart sound (or after the ejection click when present)
    - Peaks in mid or late systole
    - Ends before the second heart sound; this peak is delayed

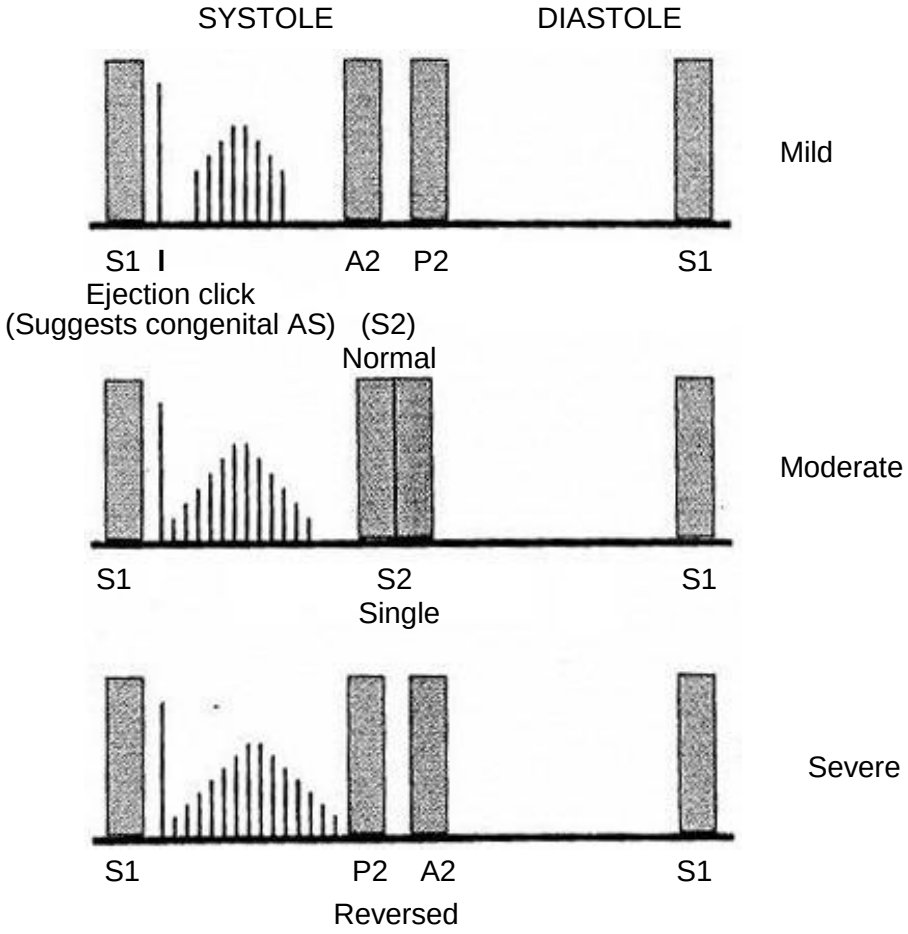
Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 19.

Precordium- Basal systolic thrill; apex displaced anteriorly and laterally.



Carotids- slow upstroke to a delayed peak. Auscultation- A2 diminished or paradoxically ejection systolic murmur radiating to carotids. Cold extremities. Reversed S2-P2-A2 in severe AS (paradoxican splitting)

Useful background: Aortic stenosis (AS) (at the aortic area)



- Soft S_2
- Reversed A_2 / P_2 (narrow or reverse split S_2)
- S_4
- Narrow pulse pressure
- Systolic thrill
- Heaving apex beat
- L- CHF

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 3.31, page 77.

Useful background: Accuracy of the physical examination for detecting aortic stenosis

Finding	PLR	NLR
➢ Slow carotid upstroke	9.2	0.56
➢ Murmur radiating to right carotid	8.1	0.29
➢ Reduced or absent S_2	7.5	0.50
➢ Murmur over right clavicle	3.0	0.10
➢ Any systolic murmur	2.6	0
➢ Reduced carotid volume	2.0	0.64

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

Source: Simel DL, et al. *JAMA* 2009, Table 33-11, page 445.

Useful background

- Causes of combined aortic and mitral valve disease
  - Rheumatic valvular disease
  - Infective endocarditis
  - Collagen degenerative disorder (e.g. Marfan's syndrome)
  - Calcific changes in the aortic and mitral valve apparatus

Source: Baliga RR. *Saunders/Elsevier* 2007, page 22.

Useful background: Increased Likelihood of Aortic Stenosis as the cause of a systolic murmur.

- Effort syncope
- Slow rate of rise of the carotid artery pulsation
- Timing of peak murmur intensity in mid or late systole
- Decreased intensity of S_2

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 65.

Useful background: The mechanism of syncope in aortic stenosis

- The left ventricle is suddenly unable to contract (transient electro-mechanical dissociation) against the stenosed valve.
- Cardiac arrhythmias (bradycardia, ventricular tachycardia or fibrilation)
- Marked peripheral vasodilatation without a concomitant increase in cardiac output, particularly after exercise.

Source: Baliga RR. *Saunders/Elsevier* 2007, page 20.

Pulmonary stenosis

- Causes of pulmonary stenosis
  - Congenital (commonest cause)
  - Carcinoid tumour of the small bowel

Source: Baliga RR. *Saunders/Elsevier*, 2007, page 81

  - Usually congenital in origin
  - Systolic ejection murmur
  - Narrowing which may be
    - Valvular
    - Subvalvular
    - Supravalvular
  - Ejection click (from post-stenotic dilation)
  - Loud splitting of P_2
  - Soft P_2

 What are the clinical findings which suggest subvalvular PS?

  - No ejection click
  - Often associated with a VSD

 Why are blood cultures usually negative for growth in the patient with PS?

  - Embolization is to the lungs, not to the peripherial blood

- Give 4 causes of P_2 which are associated with pulmonary hypertension.
  - MS
  - ASD
  - PDA
  - Carcinoid

Easy Question for our Would-be Cardiologist!

Q. In the context of PS, what are the features of the eponymous syndromes named after Noonan, Watson and Williams?

A.
- Noonan's syndrome: short stature, ptosis, downward slanting eyes, wide-spaced eyes (hypertelorism), low-set ears, webbed neck, mental retardation and low posterior hairline. About two thirds of patients with Noonan's syndrome have pulmonary stenosis due to valve dysplasia
- Watson's syndrome: café-au-lait spots, mental retardation and pulmonary stenosis
- Williams' syndrome: infantile hypercalcaemia, elfin facies and mental retardation in addition to supravalvular pulmonary stenosis. Subvalvular pulmonary stenosis, which is caused by the narrowing of the right ventricular infundibulum or subinfundibulum, usually occurs in association with a ventricular septal defect.

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 81 to 82.

- Perform a directed physical examination to distinguish between the systolic murmur of pulmonary stenosis (PS) and aortic stenosis (AS).

	AS	PS
➢ Site of maximal intensity	Apex, or 2nd ICS	L. sternal border
➢ Intensity		
➢ Inspiration	─	↑
➢ Expiration	↑	─
➢ Standing	↓	↑
➢ After release of Valsalva maneuver	Late	Early

Abbreviations: AS, aortic stenosis; ICS, intercostal space; PS, pulmonary stenosis

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 258.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What are the causes of pulmonary stenosis?

A1.
- Congenital (commonest cause)
- Carcinoid tumour of the small bowel

Q2. How can valvular pulmonary stenosis (PS) be distinguished from on a chest X-ray?

A2. Only valvular PS has post-stenotic dilation.

- Perform a physical focused physical examination to distinguish between the murmur of pulmonary stenosis (PS) and aortic stenosis (AS).

Physical sign	AS	PS
➢ Location of maximal intensity	2nd R-ICS, or apex	L-sternal border
➢ Breathing-effect on murmur	Louder in expiration	Louder in inspiration
➢ Effect on ejection click	No change during inspiration	Soften during inspiration
➢ Effect of standing	Softer	Louder
➢ Valsalva maneuver		
Staining phase	Softer	Softer
	↓	↓
Releasing phase	Louder slowly	Louder quickly
➢ S2	Paradoxical splitting of S2	Widened physiologica S2
➢ S4 inspiration	Expiration	Inspiration

Abbreviation: R, right; L, left; ICS intercostals space

Systotic Regurgitation causes: intital regurgitation (MR), tricuspid regurgitation (TR), ventricular septal defect (VSD), patent ductus arteriosus (PDA)

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 258 and 259.

Useful background: Causes of the combined aortic and mitral valve disease

- Rheumatic valvular disease
- Infective endocarditis
- Collagen degenerative disorder, e. g. Marfan's syndrome
- Calcific changes in the aortic and mitral valve apparatus

I THINK I BETTA BE A GENERALIST!

Q1. In the presence of aortic stenosis (AS) or hypertrophic cardiomyopathy (HE), what is the Brockenbrough- Braunwald- Morrow (B-B-M) sign?

A1. A fall in pulse pressure after an extrasystolic beat.

Q2. In which type of muscular dystrophy is myocardial involvement most frequent?

A2.
- Pseudohypertrophic muscular dystrophy
- Dystrophia myotonia

- Perform a directed physical examination to distinguish between the systolic murmur of aortic sclerosis (no pressure gradient; due to stiff or dilated aortic root) and aortic stenosis (AS).

	Aortic Stenosis	Aortic Sclerosis
➢ Symptoms o Dizzy, syncopy, chest pain, dyspnea	+	-
➢ Pulse o Slow, small volume	+	-
➢ Apex beat PMI	+	-
➢ Precordial thrill	+	-
➢ Heart sounds (S_2, A_2)	↓	↑
➢ Murmur o Short peaks in first half of systole		+

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 252,254; Baliga RR. *Saunders/Elsevier* 2007, page 19.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is the difference between the bronchial pulse in ventricular versus supraventricular aortic stenosis (AS)?

A1. In ventricular AS, R=L brachial pulse. In supraventricular AS, the left brachial pulse has slow uptake (pulsus tardus), but the right brachial pulse is normal (L < R).

Source: Mangione S. *Hanley & Belfus*, 2000, page 182.

Q2. How would you differentiate aortic stenosis (AS) from aortic sclerosis?

A2.
- Aortic sclerosis is seen in the elderly
- The pulse is normal volume
- The apex beat is not shifted
- The murmur is localized

Q3. How does the patient's age affect the likely cause of their aortic stenosis?

A3.
- Under the age of 60 years: rheumatic, congenital.
- Between 60 and 75 years: calcified bicuspid aortic valve, especially in men.
- Over the age of 75 years: degenerative calcification

Source: Baliga RR. *Saunders/Elsevier* 2007, page 19.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. From the palpation of a central artery (brachial or carotid), differentiate between supravalvular aortic stenosis versus either subvalvular or valvular aortic stenosis?

A.

Supra'	Sub'/ valvular
○ Rapid upstroke	○ Slow upstroke
○ ↑ Pulse pressure	○ ↓ pulse pressure
○ ↓ duration of peak (summit)	○ ↑ duration of peak

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 183.

- Perform a directed physical examination to distinguish between the systolic murmur from HOCM (hypertrophic cardiomyopathy, particularly septal component) and aortic stenosis (AS).

	AS	HOCM
➢ Early after S1	+	-
➢ Midsystole	-	+
➢ Intensity of murmur:		
○ Valsalva maneuver	-	↑
○ Squatting	↑	↓
➢ Associated murmur of MR	↓	+
➢ Timing of onset systolic murmur	Immediately after S1	Begins in mid-systole
➢ Valsalva maneuver	↓ intensity	↑ intensity
➢ Squatting	↑ intensity	↓ intensity
➢ Associated MR*	Rare	75%

*MR murmur HOCM ends before A2, and may be from MVP (mitral valve prolapsed)

MR, initiated regurgitation; S1, first heart sound; A2 the A2 components of S2, the second sound

Abbreviations: AS, aortic stenosis; HOCM, hypertrophic cardiomyopathy; MR, mitral regurgitation

Adapted from Mangione S. *Hanley & Belfus* 2000, pages 256 to 258.

Useful background: Performance characteristics of the physical examination performed by experts for detecting Hypertrophic cardiomyopathy (also known as IHSS, idiopathic subaortic stenosis)

	PLR	NLR
➢ Decreased intensity with passive leg elevation	8.0	0.22
➢ Decreased or unchanged intensity with standing to squatting	4.5	0.13

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

Source: Simel DL, et al. *JAMA* 2009, page 439.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What are the complications of HOCM?

A1.
- Sudden death
- Atrial fibrillation
- Infective endocarditis
- Systemic embolization

Q2. What is the most pathophysiological abnormality in HOCM?

A2. Diastolic dysfunction

- Auscultation: stenosis – longer, peaks in early systolic, normal or loud S2 (especially if there is associated systemic hypertention)

- Aortic Stenosis
  - Congenital, degenerative, rheumatic (bicuspid semiluminar valve)
  - Valvular, supravalvular, subvalvular
  - Arterial pulse
    - Valvular: small amplitude (parsus) with slow upstroke (tardus) may be associated thrill best heard over carotid artery
    - Supravalvular: amplitude of pulse higher R>L –sided vessels
    - Subvalvualr: brick pulse, with palpable double systolic impulse (pulsus bisferiens)

- Valvular Aortic Stenosis Impulse (Pulsus Bisferiens)
  - PMI – normal in AS, unless LV hypertrophy and L-CHF or AS plus aortic regurgitation
  - Precardial thrill – palpable, does not reflect severity of AS

- Murmur budest in "sach area" 2nd right intercoatal space (aortic area) down to 5/6th intercoatal space at the left mid clavicular line
- Crescendo – decrescendo murmur; louder and longer murmur with later peak is more severe soft or absent A2 and audible or palpable S4, suggests more. If murmur becomes softer, suspect obesity or COPD, or CHF.

- Subvalvular Aortic Stenosis (HOCM)

- Supravalvular Aortic Stenosis
  - Males, with associated congenital abnormalties
    - Typical Facies
    - Patulus lip
    - Deep, husky voice
    - Hypercalcemia
  - Pulse and BP stronger on right than left side (R > L)
  - No aortic ejection click
  - May be an associated murmur of aortic regurgitation

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 254 to 259.

- Perform a focused physical examination to distinguish hypertrophic obstructive cardiomyopathy (HOCM) from aortic stenosis (AS).

	HOCM	AS
➢ Pulse	○ Jerky ○ Rapid upstroke ○ PMI* ○ Double impulse in systole	○ Anacrotic (plateau) ○ Single impulse
➢ Heart sounds		○ ↓ A_2 ○ Ejection click
➢ Thrill	○ No	○ Yes
➢ Murmur	○ Ejection ○ Late systole ○ Best heard at apex/ L-SE* ○ May be associated mitral regurgitaion	

Abbreviations: L-SE, left sterna edge; PMI, point of maximum impulse

Useful background:

- The complications of aortic stenosis
  - Sudden death occurs in 10-20% of adults and 1% of children. It has been rarely documented to occur without prior symptoms.
  - Ventricular arrhythmias (more common than supraventricular arrhythmias)
  - Heart block (may occur because of calcification of conducting tissues).
  - Systemic embolization (disintegration of the aortic valve or concomitant aortic atheroma).
  - Infective endocarditis
  - Hemolytic anemia

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 21.

- Perform a focused physical assessment for prosthetic heart valves.

- Mitral Valve
  - Recognized by their site, metallic first heart sound, normal second heart sound and metallic opening snap
  - Systolic murmurs are often
  - Diastolic flow murmurs may be heard normally over the disc valves

- Aortic Valve
  - Be recognized by their site, normal first heart sound and metallic second heart sound

- Both mitral and aortic
  - Both the first and second heart sounds will be metallic
  - The presence of a systolic murmur does not indicate valve dysfunction
  - The presence of an early diastolic murmur indicates a malfunctioning aortic valve

- Complications
  - Thromboembolism
  - Valve dysfunction, including valve leakage, valve dehiscence and valve obstruction due to thrombosis and clogging
  - Bleeding (such as upper gastrointestinal hemorrhage) due to anticoagulants
  - Hemolysis at the valve, causing anemia
  - Endocarditis (prosthetic valve endocarditis)
    - <2 months of surgery: develops as a result of intraoperative contamination of the prosthetic valve or as a consequence of a postoperative nosocomial infection

        - >2 months of surgery: after transient bacteremia (minor skin or upper respiratory tract infections or following dental or urinary manipulations). The non-cardiac manifestations resemble those of native valve infective endocarditis
    - Structural dysfunction
        - Fracture
        - Poppet escape
        - Cuspal tear
        - Calcification
    - Non-structural dysfunction
        - Paravalvular leak
        - Suture/tissue entrapment
        - Noise

- Negative prognostic factors
    - Heart failure
    - Non-streptococcal endocarditis, especially *Staph. aureas*, fungal endocarditis
    - Infection of a prosthetic valve
    - Elderly patients
    - Valve ring or myocardial abscess

- Conditions that can simulate clinical manifestations of infective endocarditis
    - Atiral myxoma
    - Non-bacterial endocarditis
    - Systemic lupus erythematosus (SLE)
    - Sickle cell disease

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 61-63; Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.14, page 81.

Useful background: Performance characteristics of physical examination of severe aortic stenosis (AS)

The finding of S_4 gallop, a murmur best heard over the 2nd intercostal space, or a murmur radiating into the neck have no value to predict the presence of severe AS.

Finding	PLR
➢ Arterial pulse	
○ Delayed carotid artery upstroke	3.7
○ Reduced carotid artery volume	2.3
○ Brachioradial delay	2.5
➢ Apical impulse	
○ Sustained apical impulse	4.1
○ Apical carotid delay	2.6
➢ Heart sounds	
○ Absent A2	4.5
○ Absent or diminished A2	3.6
➢ Murmur	
○ Late peaking (midsystole or beyond)	4.4
○ Prolonged duration	3.9

Abbreviation: ICS, intercostal space; PLR, positive likelihood ratio

Note: The finding of S4, murmur loudest over aortic area (2nd ICS), and transmission of the murmur to the neck are not mentioned here because their PLR are < 2.

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 40-1, pages 477 and 478.

Pulmonary stenosis (PS)

Useful background: Accessing severity of PS

Pathophysiology	Mild	Moderate	Severe
Pulmonary valve area, cm^2/m^2	>1.0	0.5 – 1.0	< 0.5
Transvalvular gradient, mm Hg	< 50	50 – 80	>80
Peak RV systolic pressure, mm Hg	< 75	75 - 100	>100

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 81.

Perform a focused physical examination for pulmonary stenosis.

- General inspection
  - Plump face
- JVP
  - 'a' wave
- Peripheral
  - Normal
- Palpation
  - LSE heave
- Heart sounds
  - ↓ S_2 (from ↓ A_2)
  - S_2 split
  - Ejection click
- Murmur
  - Ejection systolic
  - Upper LSE, left lung posteriorly
  - For infundibular PS, murmur heard best at 3rd – 4th L-ICS (aka Erb's point)
- Skin
  - Cyanosis, clubbing (Fallot's tetralogy)
- Signs of CHF, SBE
- Signs of eponymous syndromes – please see Bal page 82

Abbreviation: CHF, congestive heart failure; SBE, subacute bacterial endocarditis; L-ICS, left intercostals space

Mitral Regurgitation (MR)

- Perform a focused physical examination for MR.
  - Peripheral pulse – rapid upstroke of short duration (↑ BV regurgitating into LA causes ↓ LV ejection time)
  - Apex beat
    - position: down and out
    - character: forceful
  - Heart sounds
    - ↓ S_1
    - ↑ S_2 (if PHT present)
    - S_3 present
  - Murmur
    - Pansystolic
    - Transmitted to axilla

- Diaphragm for best detection
- Expiration for ↑ loudness

- Give 10 causes of mitral regurgitation.
  - ASD (ostium primum, cleft of mitral valve)
  - Partial AV canal
  - Post – surgical correction of transposition of great vessels

- Precordium
  - Apical systolic thrill,
- Apex
  - Displaced to left.
- Auscultation-
  - Apical systolic regurgitant murmur following a ↓ S_1 radiating
  - S_1 ↓ or absent (murmur may replace S_1).
  - S_3 due to increased left ventricular end diastolic volume. Auscultating an S_3 does not reflect the severity of MR, nor does a systolic regurgitant wave in the neck weins reflect the severity of TR.
  - Diastolic flow murmur in severe MR
  - In tall persons (eg. Marfan's syndrome, maximal intensity of MR murmur is close to left sternal border)
  - Radiation
    - Left axilla or left interscapular area
    - With ruptured chordate tendinae

- Perform a focused physical examination to distinguish between the systolic murmur of mitral regurgitation due to dysfunctional papillary muscle (DPM) versus ruptured chordate tendinae (RCT).

	DPM	RCT
➢ Flash pulmonary edema		
➢ Loud S3	-	+
➢ Loud S4 (3/6 or more)	-	+
➢ Decreased early systolic murmur	-	+
➢ Murmur radiates into carotids	-	+

Source: Mangione S. *Hanley & Belfus* 2000, page 261.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. How do you make the diagnosis of MR, in the absence of a murmur? (In the patient with a thick chest, well aerated lung tissue and a large RV, even severe MR may not have an audible murmur of MR)

A.
- Large L-atrium and L-ventricle
- S_2 widely split

Useful background: In mitral regurgitation (MR), the louder the murmur, the more severe the regurgitation.

Source: Simel DL, et al. *JAMA* 2009, Table 33-12, page 445.

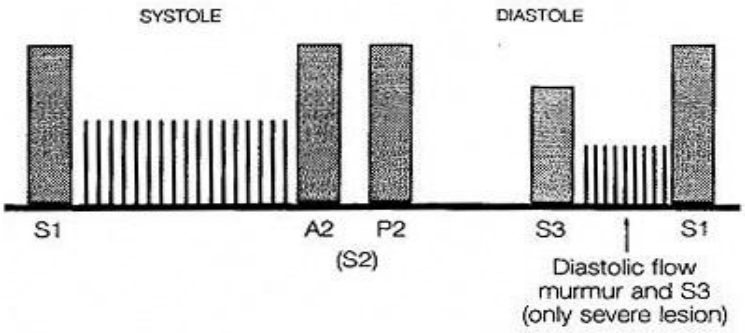
- Perform a physical focused physical examination to determine the severity of mitral regurgitation (MR).
  - Displased of apex (PMI) from large LV
  - Louder and longer apical systolic murmur
  - Loud S_3
  - Early loud diastolic flow murmur after S_3
  - S2 widened, unless pulmonary hypertension is present and the S_2split is narrow

Abbreviation: LV, left ventricle; PMI point of maximal impulse of apex of LV.

Source: McGee SR. *Saunders/Elsevier* 2007, Box 42-1 pages 494 and 495.

Mitral regurgitation (MR): Precordium- Apical systolic thrill, apex displaced to left. Auscultation- Apical systolic regurgitant murmur following a decreased S1 radiating to axilla; often hear S3 due to increased left ventricular end diastolic volume. S1 ↓ or absent (murmur may replace S1). Diastolic flow murmur in severe MR.

Useful background: Mitral regurgitation (at the apex)



Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 3.29, page 75.

Useful background: Causes of mitral regurgitation (MR)

- Acute
  - Rupture of the papillary muscle (often with MI)
  - Endocarditis (often due to perforation of the MV leaflet or the chordate)
  - Trauma
  - Myxomatous degeneration of the MV

- Chronic
  - Mitral valve leaflets
    - Annular calcification
    - Endocarditis
      - Chordal and papillary muscles
      - Rheumatic
      - Prolapse
      - Annular clacification
      - Connective tissue disease
      - Congenital cleft
      - Drug related

  - Heart
    - Cordial and papillary muscles
      - MV Prolapse
      - Rupture of chordae
      - Myocardial infarction
      - Papillary muscle rupture
    - Myocardium
      - Regional ischemia of infarctions
      - Dilated cadiomyopathy (coronary artery disease)
      - Hypertrophic cardiomyopathy
    - Left ventricular dilatation

  - Connective tissue disorders

Abbreviations: MI, mitral insufficiency; MV, mitral valve

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 9 and Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-6, page 47.

- Take a directed history and perform a focused physical examination for the causes of chronic mitral regurgitation.

    - Mitral valve prolapse
    - Rheumatic heart disease
    - Left ventricular dilatation
    - Coronary artery disease
    - Annular calcification
    - Infective endocarditis
    - Papillary muscle dysfunction
    - Cardiomyopathy
    - Connective tissue disorders

Source: Baliga RR. *Saunders/Elsevier* 2007, page 9.

- Perform a physical focused physical examination to distinguish between the murmur of MR caused by rupture of the chordate tendinae (RCT) versus papillary muscle dysfunction (PMD).

Physical sign	RCT	PMD
➢ Flash pulmonary edema	○ Yes	- No
➢ Timing of MR murmur	○ Starts immediately after S1 ○ Decreases in mid systole	- Starts at mid systole - Crescendo pattern ending at S2
➢ Radiation	○ Into carotids	- Left axilla
➢ S4	○ Yes	- No

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 261.

- Perform a focused physical examination to determine the severity of aortic regurgitation.

➢ Pulse
    - Wide pulse pressure

➢ Heart sounds
    - Soft S_2
    - Presence of S_3

➢ Murmur
    - Duration of the decrescendo diastolic murmur

- Austin Flint murmur (an apical, low-pitched, diastolic murmur caused by vibration of the anterior mitral cusp in the regurgitant jet, and is heard at the apex.)

➢ Associated signs – L-CAF

Adapted from: Baliga RR. *Saunders/Elsevier*, 2007, page 15.

- Perform a physical focused physical examination to determine the severity of mitral regurgitation (MR).

  - Displased of apex (PMI) from large LV
  - Louder and longer apical systolic murmur
  - Loud S_3
  - Early loud diastolic flow murmur after S_3
  - S2 widened, unless pulmonary hypertension is present and the S_2split is narrow

Abbreviation: LV, left ventricle; PMI point of maximal impulse of apex of LV.

Source: McGee SR. *Saunders/Elsevier* 2007, Box 42-1 pages 494 and 495.

Mitral Regurgitation (MR)

➢ Characteristics
  - Maximal intensity of murmur
    - Apex, but
    - In tall persons (eg. Marfan's syndrome, maximal intensity of MR murmur isclose to left sternal border)
  - Radiation
    - Left axilla or left interscapular area
    - With ruptured chordate tendinae

    Anterior: mid-thoracic spine, or top of head (!)
    Posterior: into the carotids

➢ Causes
  - Adults
    - Rheumatic damage to the valves
    - Pallilary muscle dysfunction (especially after acute MI)
    - Rupture of chordate tendinae (usually with infective endocarditis)
    - Myxomatous degeneration of valve
    - Mitral valve replacement
    - LV dilatation
    - Coronary heart disease
    - Annular calcification
    - Infective endocarditis

- Cardiomyopathy
- Connective tissue disorders

  - Infants
    - Endocarditis fibroelastosis
    - Congenital abnormality of anomalous left coronary artery arising from the pulmonary artery
    - Myocarditis
    - Marfan's syndrome

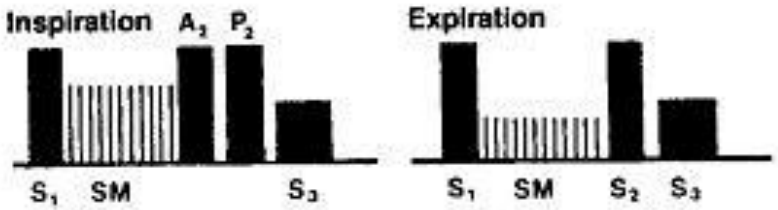
- Perform a physical focaused physical examination to distinguish between the murmur of tricuspid regurgitation (TR) and mitral regurgitation (MR).

Sign	Tricuspid regurgitation	Mitral regurgitation
➢ Pulse	○ Normal	- Jerky, or normal
➢ JVP ○ 'V' wave ○ Deep Y descents (Lancisi's sign)	○ ↑	- Normal
➢ Palpation ○ Left parasternal heave	○ +	○ +
➢ Auscultation ○ Parasystolic murmur ○ Intensity on inspiration ○ Valsava ○ Radiation ○ AJR	○ + ○ ↑ ○ in 3 sec ○ To liver ○ +	○ + ○ ↑↑ ○ in 1 sec ○ To axilla ○ -

Abbreviations: JVP. Jugular venous pressure; AJR, abdomino jugular reflux test

Adapted from: Baliga RR. *Saunders/Elsevier*, page 9; Mangione S. *Hanley & Belfus* 2000, pages 264 and 265.

<u>Tricuspid regurgitation</u>



- Usually secondary to pathology elsewhere in heart.
- Precordium – Right ventricular papasternal lift: systolic thrill at tricuspid area.
- Auscultation – Holosystolic murmur increasing with inspiration
- V wave in jugular venous pulse: systolic liver pulsation

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 251.

- Causes
  - R-CHF (large RV)
  - Cor pulmonale
  - SBE from IV drug abuse
  - Often associated with TS

- Perform a focused physical examination for TR.

- General
  - Peripheral cyanosis
- Pulse
  - May have associated atrial fibrillation
- JVP
  - ↑ 'v' waves
- Heart
  - Parasternal heave, left side
  - Heart sounds
    - ↑ P_2 (may be palpable)
    - S_3
  - Murmur
    - Pansystolic murmur
      - Lower LSE
      - Carvallo's sign
    - Mid-diastolic murmur of associated MS
- Liver
  - Pulsations/ bruit
  - Hepatomegaly
- Signs of R-CHF
- Signs of caused
  - Functional
    - CHF
    - PHT
  - Rheumatic – mitral and/ or aortic valve disease
  - Infection – R.heart endocarditis
  - Endocrine – carcinoid syndrome
  - Hereditary
    - Ebstein's anomaly
    - Endomyocardial fibrosis

- Infarction – RV papillary muscles
- Miscellaneous
  - Tricuspid valve prolopse
  - Blunt trauma

Abbreviation: LSE, left sterna edge, CHF, congestive heart failure; PhT, pulmonary hypertension; RV, right ventricle

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, pages 64 and 65.

 What are the 2 commonest causes of a palpable pulsation in the liver?
- TR
- Large angioma

- Take a directed history and focused physical examination for TR.

➢ History
- IV drug use
- Trauma to the chest
- Rheumatic fever
- Chronic obstructive pulmonary disease (COPD)

➢ Physical examination

- Skin
  - Peripheral cyanosis
  - Ankle edema
- JVP
  - Large 'v' waves in the jugular venous pulse
- Pulse
  - Atrial fibrillation
- Heart
  - Palpation
    - Left parasternal heave
    - Palpable or loud P2
  - Auscultation loud P2, S3
    - Pansystolic murmur at LLSB which ↑ in inspiration (Carvallo's sign)
    - Mid-diastolic murmur of mitral stenosis
- Abdomen
  - Hepatomegaly systolic pulsations
  - Ascites

➢ Causes
- Without pulmonary hypertension (PHT)
  - Congenital
  - Trauma
  - Endocarditis

- With (secondary to) PHT
  - Mitral stenosis plus PHT
  - ASD plus PHT
  - R-CHF plus PHT
  - R-CHF plus PHT, plus L-CHF

Abbreviation: ASD, atrial septal defect; LLSB, left lower sterna border; PHT, pulmonary hypertension; R-CHF, right-side congestive heart failure

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 64.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. Under what circumstances is the blood pressure lower in the legs than arms (normal difference: 10-15 mm Hg higher in legs than arms)?

A.
- Abnormal difference (Hill's sign, > 20 mm Hg; exaggeration of normal, indicating ↑ SV (stroke volume)' such as from tachycardia
- Atherosclerosis in the elderly
- Aortic dissection
- Aortic regurgitation (severe)

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 15.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. In the context of a systolic murmur, what is the significance if after a long diatole (such as following a premature beat), the intensity of the murmur becomes louder at the base but not at the apex?

A1. Then the systolic murmur is likely comprised of both a regurgitation murmur plus an ejection murmur.

Q2. What is the exception to this general rule?

A2. The exception is mitral valve prolapse (MVP), in which, the murmur becomes softer after a long diastole.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is the explanation for the murmur of TR (tricuspid regurgitation) not being auscultated loudest at the left lower sternal border or epigastric area?

A1.
- When the RV enlarges from TR and displaces the LV laterally and postoriorly, the murmur of TR will then be heard best at the right sternal border or apex
- If the person with TR has COPD and air trapping, the murmur will be heard over the free edge of the liver.

Source: Mangione S. *Hanley & Belfus* 2000, page 264.

Q2. In the context of tricuspid regurgitation, what is Carvallo's sign?

A2. Carvallo's sign is the pansystolic murmur of TR which increases with inspiration.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of inspiration and its effect on cardiac murmurs, what is the Rivera-Carvallo [RC] maneuver), and how does it differ from Carvallo's sign?

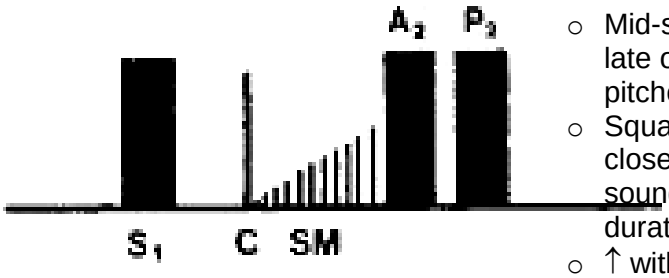
A.
- R-C maneuver
  - Inspiration cause a louder murmur across the pulmonic valve
- C. sign
  - Inspiration causes a louder pansystolic murmur of TR (tricuspid regurgitation, cluring or at the end of inspiration)
  - Carvallo's sign has high specificity but only 61% sensitivity to distinguish TR from MR (mitral regurgitation, in which inspiration does not cause a louder murmur).

Source: Mangione S. *Hanley & Belfus* 2000, page 218 and 258.

Mitral valve prolapse (MVP)

- Take a direct history and perform a focused physical examination for mitral valve prolapse.

- History
  - Palpitations associated with mild tachyarrhythmias
  - Adrenergic symptoms
  - Chest pain
  - Anxiety or fatigue
- Physical Examination



C, click

  - Mid-systolic click, followed by late or mid-systolic high pitched crescendo murmur
  - Squatting will bring the click closer to the second heart sound and decrease the duration of the murmur
  - ↑ with squatting
  - ↓ with valsalva manoeuvre, standing, bradycardia

- Complications
  - Heart
    - Murmur
      - MR
      - Endocarditis
      - TR (myxomatous degeneration of TV)
    - Arrhythmias:
      - VT (Ventricular tachycardia)
      - PST (Paroxysmal supraventricular tachycardia)
      - VPC (ventricular premature contractions)
    - Atypical chest pain
    - Transient ischemic attacks (TIAs)
    - Sudden death

- Associated conditions
  - Chronic rheumatic heart disease
  - Ischemic heart disease
  - Marfan's syndrome (high-arched palate, arm span greater than height, straight back, pectus excavatus, HOCM)
  - Cardiomyopathies
  - ASD (secundum type)

- Ehlers-Danlos syndrome
- Psoriatic arthritis
- Ebstein's anomaly
- SLE

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 251; Baliga RR. *Saunders/Elsevier* 2007, page 65; and Ghosh AK. *Mayo Clinic Scientific Press* 2008, Figure 3-9, page 49.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the patient with MR, what is the meaning of a diastolic rumble?

A.
- MR+ MS (combined mitral disease)
- ↑ BV flow across the mitral valve during diastole

Trick Questions

Q1. Distinguish between the murmur of MR due to RHD, from LV dilation and reduced contractility.

A1. MR from RHD: pansystolic murmur
MR from LV dilation: mid, late or pansystolic

Q2. Distinguish between the murmur of MR and AS with calcification.

A2. If there is a premature beat, or if there is associated AF, listen after the pause, when there is ↑ loudness of murmur in AS, but not in MR.

Abbreviation: AF, atrial fibrillation; AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; BV, blood volume; FP, filling pressure; LV, left ventricle; MR, mitral regurgitation; OS, opening snap; RHD, rheumatic heart disease; TR, tricuspid regurgitation; VSD, ventricular septal defect

Q3. In the context of MR, why does the peripheral pulse have rapid upstroke of short duration?

A3. ↑ BV regurgitating into LA causes ↓ LV ejection time.

Trick Questions

Q1. The murmur of MR is usually associated with the apex beat displaced down and out, but what is the mechanism by which the murmur of MR may radiate to the neck?

A1.
- If a stream of blood regurgitates from the LV into the LA near the aortic root, the murmur may radiate into the neck.
- This get of blood regurgitating to the aortic root may be seen with a ruptured cord as tendinae, or with disease involvement of the posterior leaflet of the mitral valve leaflet.

Q2. From the examination of the heart, how do you access the severity of MR?

A2. An S_3 suggests ↑ MR severity
A diastolic rumble (in the absence of associated MS) indicates ↑ BV flow across the mitral valve during diastole.

Q3. When does the absence of a mitral area murmur or a late systolic/ holosystolic murmur significantly reduce the likelihood of mitral regurgitation?

A3. In the setting of an acute myocardial infarction.

Trick Questions

In the patient with MR and S_3, the S_3 arises from rapid LV filling, and the S_3 in MR does not suggest ↑ FP of LV or LV dysfunction.

Another, really tricky question

Q. In the patient with combined MR and MS, (usually due to RHD), what is the significance of the presence of an S_3 or a large LA?

A. MR + MS + S_3 – indicates the MS is mild, and the dominant murmur is the MR.
MR + MS + large LA – samething: MS is not clinically significant, and the main problem is the MS.

Source: Baliga RR. *Saunders/Elsevier* 2007, page 12.

YOU HAVE DECIDED NOT TO BE A PEDIATRIC BUT RATHER AN ADULT CARDIOLOGIST!

Q. In the context of an ejection systolic murmur, what is the 'Gallavardin phenomenon'?

A. The high-frequency components of the ejection systolic murmur may radiate to the apex, falsely suggesting mitral regurgitation

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 32 and 33.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. In persons with mitral regurgitation (MR), what is the meaning of a diastolic rumble?

A1. Coexistent mitral stenosis (MS)

Q2. OK. In persons with MR, a diastolic rumble and a large left atrium, what is the interpretation?

A2. No MS

Source: Baliga RR. *Saunders/Elsevier*, 2007, page 13.

Q. Give the causes of a precordial pansystolic murmur

A.
- MR
- TR
- VSD

SO YOU WANT TO BE A CARDIOLOGIST!

Q. How do you make the diagnosis of MR, in the absence of a murmur? (In the patient with a thick chest, well aerated lung tissue and a large RV, even severe MR may not have an audible murmur of MR)

A.
- Large L-atrium and L-ventricle
- S2 widely split

SO YOU WANT TO BE A CARDIOLOGIST!

Q. You auscultate a systolic murmur which is suggestive of MR (mitral regurgitation). From the auscultation, how would you distinguish a MR murmur caused by (rheumatic heart disease), versus MVP (mitral valve prolapse) or PMA (papillary muscle dysfunction)?

A. When
- RHD: platform murmur
- MVP or PMA
  - Systolic murmur of MR begins in mid-systole, and extends to A_2
  - Soft murmur, heard best at apex
  - Crescends pattern towards S_2
  - "Cooing" sound
  - "Honking" sound (like Canada geese)
  - Myxomatous degeneration of posterior leaflet
  - MVP syndrome:
    - Atypical chest pain
    - Arrhythmias
    - Abnormal ECG
  - Mimics PMD from MI or HOCM
  - Sharp systolic click (chordal snap) in either mid or late systole, followed by murmur is typical of MVP, and can be made buder by exercise.

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 261 and 263.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. During the strain phase of the Valsalva maneuver, there is increased intrathoracic pressure, which leads to a decrease in venous return and therefore a reduction of the blood volume moving into the LV. Thus, straining reduces the loudness of heart sounds and murmurs, because of the decrease in cross-Valvular gradients. So what is the question? What are the two exceptions to the Valsalva maneuver softening heart sounds/murmurs during the held phase?

A.
- HOCM (hypertrophic obstructive cardiomyopathy)
- MVP (mitral valve prolapse)

Source: Mangione S. *Hanley & Belfus* 2000, page 257 and 268.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. When does the absence of a mitral area murmur or a late systolic/ holosystolic murmur significantly reduce the likelihood of mitral regurgitation?

A. In the setting of an acute myocardial infarction.

Source: Simel DL, et al. *JAMA* 2009, page 439.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What is the mechanism of the click in MVP?

A. Clicks result from sudden tensing of the mitral valve apparatus as the leaflets prolapse into the left atrium during systole.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What are the complications of hypertrophic cardiomyopathy?

A1.
- Sudden death
- Atrial fibrillation
- Infective endocarditis
- Systemic embolization

Q2. What is the most characteristic pathophysiological abnormality in hypertrophic cardiomyopathy?

A2. Diastolic dysfunction

Source: Baliga RR. *Saunders/Elsevier* 2007, page 76.

Mitral (or tricuspid) valve prolapsed (MVP)

- Mid-to-late systolic click, best heard at the apes in the left decubitis position, varying from cycle to cycle, Valsalva's maneuver lengthens click
- Backward snapping of prolapsed mitral leaflet, and sudden distention of chordal apparatus, from mitral or tricuspid valve prolapsed.
- Which two and only two murmurs are enhanced by Valsalva's maneuver? – mitral valve prolapsed) and HOCM (idiopathic hypertrophic subaortic stenosis)
- Mid-to-late systolic click plus late systolic murmur suggests mitral valve prolapse plus mitral regurgitation.

Source: McGee SR. *Saunders/Elsevier* 2007, page 498 to 501.

- Mitral valve prolapse (MVP, not to be confused with most valuable [Sports] player)

- Perform a focused physical examination for MVP (mitral valve prolapse).

- Case
  - Mid-systolic click (MSC)
  - Mid- or late systolic murmur
  - Squatting ↓ duration of systolic murmur
  - Standing, valsalva
    - ↑ MSC and S2
    - ↑ duration of systolic murmur

- Causes or associations
  - Hereditary
    - Marfan syndrome
    - ASD, secundum (atrial septal defect)
    - Ehlers – Danlos syndrome
    - Ebstein's anomaly
  - Rheumatic
    - Rheumatic heart disease
    - Systemic lupus erythematosis
  - Ischemic heart disease
  - Idiopathic – cardiomyopathics

- Complications
  - Murmurs
    - Associated MR ±
    - SBE
  - Arrhythmias
    - VPC (ventricular premature contractions)
    - VT (Ventricular tachycardia)
    - PST (paroxysmal supraventricular tachycardia)
  - CNS
    - TIA (transient ischemic attack)
    - CVA (cerebrovascular accident)
  - Atypical chest pain
  - Sudden death

Adapted from: Baliga RR. *Saunders/Elsevier*, 2007, page 66.

Useful background: Performance characteristics of physical examination for determining the severity of characteristics systolic murmur of moderate to severe mitral and tricuspid regurgitation

- Auscultating the murmur of mitral regurgitation (MR) has a positive likelihood ratio (PLR) of 4.4 that the MR is moderate – to – severe, whereas for tricuspid regurgitation (TR), palpating a pulsative liver has a PLR of 3.9 that the regurgitation is moderate – to – severe.

- Auscultating an S_3 does not reflect the severity of MR, nor does a systolic regurgitant wave in the neck weins reflect the severity of TR.

Finding	PLR
➢ Mitral Regurgitation (MR)	
o Detecting MR	4.4
➢ Tricuspid regurgitation (TR)	
o Pulsatile liver	3.9

Abbreviations: PLR, positive likelihood ratio; MR, mitral regurgitation; TR, tricuspid regurgitation

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 42-1, page 497.

Diastolic murmurs

SO YOU WANT TO BE A CARDIOLOGIST!

Q.Give 5 causes of diastolic murmurs not due to valvular disease.

A.
- Atrial myxoma
- Ventricular septal defect
- Atrial septal defect
- Normal cardiac structure, increased flow
- Renal failure with volume overload
- Thyrotoxicosis
- Anemia
- Sepsis

Source: Simel DL, et al. *JAMA* 2009, Table 32-1, page 420.

Useful background: Diastolic murmurs are classified according to the time of onset of the murmur

- Early
  - Begins with the second heart sound (S_2).
  - Decrease in intensity (decrescendo) and disappear before the first heart sound (S1)
  - Can continue through diastole.

- Mid
  - Begins clearly after S_2 (in mitral stenosis, classically after an opening snap [OS]).

- Late
  - Begins in the interval immediately before S_1.
  - In mitral stenosis, the mid diastolic murmur may merge with the late diastolic (presystolic) murmur.

Abbreviations: OS, opening snap

Source: Simel DL, et al. *JAMA* 2009, Figure 32-2, page 421.

- Mitral or tricuspid stenosis
  - Degree of stenosis indicated by duration of murmur, not intensity
  - Mitral stenosis- use bell, lightly applied at apex with patient on L side after exercise. Presystolic accentuation is often a sign of pure stenosis, but is absent in atrial fibrillation
  - Tricuspid stenosis- murmur louder on inspiration
  - Mitral or tricuspid distortion eg Carey-Coombs murmur of active rheumatic carditis

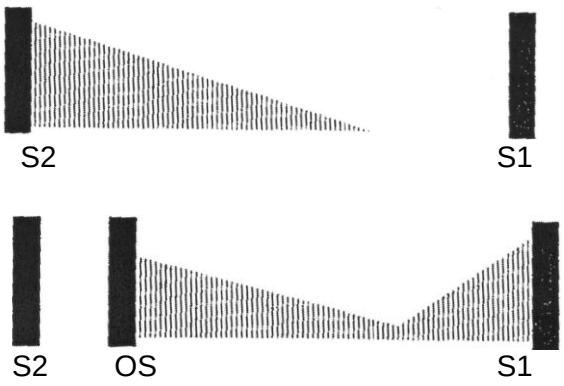
- Mitral Stenosis
  - Calcification of mitral annulus and leaflets
  - Rheumatic heart disease
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Malignant carcinoid
  - Congenital stenosis

- Conditions that Simulate Mitral Stenosis
  - Left atrial myxoma
  - Ball valve thrombus in the left atrium
  - Cor triathriatum (a rare congenital heart condition where a thin membrane across the left atrium obstructs pulmonary venous flow).

Adapeted from: Mangione S. *Hanley & Belfus* 2000, pages 266 to 269.

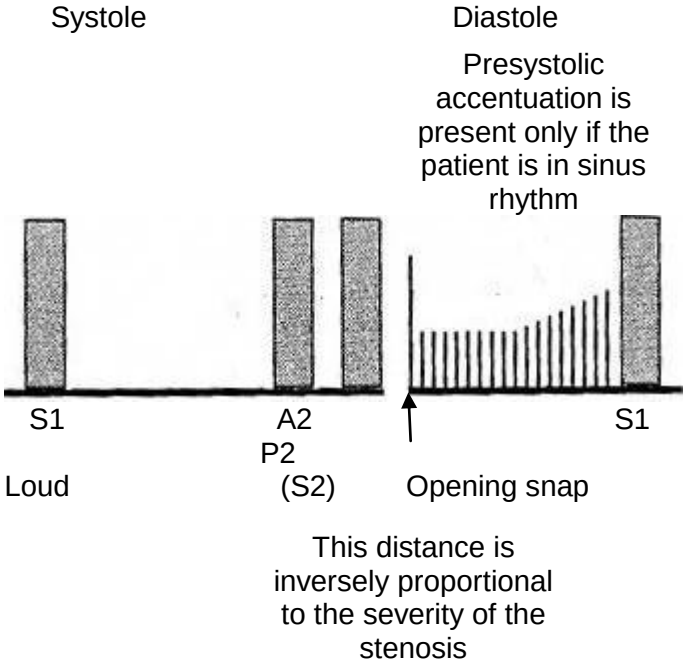
Mitral stenosis

Useful background: Selected features of diastolic murmurs



Adapted from: Simel DL, et al. *JAMA* 2009, Figure 32-2, page 421.

Useful background: Mitral stenosis (MS) (at the apex)



Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 3.28, page 74

Mitral Stenosis (MS)

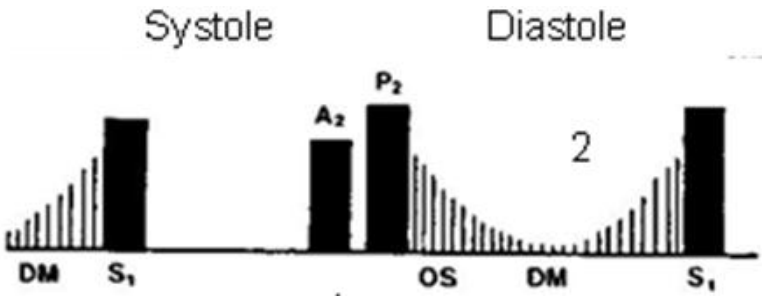
- Head/ neck
  - Malar flush
  - ↑ JVP
- Peripheral pulse – sinus or AF
- Apex
  - Tapping (5th ICS, MCL)
  - Left parasternal heave (RV large)
- Heart sounds
  - ↑ S_1
  - OS (apex, left decubitus position)
  - ↑ S_2 (from ↑P_2)
  - ↑ S_3 (rapid LV filling)
- Murmur
  - Rumbling
  - Low-pitched
  - Mid-diastolic
  - Left lateral position
  - During expiration
  - Presystolic accentuation
  - Louder after sit-ups or hopping

Useful background:

The normal area of the mitral valve is 4 to 6 cm^2. The flow across the valve becomes turbulent when the cross sectional area is < 2 cm^2. The MS is said to be “tight” when this area is < 1 cm^2.

- Give 4 complications of MS.
  - LA enlargement
  - AF
  - Emboliaztion (eg CVA)
  - PHT
  - TR
  - R-CHF

Abbreviation: AF, atrial fibrillation; LA, left atrium; PHT, pulmonary hypertension; R-CHF, right-sided conjestive heart failure; TR, tricuspid regurgitation.



Precordium- tapping apex beat; diastolic thrill at apex; parasternal lift. Auscultation- loud S1, P2 diastolic opening snap followed by rumble with presystolic accentuation. Atrial fibrillation may be pulse pattern. Cold extremities. 1) This distance is inversely proportional to the severity of the stenosis; 2) Presystolic accentuation is present only if patient is in sinus rhythm

Useful background: physical examination for MS

- Assessment of severity
  - The louder the murmur and the thrill, the more severe the MS
  - Conditions making murmur louder without necessarily a greater pressure gradient(false positive), unless there is associated pulmonary hypertension which softens the murmur of severe MS, and unless there is associated mitral regurgitation (which increases diastolic flow across the mitral valve making a louder murmur of MS)
  - Conditions making murmur softer, causing overestimation of severity (false negative)
    - Emphysema
    - Very severe stenosis mitral or tricuspid valve
    - Severe pulmonary hypertension
    - Atrial fibrillation

Useful background: Performance characteristics of other cardiac findings in mitral stenosis.

Finding (Ref)	PLR
➢ Graham Steell murmur	
o Detecting pulmonary hypertension	4.2
➢ Hyperkinetic apical movement	
o Detecting associated mitral regurgitation or aortic valve disease	11.2
➢ Hyperkinetic arterial pulse	
o Detecting associated mitral regurgitation	14.2

Source: McGee SR. *Saunders/Elsevier* 2007, page 506.

- Causes
  - Rheumatic fever
  - Rheumatoid arthritis
  - Systemic lupus erythematosis
  - Malignant carcinoid (carcinoid syndrome)
  - Congenital: parachute mitral valve with one papillary muscle having chordate attached to both leaflets of mitral valve
  - Myxoma of left atrium
  - Calcified bacterial vegetation of mitral valve
    - Mitral annulus and leaflets
  - Mimics
    - Severe MR
    - VSD
    - Austin Flint murmur* of severe AR
    - Ball valve thrombus in LA
    - Cor triatriatum (a rare congenital heart condition where a thin membrane across the left atrium obstructs pulmonary venous flow)

Abbreviations: MR, mitral regurgitation; VSD, ventricular septal defect; AL, left atrium

*Definition: Austint Flint murmur: diastolic murmur (rumble) caused by functional closure of the anterior leaflet of mitral valve when there is moderate-to-severe aortic regurgitation, Distinguish from MS by the absence of an opening snap in a non-calcified valve, and the presence of S3 (rare in mitral stenosis).

Adapted from: Mangione S. *Hanley & Belfus* 2000. page 266 to 269; and Baliga RR. *Saunders/Elsevier* 2007, pages 4 and 7.

- Mitral or tricuspid stenosis
  - Degree of stenosis indicated by duration of murmur, not intensity
  - Mitral stenosis- use bell, lightly applied at apex with patient on L side after exercise. Presystolic accentuation is often a sign of pure stenosis, but is absent in atrial fibrillation
  - Tricuspid stenosis- murmur louder on inspiration

- Increased AV flow rate
  - Mitral area VSD and PDA
  - Tricuspid area ASD and TAPVD

Source: Burton JL. *Churchill Livingstone* 1971, page 7.

- Perform a focused physical examination to distinguish between the diastolic murmurs of mitral stenosis (MS) versus tricuspid stenosis (TS).

Physical finding	TS	MS
➢ Location	○ epigastric and R/L parastenal area ○ over apex if RV is very large	
➢ effect on murmur of inspiration	Louder	softer
➢ position to best hear murmur	R lateral decubitus	L lateral decubitus
➢ quality	"scratchy"	Low pitch
➢ presystolic accentuation	Absent	present

Source: Mangione S. *Hanley & Belfus* 2000, pages 266 to 269.

HAVE YOU GIVEN UP YET AND DECIDED TO BE A CARDIOLOGIST?

Q1. What causes the tapping apex beat in mitral stenosis?

A1. An accentuated S1

Q2. What does a soft S1 mean in MS?

A2. Loss of mobility of the valve leaflets

HAVE YOU GIVEN UP YET AND DECIDED TO BE A CARDIOLOGIST?

Q1. What does the opening snap indicate?

A1.
- Cause by the opening of the stenosed mitral valve and indicates that the leaflets are pliable
- Usually accompanied by a sound S1
- Absent when the valve is diffusely calcified (when only the tips of the leaflets are calcified, the opening snap persists)

Q2. What does a soft S_1 mean in MS?

A2. Loss of mobility of the valve leaflets

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 4 and 7.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. A mid-diastolic murmur is auscultated, and MS is suspected. Give the differential of the causes of a murmur which simulates MS.

A1.
- LA myxoma
- Ball valve thrombus of LA
- ASD
- Cor tri atriatum (a membrane across the LA which partially blocks the pulmonary venous flow)

Q2. In the context of a mid-diastolic murmur which must be differentiated from MS, what is Lutembacher's syndrome, and Ortner's syndrome?

A2.
- Lutembacher's syndrome : ASD + MS
- Ortner's syndrome: Large LA in MS causing paralysis of left vocal cord, leading to hoarsensess.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. The commonest cause of mitral stenosis is .....?

A1. Rheumatic heart disease.

Q2. The commonest cause of MS is RHD. Give 4 rare causes of MS.

A2.
- Congenital
- Rheumatoid arthritis
- SLE
- Malignant carcinoid
- Mitral valve calcification

Abbreviation: SLE, systemic lupus erythematosis; MS, mitral stenosis

Q3. A tapping apex beat in MS is caused by .....?

A3. A pronounced S_1.

Q4. A loud S_1 in MS is caused by ...?

A4. Sudden closing of the valve leaflets during ventricular contraction in systole.

Q5. An opening snap in MS is caused by ...?

A5. Opening of the stenosed but pliable mitral valve leaflets.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of mitral stenosis, what is Ortner's Syndrome?
A.
- Hoarseness of voice caused by left vocal cord paralysis associated with enlarged left atrium in mitral stenosis.

Source: Baliga RR. *Saunders/Elsevier* 2007, page 7.

Trick Question

Q1. In the patient with known MS, what is the implication of the loss of the opening snap (OS)?

A1. The OS is caused by the opening of the stenosed valve when the leaflets are pliable. Once the leaflets become calcified, the OS disappears.

Q2. The high-pitched OS occurs shortly after S_2, and the shorter the interval between S_2 and OS, the higher the LA pressure.
➔ What is the clinical significance of a short interval between S_2 and OS?

A2. A short interval between S2 and OS signifies ↑ LA pressure, and greater severity of MS.

Q3. The rumbling, low-pitched, mid-diastolic murmur of MS may be associated with presystolic accentuation what is the cause of the presystolic accentuation, first when the patient is in sinus arythm, and secondly in atrial fibrillation (AF)?

A3.
- Sinus rhythm: increased flow during atrial systole across the narrowed.
- AF: turbulent flow across the mitral valve at the start of ventricular systole

Q4. Give 3 findings suggesting that the MS is severe.

A4.
- Short distance between S_2 and OS
- Long duration of MS murmur
- Murmur of MS becoming softer
- Signs of pulmonary hypertension (PHT)

Trick Question

Q1. What is the clinical significance of the diastolic murmur of MS becoming softer?

A1. When the stenosis across the mitral valve becomes tighter, the murmur becomes less prominent, even to the point of disappearing.

Q2. Perform a focused physical examination for PHT.

A2.
- ↑ P_2
- RV lift (L parasternal heave)
- ↑ JVP
- Ascites
- Peripheral edema
- Signs of etiology eg MS, COPD

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is the effect of pregnancy on MS?

A1.
- Patients usually become symptomatic in T_2
- Blood volume increases

Q2. In the context of MS, what is Ortner's syndrome?

A2. Hoarseness of voice cause by keft vocal cord paralysis associated with enlarged left atrium in mitral stenosis

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 4 and 7.

Q. Give two circumstances when an opening snap does not occur with mitral stenosis (MS)

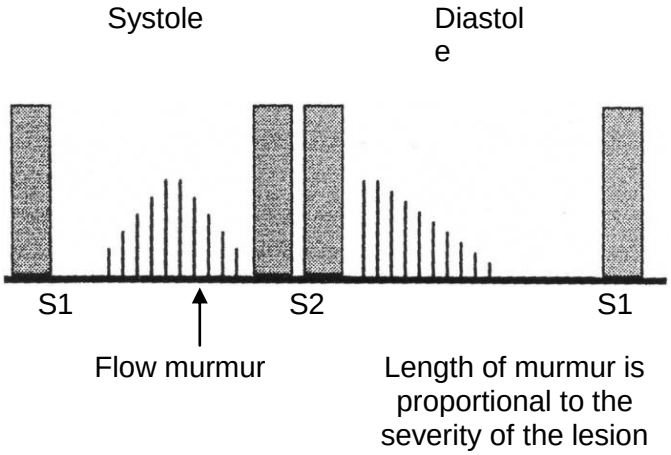
A.
- Combined MS and MR (mitral regurgitation)
- Calcified mitral stenosis

Tricuspid stenosis (TS)

- Causes
  - Associated with
    - TR
    - MS
  - SLE
  - Carcinoid tumor

Aortic regurgitation

Useful background: Aortic regurgitation (at the left sternal edge)



Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 3.32, page 79.

- Perform a focused physical examination for the patient with aortic regurgitation (AR).

- Extra-cardiac
  - Head & neck
    - Head-nodding (in timed with systole; de Musset's sign)
    - Eyes – Argyll Robertson pupils (syphilis)
    - Uvula – movement (timed with systole; Muller's sign)
    - Palate – high arch (Marfan's syndrome)
    - Carotids – Corrigan's sign (visible pulsating carotids)
  - Pulse
    - Large volume, rapid fall
    - Wide pulse pressure
  - MSK
    - Hands – rheumatoid arthritis
    - Capillary – pulsation in nail beds (Quincke's sign)

- Arm span > height (Marfan's syndrome)
- Back – ankylosing spondylitis

- Heart
  - Heart sounds
    - S_1, S_2 usually normal
    - ↑ S_2 pulmonary hypertension
    - ↓ S_2 severe AR
    - S_3 (bicuspid aortic valve, or severe AR)
  - Apex beat
    - Outward displacement
    - forceful
  - Murmur
    - Diastole, early
      - High-pitched
      - LSE
      - Leaning forward
      - End of expiration
    - Diastole, mid
      - Apex of heart
      - Low-pitched
    - Austin Flint murmur
      - Mimicking MS, but with no OS
      - Sean in severe AR
      - The regurgitant jet of blood in AR causes the anterior cusp of the mitral valve to vibrate
    - Systole
      - Base of heart
      - Ejection-like crescendo – decrescendo murmur

Abbreviation: LSE, left sterna edge; OS, opening snap

Useful background: Causes of aortic regurgitation

➢ Inherited/ congenital	○ Bicuspid aortic valve ○ Marfan's syndrome
➢ Idiopathic	○ Dilation of aortic root and annulus ○ Cystic medial necrosis
➢ Infection	○ Rheumatic fever ○ Bacterial endocarditis ○ Syphilis
➢ MSK	○ Ankylosing spondylitis ○ Reiter's syndrome

- Cardiac
  - Atherosclerosis
  - Hypertension
  - Aortic dissection
  - Rupture of sinus of valsalva
  - Non-functioning prosthetic valve

Useful background: Aortic regurgitation: Symptoms and findings on examination

	Acute	Chronic
➢ Symptoms	○ Shock ○ Arrhythmia ○ Chest pain - Dissection, RCA - Infarct	○ Dyspnea ○ Fatigue ○ Exercise intolerance ○ Night sweats ○ Palpitations
➢ Examination	○ Faint, short diastolic murmur ○ Pulmonary edema dyspnea	○ Peripheral pulses - Quincke and Duroziez signs - Pistrol-shot pulse - Enlarged, diffuse, hyperdynamic LV ○ Murmur etiology - LSB – valve - RSB – root ○ Enlarged heart ○ Enlarged aorta ○ LVA ○ ST elevation II, III, F (if aortic dissection into RCA)

Abbreaviation: LSB, left sterna border; LV, left ventricle; LVH, left ventricular hypertrophy; RCA right coronary artery; RSB, right sterna border

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-3, page 44.

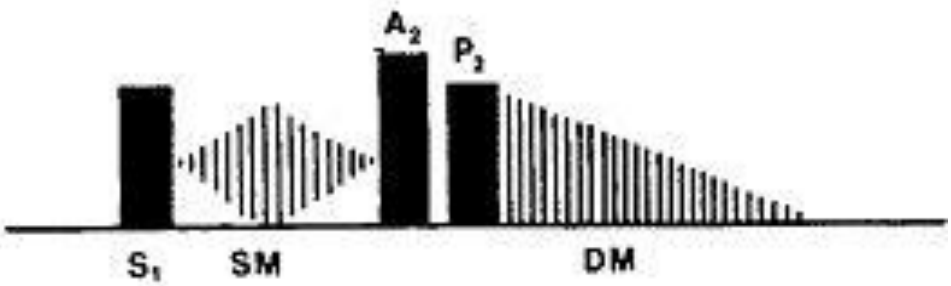
- Perform a focused physical examination to access the severity of AR.

➢ Heart sounds	○ ↓ S_2 ○ S_3
➢ Pulse	○ ↑ Pulse pressure
➢ Apex	○ Extensive outward displacement from LVH/ LVD (cor bovinum)
➢ Murmur	○ Long decrescendo diastolic murmur ○ Extention of murmur to fill all of diastole ○ Louder murmur ○ Presence of Austin Flint murmur

➢ Signs of L-CHF

Abbreviations: LVD, left ventricular dilation; LVH, left ventricular hyperteophy

- Perform a focused physical examination for aortic regurgitation.



- ○ Often associated with Marfan's syndrome, rheumatoid spondylitis.
- ○ Precordium – Apex displaced laterally and anteriorly
- ○ Thrill often plapable along left sterna border and in the jugular notch.
- ○ Carotids – Double systolic wave
- ○ Auscultation – Decrescendo diastolic murmur along left sternal border
- ○ M_1 and A_2 are increased

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 251.

Useful background: Causes

➢ Acute Aortic Regurgitation
- ○ Infective endocarditis
- ○ Aortic dissection
- ○ Trauma

- Failure of prosthetic valve
- Rupture of sinus of Valsalva

- Take a directed history and perform a focused physical examination for aortic regurgitation.

- General
  - Dyspnea
  - Fatigue
  - Exercise intolerance
  - Night sweats

- Lung
  - Pulmonary edema

- Heart
  - Shock
  - Arrhythmia
  - Chest pain
    - Dissection
    - Infarct
  - Palpitations
  - Peripheral pulses
    - Quincke and Duroziez signs
    - Enlarged, diffusely hyperdynamic LV
  - Murmur, etiology
    - LSB – valve
    - RSB – root

Abbreviation: LSB, left sterna border; LV, left ventricle; LVH, left ventricular hypertrophy; RSB, right sternal border

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 3-3, page 44.

- Give 3 clinical features that suggest that a patient's AR is not due to the commonest cause (rheumatic fever), but rather is due to syphilis.

  - No murmurs other than just AR
  - Angina, not relieved with nitrates
  - Calcified ascending aorta

- The murmur of AR is diastolic, but what may cause a systolic murmur together with the typical diastolic murmur of AR?
  - AR plus AS
  - AR plus MR
  - Aneurysm
  - Systolic hypertension

- What are the clinical findings which help to distinguish PDA (patent ductus arteriosis) from the murmur of AR?
  - Diastolic murmur in PDA is
    - Late (rather than early as in AR)
    - Loudest anteriorly, left side
    - May be heard posteriorly
  - Associated with a thrill

Adapted from: Mangione S. *Hanley & Belfus* 2000. page 271 and 272.

- MSK
  - Reiter's syndrome
  - Ankylosing spondylitis
- Rheumatic fever
- Endocarditis
- Conditions associated with aortic valve leaflet abnormalities
  - Marfan syndrome
  - Rheumatoid arthritis
  - Ankylosing spondylitis
- Diseases that affect the aortic root
  - Hypertension
  - Syphilis
  - Inherited connective tissue disorders
  - Aortic aneurysm (dissection of descending aorta)
- Misdiagnosed AR
  - Easily confused with similar murmur of pulmonary regurgitation or tricuspid regurgitation (Graham Steell murmur): early diastole, 2nd L-ICS due to pulmonary hypertension.
  - Sudden onset AR is different from chronic AR by having a soft/absent S1, and a diastolic murmur which is never holodiastolic (only early-to-mid diastole)

Abbreviaton: AR, aortic regurgitation

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 14 to 16; Simel DL, et al. *JAMA* 2009, page 430.

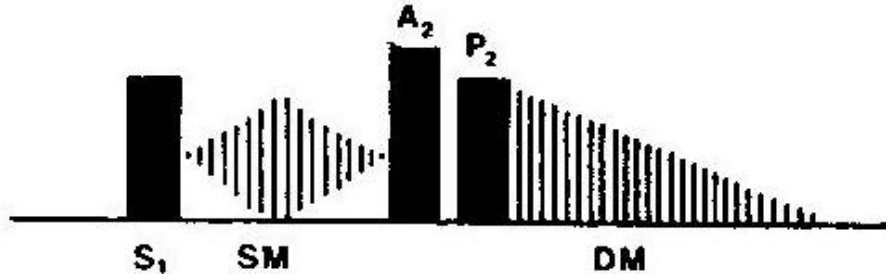
SO YOU WANT TO BE A CARDIOLOGIST!

Q1. In which cardiac phases are the diagnosis and severity of AR and MR made?

A1. Curious comparison: AR is diagnosed in diastole, but its severity assessed in systole; MR is diagnosed in systole, but its severity is assessed in diastole

Q2. In the context of aortic regurgitation (AR), what is Landolfi's sign?

A2. The pupil contracts in systole, and dilates in diastole



- Apex
  - Displaced laterally and anteriorly
  - Thrill often palpable along left sternal border and in the jugular notch.
- Carotids
  - Double systolic wave.
- Auscultation-
  - Decrescendo diastolic murmur along left sternal border; S1 and A2 are increased.
  - Length of murmur is proportional to severity
- Associations
  - Marfan's syndrome,
  - Rheumatoid spondylitis.

- Causes of acute aortic regurgitation
  - Infective endocarditis
  - Aortic dissection
  - Trauma
  - Failure of prosthetic valve
  - Rupture of sinus of Valsalva

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 16; and Burton JL. *Churchill Livingstone* 1971, page 9 and Mangione S. *Hanley & Belfus* 2000. page 251.

- Perform a physical examination to determine the severity of aortic regurgitation.

    - Wide pulse pressure
    - Soft S2
    - Duration of the decrescendo diastolic murmur
    - Austin Flint murmur (an apical, low pitched, diastolic murmur caused by vibration of the anterior mitral cusp in the regurgitation jet, and is heard at the apex)
    - Signs of left ventricular failure
    - Hill's sign

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 1; Burton JL. *Churchill Livingstone* 1971, page 9.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of Aortic regurgitation, what is "Hill's" sign?

A.
- Higher systolic pressure in the leg than in the arm, and
- An indicator of severity of aortic regurgitation

Useful background: Performance characteristics for aortic regurgitation (AR)

Finding	PLR
➢ Characteristic diastolic murmur	
o Detecting mild aortic regurgitation or worse	9.9
o Detecting moderate-to-severe aortic regurgitation	4.3
➢ Early diastolic murmur loudest on right side of sternum	
o Detecting dilated aortic root or endocarditis	8.2
➢ The finding of an early diastolic murmur which becomes softer with amyl nitrite inhalation is not of significant use to distinguish AR versus Graham Steell murmur	NS

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 41-1, page 486.

- Characteristics of moderate-to-severe AR

Finding	Sensitivity (%)	Specificity (%)	PLR	NLR
➢ Diastolic murmur				
○ Murmur grade 3 or louder	30-61	86-98	8.2	0.6

Only when the diastolic blood pressure is ≤ 50 mm Hg, the pulse pessure is ≥ 80 mm Hg, or Hill's test is ≥ 60 mm Hg are these findings have a positive likelihood ratio (PLR) which makes then clinically useful (PLR, 19.3, 10.9 and 17.3 , respectively). Duroziez's sign, femeral pistol shot bruit, and the water hammer pulse do not signify sevee AR. Modest PLRs are associated with S3 gallop (5.9), and enlarged or sustained apical impulse (2.4).

Source: McGee SR. *Saunders/Elsevier* 2007, Box 41-2, page 488.

- Likelihood ratios of the physical examination for detecting aortic regurgitation

	Patient Population	PLR	NLR
➢ Overall cardiac examination	Referred for evaluation of systolic murmur	5.1	0.82
➢ Third heart sound (to identify severe AR)	Patients with isolated aortic insufficiency, referred for echocardiography	5.9	0.83

Abbreviations: AR, aortic regurgitation; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

Source: Simel DL, et al. *JAMA* 2009, Table 32-4, page 429.

Useful background: Likelihood ratios for typical murmur to predict aortic regurgitation (AR), or an S_3 to predict severe AR

Finding (type of clinician)		PLR	NLR
➢ Typical murmur	Mild or greater	8.8-32	0.2-0.3
○ Cardiologist	Moderate or greater	4.0-8.3	0-0.1
○ Murmur intensity (generalist or cardiologist)	Grade 3	4.5	
	Grade 2	1.1	
	Grade 1	0	
	No murmur	0	

Finding (type of clinician)		PLR	NLR
➢ Third heart sound (S_3) (cardiologist)	Severe	5.9	0.83

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

Source: Simel DL, et al. *JAMA* 2009, Table 32-5, page 430.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of aortic regurgitation (AR), what is Duroziez' double murmur?

A.
- Application of gradual pressure over femoral artery in persons with aort regurgiatation (AR) results in a to-and-fro systolic and diastolic murmur
- Sensitivity of 58-100% for AR (false positive in all high output states).
- False negative Duroziez' murmur in mild AR, AR+AS, mitral stenosis o regurgitation, or coarctation of aorta.

- Causes of collapsing pulse: Hyperdynamic circulation due to
  - Aortic regurgitation
  - Thyrotoxicosis
  - Severe anaemia
  - Paget's disease
  - Complete heart block

Source: Baliga RR. *Saunders/Elsevier*, 2007, page 78.

Useful background: Aortic regurgitation

- If the examiner does NOT hear an AR murmur, the likelihood that the patient has AR is diminished as follows:
  NLR 0.1 for moderate or greater AR
  NLR 0.2 to 0.3 for mild or greater AR

- If the examiner DOES hear an AR murmur, the likelihood that the patient has AR is increased as follows:
  PLR 4.0 to 8.3 for moderate or greater AR
  PLR 8.8 to 32.0 for mild or greater AR

Abbreviations: AR, aortic regurgitation; PLR, positive likelihood ratio; NLR, negative likelihood ratio

Source: Choudhry NK, et al. *JAMA* 1999; 281:2231-38.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What causes a systolic murmur to accompany to the typical diastolic murmur of AR?

A. Severe AR, or concurrent AS (i.e. AR+AS)

Trick Questions!

Q1. Aortic regurgitation (AR) has both a forward flow and a reverse flow component leading to the pulsus bisferiens and the "pistol shot" femoral bruit as well as the Duroziez' double murmur over the femoral artery. You auscultate a double murmur over the femoral artery, and pressure over the caudad portion of the compressing diaphragm of the stethoscope enhances the reverse flow murmur. But the patient does not have AR. What condition do they have?

A1. PDA (patent ductus arteriosus)

Q2. When a patient with AR was admitted, you discovered that she he had pulsus bisferiens. A week later the consultant cannot palpate this abnormal pulse. Did you overcall the presence of this abnormal pulse, because you knew they had AR and you thought they "should" have this kind of pulse?

A2. Not necessarily. The pulsus bisferiens lessens and then disappears when L-CHF develops.

Trick Question

Q. The early diastolic murmur of AR is usually heard best with the diaphragm and at the LSE. What is the significance of this murmur being auscultated at both the right and the left sterna edge?

A. As a result of the AR, the ascending aorta becomes dilated and displaced, so that this high pitched early diastolic murmur becomes audible on both sides of the sternum.

SO YOU WANT TO BE A WHIZ-KID CARDIOLOGY RESIDENT!

Q1. The sensitivity of Duroziez's maneuver for aortic regurgitation (AR) is 58 to 100%.

- Give 4 causes of false megative Duroziez's maneuver.

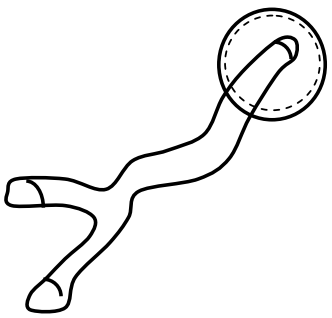
A1.
- Mild AR
- AR plus AS
- AS plus MS (↓ LV filling from mitral stenosis [MS])
- AS plus MR (↓ LV emptying from mitral regurgitation [MR])
- Coarctation of the aorta

Q2. Perform a focused physical examination to distinguish between the Duroziez' double murmur of AR, and "false positive" Duroziez's sign, not due to AR.

A2.
- This sign is AR is due to one murmur from forward flow, and one from reverse flow
- Any high – output state may cause a pulsus bisferiens as well as the Duroziez double murmur.
- The double murmur in high- outflow states one both due to forward flow
  - Auscultate over the femoral artery, and hear the to – and – fro murmur
  - Pressure over the cephalad edge of the compression stethoscope diaphragm increases both murmurs in high-output states
  - Pressure over the caudad edge of the diaphragm increases only the murmur from the reverse flow, as occurs in AR
- Distinction method

Cephalad pressure

↑ forward flow of both murmurs in high-output states



Caudad pressure

↑ reverse flow murmur position of the double murmur of AR

- Aortic or pulmonary regurgitation
  - Aortic regurgitation – often missed. Listen with diaphragm all down L sternal edge for soft 'whispered R' murmur with patient leaning forward in expiration
  - Pulmonary regurgitation- usually due to pulmonary hypertension
  - Austin-Flint due to Aortic Incompetence mimics mitral stenosis
  - Graham Steell due to mitral stenosis, mimics pulmonary regurgitation

- Continuous ('Machinery murmur')
  - Patent ductus arteriosus (PDA)
  - Aortico-pulmonary septal defect
  - Pulmonary AV fistula
  - Bronchial artery anastomosis in pulmonary atresia
  - Venous hum
  - Combined AS and AI, or MR and AR

SO YOU WANT TO APPLY FOR A CARDIOLOGY RESIDENCY!

Stump Your Staff – See if they know more than four of the eponymous signs of aortic regurgitation

- Quincke's sign: capillary pulsation in the nail beds- it is of no value, as this sign occurs normally
- Corrigan's sign: prominent carotid pulsations
- De Musset's sign: head nodding in time with the heartbeat
- Hill's sign: increased blood pressure in the legs compared with the arms
- Mueller's sign: pulsation of the uvula in time with the heartbeat
- Duroziez's sign: systolic and diastolic murmurs over the femoral artery on gradual compression of the vessel
- Traube's sign: a double sound heard over the femoral artery on compressing the vessel distally; this is not a 'pistol shot' sound that may be heard over the femoral
- Corrigans neck pulsation
- De Mussetts head nodding
- Duroziez's femoral diastolic murmur
- Quincke's capillary pulsation (nails)

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3-13, page 78.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. Under what circumstances is the blood pressure lower in the legs than arms (normal difference: 10-15 mm Hg higher in legs than arms)?

A.
- Abnormal difference (Hill's sign, > 20 mm Hg; exaggeration of normal, indicating ↑ SV (stroke volume)' such as from tachycardia
- Atherosclerosis in the elderly
- Aortic dissection
- Aortic regurgitation (severe)

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 15.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the setting of severe aortic regurgitation, what is Duroziez' murmur?

A. Auscullation of the femoral artery with slowly increasing pressure of the diaphragm of the stethoscope on the artery causes a systolic and diastolic back – and – forth murrmur.

Cardiomyopathy

- Perform a focused physical examination for hypertrophic cardiomyopathy (HC).

Pathophysiology outflow tract obstruction leading to diastolic dysfunction

- JVP
  - 'a' wave
- Pulse
  - Carotid, bifid
  - Peripheral, may have associated AF
- Palpation
  - Double apical impulse
  - ↓ PP (pulse pressure) after an extrasystolic beat; aka (B-B-M sign)
- Heart sounds
  - S_4
- Murmur
  - Ejection systolic murmur
  - LSE (left sterna edge)
  - Intensity
    - ↓ by squatting
    - ↑ by standing, valsalva maneuver
- Signs of SBE (subacute bacterial

endocarditis)
- Signs of systemic embolization
- Signs of associated Friedreich's ataxia

- Perform a focused physical examination for the type and cause of cardiomyopathy.

➢ Congestive
- Large flask-shaped heart
- Atrial fibrillation or LBBB common
- Tricuspid regurgitation (TR)

➢ Constrictive (often due to amyloidosis)

➢ HOCM
- Jerky, arterial pulse, S3; variable late systolic murmur down LSE

Abbreviations: ECG, electrocardiography; HOCM, hypertrophic obstructive cardiomyopathy; LBBB, left bundle branch block; LSE, left sternal edge.

Source: Burton JL. *Churchill Livingstone* 1971, page 17.

Useful background: Causes of cardiomyopathy

➢ Primary
- Idiopathic
- Endomyocardial fibrosis or fibro-elastosis
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Pregnancy and puerperium

➢ Secondary
- Toxins, drugs – alcohol, anthracyclines
- Anemia
- Endocrine
  - Pheochromocytoma
  - Thyrotoxicosis
  - Hypothyroidism
  - Hypoadrenalism
- Infection- viral (Coxsachie)
  - Toxoplasmosis
  - Schistosomiasis
  - Chagas disease (trypanosoma)
  - Sarcoidosis
  - TB

- Infiltration
  - Amyloidosis
  - Leukemia
  - Hemochromatosis
- Metabolic
  - Beri-beri
  - Iron overload
  - Carcinoid
  - Porphyria
  - Glycogen storage disease
  - Cobalt or antimony poisoning
- 'Collagen-vascular' disease
  - SLE
  - Arteritis
  - Systemic sclerosis
  - Rheumatoid disease
  - Ankylosing spondylitis
- Neuromuscular
  - Friedreich's ataxia
  - Myopathies (eg dystrophia myotonica, Duchenne)

Abbreviations: HOCM, hypertrophic obstructive cardiomyopathy; SLE, systemic lupus erythematosus; TB, tuberculosis

Adapted from: Burton JL. *Churchill Livingstone* 1971; and Davey P. *Wiley-Blackwell*, 2006, page 162.

Useful background: Effort of inspiration on cardiac murmurs

- Increases: TS, TR, PS
- Decreases: MS, MR, AS, AR, L→ R shunts

Abbreviations: AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; PS, pulmonary stenosis; TS, tricuspid stenosis; TR, tricuspid regurgitation.

Source: Burton JL. *Churchill Livingstone* 1971, page 7.

"Trustworthiness is a gating mechanism for social interactions."

Grandad

Useful background: Abnormal diastolic function in myocardial disease

Phase	Influencing Factors
➢ Relaxation	○ Age ○ Ischemia ○ Hypertrophy
➢ Passive filling	○ Myocardial compliance ○ Heart rate
➢ Atrial contraction	○ Atrial contraction ○ Atrioventricular synchrony

Source: Ghosh AK. *Mayo Clinic Scientific Press*, 2008, Table 3-30, page 112.

Useful background: Classification of Cardiomyopathies

➢ Infection	○ Viral ○ Bacterial ○ Parasitic
➢ Infiltration	○ Amyloidosis ○ Hemochromatosis ○ Glycogen storage disease ○ Sarcoidosis ○ Fat
➢ Inherited ○ Obstructive Endomycardial Fibrosis ○ Fibroelastosis Puerperal Idiopathic	○ Friedreich's ataxia ○ Muscular dystrophies ○ Gargoylism
➢ Nutritional	○ Starvation ○ Kwashiorkor
➢ Toxic	○ Alcohol ○ Drugs
➢ Immune	○ Rheumatoid arthritis ○ SLE ○ Scleroderma
➢ Endocrine	○ Polyarteritis nodosa ○ Myxedema ○ Acromegaly
➢ Congenital	○ Myasthenia gravis

Adapted from: Davies IJT. *Lloyd-Luke LTD* 1972, Table III, page 84.

- Take a directed history and perform a focused physical examination for the three types of cardiomyopathy.

- Congestive failure
  - Often tricuspid regurgitation
  - Large flask-shaped heart
  - Low voltage ECG
  - Atrial fibrillation and LBBB common

- Constrictive (often due to amyloidosis)

- HOCM
  - Angina, syncope
  - Dyspnea
  - Jerky arterial pulse
  - 3rd heart sound
  - Variable late systolic murmur down LSE
  - Decreased by negative inotropic drugs

Source: Burton JL. *Churchill Livingstone* 1971, page 17.

Pericardial diseases

Useful background: Pericardial friction rubs

- Systolic as well as diastolic components (one near S3, early in diastole; the second diastolic component is at time of S4)
- May resemble a S3 gallop
- Best heard 3/4th LSB (left sterna boarder); sitting up, leaning forward, holding breath in inspiration
- Caused by pericarditis:
  - All pericardium
    - Viral
    - Lupus
    - Uremia
  - Focal pericarditis
    - Myocardial infarction
    - Tumor

Source: Mangione S. *Hanley & Belfus* 2000, page 272 to 273.

Useful background: Pericardial Friction Rub

- Softening or rub suggests development of pericardial effusion
- May be diffuse or localized (eg. MI, trauma, metastatic tumor)
- Effect of breathing:
    - Pericardial rub persists in inspiration, expiration, or both.
    - Pleural rub disappears when breathing held in either inspiration or expiration
- The “Big 3” for the diagnosis of chest pain, pericardial rub, characteristic ECG changes

Adapted from: McGee SR. *Saunders/Elsevier* 2007, page 510 to 512 and Mangione S. *Hanley & Belfus* 2000, page 234.

 Perform a focused physical examination to determine if a patient’s pericardial rub has progressed to the development of a pericardial effusion.

 Rub
- Transient
- Localized
- Present in both systole and diastole
- Louder when
    - Sitting forward
    - Pressing more firmly with stethoscope

 Effusion
- Pulsus paradoxicus (inspiration decreases rather than the normal increase in pulse rate & volume).
- Dullness, 2nd left ICS (intercostals space)
- 2nd L. ICS dullness disappears on sitting.
- Collapse of base of L. lung

Note: At lease 250 mL of fluid is necessary in pericardial sac before a clinical diagnosis of effusion can be made.

 Perform a focused physical examination to determine if a patient’s elevated JVP is due to SVC (superior vena caval) obstruction?

- Face
    - Edema
    - Cyanosis
    - Collateral vessels
- Eyes
    - Exophthalmosis
    - Papilledema
- Signs in face and eyes become worse when the patient leans forward.

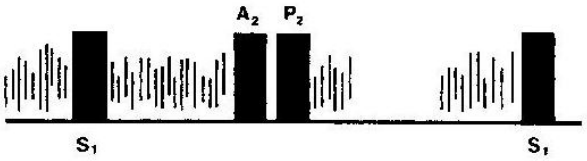
 Perform a focused physical examination to determine if a patient’s elevated

JVP is not due to congestive heart failure.

- Heart
  - CHF (congestive heart failure)
  - TR (tricuspid regurgitation)
  - □ blood volume
  - Bradycardia

- VC (vena cava)
  - SVC obstruction
  - □ intra-abdominal pressure on IVC
- Neck
  - Compression of neck veins
- Lung
  - Pleural effusions
  - □ intrathoracic pressure

Pericarditis



- Pulse
  - PR ↑
  - PP (pulsus paradoxicus) ↓
- Blood pressure
  - SBP ↓ (↓ PP and ↓ BP with tamponade)
- JVP
- HEART
  - Percussion
    - Enlarged, with effusion
  - Auscultation
    - Friction rub
    - Heart sounds may be reduced

Abbreviations:
JVP, jugular venous pressure;
PP, pulse pressure;
PR, pulse rate;
SBP, systolic blood pressure

Source: Mangione S. *Hanley & Belfus* 2000, page 246-251; pages 74 and 75.

- Take a directed history for the causes of pericarditis.

- Immune
  - Collagen vascular disease

- Metabolic
  - Rh. Fever
  - Uremia
  - Myxedema

- Tumor
  - Neoplasm
  - Radiation

- Trauma
  - Post – surgery

- Idiopathic
  - Endomyocardial fibrosis (EMF)

- Drug (phenylbutazone)

- Infective
  - Viral
  - Bacterial (pyogenic or TB)
  - Mycotic
  - Parasitic
  - Post – purulent constriction

- Post - myocardial infarction (Dressler's syndrome; pericarditis may be focal)

Abbreviations: EMF, endomyocardial fibrosis; TB, tuberculosis

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 18; Baliga RR. *Saunders/Elsevier* 2007, page 96.

Useful background: Causes of constrictive pericarditis

- Tuberculosis (<15% of patients)
- Connective tissue disorder
- Neoplastic infiltration
- Radiation therapy (often years earlier)
- Postpurulent pericarditis
- Hemopericardium after surgery
- Chronic renal failure

- Perform a focused physical examination for constrictive pericarditis.

➢ General	o Dyspnea o Momiting o Cough o Cachectic
➢ JVP	o Prominent x and y descents o Kussmaul's sign (↑ JVP with inspiration)
➢ Pulse	o 1/3 have AF
➢ Apex beat	o Not palpable
➢ LSE	o Early diastolic knock which ↑ with inspiration o Differentiate from - ↑ P2 - S3 gallop - OS of MS - Pericardial sound - Atrial myxoma (tumor "plop") o No pericardial rub
➢ Lungs	o Associated pleural effusion
➢ Abdomen	o Hepatomegaly o Ascites
➢ Lower legs	o Pitting edema

Abbreviations: AF, atrial fibrillation; JVP, jugular venous pressure; LSE, left sterna edge; MS, mitral sternosis; OS, perning snap

- Perform a focused physical examination for acute cardiac tamponade.

➢ Inspection
  - o Tachypnea
    - Anxiety
    - Restlessness
    - Syncope

➢ JVP ↑, Kussmaul's sign, prominent x but absent y descent

➢ Pulse and blood pressure
  - rapid pulse rate

  - pulsus paradoxus
  - hypotension

- Apex beat: not palpable
- Auscultation: reduced heart sounds
- Lungs: dullness and bronchial breathing at the left base (due to lung compression by the distended pericardial sac).

Abbreviation: JVP, jugular venous pressure

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, page 69.

- Perform a focused physical examination to distinguish between the jugular venous pulse and the carotid artery pulse.

Kussmaul's signs

- Paradoxical elevation of CVP during inspiration
- In addition to causing an elevated CVP, venoconstriction probably also contributes to the positve abdominojugular test and Kussmaul's sign, two signs that often occur together
- Most patients with constrictive pericarditis and Kussmaul's sign also have a notably positive abdominojuglar test

Source: McGee SR. *Saunders/Elsevier* 2007, page 382

- Take a directed history and perform a focused physical examination for chronic constrictive pericarditis.

- History
  - Tiredness
  - Exertional dyspnoea
  - Effort syncope
  - Symptoms due to ascites
  - Ankle swelling
  - Nausea, vomiting, dizziness,cough

- Physical signs: cachexia
  - Pulse and blood pressure: Pulsus paradoxus (more than the normal 10 mm Hg fall in the arterial pulse pressure on inspiration, because increased right ventricular filling compresses the left ventricle); low blood pressure
  - The JVP ↑, Kussmaul’s sign (uncommon); prominent x and y descents

- Apex beat: not palpable
- Auscultation: Heart sounds distant, early S3, early pericardial knock (rapid ventricular filling abruptly halted)
- Abdomen: hepatomegaly, splenomegaly,ascites
- Peripheral edema
- Causes of chronic constrictive pericarditis:
  - Cardiac operation or trauma
  - Tuberculosis
  - Histoplasmosis or pyogenic infection
  - Neoplastic disease
  - Mediastinal irradiation
  - Connective tissue disease (especially rheumatoid arthritis)
  - Chronic renal failure.

Abbreviation: JVP, jugular venous pressure

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 96; Burton JL. *Churchill Livingstone* 1971, page 18.

- Perform a focused physical examination to distinguish between the presence of chronic pericarditis with constriction constructive pericarditis (CP) and cardiac tamponade (CT).

➢ Inspection	-	Cachexia, in chronic tachypnea
	-	Anxiety, restless (CT)
	-	Syncope (CT)
➢ Palpation		
o Pulse	-	Increased rate
	-	Pulsus paradoxus
	-	(↓ BP on inspiration > 10 mmHg)
	-	(JVP ↑, Kussmaul's sign, prominent x and y descents)
o Blood pressure	-	Reduced
o Apex beat	-	Difficult to feel
➢ Auscultation	-	Difficult to hear heart sounds
	-	Early S_3
	-	Pericardial knock
➢ Associations	-	Hepatosplenomegaly
	-	Peripheral edema
		Left lung base dull, with bronchial breathing due to lung compression (CT)

- Signs of pericardial disease: ↑ JVP, dyspnea, pericardial rub or effusion

- Signs of cardiac tamponade: pulsus paradoxus: ASA, severe LV dysfunction (especially those with uremic pericarditis), regional tamponade (tamponade affecting 1 or 2 heart chambers, such as following heart surgery), severe hypotension, aortic regurgitation.

- Cardiac tamponade without pulsus paradoxus: ASD, severe LV dysfunction (especially those wtih uremic pericarditis), regional tamponade (tamponade affecting 1 or 2 heart chambers, such as following heart surgery), severe hypotension, aortic regurgitation

Abbreviations: ASA, American Society of Anesthesiologists; ASD, atrial septal defect; CPC, chronic pericarditis with constriction; CT, cardiac tamponade; JVP, jugular venous pressure; LV, left ventricle

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Table 43-1, 43-2, page 513, 514.

Useful background: Causes of pericardial effusion

- Exudates
  - Acute pericarditis
  - Metastatic malignancy
- Transudates
  - CHF
  - Liver failure
  - Nephrotic syndrome
  - Myxedema
- Hemopericardium
  - Aortic dissection
  - Trauma

Source: Davey P. *Wiley-Blackwell*, 2006, page 163.

"Science is never cast in stone and ideas are written with a finger on shifting sand."

Anonymous

- Perform a focused physical examination for constrictive pericarditis (CP) and cardiac tamponade (CT).

Physical finding	Frequency (%) CP	CT
➢ JVP ↑		
○ ↑ y descent	98	100
○ (Friedrich's sign)	57-94	-
○ Kussmaul's sign	50	0
➢ Pulse		
○ AF tachycardia > 100 bpm	36-70	0
➢ BP		
○ Pulsus > 10 mmHg	17-43	81-100
○ Paradoxicus	>20	98
	>30	78
	>40	49
		38
➢ Auscultation of precordium		
○ Pericardial knock	28-94	23
○ Rub	4	
○ ↓ heart sounds	-	36-84
➢ Other		
○ Hepatomegaly	87-100	58
○ Edema	63	27
○ Ascites	53-89	-

Abbreviations: AF, arterial fibrillation; BP, blood pressure; CP, constrictive pericarditis; CT, cardiac tamponade; JVP, jugular venous pressure

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Table 43-1, 43-2, pageS 513 and 514.

SO YOU WANT TO BE A CARDIOLOGIST!

Q. In the context of cardiac tamponade, what is Beck's triad?

A.
- Low arterial blood pressure
- High venous pressure
- Absent apex in cardiac tamponade is known as Beck's triad

Source: Baliga RR. *Saunders/Elsevier* 2007, page 100.

SO YOU WANT TO BE A CARDIOLOGY RESIDENT!

Q1. Which 2 causes of pericardial rub do not usually progress to a pericardial effusion?

A1. Pericardial rub caused by myocardial infarction, or uremia.

Q2. What are the ECG changes which suggest that a rub has progressed to an effusion?

A2.
- Low voltage
- ↑ ST
- Changes occur in all limb leads

Q3. What is the easy way to distinguish between the ECG changes of a myocardial infarction (MI) versus pericardial effusion?

A3. Low voltage and ↑ ST changes do not occur in all limb voltages in mL.

Q4. Which cause of constrictive pericarditis does not usually cause cardiomegaly, murmurs or atrial fibrillation (AF).

A4. Tuberculous pericarditis

Q5. In the context of the patient with constrictive pericarditis, what is Broadbent's sign?

A5. Intercostal indrawing during systole.

Q6. What are the types of pulmonary stenosis (PS)?

A6.
- Valvular
- Subvalvular: infundibular and subinfundibular
- Supravalvular

Source: Baliga RR. *Saunders/Elsevier* 2007, page 82.

Useful background: Causes of constrictive pericarditis

- Infection
  - Tuberculosis (<15% of patients)
  - Postpurulent pericarditis

- Infiltration
  - Neoplasm
  - Connective tissue disorder
- Immune
- Radiation
  - Often years earlier
- Surgery
  - Hemopericardium
- Chronic renal failure

Adapted from: Baliga RR. *Saunders/Elsevier*, 2007, page 96.

- Perform a focused physical examination for acute cardiac tamponade.

- General signs
  - Tachypnea
    - Anxiety
    - Restlessness
    - Syncope
  - Pulse and blood pressure: rapid pulse rate, pulsus paradoxus; hypotension
  - JVP ↑, Kussmaul's sign, prominent x but absent y descent
  - Apex beat: not palpable
  - Auscultation: reduced heart sounds
  - Lungs: dullness and bronchial breathing at the left base (due to lung compression by the distended pericardial sac).

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited*, 2003, page 69.

Useful background: Performance Characteristics for coronary artery disease

The only historical points with significant characteristics for coronary artery disease is typical angina (positive likelihood ratio, 5.8), a previous myocardial infarction, and age over 70 years (2.6). Three curious physical findings include ankle – to - arm pressure index < 0.9 (PLR, 4.1), arcus senilis (3.0), and ear lobe crease (2.3).

Source: McGee SR. *Saunders/Elsevier* 2007, Box 45.1, page 531.

- Perform a focused physical examination to distinguish a chronic constrictive pericarditis (CP) from acute cardiac tamponade (CT).

Vital Signs		CT	CP
➢ Pulse and blood pressure	Pulsus paradoxus	✓	✓
	Pulse rate	↑	✓
➢ Respiratory Rate		↑	↑
➢ Kussmaul's Sign		✓	↑
➢ JVP	↑x absent y descent	+	+
➢ Apex Beat	Impalpable	✓	✓
➢ Heart sounds	Loudness	↓	↓
	S3	-	-
	Pericardial knock	-	-
➢ Lungs	Left base dull	✓	-
	Bronchial breathing	✓	-
➢ Abdomen	Hepatomegaly	-	+
	Splenomegaly	-	+
➢ Lower leg Edema		-	+

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, page 69.

<u>Diseases of the aorta</u>

- In the patient with coarctation of the aorta and notching of the ribs, which ribs are not affected?
  - Ribs 1 & 2: intercostals arteries arise from the subclavian artery,
  - Remainder of ribs: intercostals arteries arise from the aorta belo/ abuse (?) the coarctation.

- What condition causes cyanosis of the legs and clubbing of the toes, and why?
  In childhood type coarctation, the narrowing is above the ductus arteriosus. As a result of the associated pulmonary hypertension, unsaturated bloody flows from the pulmonary artery, and is shunted through the ductus arteriosis to the lower aorta.
  - Childhood coarctation

- What condition causes cyanosis of the left but not the right hand and arm?
  - Childhood coarctation, with the left subclavian artery arising below the patent ductus arteriosus.

- Name two conditions which cause a systolic bruit heard best at the left scapular region, or then post – axillary region?
  - Coarctation of the aorta
  - Pulmonary AV aneurysm

- What bedside sign helps to distinguish between the two?
  - With pulmonary AV aneurysm, there is associated cyanosis

- Systemic hypertension is commonly associated with coarctation of the aorta. In which arteries do they develop thrombosis?
  - Not in brain, heart or kidney
  - Why – no associated atherosclerosis (ie, while the cause of the hypertension in coarctation is not clear, it is not due to atherosclerosis)

- What are the commonest causes of death in the patient with coarctation of the aorta?
  - Brain – ruptured cerebral aneurysm
  - Heart
    - SBE
    - CHF
    - Rupture of aorta

- Perform a focused physical examination for syphilitic aortitis with saccular aneurysm of aorta.

- Nerves
  - L. recurrent laryngeal nerve
    - Hoarseness or aphonia
  - Cervical sympathetic nerve
    - Unequal pupils (Horner's syndrome)
- Trachea
  - Tug, displacement, stridor
- Bronchi
  - Cough, atelectasis
- Brachial artery
  - Difference in BP in arms > 20 mmHg
- Heart
  - Aortic dilation, AR

- Signs of MI, from obstruction of coronary arteries
- Signs of myocarditis
- Conduction defects (syphilitic gamma)

- Bone
  - Erosion of spine, pulsation in region of L. scapula, bulging of aortic area of chest wall

Abbreviations: AR, aortic regurgitation; BP, blood pressure; MI, myocardial infarction

Source: Davies IJT. *Lloyd-Luke LTD*., 1972, page 38.

- What are the clinical findings which help to distinguish the murmur from an aortic aneurysm from the similar murmur of AS? In aortic aneurysm,
  - No thrill
  - No plateau pulse
  - A_2 (not , as with AS)

- Besides the murmur which sounds like AS, what other clinical findings suggest the murmur is due to dissecting aortic aneurysm?
  - Expansile pulsation in right 2nd, 3rd intercostals spaces
  - Right-sternal dullness
  - Expansile pulsation on right side of neck
  - Tracheal tug in suprasternal notch

Useful background: Abdominal Aortic Aneurysm (AAA)

Width of aorta by palpation	Sensitivity (%)	PLR	NLR
≥3.0 cm (all)	39	12.0	0.72
3.0 cm –3.9 cm	29		
≥4.0 cm		15.6	0.51
4.0 cm-4.9cm	50		
≥5.0 cm	76		

Physical sign	Sensitivity (%)	Specificity (%)
Definite pulsatile mass	28	97
Definite or suggestive pulsatile mass	50	91
Abdominal bruit	11	95
Femoral bruit	17	87
Femoral pulse deficit	22	91

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. The pulse rate determined in the right radial artery is slower than on the left side. What is the likely explanation?

A1. An aneurysm of the ascending aorta, or common carotid artery.

Q2. A patient has a higher blood pressure taken from the right as compared with the left arm, what are the explanations?

A2.

- R. brachial artery
  - Occlusion/ stenosis
- Aorta
  - Coarctation
  - Dissection
- Thoracic outlet syndrome
- Heart
  - Aortic stenosis (supraventricular)
  - Patent ductus arteriosus

Useful background: Performance characteristics of clinical findings for thoracic aortic dissection

Symptom or sign	PLR	NLR
➢ Focal neurologic deficit	6.6-33	0.7-0.9
➢ Pulse deficit	5.7	0.7
➢ Enlarged aorta or wide mediastinum	2.0	0.3

All other symptoms/signs (including pulse deficit, murmur of aortic indufficiency and widened mediasternum on chest X-ray have low sensitivity – [Simel David L, Rennie Drummond, Keitz Sheri A. The Rational Clinical Examination: Evidence- based clinical diagnosis. *JAMA* 2009, Table 50-8, page 672.])

Note that many historical symptoms and signs on physical examination have a PLR < 2 (and are not included here)

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

Source: Simel DL, et al. *JAMA* 2009, Chapter 50, Table 50-9, page 673.

Useful background: Sensitivity of findings for thoracic aortic dissection (TAD)

Finding	Sensitivity
➢ History	
o Hypertension	0.65
o Hypertension, age <40 y	0.34
➢ Symptoms	
o Abrupt onset	0.84
o Abrupt onset < 40 y	0.96
o Chest pain	0.71
o Chest pain, age <40 y	1.0
➢ Chest radiograph	
o Widened mediastinum	0.63

Note: Some possible findings in TAD are not included because the sensitivity is < 66%. These would include Marfan syndrome, age < 40 y (0.05); Marfan syndrome (0.04); Pulse deficit (0.32); Murmur of aortic insufficiency (0.28) and Back pain (0.30).

Source: Simel DL, et al. *JAMA* 2009, Table 50-8, page 672.

- Take a directed history and perform a focused physical examination to distinguish between aortic dissection (AD) and valvular aortic regurgitation.

Finding	PLR	NLR
➢ Chest pain		
➢ Pulse pressure deficit between arms (SBP > 20 mmHg between right and left arms)	6.0	NS
➢ Focal neurological signs (obstruction of cranial or vertebral arteries)	33.4	NS
➢ 2 of above findings	5.3 (> 30% ↑ probablility of AD)	-
➢ 3 of above findings	65.8 (> 50% ↑ probablility of AD)	

➢ Differences in SBP > 20 mmHg between right and left arms

Note: The presence of aortic regurgitation is not mentioned here, since its PLR is < 2.

Abbreviation: AD, aortic dissection; PLR, positive likelihood ratio; NLR, negative likelihood ratio; NS, not significant; SBP, systolic blood pressure

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 15.2, page 163.

SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q1. What causes rib notching?

A1.
- Coarctation of the aorta
- Pulmonary oligemia
- Blalock-Taussig shunt
- Subclavian artery obstruction
- Superior vena caval syndrome
- Neurofibromatosis
- Arteriovenous malformations of the lung or the chest wall

Source: Baliga RR. *Saunders/Elsevier* 2007, page 86.

Q2. What are the types of aortic coarctation?

A2.
- Common:
  - Infantile or preductal where the aorta between the left subclavian artery and patent ductus arteriosus is narrowed. Its manifests in infancy with heart failure. Associated lesion include patent ductus arteriosus, aortic arch anomalies, transposition of the great arteries, ventricular septal defect.
  - Adult type: the coarctation in the descending aorta is juxtaductal or slightly postductal. It may be associated with bicuspid aortic valve or patent ductus arteriosus. It commonly between the age of 15 and 30 years.
- Rare
  - Localized juxtaductal corctation
  - Coarctation of the ascending thoracic aorta

Source: Baliga RR. *Saunders/Elsevier* 2007, page 85.

Q3. What are the fundal findings in coarctation of aorta?

A3. Hypertension due to coarctation of aorta causes retinal arteries to be tortuous with frequent 'U' turns; curiously, the classical signs of hypertensive retinopathy are rarely seen.

Q4. Young persons may be diagnosed with coarctation of the aorta, whereas in older persons aortic disease may be from dissection or obstruction from atherosclerosis. What abnormalities found on physical examination will suggest these diseases of the aorta?

A4.
- Asymmetry
  - R. vs L. arm
  - Arm vs Leg

  → Pulse strength, timing; Systolic blood pressure

Useful background: Performance characteristics of aortic dissection

Finding	Sensitivity (%)	Specificity (%)	PLR	NLR
➢ Individual findings				
○ Pulse deficit	12-49	82-99	6.0	NS
○ Aortic regurgitation murmur	15-49	45-95	NS	NS
○ Focal neurologic signs	14	100	33.4	NS
➢ Combined findings				
0 predictors	4	47	0.1	...
1 predictor	20	...	0.5	...
2 predictors	49	...	5.3	...
3 predictors	27	100	65.8	..

Source: McGee SR. *Saunders/Elsevier* 2007, Box 14.1, page 149.

Coarctation of the aorta (adult type)

- Perform a focused physical examination of the heart and cardiovascular system for coarctation of the aorta presenting in an adult.

➢ Definition: narrowing of aorta just at or slightly after the ductus

➢ Body habitus: the torso of the body is better developed in the upper than the lower part of the body

➢ Pulses
- ○ Radial arterial pulse R > L
- ○ Femoral arterial pulse weak and delayed, compared to brachial arteries

➢ BP
- ○ SBP – arms > legs
- ○ DBP – arms = legs
- ○ PP - ↑ in arms compared to legs
  - R = L arm

➢ Suprasternal notch
- ○ Systolic thrill

➢ PMI
- ○ Heaving, if associated enlargement of LV

- Heart
  - If associated bicuspid aortic valve (50% of persons)
  - systolic ejection click
  - May have associated PDA, VSD, MS, MR, SBE
  - Systolic murmur at base of heart
- L. sterna border
  - Harsh, systolic ejection murmur
- Back
  - Harsh, systolic ejection murmur
  - Collaterals over scapula
  - Systolic murmur over scapular collaterals
- Associations
  - Congestive heart failure
  - Aortic dissection (especially in pregnancy)
  - Systemic hypertension
  - Turner syndrome
  - Berry aneurysm (circle of Willis) pressure on cranial nerve III

Abbreviation: DBP, diastolic blood pressure; L, left side; LV, left ventricle; MR, mitral regurgitation; MS, mitral stenosis; PDA, patent ductus arteriosus; PMI, point of maximum impulse; PP, pulse pressure; R, right side; SBE, subacute bacterial endocarditis; SBP, systolic blood pressure; VSD, ventricular septal defect

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What are the complications of aortic coarctation?

A.
- Severe hypertension and resulting complications:
  - Stroke
  - Premature coronary artery disease

Bacterial Endocarditis

- Definition: Infective endocarditis (IE) is a life-threatening infection of the cardiac endothelium associated with significant morbidity and mortality.
  - Occur as a result of
    - Injury or trauma to the cardiac andothelial surface, e.g.
      - Turbulent blood flow
      - Fibrin deposition
      - Bacterial adherence
  - Complications

- Heart
  - HF (heart failure)
  - Peri-annular abscess
- Vessels
  - Aneurysm
- Kidney
  - Glomerulonephritis
- Embolization

Gin AS, et al. Chapter 113. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 1474.

- Perform a focused physical examination for embolization to extra-cardiac sites in a patient with infective endocarditis.

Eyes	Roth spots ↓ visual acuity Conjunctival petechiae
Fingers	Janeway lesions Clubbing
Mucosal surfaces	Petechiae
Skin	Splinter hemorrhages Osler nodes
Lung	Pulmonary edema Pleuritic rub
CNS	Numerous defects
Spleen	Splenomegaly

- Perform a focused physical examination for infective endocarditis

- General signs
  - Fever
  - Weight loss
  - Pallor (anemia)

- Eyes
  - Pale conjunctivae (anemia)

- Retinal or conjunctival hemorrhages (Roth's spots are fundal vasculitic lesions with a yellow centre surrounded by a red ring).

- Hands
  - Splinter hemorrhages
  - Clubbing (within six weeks of onset)
  - Osler's nodes
  - Janeway lesions

- Arms
  - Evidence of intravenous drug use

- Heart
  - Signs of underlying heart disease
    - Acquired (mitral regurgitation, mitral stenosis, aortic stenosis, aortic regurgitation)
    - Congenital (patent ductus arteriosus ventricular septal defect, coarctation of the aorta
    - Prosthetic valves
- Abdomen: splenomegaly

- Peripheral evidence of embolisation to limbs or central nervous system

- Take a directed history and perform a focused physical examination for bacterial endocarditis (BE) (pathophysiological approach).

- Systemic disease
  - Fever
  - Pallor (anemia)
  - Weight loss

- Vasculitis
  - CNS – CVA (embolic)
  - Eye – Roth spots
  - Heart
    - New, or change in pre-existing murmur
    - CHF (congestive heart failure)
    - Conduction defects
    - Pericarditis
    - Endocarditis
    - Infection of prosthetic valves
      - Valve dysfunction
      - Structural or non-structural dysfunction
      - Endocarditis
  - Artery
    - Mycotic aneurysm
    - Rupture of aneurysm

- Skin
  - Finger clubbing splinter hemorrhages in beds of nails
  - Osler's nodes
  - Janeway lesions
  - Petechiae
- GI – ischemic bowel disease

- Immune changes
  - MSK
    - Arthralgias
    - Clubbing
    - Anemia

- Differential
  - SBE (subacute bacterial endocarditis)
  - Non-bacterial endocarditis
  - Atrial myxoma
  - SLE (systemic lupus erythematosus)
  - Sickle cell disease

- Complications
  - Heart
    - CHF
    - Conduction defect
    - Valve damage
    - Coronary artery embolization
    - Infection of
      - Valve ring (abscess)
      - Myocardium
      - Fungal endocarditis
      - Pericarditis
      - Aortic root
      - Fistula in sinus valsalva
  - Arteries
    - Septic emboli to vasa vasorum
    - Mycotic aneurysms
    - Rupture of aneurysms (eg cerebral vessels, and hemorrhage)
  - CNS
    - Brain abscess
    - Fungal endophthalmitis
  - Spleen – infarcts
  - GI tract – mesenteric ischemia
  - Kidney – diffuse or focal glomerulonephritis

Useful Terms

- Osler's nodes
  - Small, red, tender nodules in pulp of fingers
  - Arise from inflammation around infected embolization
- Janeway lesions
  - Red, non-tender flat lesions on palms of hands and soles of feet
  - Blanch on pressure

In a person with suspected bacterial endocarditis, perform a focused physical examination to distinguish between Osler's nodes, and janeway lesions.

	Osler's nodes	Janeway lesions
➢ Small	✓	✓
➢ Red	✓	✓
➢ Tender	✓	No
➢ Nodules	✓	Flat lesions
➢ Blanch	No	✓
➢ Finger tips	✓	No
➢ Palms/ soles	No	✓

Useful background: Definition of infective endocarditis according to the modified Duke Citeria

- Definitive infective endocarditis
  - Pathological criteria
    - Microorganisms demonstrated by culture or histological examination of a vegetation
    - A vegetation that has embolized
    - An intracardial abcess specimen
    - Pathological lesions
    - Vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
  - Clinical criteria
    - 2 major criteria; or
    - 1 major criteria and 3 minor criteria; or
    - 5 minor criteria

- Possible infective endocarditis
  - 1 major criterion and 1 minor criterion; or
  - Minor criteria

- Rejected diagnosis of infective endocarditis
  - Firm alternative diagnosis explaining evidence of IE; or
  - Resolution of IE syndrome with antibiotic therapy for ≤ 4 days; or
  - No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
  - Does not meet criteria for possible IE as above

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 1476.

Useful background: Definition of terms used in Modified Duke Criteria for the diagnosis of infective endocarditis

- Major criteria
  - Blood culture positive for IE
    - Typical microorganisms consistent with IE from 2 seperae blood cultures: Viridans streptococci, Streptococcus bovis, HACEK group, Saphylococcus aureus; or community-acquired enterococci in the absence of a primary focus; or
    - Microorganisms consistent with iE from persistently positive blood culture defined as follows: At least 2 positive cultures of blood samles drawn > 12 hour apart; or all of 3 or a majority of ≥ 4 separate culture of Coxiella burnetii or anti-phase 1 IgG antibody titer > 1:800
  - Evidence of endocardial involvement
  - Echocardiogram positive for IE (TEE recommended for patients with prosthetic valves, rated at least “possible IE” by clinical criteria, or complicated IE (paravalvular abscess); TE as first test in other patients) defined as follows:
    - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic value.
  - New valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 2, page 1476.

Useful background: Modified Duke Criteria for the diagnosis of infective endocarditis

- Definite infective endocarditis

- Diagnosis accepted
  - Pathologic criteria
    - Microorganism on culture or histologic examination of a vegetation, a vegetation that has embolize, or an intracardiac abcess specimen; or
    - Pathological lesion; vegetation or intracardiac abcess confirmed by histologic examination showing active endocarditis.
  - Clinical criteria[a]
    - 2 major criteria, or
    - 1 major criterion and 3 minor criteria, or
    - 5 minor criteria
  - Possible infective endocarditis
    - 1 major criterion and 1 minor criterion, or
    - 3 minor criteria

- Diagnosis rejected
  - Firm alternative diagnosis explaining evidence of infective endocarditis, or
  - Resolution of infective endocarditis syndrome which antibiotic therapy for ≤ 4 days, or
  - No pathological evidence of infective endocarditis, as above

Modified Duke criteria, as quoted in: Ghosh AK. *Mayo Clinic Scientific Press*, 2008, Table 15-5, page 598.

- Perform a focused physical examination for bacterial endocarditis.

- Clinical features of subacute bacterial endocarditis
  - Fever, tachycardia, arthralgia, pallor with café au lait complexion
  - Microscopic hematuria
  - Oslers nodes- pink, tender, on digits, palms or soles
  - Splinter hemorrhages and petechiae
  - Clubbing
  - Splenomegaly
  - R- CHF or other endocardial damage

- Acute damage
  - Cusps
  - Chordae tendinae
  - Endo cardium
    - Pneumococcus, haemolytic streptococcus, staphylococcus, gonoccus
  - Pericardium
    - Pneumonia
    - Strep'
  - Myocardium
    - Staph'
  - Affects either a previously normal or abnormal valve
- Subacute damage
  - Cusps, chordae tendinae, endocardium, aorta
  - Usually affects a previously abnormal valve
  - New murmur, or changing murmur
  - Fever
  - Joint pain and tenderness
  - Anemia
  - Petechial hemorrhage
  - Embolism
  - Clubbing
- Risk factors

Stratify risk of having bacterial endocarditis

- High risk factors
  - Rheumatic fever
  - Artificial valves
  - Previous IE
  - IV drug users
  - Intravascular devices (e.g. arterial lines)
- Moderate risk factors
  - Most congential heart
  - Malformations
  - Valvular dysfunction
  - HCM
  - MVP with MR
- Constitutional risk factors
  - Fever
  - Chills
  - Malaise
  - Night sweats
  - Anorexia
  - Arthralgias
- Cardiac risk factors
  - Murmur
  - Palpatation
  - CHF
- Pulmonary risk factors
  - Septic pulmonary embolism

Stratify risk of having bacterial endocarditis

- Ask the patient about:
  - Prosthetic heart valves
  - Recent surgeries
  - Indwelling catheters or hemodialysis
  - Recent IV drug use
- Neurological risk factors
  - Immune mediated phenomena
  - Focal deficit
  - Headache
  - Meningitis
- Metastatic infection
  - Organ infarction
  - Embolic manifestations
- Peripheral signs
  - Petechiae
  - Conjunctivae
  - Buccal mucosa
  - Palate
  - Splinter hemorrhages: linear dark red streaks (nails)
  - Janeway lesions: ~ 5mm non-tender hemorrhagic macules on palm and soles
  - Osler's nodes: small painful nodules on fingers, toe pads, lasing hours-days
  - Roth spots: retinal hemorrhage with pale center near optic disc
- MSK
  - Splenomegaly
  - Synovitis
  - Vasculitis
  - Glomerulonephritis

Abbreviations: R-CHF, right side congestive heart failure; HCM, hypertrophic cardiomyopathy; IE, infectious endocarditis; MR, mitral regurgitation; MVP, mitral valve prolapse.

Adapted from: Burton JL. *Churchill Livingstone* 1971; Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 13, page 66.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. In the context of the patient with suspected SBE (subacute bacterial endocarditis), how do you differente Roth spots from other types of red lesions of the retina?

A1. Red lesions of the retina are caused by

- Microaneurysm
- Blot an dot hemorrhages
- Flame and splinter hemorrhages
- Preretinal hemorrhages, including subhyaloid hemorrhages space
- Roth spots are hemorrhages with a fibrinous centre which gives them a white spot with a red halo.
- White- Centered hemorrhages are associated with
  - SBE
  - Diabetes
  - Intracranial hemorrhage
  - Leukemias
  - Various infectious processes

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 99.

Q2. In the context of reddish lesions on the palms of the hands or soles of the feet, distinguish between Janeway lesions and Osler's nodes.

A2. Janeway lesions are small and non-tendon whereas, Osler's nodes are swollen, tender. Janeway lesions arise from septic emboli or sterile vasculitis in endocarditis (with or without bacteremia, gonococcal sepsis, or lupus (SLE).

SO YOU WANT TO BE A CARDIOLOGIST!

Q. What is the most common cause of death in persons with SBE?

A. CHF, secondary to

- Perforation of a valve cusp
- Rupture of a chorda tendinea

- Perform a focused physical examination for subacute bacterial endocarditis (SBE).

- General
  - Fever

- CNS signs from emboli

- Eye
  - Petechiae in
    - Conjunctiva
    - Soft/ hard palate
    - Retina (crops of red spots with white centres; aka Roth spots)

- Teeth
  - Possible source of infection usually microscopic

- Heart
  - New murmur
  - Changing murmur

- Renal
  - Hematuria (from small renal infarcts)

- Skin
  - Petechiae
  - Clubbing
  - Café-aulait spots

- MSK
  - Palor (hemolytic anemia)
  - Splenomegaly

Useful background: Valve disease predisposing to endocarditis

- Patient
  - Prosthetic valves*
  - Previous endocarditis*

- Valves
  - Mitral or aortic regurgitation (MR, AR)*
  - Ventricular septal defect (VSD)*
  - Patent ductus arteriosus (PDA)*
  - Aortic stenosis (AS)
  - Hypertrophic cardiomyopathy

- Atrial septal defect (ASD)
- Pure mitral stenosis (MS)

*high risk

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 166.

Useful background: Antibiotic regimen for endocarditis prophylaxis in dental procedures

Drug	Adult dose	Pediatric dose
Standard regimen		
Amoxicillin	2 g Po	50 mg/kg
➢ Unable to take oral medications		
○ Ampicillin	2 g IM or IV	50 mg/kg IM or IV
or		
○ Cefazolin	1 g IM or IV	50 mg/kg IM or IV
or		
○ Ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
➢ Allergic to Penicillins		
○ Cephalexin	2 g po	50 mg/kg
or		
○ Clindamycin	600 mg po	20 mg/kg
or		
○ Azithromycin	500 mg po	15 mg/kg
or		
○ Clarithromycin	500 mg po	15 mg/kg
➢ Allergic to penicillins and unable to take oral medications		
○ Cefazolin	1g IM or IV	50 mg/kg IM or IV
○ Ceftriaxone	1g IM or IV	50 mg/kg IM or IV
○ Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 8, page 1482.

Useful background: Modified Duke Criteria for the diagnosis of infective endocarditis

- Definite infective endocarditis
  - Pathologic criteria
    - Microorganism on culture or histologic examination of a vegetation, a vegetation that has embolize, or an intracardiac abcess specimen; or
    - Pathological lesion; vegetation or intracardiac abcess confirmed by histologic examination showing active endocarditis
  - Clinical criteria
    - 2 major criteria, or
    - 1 major criterion and 3 minor criteria, or
    - 5 minor criteria
  - Possible infective endocarditis
    - 1 major criterion and 1 minor criterion, or
    - 3 minor criteria

  - Rejected
    - Firm alternative diagnosis explaining evidence of infective endocarditis, or
    - Resolution of infective endocarditis syndrome which antibiotic therapy for ≤ 4 days, or
    - No pathological evidence of infective endocarditis, as above

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 15-5, page 598.

Congenital heart disease

Useful background: Anatomic classification of congenital heart disease

- Shunts (R → L or L → R)
  - R and L heart shunts
- Valvular defects
  - Aortic or pulmonary stenosis
  - Bicuspid aortic valve (predisposes to later aortic stenosis)
  - Tricuspid atresia
- Complex lesions
  - Fallot's tetralogy
  - Transposition of the great vessels
  - Ebstein's anomaly
  - Combinations of defects

Source: Davey P. *Wiley-Blackwell* 2006, page 174.

- Secundum ASD
  - Persistent hole in ostium secundum (second hole in the septum premum in not blocked off in the normal manner by the septum secundum)

- Primum
  - Persistal hole in ostium primum, with incompetence of the AV valves.

- Perform a focused physical examination to distinguish between dextrocardia, situs inversus, dextroversion, and levoversion.

	Dextrocardia Side	Situs inversus	Dextro-version	Levo-version
➢ Apex beat	R	R	R	L
➢ Heart sounds	R	R	R	L
➢ R. atrium	L	L		
➢ Descending aorta	R	R	L	R
➢ Lung		R, 2 lobes; L, 3 lobes		
➢ Liver dullness		L		
➢ Stomach	L	R	L	R
➢ Associated				
o Bronchiectasis and dysplasia of the frontal sinuses (Kartagener syndrome)	✓	✓	-	-
o Cardiac malformation (CM)	✓	-	-	-
o CM plus Turner syndrome*	✓	-	-	-
o Asplenia	✓	-	-	-

*Turner syndrome: female, webbing of neck, ↑ carrying angle of elbow joint, gonadal dysgenesis

- Give the chest X-ray findings seen in 3 common causes of congenital heart disease.

➢ Causes
  - VSD
  - ASD (of the secundum type)
  - Patent ductus arteriosus (PDA)
  - Fallot's tetralogy (in order of frequency)

➢ Chest X-Ray Findings
  - Boot-shaped heart
  - Enlarged right venticle
  - Decreased pulmonary vasculature
  - Right-sided aortic arch (in 30% of cases).

- Perform a focused physical examination for ASD.

➢ Pulse	o Usually normal o May be associated with atrial fibrillation
➢ Palpation	o PMI – normal, or diffuse o Heave – LSE (left sterna edge)
➢ Heart sounds	o S_2 - Wide - Split - Fixed
➢ Murmur	o Large L → R shunt o Mid – diastolic o Tricuspid area o Murmur of TR, often with onset of AF
➢ Signs of PHT	o Eisenmenger syndrome
➢ Hand (Holt-oram syndrome)	o Hypoplastic thumb o Thumb is in line with other digits o Accessory phalanx
➢ Associated syndromes	o Fallot's trilogy - ASD - PS - RVH o Lutembacher syndrome - ASD - MS (rheumatic)

Abbreviation: PS, pulmonary stenosis; MS, mitral stenosis; RVH, right ventricular hypertrophy; PMI, apex impulse, point of maximum impulse; AF, atrial fibrillation; TR, tricuspid regurgitation.

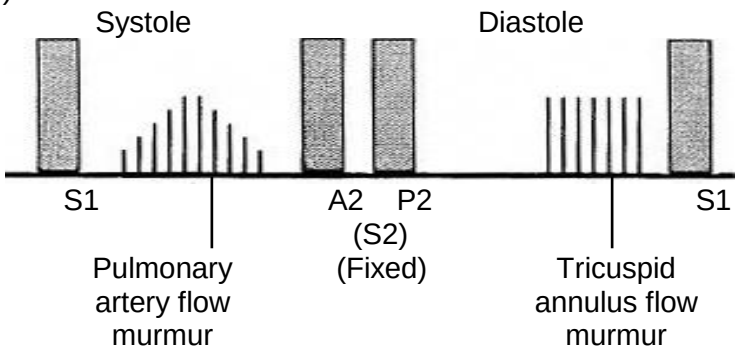
SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q. What is the Taussing-Bing syndrome?

A.
- The aortic arises from the right ventricle
- The pulmonary trunk overrided both ventricles at the site of an interventricular septal defect

Source: Baliga RR. *Saunders/Elsevier* 2007, page 93.

Useful background: Atrial septal defect (ASD): ostium secundum (at the left sternal edge)



Adapted form: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 3.34, page 84.

- Perform a focused physical examination to distinguish between a secundum and a primum ASD.

Secundum

- JVP
  - ↑ a wave
- Murmur
  - Tricuspid diastolic murmur
  - Pulmonary systolic ejection murmur
- Sounds
  - ↑ P_2
  - P_2 widely split
- ECG
  - RBBB plus right axis deviation

- Primum is also accompanies by pansystolic murmur (due to incompetent AV valves)
  - RBBB plus left axis deviation

ASD itself is not associatied with a murmur.

The murmur of a VSD is usually

- Pansystolic Q loudest in the L- ICS 3,4 (left third and fourth left intercostals spaces)
- Radiates over the precordium
- Associated thrill
- Radiates to the axilla
- Associated with a S_3

- Perform a focused physical examination for VSD.

  - Pulse
    - Usually normal
  - Palpation
    - PMI
      - Dynamic
      - Displaced - laterally
    - Pulsation over pulmonary trunk and RV heave (with PHT)
    - Thrill
      - L-LSE (left lower sterna edge)
  - Heart sounds
    - S_2 normal – with small defects
    - S_2 split
    - $A_2 \downarrow$ - with large defects
    - P_2 only – RV = LV pressure
    - $\uparrow P_2$ – PHT (pulmonary hypertension)
  - Murmurs
    - Small defect (muscular VSD)
      - Ejection murmur
      - High frequency
    - Moderate defect
      - Systolic
        - Pansystolic
        - L-LSE
        - Diminishes with development of PHT
      - Diastole
        - Mid-diastole
        - Rumple
        - Apex
        - Decrescendo if VSD associated with AR

- Signs of pulmonary hypertension (PHT)
- Signs of bacterial endocarditis
- Signs of myocardial infarction (VSD from rupture of interventricular septum)
- Signs of CHF (congestive heart failure)
- Signs of associated conditions
  - VSD as part of a syndrome
    - Fallot's tetralogy
    - TA (truncus arteriosus)
    - Double – outlet RV
    - AV canal defects
  - VSD as an association
    - Down's syndrome
    - Transposition of the great arteries
    - PDA (patent ductus arteriosus)
    - ASD, secundum (arterial septal defect)
    - Coarctation of the aorta
    - Valvular defects
      - Pulmonary stenosis
      - Pulmonary atresia
      - Tricuspid atresia
- Changes in signs of VSD when VSD complicated by PHT
- Palpation
  - ↓ LV impulse
  - ↓ thrill
  - ↑ RV impulse
  - Pulsation over pulmonary trunk
- Heart sounds
  - ↑ P_2
- Murmur
  - ↓ pansystolic murmur (reversal of VSD shunt, aka Eisenmenger complex)
  - New murmur of pulmonary regurgitation (Graham Steell's murmur)
- Skin
  - Cyanosis
  - Clubbing

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, pages 67 and 68.

Useful background: What are the types of VSD?

- The supracristal type (above the crista supraventricularis):
  - A high defect just below the pulmonary valve and the right coronary cusp of the aortic valve
  - The latter may not be adequately supported, resulting in aortic regurgitation
  - In Fallot's tetralogy this defect is associated with the rightward shift of the interventricular septum
  - In double-outlet left ventricle with subaortic stenosis the supracristal defects associated with a leftward shift of the septum
- The infracristal defect, which may be in either the upper membranous portion of the interventricular septum, or the lower muscular part
  - Small defects (maladie de Roger; curiously, a very loud murmur)
  - Swiss cheese appearance (multiple small defects)
  - Large defects
  - Gerbode defect (defect opening into the right atrium

Source: Baliga RR. *Saunders/Elsevier* 2007, page 169.

- Perform a focused physical examination for a ventricular septal defect (VSD).

- Murmur
  - Continuous in systole and diastole, with no interval of a silent pause
  - May cover entire systole, or be decrescendo, crescendo, or mixed crescendo/decrescendo
  - Best heard L. LSB
  - If there is a crescendo pattern, it starts after S_1
  - Usually due to PDA (patent ductus arteriosus)
  - When pulmonary hypertension (PHT) develops, diastolic component disappears.
  - With further worser PHT, the continuous murmur completely disappears.

- Complications
  - CHF
  - RV outflow obstruction (muscular infundibular obstruction)
  - Aortic regurgitation
  - Infective endocarditis
  - Pulmonary hypertension and reversal of shunt L → R ➔ R → L (Eisenmenger complex)

- Causes (defect in the membranous portion of the interventricular septum)
  - Congenital
  - Rupture of the interventricular septum (e.g. complication of myocardial infarction)

- Associations
  - Heart
    - Fallot's tetralogy
    - Double-outlet right ventricle
    - AV canal defects
    - Patent ductus arteriosus (PDA)
    - Pulmonary stenosis
    - Secundum atrial septal defects
    - Tricuspid atresia

  - Vessels
    - Truncus arteriosus
    - Coarctation of aorta
    - Transposition of the great arteries
    - Pulmonary atresia

Abbreviation: L. LSB, left lower sternal border

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 265-266; Baliga RR. *Saunders/Elsevier* 2007, page 60.

- Physiological classification of congenital heart disease based on the presence or absence of cyanosis

- Acyanotic

- With L → R shunt
  - Ventricular septal defect (VSD)
  - Atrial septal defect (ASD)
  - Patent ductus arteriosus (PDA)

- With no shunt
  - Bicuspid aortic valve, congenital aortic stenosis
  - Coarctation of aorta
  - Dextrocardia
  - Pulmonary stenosis, tricuspid stenosis
  - Ebstein's anomaly

- Cyanotic
  - Ebstein's anomaly (if an atrial septal defect (ASD) and R → L shunt are also present)
  - Truncus arteriosus
  - Transposition of the great vessels
  - Tricuspid atresia

- Total anomalous pulmonary venous drainage
- Eisenmenger's syndrome (pulmonary hypertension and a right – to - left shunt)
- Tetralogy of Fallot

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.15, page 85.

Patent ductus arterosus (PDA)

- Perform a focused physical examination for PDA.

➢ Pulse	o Collapsing o Differentiate from - AR (aortic regurgitation) - CHB (complete heart block) - Anemia - Hyperthyroidism - Paget's disease
➢ Palpation	o Heaving apex beat o Thrill, 2nd L-ICS
➢ Heart sounds	o S_2 absent o ↑ P_2 with development of PHT
➢ Murmur	o Pansystolic (continuous "machinery") murmur o Systolic murmur begins after S_1, peaks with S_2, and may extend into early diastole (Gibson murmur) o LSE, outer border of clavicle o Differentiate from - Venous ▪ Venous hum ▪ AV anastomosis – intercostals vesssels, post rib fracture ▪ AV fistula – coronary, pulmonary - Rupture sinus of valsalva - Murmur ▪ MR plus AR ▪ VSD plus AR
➢ Associations	o VSD (ventricular septal defect) o PS (pulmonary stenosis) o Coarctation of aorta o Hypoplastic left heart syndrome o Critical congenital aortic stenosis

- Signs of development of PHT (pulmonary hypertension)
  - Signs of PHT
    - ↑ P_2
    - Clubbing and cyanosis of toes
  - Diastolic and then systolic murmur disappear
- Signs of CHF
- Signs of septic emboli
  - Pulmonary artery endarteritis
  - Pulmonary emboli
- Signs of
  - Intraventricular bleeding
  - Broncho-pulmonary dysplasia
  - NEC (necrotizing enterocolitis)
  - Rupture of aneurysmal and calcified ductus

Abbreviation: L-ICS, left intercostals space; PHT, pulmonary hypertension; LSE, left sterna edge; AR, aortic regurgitation; VSD, ventricular septal defect.

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, pages 78 and 79.

- Perform a focused physical examination for PDA (patent ductus arteriosis).
  - Heart sounds
    - wide splitting of S_2
  - Murmur
    - machinery – murmur, L-ICS-2 *
    - rarely only a systolic murmur
  - Cyanosis, clubbing – see below

*L-ICS-2, left second intercostals space

- Give the clinical findings of 5 causes of congenital heart disease associated with cyanosis.
  - Pulmonary stenosis (PS) – pulmonary conus normal size, or enlarged due to post-stenotic dilation of pulmonary artery.
  - Tetralogy of Fallot
    - PS
    - RVH (right ventricular hypertrophy)
    - VSD (ventricular septal defect)
    - DPA (dextroposition of the aorta: L → R)

- Eisenmenger complex
  - RVH
  - VSD
  - DPA
- Transposition of the great vessels
- Tricuspid atresia

Useful background: Causes of cyanosis

- Central cyanosis
  - ↓ arterial oxygen saturation
    - ↓ concentration of inspired oxygen: high altitude
    - ↓ cardiac output: left ventricular failure or shock
    - Lung disease: chronic obstructive pulmonary disease with cor pulmonale, massive pulmonary embolism
    - Right-to-left cardiac shunt (cyanotic congenital heart disease)
  - Polycythemia
  - Hemoglobin abnormalities (rare): methemoglobinemia, sulphemoglobinemia

- Peripheral cyanosis
  - All causes of central cyanosis cause peripheral cyanosis
  - Exposure to cold
  - Arterial or venous obstruction

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 2.2, page 19.

- Perform a focused physical examination to determine the cause of acyanotic, cyanose tardive, and cyanotic congenital cardiovascular disease.

- Acyanotic – coarctation of the aorta; aortic stenosis (valve or infundilonlum 1-2 cm below the valve); dextracardia

- Cyanose tardive - (< 30% R→ L shunt; > 30% with exercise, CCF) ASD, VSD (Roger's disease; Eisenmenger complex), PFA, PDA, PS

- Cyanotic – tetrology of Fallot, transposition of great vessels

- Coarctation of the aorta
  - Visible or palpable pulsation above the episternal notch
  - Systolic murmur (front, back)
  - SBP in arms > legs

- Collateral circulation (internal mammary, interstitial, scapillary arteries)
- Chest x-ray
  - ↓ aortic knuckle
  - Indentation of aortic shadow at point of contraction
  - Notching of lower borders of ribs (erosion by dilated intercostal arteries)

- Patent forman ovale (PFA)
  - Persistent valve-like opening covered by a membrane on the left side
  - May cause paradoxic embolus (peripheral vein or RA embolus goes to systolic circulation, e.g. brain, kidney rather than lung
  - With RAH and LAH, large defect produced like ASD

- Atrial septal defect (ASD)
  - Early LA → RA: no cyanosis or clubbing (one of the few causes of R-side enlargement without cyanosis)
  - Murmur of PS (↑ flow)
  - ↑P_2
  - Late RA→ LA: cyanosis, clubbing

- Chest x-ray
  - RVH
  - Prominent, pulsating pulmonary arteries
  - Hilar dance (prominent, pulsating hilar shadows)
  - Small aorta
- Lutenbacher syndrome
- Interventricular defects (IVD)
  - Roger's disease
    - Small IVD
    - Harsh systolic murmur, L-3rd, ICS
    - Thrill (in 90%)
  - Eisenmenger complex
    - Dextraposed aorta (partially arising from RV)
    - Large high VSD
    - Systolic murmur with a thrill; may have associated AR
    - Distinguish from tetrology of Fallot

- Patent ductus arteriosus (PDA)
  - Persistance of fetal connection between pulmonary artery into aorta
  - Continuous (systolic and diastolic) all over precordium, or medial to left midscapula
  - Thrill
  - LVH, RVH; late, RV → LV shunt, with cyanosis

- ↑ PP due to ↓ DBP (PP = SBP-DBP)
- Corrigan pulse (also seen in AR)

➢ Tetralogy of Fallot
- VSD, RVH, PS, dextra posed aorta
- Cyanosis, clubbing, retarded growth, polycythamin
- $A_2 > P_2$
- Distinguish from Eisenmenger complex

➢ Transposition of the great vessels
- RV → aorta, LV → pulmonary artery
- Survival only with a shunt: PFA, VSD, PDA

Abbreviations: AR, aortic regurgitation; ASD, atrial septal defect; CCF, congestive cardiac failure; DBP, diastolic blood pressure; IVD, interventricular defects; LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; MS, mitral stenosis; PDA, patent ductus arteriosus; PFA, patent forman ovale; PP, pulse pressure; PS, pulmonary stenosis; RA, right atrium; RV, right ventricle; RVH, right ventricle hypertrophy; SBP, systolic blood pressure; VSD, ventricular septal defect

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 3.15, page 85.

- Perform a focused physical examination for tetralogy for Fallot's.

➢ Necessary finding
- VSD with R → L shunt
- PS (infundibular or valvular)
- RVH
- Dextroposition of the aorta, with overriding of the VSD

➢ Physical examination

➢ Skin/ handsClubbing
- Clubbing
- Central cyanosis

➢ Precordium
- Palpation
  - Left parasternal heave with normal left ventricular impulse
- Auscultation
  - Ejection systolic murmur heard in the pulmonary area
- After Blalock-Taussing shunt
  - Radial pulse L < R
  - The arm on the side of the anastomosis (usually the left) may be smaller than the other arm
  - Blood pressure difficult to obtain (narrow pulse pressure in the arm supplied by the collateral vessels)

- Thoracotomy scar

- Complications
  - Cyanotic and syncopal spells
  - Cerebral abscess
  - Endocarditis

- Associations - Conditions associated with Fallot's (Stenson's) tetralogy
  - Right-sided aortic arch
  - Double aortic arch
  - Left-sided superior vena cava (
  - Hypoplasia of the pulmonary arteries
  - ASD

Abbreviation: PS, pulmonary stenosis; RVH, right ventricular hypertrophy

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 91.

- Perform a focused physical examination for dextrocardia.

- Apex beat is on the right side.
- Heart sounds heard on the right side of the chest
- Liver dullness on the left side
- Possible bronchiectasis
- Mazinkonski's sign – not named after this person!
  - Dextrocardia without evidence of situs inversus, usually associated with cardiac malformation
  - May occur with cardiac malformation in Turner's syndrome

Source: Baliga RR. *Saunders/Elsevier*, 2007, page 83.

- Perform a focused physical examination to distinguish between acquired versus congenital dextrocardia.

- Congenital dextrocardia may be associated with
  - Basal bronchiectasis
  - Malformed frontal sinuses
  - Situs inversus (transposition of viscera, with dullness over left ribs anteriorly, and tympany over right ribs anteriorly
- Acquired right lung disease
  - Collapse
  - Effusion (large)
  - Pneumothorax (large)

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. What is the difference between Eisenmenger syndrome and complex?

A1.
- Eisenmenger syndrome
  - PHT plus reversed or bidirectional shunt from one of many cardiac defects (ASD, VSD, PDA)
- Eisenmenger complex
  - VSD plus R → L shunt, without, or common associated PS

Q2. In the context of Eisenmenger syndrome, with which type of associated shunt is the right ventricle enlarged?

A2. With ASD causing Eisenmenger syndrome, the RV is enlarged.

Q3. Which findings on physical examination of the heart suggest that the Eisenmenger complex is progressing to the Eisenmenger syndrome?

A3.
- ↑ P2
- Murmur becomes softer
- L-side of heart becomes smaller

I haven't given up yet: I STILL WANT TO BE A CARDIOLOGIST!

Q. What is Lutenbacher syndrome?

A. ASD plus mitral stenosis.

- Take a directed history and perform a focused physical examination for Eisenmenger syndrome.

➢ Definition
- Pulmonary hypertension with a reverse or bidirectional shunt
- Shunt (VSD, ASD, patent ductus arteriosus, persistent truncus arteriosus, single ventricle or common artrioventricular canal

➢ History
- CNS
  - Cerebrovascular accidents (as a result of paradoxical embolization, venous thrombosis of cerebral vessels, or intracranial haemorrhage)
  - Sudden death
  - Brain abscess
- Lung
  - Pulmonary embolization
  - Hemoptysis
- Heart
  - Right ventricular failure

    - Paradoxical embolization
    - Infective endocarditis
  - Kidney
    - Hyperuricemia

- Physical examination
  - Clubbing of fingers
  - Central cyanosis
  - JVP 'a' waves ; 'v' wave if tricuspid regurgitation is present
  - Left parasternal heave
  - Palpable P2
  - Loud P2
  - Pulmonary ejection click
  - Early diastolic murmur of pulmonary regurgitation (Graham Steell murmur)
  - Tricuspid regurgitation
  - S2
    - VSD: single second sound
    - ASD: fixed, wide split second sound
    - PDA: reverse split of second sound, and lower-limb cyanosis

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, pages 88 and 89.

- Perform a focused physical examination of the cardiovascular system for Eisenmenger syndrome (ES).

➢ General appearance	○ Central cyanosis (when R → L shunting occurs) ○ Cyanosis of lower torso > upper torso ○ Clubbing of fingers
➢ JVP	○ 'a' waves
➢ Pulse	○ 'v' waves if ES is associated with TR ○ Atrial arrhythmias
➢ Heart palpation	○ L. parasternal heave ○ Palpable P2
➢ Heart sounds	○ ↑ P2 ○ Single S2 - VSD ○ Wide, fixed splitting of S2 - ASD ○ Reversed S2 splitting (A2 P2 → P2A2) ○ Pulmonary ejection click
➢ Murmurs	○ PR - early diastolic murmur (aka Graham Steell murmur) ○ TR - loud pansystolic murmur

- Complications
  - R. CHF
  - CVA
  - Brain SOL (abscess)
  - SBE
  - Hemoptysis
  - Bleeding, thrombosis

Abbreviation: ASD, atrial septal defect; L, left side; PDA, patent ductus arteriosus; PHT, pulmonary hypertension; PR, pulmonary regurgitations; PTA, persistent truncus arteriosus; R, right side; RV, right ventricle; SBE, subacute bacterial endocarditis; SOL, space-occupying lesion; TR, tricuspid regurgitation; VSD, ventricular septal defect

HAVE YOU DECIDED NOT TO BE A PEDIATRIC BUT RATHER AN ADULT CARDIOLOGIST? NO WONDER!

Q. In the context of a systolic murmur, what is the 'Gallavardin phenomenon'?

A. The high-frequency components of the ejection systolic murmur may radiate to the apex, falsely suggesting mitral regurgitation

! Trick Questions!

Q1. Under what circumstances does the person with PDA develop cyanosis (cyanosis tardive)?

A1. With
- Exercise
- CHF
- Infection

Q2. Under what circumstances does the person with PDA develop clubbing?

A2. With
- SBE (subacute bacterial endocarditis)
- Pulmonary infection

Q3. What are the typical changes on the chest X-ray of the person with PDA?

A3.
- Large right atrium
- Large pulmonary conus and arteries ("hilar dance")
- Aorta normal size

SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q1. What are the types of aortic coarctation?

A1.
- Common:
  - Infantile or preductal where the aorta between the left subclavian artery and patent ductus arteriosus is narrowed. Its manifests in infancy with heart failure. Associated lesions include patent ductus arteriosus, aortic arch anomalies, transposition of the great arteries, ventricular septal defect.
  - Adult type: the coarctation in the descending aorta is juxtaductal or slightly postductal. It may be associated with bicuspid aortic valve or patent ductus arteriosus. It commonly between the age of 15 and 30 years.
- Rare
  - Localized juxtaductal corctation
  - Coarctation of the ascending thoracic aorta

Source: Baliga RR. *Saunders/Elsevier*, 2007, page 85.

Q2. What are the fundal findings in coarctation of aorta?

A2. Hypertension due to coarctation of aorta causes retinal arteries to be tortuous with frequent 'U' turns; curiously, the classical signs of hypertensive retinopathy are rarely seen.

Source: Baliga RR. *Saunders/Elsevier* 2007, page 87.

SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q1. Why does the hemodynamic severity of a VSD not reflect its size?

A1. The hemodynamic severity is reflected by the L → R shunt. The magnitude of this shunt may be reduced by
- ↑ pulmonary arteriolar resistance
- Hypertrophy of pulmonary outflow tract, leading to pulmonary stenosis (from functional muscular hypertrophic subvalvular pulmonary stenosis)

Q2. When does the typical pansystolic murmur of VSD occur only in early systole?

A2. The VSD is usually in the membranous portion of the ventricular septum. If the muscular part of the septum contracts, the murmur occurs only in early systole.

SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q1. What are the complications of aortic coarctation?

A1.
- Severe hypertension and resulting complications:
  - Stroke
  - Premature coronary artery disease

Q2. What do Turner's syndrome, Noonan's syndrome and Bonnevie-Ullrich syndrome have in common?

A2. Webbed neck. Now let's consider these three syndromes.

Turner syndrome
- Phenotypic females
- Cvarian dysgenesis
- Short stature
- Low-set ears
- "shield chest|
- Café-au-lait spots
- Freckles
- Heart congenital coarctation of aorta

Bonnevie- Ullrich syndrome
- Lymphedena of hands & feet
- Nail dystrophy
- Lax skin
- Short stature

Noonan syndrome
- Congenital pulmonary stenosis
- Pectus carinatum (forward projection of sternum
- Short stature
- Mildly mentally challenged
- Hypertelevision
- Bleeding
- Skin changes

Q3. What is Kartagener's syndrome?

A3. A type of immotile cilia syndrome in which there is dextrocardia situs inversus, bronchiectasis and dysplasia of the frontal sinuses.

Q4. Which other abnormality has been associated with dextrocardia?

A4. Asplenia (blood smear may show Heinz bodies, Howell-Jolly)

Q5. What is Kartagener's syndrome?

A5.
- Dextrocardia or situs inversus bronchiectasis
- dysplasia of the frontal sinuses

Q6. What are the congenital disorders in which atrial fibrillation is common?

A6.
- Atrial septal defect
- Ebstein's anomaly

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 32 and 33.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. Under what clinical circumstances should heart disease be suspected as being congenital in origin?

A1.
- Young person
- Murmur down left sterna edge
- Presence of both cyanosis and clubbing
- Presence of other congenital conditions:
  - Down's syndrome : ASD (ostium primuim type of atrial septal defect)
  - Turner's syndrome: coarctation of the aorta, pulmonary stenosis
  - Gargoylism: fibroelastosis
  - Marfan's syndrome : ASA, dissecting aneurysm
- Depending upon underlying history, presence of
  - Cyanosis
  - Clubbing
  - Polycythemia (secondary to low pO2)
  - Drawfism, or infantilism (retention in adult life of sexual characteristics of childhood)

Q2. What are the commonest types of congenital heart disease?

A2. VSD (ventricular septal defect), ASD (atrial septal defect, secundum type) and Fallot's tetralogy

Q3. Congenital heart disease may be cyanotic or non-cyanotic in nature. What is cyanosis tardive?

A3. Persons with a congenital shunt (PDA, VSD, ASD) have the potential to develop cyanosis when the shunt reverses secondary to
- CHF
- Pulmonary infection
- Exercise

Q4. In the context of ASD, what is the "Lutembacher complex", and what is the significance of this physical finding to the prognosis of the associated murmur".

A4. The lutembacher complex is ASD plus mitral stenosis (MS). When MS occurs with ASD, its prognosis is better than MS by itself.

Q5. In the context of a congenital or acquired VSD, what are Graham Steell's murmur, and Eisenmenger complex?

A5.
- Graham Steell's murmur - Murmur of PR (pulmonary regurgitation) in person with a VSD in which the flow through the defect decreases from the development of PHT, and the usual left - to- right shunting falls)
- Eisenmenger complex - The left - to – right flow in the VSD reverses with the development of pulmonary hypertension

SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q1. What are the types of VSD?

A1.
- The supracristal type (above the crista supraventricularis):
  - A high defect just below the pulmonary valve and the right coronary cusp of the aortic valve
  - The latter may not be adequately supported, resulting in aortic regurgitation
  - In Fallot's tetralogy this defect is associated with the rightward shift of the interventricular septum
  - In double-outlet left ventricle with subaortic stenosis the supracristal defects associated with a leftward shift of the septum
- The infracristal defect, which may be in either the upper membranous portion of the interventricular septum, or the lower muscular part
  - Small defects (maladie de Roger; curiously, a very loud murmur)
  - Swiss cheese appearance (multiple small defects)
  - Large defects
  - Gerbode defect (defect opening into the right atrium

Source: Baliga RR. *Saunders/Elsevier* 2007, page 169.

Q2. With regards a VSD, what is the "Maladic de Roger"?

A2. Maladie de Roger is a VSD with no hemodynamic consequences (no symptoms, no changes on chest X-ray or ECG).

Q3. With regards to a VSD, what is the importance of also auscultating a mitral diastolic murmur and a pulmonary systolic murmur?

A3. These murmurs are caused by an increase in the flow of blood throung these mitral and pulmonary valves, indicating that the shunt is large and hemodynamically significant.

Q4. With regards to a VSD accompanied by a mitral diastolic murmur and a pulmonary systolic murmur, what is the hemodynamic significance of the lessening of these murmurs (loss of mitral murmur and lessening of pulmonary murmur)?

A4. With the increased blood flow through the mitral and pulmonary valves as the result of a large VSD shunt, the pressure in the right ventricle (RV) will increase and will reduce the flow which caused the murmurs.

Q5. With regards to VSD, what is "Eisenmenger's syndrome"?

A5. Eisenmenger's syndrome is a VSD with R → L shunt causing central cyanosis (the reversal of the L → R shunt to a R → L arises from the marked ↑ RV pressure.

Q6. What is the effect of pregnancy in women with VSD?

A6. Small defects should be present no problems.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. Which congenital cardiac lesions are dependent on a PDA?

A1.
- Hypoplastic left heart syndrome
- Complex coarctations of aorta
- Critical congenital aortic stenosis

Q2. What happens to the continuous murmur of patent ductus arteriosus (PDA) in pulmonary hypertension?

A2. First the diastolic murmur, then the systolic murmur becomes softer and shorter, P2 increases in intensity

Source: Baliga RR. 250 *Saunders/Elsevier* 2007, pages 78 and 81.

Q3. In the context of a continuous cardiac murmur present from birth, what lesion causes cyanosis and clubbing of the toes, but not the hands?

A3. Cyanosis and clubbing of the toes but not the hands is a "differential" finding due to PDA.

Q4. Which cardiac lesions are dependent on PDA?

A4.
- Hypoplastic left heart syndrome
- Complex coarctation of aorta
- Critical congenital aortic senosis

Q5. What happens to the continuous murmur of patent ductus arteriosus (PDA) in pulmonary hypertension?

A5.
- First the diatolic murmur, then the systolic murmur, becomes softer and shorter
- P_2 increases intensity

SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q1. What are the four commonest causes of cyanotic heart diseases of infancy?

A1. The Four T's:

- **T**etralogy of Fallot
- **T**ransposition of the great vessels
- **T**ricuspid regurgitation
- **T**otal anomalous pulmonary venous connection

Source: Baliga RR. *Saunders/Elsevier* 2007, page 89.

Q2. Give an example of a cyanotic cardiac condition where the cyanosis is more pronounced in the feet than in the hands.

A2. Eisenmenger's syndrome

Q3. Do you know all about Fallot and his tetralogy?

A3. Well, yes: ASD, pulmonary stenosis and right ventricular hypertrophy

Q4. Well then, what is Fallot's pentatoly?

A4. Fallot's tetralogy with associated ASD is known as Fallot's pentology

Source: Baliga RR. *Saunders/Elsevier* 2007, page 92.

SO YOU WANT TO BE A PEDIATRIC CARDIOLOGIST!

Q1. What are the pathognomic "Coeur de sabot" finding on chest X-ray which suggest tetralogy of Fallot?

A1. Pathognomic

- Aortic knuckle - normal
- Pulmonary conus – concavity
- Lower left heart border – upturned (due to RVH)
- Hilum – enlarged right atrium and pulmonary artery
- Lung fields – poorly seen

Abbreviation: RVH, right ventricular hypertrophy

Q2. What do you understand by the term 'situs inversus'?

A2. Right-sided cardiac apex, right stomach, right-sided descending aorta. The right atrium is on the left. The left lung has three lobes and the right lung has two.

Q3. What do you understand by the term 'dextroversion'?

A3. Right-sided cardiac apex, left sided stomach and left-sided descending aorta.

Q4. What do you understand by the term "levoversion'?

A4. Left-sided apex, right-sided stomach and right descending aorta

Source: Baliga RR. *Saunders/Elsevier* 2007, page 84.

Cardiac risk stratification

Useful background: American Society of Anesthesiologist Classification of Anesthetic Mortality within 48 hours postoperatively

Class	Physical Status	48-Hour Mortality
I	Healthy persons younger than 80 y	0.07%
II	Mild systemic disease	0.24%
III	Severe but not incapacitating systemic disease	1.4%
IV	Incapacitating systemic disease that is constant threat to life	7.5%
V	Moribund patient not expected to survive 24 hours, regardless of surgery	8.1%
E	Suffix added to any class to indicate emergency procedure	Double risk

Printed with permission: MXSAP IX: Part C, Book 4. *American college of Physician* 1991.

Source: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 8-8, page 336.

- Take a focused history to determine the cardiac risk stratification for noncardiac surgical procedures.

Cardiac risk	Procedure
➢ High	○ Emergency operations ○ Elderly patient ○ Aortic and other major vascular procedures ○ Peripheral vascular procedures ○ Prolonged surgical procedures associated with large fluid shifts or blood loss (or both)
➢ Intermediate	○ Carotid endarterectomy ○ Head and neck operations ○ Abdominal and intrathoracic procedures ○ Orthopedic procedures ○ Prostate operations
➢ Low	○ Cataract extraction ○ Breast operation ○ Endoscopic procedures

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 8.9, page 337.

Useful background: Odds ratios (OR) > 2 for perioperative pulmonary complications.

Risk Factors	Odds ratio
➢ Patient	
○ ASA class ≥ II	4.9
○ Chronic obstructive pulmonary disease	2.4
○ Age (2.3 for 60-69, increasing to 5.6 for ≥ 80 years)	
○ Total functional dependence	2.5
➢ Co-morbidities	
○ Congestive heart failure	2.9
○ Serum albumin <35 g/L	2.5
➢ Impaired sensorium	
➢ Cigarette use	
➢ Procedure-related	
○ Surgical site or type of procedure	6.9
○ Open abdominal aortic repair	4.2
○ Thoracic	3.1
○ Abdominal	2.5
○ Neurosurgical	2.2
○ Head and Neck	2.1
○ Vascular	2.5
○ Emergency surgery	2.3
○ Prolonged surgery (>3 h)	
➢ General anesthesia	2.4

Note that the OR < 2 for age 50-59; partial functional dependence, unpaired sensorium, smoking; blood transfusion > 4 units.

Abbreviation: ASA, American Society of Anesthesiologists

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 18-11, page 341.

- Take a directed history and perform a focused physical examination for superior vena cava (SVC) obstruction.

➢ History
  - Headache
  - Blackouts
  - Edema of the face
  - Dysphagia
  - Dyspnea
  - Wheezes

➢ Examination
  - General dyspnea
  - Face
    - Plethora
    - Dyspnea
  - Eyes
    - Horner's syndrome
    - Signs of radiation marks
  - Signs of brochogenic carcinoma
    - Clubbing
    - Tar staining
    - Lymph nodes
    - Chest signs
  - Neck
    - Tortuous, visible and dilated veins on the chest wall and neck
    - Neck veins non pulsatile

➢ Causes
  - Bronchogenic carcinoma (commonest cause, 70% of cases)
  - Lymphoma – in young adults
  - Other causes:
    - Aortic aneurysm
    - Mediastinal goitre
    - Mediastinal fibrosis (due to methysergide, histoplasmosis or TB)
    - Constrictive pericarditis

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, pages 593 and 594.

Useful background: Selected quality measures

Clinical Condition	Selected Quality Measures
➢ Acute coronary syndrome	○ Aspirin at arrival & discharge ○ B-blocker at arrival & discharge ○ ACE inhibitor for LVSD
➢ Congestive heart failure	○ Left ventricular function assessment ○ ACE inhibitor for LVSD ○ Smoking cessation advice & counseling
➢ Community-acquired pneumonia	○ Oxygenation assessment within 24 h ○ Pneumococcal screening & vaccination ○ Antibiotic timing (first dose in < 4 h) ○ Smoking cessation advice & counseling
➢ CRC screening	○ Risk: age, family history, IBA, smoking, obesity (sporadic, familial poly syndromes) ○ Adequacy of preparation & sedation ○ Reporting of cecal landmarks ○ Withdrawal time ○ Personal polyp detection rates (M, 25%, F,15%)

Abbreviation: ACE, angiotensin-converting enzyme; LVSD, left ventricular systolic dysfunction; CRC, colorectal cancer

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 13-2, page 505.

Remember

- Even women with well controlled hypertension have an increased risk of pre-eclampsia
- There is an increased risk for a woman to develop pre-eclampsia if she has been a sufferer of migraine headaches

ENDOCRINOLOGY

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Diabetes mellitus

- Take a directed history for diabetes mellitus.

➢ Glucose control

- Method and frequency of glucose monitoring, and by whom (patient, caregiver, health care worker)
- Typical levels of HbA1c, blood glucose at different times
- Dietary pattern, spacing of meals and snacks, quality and quantity of intake (CDA diet/calories/day); alcohol.
- Hypoglycemic reactions (frequency, symptoms); anxiety, tremor, seizures, palpitations, sweating, hunger
- Hyperosomolar non-ketotic coma (HONC)
- Diabetic ketoacidosis (DKA)
  - Symptoms of hyperglycemia (polyuria, polyphagia, polydypsia)
  - Anorexia, nausea, vomiting, abdominal pain
  - Fatigue
  - Kussmaul breathing
  - Precipitation: D/C insulin, infection, altered exercise/diet
- Medications (type, dose, frequency and adverse effects) Insulin, oral hypoglycemics, antagonistic medications (thiazides, corticosteroids)

➢ Causes/associated conditions

- Hormone-induced states (rare)
  - Acromegaly
  - Cushing's syndrome
  - Pheochromocytoma
  - Glucagonoma
- Drugs
  - Steroids
  - Oral contraceptive agents
  - Streptozotocin, diazoxide, phenytoin, thiazide diuretics
- Pancreatic disease
  - Chronic pancreatitis, carcinoma
  - Haemochromatosis
- Syndromes
  - Lipoatrophic diabetes (characterized by generalized lipoatrophy, hyperglycemia, hepatomegaly, hirsutism, acanthosis nigricans, hyperpigmentation and hyperlipidemia)
- Family history

- Having one sibling or parent with T2 diabetes increases the lifetime risk for developing T2 diabetes to 10-15 %

- Complications
  - Hyperglycemia
    - Polyphagia
    - Weight changes
    - Polydipsia (+/- nocturia)
    - Polyuria
    - Blurred vision
    - Yeast infections
  - Hypoglycemia (adrenergic symptoms and signs)
    - Hunger
    - Palpitations
    - Sweating
    - Anxiety
    - Tremors
    - Seizures
  - Neuropathy
  - ANS neuropathy
  - Impotence
  - Neurogenic bladder: retention overflow incontinence
  - Orthostasis hypotension (gastroparesis),
  - Bowel dysmobility (diarrhea/constipation)
  - PC bloating, fullness
  - Autonomic neuropathy
    - Orthostatic hypotension, gastroparesis (nausea, vomiting, postprandial bloating and early satiety), diarrhea, constipation, neurogenic bladder (retention and overflow incontinence), and impotence
  - Sensory neuropathy
    - Vibration sense (first lost), proprioception and light touch in glove-and-stocking distribution, Charcot's joints, foot ulcerations
  - Radiculopathy
    - Shooting or burning pain, often radiating down lower extremities
  - Mononeuropathy
    - Cranial nerve (CN) palsies; often CN III (but pupils spared), CN IV, CN VI

- Amyotrophy
  - Atrophy of the pelvic girdle and large leg muscles that can spontaneously remit. Often affects older males
- Mononeuritis multiplex
  - Peripheral nerve palsies that can cause sensory or motor neuropathies such as foot drop
- Peripheral neuropathy:
  - Anesthetic/paresthetic/hyperesthetic feet
  - Sensory: vibration, proprioception, light touch (glove-in stocking)
  - Charcot's joints
- Retinopathy
  - Fundoscopic examinations; visual acuity – blurred vision; cataracts
- Nephropathy
  - Known renal disease or proteinuria, date of last urinalysis
- Cardiovascular
  - Cardiac: angina, MI, Hx or symptoms of CHF or pulmonary edema
  - Peripheral vascular disease: claudication, rest pain, foot ulcers or infections, amputations, foot care

Abbreviation: CN, cranial nerve

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 280; and Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.17, page 336.

- What's "the best"? The "best" clinical findings for diabetic foot in a diabetic patient are a foot ulcer >2cm, a foot ulcer with bone exposed, or a positive probe test.

Useful background: risk factors of diabetes mellitus

- Abdominal obesity
- Acanthosis nigricans
- Age ≥ 40 years
- Dyslipidemia[a]
- First degree relative with T2DM
- History of
  - Delivery of a macrosomic infant
  - IFG or IGT
  - Gestational diabetes mellitus
- Hypertension

- Member of high-risk population
  - Aboriginal
  - Hispanic
  - South Asian
  - Asian
  - African descent
- Overweight
- Polycystic ovary syndrome
- Presence of complications associated with diabetes
- Schizophrenia
- Vascular disease (coronary cerebrovascular or peripheral)

[a] Associated with insulin resistance

Abbreviations: IFG, impaired fasting glucose; IG, impaired glucose tolerance; T2DM, type 2 diabetes mellitus

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 2, page 383.

Useful background: Risk and management

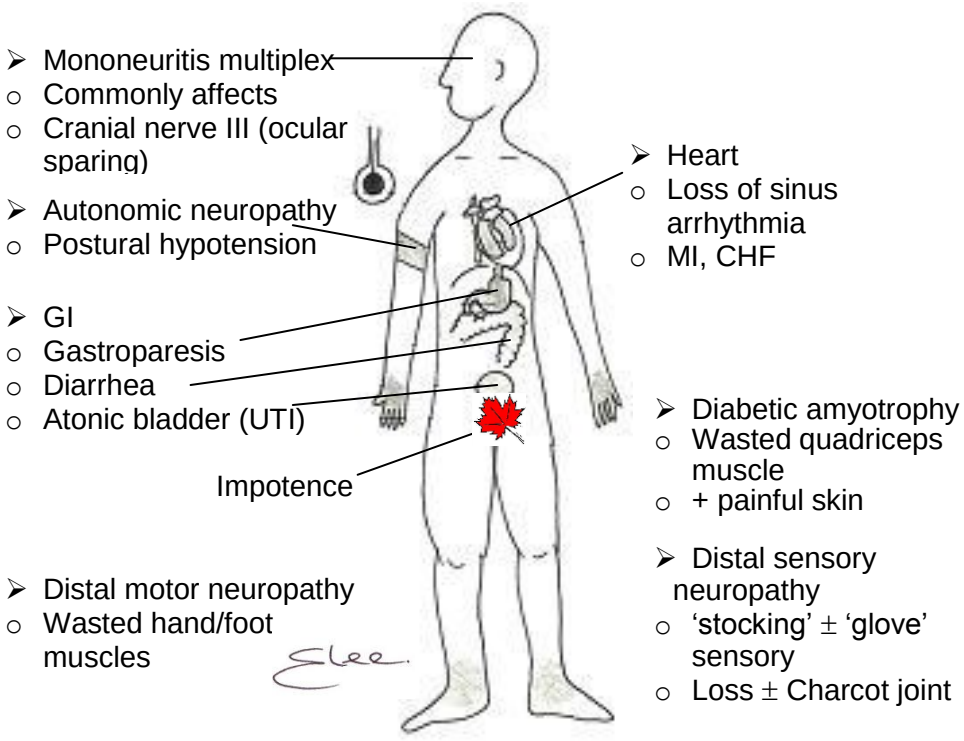
- Modifiable risk factors
  - Hypertension
  - Smoking
  - Hyperlipidemia
  - Obesity
  - Exercise
  - Substance abuse
  - Personal history of gestational diabetes

- Management
  - Diet
    - Caloric intake
    - Amount and types of fats, protein, fibre, and sugar
  - Lifestyle
    - Weight
    - Smoking
    - Alcohol or substance use
    - Exercise (type and amount)
  - Drug treatments
    - All medications
    - Insulin (type, amount, dosing schedule, side effects)
    - Hypoglycemic agents (type, frequency, side effects)

- Monitoring (type [blood/urine], frequency, HbA_{1c})
- Adherence to recommendations
- Family history of diabetes

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 20 and 21.

- Perform a focused physical examination for diabetic nephropathy.



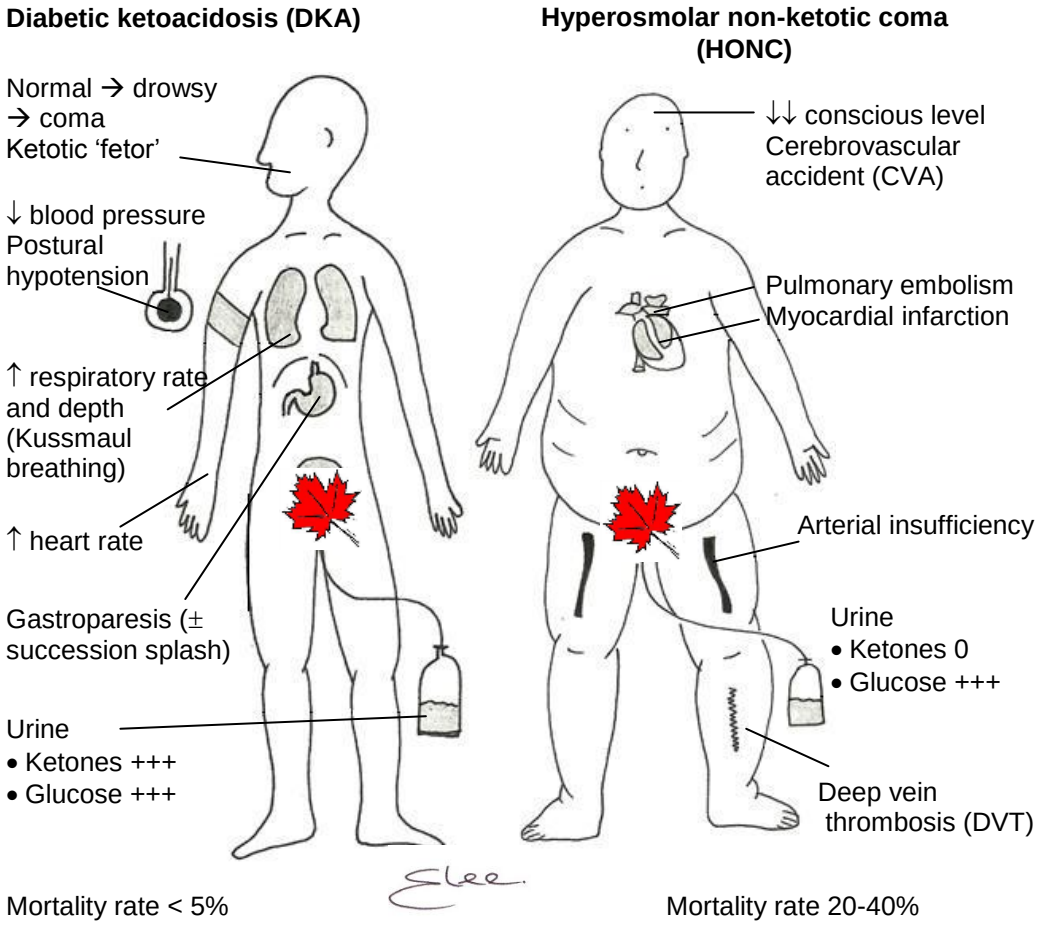
Abbreviations: CHF, congestive heart failure; MI, myocardial infarction; UTI, urinary tract infection

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 280.

People must retire at age 65, to have enough time to wait for their public Health Care!

Anonymous

Useful background: DKA and HONC



Management of DKA
- IV fluids
- IV insulin
- IV KCl (after insulin and fluids)
- Treatment of underlying cause

Investigations	DKA	HONC
Glucose	↑	↑↑
Na	→	↑↑
Urea	↑	↑↑
pH	↓	→
Serum osmolality	↑	↑↑

Abbreviations: CVA, cerebrovascular accident; DVT, deep vein thrombosis

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 282.

➢ What's "the best"? The "best" clinical tests for hypothyroidism are: slow speech, cool, dry and course skin, and brachycardia or a Billewicz diagnostic scale ≥ 30 points.

- Perform a focused physical examination of the diabetic foot.

- Skin (look between toes)
  - Dry cracked skin
  - Necrobiosis diabeticorum
  - Blisters, corns, bunions
  - Ingrown or dystrophic nails
  - Cellulitis
  - Ulcers
  - Infection between toes

- Vascular insufficiency
  - Pallor, red cool skin
  - Loss of hair
  - Ulcers, with or without infection
  - Gangrene or amputations
  - Reduced posterior tibial and dorsalis pedis pulses

- Neuropathy
  - Sensory
    - Reduced vibration sense (use 128 Hz fork)
    - Reduced pin prick/fine touch (5.07 monofilament)
    - Glove/stocking distribution in legs
  - Motor
    - Claw-hammer toes, foot drop, pes cavus, ankle deformity
  - Reflex
    - Ankle jerk reduced

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 554; McGee SR. *Saunders/Elsevier* 2007, pages 605 to 609.

Useful background: Performance characteristics of clinical tests for the diabetic foot

Finding	PLR
Predictors of subsequent foot ulceration	
Unable to sense the 5.07 monofilament	2.4
Predictors of osteomyelitis, in patients with foot ulcers	
Ulcer area >2 cm	7.2
Positive probe test	4.3
Ulcer depth >3 mm or bone exposed	3.6

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 51-1, page 608.

Useful background:

- Skin lesions seen in diabetes
  - Granuloma annulare
  - Chronic pyogenic infections and carbuncles
  - Eruptive xanthomata
  - Lipoatrophy and lipohypertrophy
  - Leg ulcers and gangrene
  - Acanthosis nigricans
  - 'Pebbles' on the dorsal aspect of the fingers
  - Peripheral anhidrosis (due to autonomic neuropathy)
  - Vulval candidiasis
  - Necrobiosis lipoidica diabeticorum*

* Sharply demarcated plaques with shiny surface, yellow waxy centres, and red margins with surrounding to angiectasia, sometimes complicated by ulceration of plaque, usually seen on the shin

- Skin lesions on shins
  - Necrobiosis lipodica diabeticorum
  - Erythema nodosum
  - Pretibial myxedema
  - Diabetic dermopathy
  - Erythema ab igne
  - Livedo reticularis

Printed with permission: Baliga RR. *Saunders/Elsevier* 2007, pages 442 and 443.

- Perform a focused physical examination to differentiate DKA from HONC.

	DKA	HONC
➢ CNS	○ Normal to coma	○ Drowsy ○ CVA
➢ CVS	○ Hypotension (including postural changes) ○ Tachycardia	○ Myocardial infarction ○ Peripheral vascular disease ○ DVT
➢ Respiratory	○ Rate ↑ ○ Depth ↑ (kussmaul breathing) ○ Ketotic breath	○ Pulmonary embolus
➢ GI	○ Succussion splash (gastroparesis)	

Abbreviations: CVA, cerebrovascular accident; DKA, diabetic ketoacidosis; DVT, deep vein thrombosis; HONC, hyperosmolar non-ketotic coma

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 282.

Useful background: Drugs that can cause dysglycemia

- Atypical antipsychotic agents, e.g.
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Paliperidone
  - Risperidone

- Beta-adrenergic antagonists, e.g.
  - Atenolol
  - Metoprolol
  - Propranol[a]

- Diazoxide
- Glucocorticoids, e.g. prednisone
- Interferon alfa
- Isoniazid
- Niacin
- Pentamidine
- Protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tiprenavir)
- Tacrolimus
- Thiazide or loop diuretics, e.g.,
  - Furosemide
  - Hydrochlorothiazide

[a] Medication-induced dysglycemia should not preclude the se of these medications if clinically indicated

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 381.

Obesity

Useful background: WHO Classification of overweight and obesity in adults according to body mass index

Classification	BMI[a]	Risk of Comorbidities[b]
➢ Underweight	< 18.5	Mildly increased
➢ Normal	18.5-24.9	Average
➢ Overweight	25-29.9	Mildly increased
➢ Obese	≥ 30	
○ Class I	30-34.9	Moderate
○ Class II	35-39.9	Severe
○ Class III	≥ 40	Very severe

[a] Values are aged and gender independent
[b] Both BMI and a measure of fat distribution (e.g., waist circumference) are important in estimating the risk of comorbidities (type 2 diabetes, hypertension, dyslipidemia)

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 412.

Hypoglycemia

- Give a systematic approach to hypoglycemia.

➢ Functional

➢ Stomach
  ○ Rapid emptying (e.g. "dumping" syndrome)

➢ Liver disease

➢ Drugs/ toxins
  ○ Insulin
  ○ Oral hypoglycemias
  ○ Alcohol
  ○ Tobacco
  ○ ASA
  ○ Antihistamines

➢ Diet
  ○ Galactose
  ○ Fructose
  ○ Leucine

- Endocrine
  - Early diabetes
  - Hypothyrodism
  - Addison's disease
  - Pituitary failure

- Tumors
  - Insulinoma
  - Sarcoma (mediastinal, retroperitoneal)
  - Hepatocellular (HCC)
  - Adrenal tumor

- Hereditary
  - Inborn errors of metabolism

- Take a directed history and perform a focused physical examination in the adult to determine the causes of hypoglycemia.

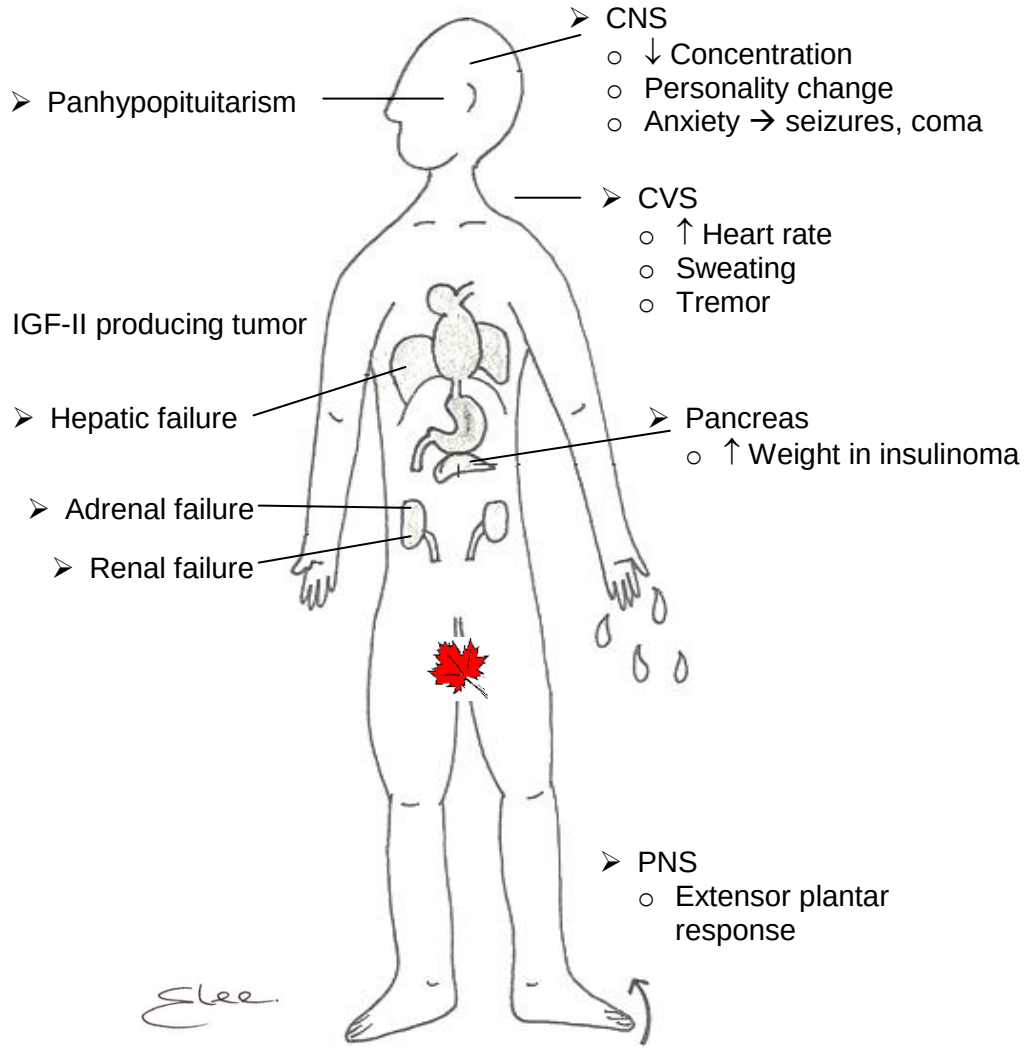
- Starvation and exercise
- Reaction to glucose ingestion
  - Functional
  - Early diabetes mellitus
  - Post gastrectomy
- B cell overactivity
  - Insulinoma
  - Hyperplasia
- Endocrine disease
  - Early diabetes mellitus
  - Hypothyroidism
  - Hypopituitarism
  - Hypoadrenalism
  - Insulinoma
  - B-cell hyperplasia
- Drugs
  - Insulin
  - Sulphonylureas and diguanides
  - Salicylates
  - Antihistamines
- Sensitivity to:
  - Leucine
  - Galactose, fructose
  - Alcohol
  - Tobacco

- Liver disease
  - Glycogen storage disease
  - Hepatoma
- Fibrosarcoma

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 93.

Useful background: Complications of hypoglycemia

Usually related to diabetic treatment



Abbreviations: CNS, central nervous system; CVS, cardiovascular system; PNS, peripheral nervous system

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 280.

- Definition: Diabetes is
  - A chronic metabolic disturbance…..a heterogeneous syndrome
  - Characterized by fasting and/or postprandial hyperglycemia
  - Caused by an absolute or relative lack of insulin, resistance to the action of insulin, or both
  - Complications involving small blood vessles (microangiography), larger blood vessels (macroangiopathy) and nerve damage (neuropathy), affecting multiple organs and systems.
  - Classification
    - T1DM (Type 1 diabetes mellitus)
      - Autoimmune destruction of pancreatic beta cells, resulting in an absolute deficiency of insulin
      - Often presents with acute metabolic symptoms

    - T2DM
      - Insulin resistance, with some insulin deficiency
      - (GDM) gestational diabetes mellitus – "….onset ot recognition of glucose intolerance in pregnancy…."
      - MODY (maturity-onset diabetes of the young
      - Damage / loss of pancreas from disease, drugs, infection, metabolic disorders, trauma, surgery

Diabetic Foot

- Definition:
  - The diabetic foot refers to the development of diabetic peripheral neuropathy leading to reduced sensation, leading to trauma, ulceration, infection, gangrene, and deformities (Charcot arthropathy) may develop.

<u>Thyroid disease</u>

Definition: Pemberton's sign " a reversible superior vena cava obstruction produced by a retroclavicular goitrous thyroid rising into the thoracic inlet"

- If after raising the hands above the head for 3 minutes the person does not develop signs or symptoms of SVC obstruction, the sign is negative.
- Other causes of SVC obstruction, such as lymphoma, or other tumors causing reversible may cause a positive Pemberten's sign, with blue/ pink face, dizziness, nasal congestion, obstruction of the thoracic outlet, dyspnea.

Source: Mangione S. *Hanley & Belfus* 2000, page 157

- Take a directed history for thyroid disease.

➢ Condition
  - Medications, allergies, smoking
  - History of major illnesses (especially autoimmune)
  - Hospitalizations/surgeries
  - Radiation exposure (especially neck)
  - Family history of multiple endocrine neoplasia, medullary cancer or other cancers/lumps
  - Person history of goiter or nodules
  - Family history of goitre or nodules

➢ History of HIV status/risk factors, smoking, alcohol, drug usage.

➢ Causes /associations
  - Diabetes mellitus
    - Polyuria, polydipsia, thirst, blurred vision, weakness, infections, groin itch, rash (pruritus vulvae, balanitis), weight loss, tiredness, lethargy, and disturbance of conscious state
  - Hypoglycemia
    - Morning headaches, weight gain, seizures, sweating
  - Primary adrenal insufficiency
    - Pigmentation, tiredness, loss of weight, anorexia, nausea, diarrhea, nocturia, mental changes, seizures (hypotension, hypoglycemia)
  - Acromegaly
    - Fatigue, weakness, increased sweating, heat intolerance, weight gain, enlarging hands and feet, enlarged and coarsened facial features, headaches, decreased vision, voice change, decreased libido, impotence.

➢ Complications
  - Goiter
    - Dysphagia
    - Neck swelling
    - Stridor
  - CNS
    - Fatigue, weakness, tremor
    - Dysphagia
  - GI
    - Diarrhea/constipation
    - Weight change
  - GU
    - Decreased menses or fertility
    - Polyuria

- Thyrotoxicosis
  - Preference for cooler weather
  - Weight loss
  - Increased appetite (polyphagia)
  - Palpitations
  - Increased sweating
  - Nervousness
  - Irritability
  - Diarrhea
  - Amenorrhea
  - Muscle weakness
  - Exertional dyspnea
- Hypothyroidism (myxedema)
  - Fatigue
  - Cold intolerance
  - Slowing of mental and physical performance
  - Hoarseness
  - Enlarged tongue
  - Slow pulse
  - Pericardial effusion
  - Anorexia
  - Weight gain
  - Constipation
  - Paresthesia
  - Slow speech
  - Muscle cramps
  - Slow relaxation of reflexes
  - Menorrhagia
  - Amenorrhea
  - Anovulatory cycles
  - Periorbital edema
  - Rough skin
  - Dry coarse hair
  - Anemia
- Differential diagnosis
  - Thyroid tumor (benign vs. malignant)
  - Goitre
  - Thyroid cyst
  - Thyroglossal duct cyst

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited*, 2003, Table 9.5, page 318; and Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 152 and 153.

- Perform a focused physical examination for thyroid disease.

- Neck mass
  - Inspection
    - Nutritional status
    - General appearance
    - Anatomical landmarks of thyroid
    - Mass, tenderness
    - Effect of swallowing
  - Palpation
    - Positioning, with and without swallowing
    - Gland size, consistency, tenderness and nodularity
    - Module location, size and number, character, tenderness
  - Auscultation
- Eyes
  - Chemosis (conjuntival edema) and hyperemia, periorbital edema
  - Corneal exposure with ulceration
  - Widening of the palpebral fissure (thyroid stare)
  - Lid retraction (widening of palpebral fissure) or lid lag on downgaze (von Graefe's sign)
  - Exophthalmos
  - Proptosis
  - Double vision
  - Visual loss from optic nerve compression and edema)
- Voice
  - Hoarse
  - Stridor
- CVS
  - Palpitations, hypertension, tachycardia
  - Deep tendon reflexes
- GI
  - Dysphagia
  - Diarrhea/constipation
  - Weight change
- CNS
  - Tremor
  - Weakness
  - Hypo-/ hyperreflexia
- Skin
  - Sweating
  - Pretibial, myxedema
  - Thinning of hair
  - Pigmentation

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.1, page 308; Table 9.2, page 311, Table 9.5, page 318; Baliga RR. *Saunders/Elsevier* 2007, page 353- 356; Jugovic PJ, et al. *Saunders/ Elsevier* 2004, page 152; Mangione S. *Hanley & Belfus* 2000, pages 81 and 82.

Useful background: The performance characteristics for palpation of the thyroid.

Sens (PID)	Spec (NIH)	PLR	NLR
70%	82%	3.8	0.37

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

- PLR (positive likelihood ratio) = sensitivity/ (1-specificity) [PID/ (1-NIH)] the finding is more likely with than without the target disorder (probability of disease increases)
- NLR (negative likelihood ratio) = 1- sensitivity/ specificity [(1-PID)/ NIH] the finding is less likely without than with the target disorder (probability of disease decreases)
- Sensitivity – PID (positive in disease)
- Specificity – NIH (negative in health)

PGT-BN

- Auscultate the thyroid gland of the patient has a goiter, or consideration of the patient having Grave's disease, or other symptoms/ signs of hyperthyroidism.
- Distinguish between venous hum (compress neck veins on that side), carotid bruit (different position than thyroid), aortic stenosis/ sclerosis.

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q1. From the clinical examination, how might you suspect that you are dealing with hypothyroidism due to pituitary failure, rather than primary failure of thyroid?

A1. Persons with hypopituitarism have

- Smooth skin
- Loss of body hair
- Long-term, there may be atrophy of the thyroid

Q2. The less important eponyms related to thyroid eye disease.

A2.

- Infrequent blinking – Stellwag's sign
- Tremor of gently closed eyelids – Rosenbach's sign
- Difficulty in everting upper eyelid – Gifford's sign
- Absence of wrinkling of forehead on sudden upward gaze – Joffroy's sign
- Impaired convergence of the eyes following close accommodation – Möbius' sign
- Weakness of at least one of the extraocular muscles – Ballet's sign
- Paralysis of extraocular muscles – Jendrassik's sign

Source: Baliga RR. *Saunders/Elsevier* 2007, page 36.

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q1. Under what circumstances may a bruit be head over a carcinoma of the thyroid?

A1. When the uptake of radioactive iodine into the papillary or follicular carcinoma has been enhanced by increasing the blood supply to the thyroid with a drub such as carbimazole.

Q2. What is the way on physical examination when you find a midline mass to distinguish between a thyroid lesion and a thyroglossal cyst?

A2. Both move on swallowing, but only the thyroglossal cyst moves when the tongue is protruded.

Q3. What is the way to demonstrate a laryngocele?

A3. A laryngocele may be demonstrated by performing the valsalva maneuver ("forced expiration against a closed glottis [bearing down], which increased intrathoracic and central nervous pressure, pushing on the diverticulum and making it more prominent in the area of the hyoid and thyroid cartilages.

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q1 Distinguish clubbing and bony enlargement from thyroid acropachy from pulmonary hypertrophic osteoarthropathy (periostits)

A1.
- Thyroid periostitis – hands and feet, asymptomatic
- Pulmonary hypertrophic osteoarthropathy – long bones

Source: Mangione S. *Hanley & Belfus* 2000, page 163.

Q2. In the context of thyroid disease, what is Berry's sign?

A2 Berry's sign is the loss of the carotid pulse due to a thyroid malignancy causing enlargement of the thyroid to the point of blocking the carotid artery.

Q3. What is the usual cause of unilateral proptosis?

A3. Malignancy, not Grave's disease (bilateral in 95%, thus unilateral in only 5%)

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q. In the context of examining the thyroid gland, distinguish between Oliver's sign, Cardarelli's sign, and Campbell's sign

A.

- Oliver's sign
  - "tracheal tug"
  - Downward displacement of the cricoids cartilage with each contraction of the ventricles
  - In a person with an aneurysm of the aortic arch each systolic ejection is transmitted by the dilated aortic arch onto the left bronchus, and from the left main bronchus to the trachea, pulling it downwards with each contraction of the ventricles.
- Cardarelli's sign
  - When pressing on the thyroid cartilage to displace the thyroid to the left, a transverse pulsation is noted from the contact created between the left bronchus and the aorta, suggesting an aneurysm of the aortic arch.
- Campbell's sign
  - When breathing in , the cartilage of the thyroid moves downwards (tracheal tug)
  - Associated with chronic obstructive pulmonary disease (COPD)
  - The degree of downward displacement ("tug") on the cartilage and therefore on the thyroid and the trachea
  - In COPD, there is strong contraction of the diaphragm, which pulls on the trachea during inspiration.

Remember, thyrotoxicosis may be due to

- Graves' disease – diffuse hyperplasia of thyroid gland
- Toxic nodule (adenoma, single or multiple)

Trick Questions!

- Which signs of Grave's disease are not due to the associated hyperthyroidism?
  - Pretibial myxedema
  - Exophthalmos
- Which two functional thyroid disorders are associated with pretibial myxedema?
  - Grave's disease
  - Hypothyroidism
- In the patient with diffuse thyromegaly and unilateral proptosis, what are the causes of the ophthalmopathy?
  - Although bilateral proptosis is the commonest cause of proptosis in adults, unilateral proptosis occurs in only 5% of Grave's patients, so the correct answer is – lack for a cause of unilateral proptosis other than Grave's disease.

SO YOU WANT TO BE A GOOD GENERAL PHYSICIAN!

Q1. In the context of the eyebrows, what is Queen Anne's sign?

A1. Thinning of the hair of the eyebrows

Q2. What conditions other than cosmetic practice and hypothyroidism are associated with thinning of the eyebrows?

A2.
- Systemic Lupus Erythematosis (SLE)
- Miscellaneous drugs and skin diseases

Q3. Stump the staff! How do you distinguish between thinning of the brows from SLE versus hypothyroidism?

A3. In hypothyroidism, it is the later portion of the brow which is thinned. Adapted from: Mangione S. *Hanley & Belfus* 2000, page 11.

Q4. What is thyroid acropacly, and how is it distinguished from a pulmonary etiology?

A4.

	Thyroid	Pulmonary
○ Painful periostitis	No	✓
○ Long bones	No	✓
○ Hands, feet	✓	No

Thyroid nodule and goiter

Definition: Goiter, a chronically enlarged thyroid gland due to hypertrophy or degeneration, not due to neoplasia or inflammation, and the term goiter does not reflect the functional status of the gland.

- The performance characteristics of physical examination for detecting goiter are good
  - Sensitivity 70% (95% CI = 68 to 73%)
  - Specificity 82% (95% CI = 79 to 85%)
  - PLR = 3.8
  - NLR = 0.37

	➢ For assessing thyroid size PLR
o Normal (0-20 gm)	0.15
o Small (1-2x normal: 20 to 40 gm)	1.9 (size tends to be overestimated)
o Large > 2x normal (> 40 gm)	25 (size tends to be underestimated)

These characteristics are not influenced by the presence of thyroid nodules.

- A bruit auscultated over a goiter is highly suggestive of Graves disease, (↑ vascularity), but not for other causes of hyperthyroidism.

- Give 4 causes of a bruit in the neck.
  - Grave's thyrotoxemia
  - Venous hum
  - Carotid bruit
  - Aortic stenosis/ sclerosis

- Take a directed history and perform a focused physical examination to determine if a thyroid nodule is likely to be malignant.

- History
  - Age < 30 years old or > 60 years old
  - Single nodules
  - History of head or neck irradiation
  - Compressive symptoms (pain, dysphagia, stridor, hoarseness)

- Physical exam
  - Fixed and firm solitary nodule with enlarged regional lymph nodes

- Type of thyroid disease
  - Benign nodules
    - Hashimoto's thyroiditis
    - Hürthle adenoma
    - Follicular adenoma
    - Multinodular goitre
  - Malignant nodules
    - Papillary
    - Follicular
    - Medullary, anaplastic
    - 1˚ lymphoma
    - Metastatic (breast or kidney tumors)

- Causes of a diffuse goitre (patient often euthyroid)
  - Idiopathic (majority)
  - Puberty or pregnancy
  - Thyroiditis
    - Hashimoto's
    - Subacute (gland usually tender)
  - Simple goitre (iodine deficiency)
  - Goitregens, e.g. iodine excess, drugs (lithium, phenylbutazone)
  - Inborn errors of thyroid hormone synthesis, e.g. Pendred's syndrome (an autosomal recessive condition associated with nerve deafness)

- Causes of a solitary thyroid nodule
  - Benign
    - Dominant nodule in a multinodular goitre
    - Degeneration or hemorrhage into a colloid cyst or nodule
    - Follicular adenoma
    - Simple cyst (rare)
  - Malignant
    - Carcinoma – primary or secondary)e.g. renal wall carcinoma)
    - Lymphoma (rare)

- Ultrasound
  - Solitary nodule
  - Irregular halo
  - Hypoechoic
  - Punctuate calcification
  - Increased blood flow

Adapted from: Scenarios for directed histories and physical examinations, Fundamental clinical situations, page 152 and 153; Talley N. J., et al. Clinical Examination: a Systematic Guide to Physical Diagnosis. *Maclennan & Petty Pty Limited*, East gardens, Australia, 2003, Table 9.3, page 314.

Useful background: Likelihood ratios for palpable thyroid gland indicating a goiter

➢ Palpable thyroid	PLR	NLR
○ Adults*	3.8	0.37
○ Children	3.0	0.30
○ Pregnancy	4.7	0.08

* Sensitivity 70% (95% CI 68%-73%), Specificity 82% (95% CI 79%-85%)

Source: Simel DL, et al. *JAMA* 2009 Chapter 21, Table 21-10, page 287.

Useful background:

- ➢ A normal thyroid gland weighs <20 gm (in iodine non-deficient regions), and is usually not palpable
- ➢ Goiter does not reflect function or neoplasia; goiter is hypertrophy or degeneration of the thyroid gland, with normal or abnormal thyroid function.
- ➢ Pemberton's sign
  - ○ Hands above the head for 30 min causing
    - Blue/ pink face/ neck from venous stasis and ↑JVP
    - Head congestion, dizziness, stiffness
  - ○ From a retrosternal goiter, or any cause of reversible SVC syndrome (tumor)
- ➢ Compression complications of a thyroid goitre
  - ○ Trachea (stridor)
  - ○ Esophagus (dysphagia)
  - ○ Recurrent laryngeal nerve (palsy)

- Take a directed history for the factors which increase the pretest probability of a goiter being present.

- ➢ Children, especially those in endemic iodine deficiency locales
- ➢ Pregnant and lactating women
- ➢ Elderly patients
- ➢ Symptoms of hyperthyroidism or hypothyroidism
- ➢ Patients with excessive radiation exposure
- ➢ Patients with Down Syndrome

Source: Simel DL, et al. *JAMA* 2009 Chapter 21, page 287.

- Perform a focused physical examination to distinguish between Grave's disease (GD) and Toxic Nodular Goitre (TNG).

Sign	GD	TNG
➢ Age	○ Younger	- Older
➢ Thyroid	○ Diffuse goiter	- Nodular, enlarged thyroid gland
➢ Eye signs	○ Common	- Rare
➢ Atrial fibrillation	○ Rare	- Common (~40%)
➢ Associated autoimmune disease	○ Common	- Rare

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 369.

- Perform a focused physical examination for Grave's disease.
    - ○ Symptoms and signs of hyperthyroidism
    - ○ Diffuse goiter
    - ○ Pretibial myxedema
        - Local thickening of the skin due to infiltration of lymphocytes, other inflammatory cells, as well as mucopolysaccharides
        - May be itchy
        - May be pigmented
    - ○ Thyroid ophthalmopathy
        - Exophthalmos
        - Proptosis (> 18mm forward protrusion of the age) (bilateral in 95%)
        - Congestion
            - Conjunctivitis
            - Chemosis
            - Periorbital edema
            - Papilledema
            - Optic atrophy
        - Ophthalmoplegia
            - Medial rectus
            - Inferior rectus
            - Amblyopia ↓ gaze upwards ↓ convergences
            - Double vision
            - ↓ usual acuity ↓ blinking
            - Tremor of upper eyelids when eyes are closed
            - Brown pigment on eyelids
    - ○ Association with other autoimmune disorders
        - Hyper-/ hypopigmentation (vitiligo)
        - Premature greying (!)

- Miscellaneous - Plummer's nails
  - Separation of the nail from the nailed (onycholysis)
  - Separation is usually in the 4th digit

Pretibial myxedema is not caused by hyperthyroidism; i.e. is not related to the active thyroid; PM is only an association.

Hypothyroidism

- Definition: "Hypothyroidism is a clinical syndrome that usually results from a deficiency of thyroid hormone, [OR] rarely it can be due to resistance to thyroid hormone". (Lochnan H, et al. Chapter 30. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 365).

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Q4. With the development of thyroid-stimulating immunoglobulins, the TSH receptors are activated and hyperthyroidism (Graves' disease) develops. This often associated with eye disease as well as pretibial myxedema. Treatment with propylthiouracil (PTU) is usually indicated.

Give the recommended monitoring when a woman with Graves' disease, on PTU, becomes pregnant.

A4.
- Untreated hyperthyroidism in mother
  - ↑ risk of fetal loss
- Hyperthyroidism in mother, pregnant mother treated with
  - Eurothyroid
  - Titre of stimulating thyroid antibodies may still be increased and cause hyperthyroidism in the fetus
- Same as above, but over treatment of hyperthyroidism in mother, using PTU
  - Hypothyroidism may develops in fetus

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Q1. An increased serum TSH (thyroid-stimulating hormone) is usually a sensitive indicator of hypothyroidism.

- Give two clinical situations in which the patient may be clinically hypothyroid, but the TSH concentration is normal or low, rather than increased.

A1. In the patient with clinical hypothyroidism, the TSH may be normal or low in disease of the pituitary (secondary hypothyroidism) or hypothalamus (tertiary hypothyroidism).

Q2. Define "subclinical hypothyroidism", and give 4 indications for it to be treated.

A2.
- Definition: "Subclinical hypothyroidism is defined by an elevated TSH with normal thyroid hormone levels" (Lochnan H, et al. Chapter 30. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 365).

- Indications for treatment of subclinical hypothyroidism:
  - ↑↑ TSH (> 10 mU/L)
  - Symptoms of hypothyroidism
  - Anti-TPO (anti-thyroid peroxidase) positive
  - Abnormal lipid profile
  - Planned pregnancy

Q3. On the basis of TSH (thyroid-stimulating hormone), anti-TPO (thyroid peroxidase antibodies), fT_3 (free triiodothyronine) and fT_4 (free thyroxin), distinguish primary (1^o), hypothyroidism from secondary (2^o) and tertiary (3^o) hypothyroidism, and from resistance to thyroid hormone.

A3.

	Causes of Hypothyroidism		
	1^o	2^o / 3^o	Resistance
➢ TSH	↑	↓ / N	↑
➢ Anti-TPO	+	-	
➢ fT_4	↓	↓	↑

Useful background: Causes of hypothyroidism

Cause	Comments
➢ Hashimoto's thyroiditis	o Most common cause o Anti-PO leels very high
➢ Hypothyroid phase of subacute thyroiditis	o Usually transient
➢ Congenital	o Aplasia of thyroid o Dyshormogenesis
➢ Iodine deficiency	o Rare in North America
➢ Recovering phase of non-thyroidal illness	o Transiently elevated TSH
➢ Pituitary disorder	o Secondary hypothyroidism o TSH low or normal o fT_4 usually low
➢ Hypothalamic disorder	o Tertiary hypothyroidism o TSH low or normal o fT_4 usually low
➢ Resistance to thyroid hormone	o High TSH, fT_3 and fT_4

Abbreviations: anti-TPO, thyroid peroxidase antibodies; fT_3, free triiodothyronine; fT_4, free thyroxine

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 366.

Thyroid nodules

Q. The patient with a thyroid nodule may have a normal, increased or decreased TSH level. A thyroid scan and a FNAB (fine needle aspiration biopsy) may be necessary to help determine if the nodule is malignant, and if surgical resection is indicated. It is suggested to "….consider surgery if 2 or more risk factors for malignancy are present" (Lochnan H, et al. Chapter 30. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 372).

- Give the risk factors for thyroid cancer.

A.
- The patient
  - < 20 or > 60 years of age
  - Male
  - Previous
    - Malignancy
    - Radiation exposure
  - Family history of thyroid cancer
- The nodule
  - Nodule
    - > 4 cm
    - Becoming rapidly larger
    - Fixed to soft tissue
  - Spread
    - Vocal cord paralysis
    - Lymphadenopathy

- Perform a focused physical examination for hypothyroidism.

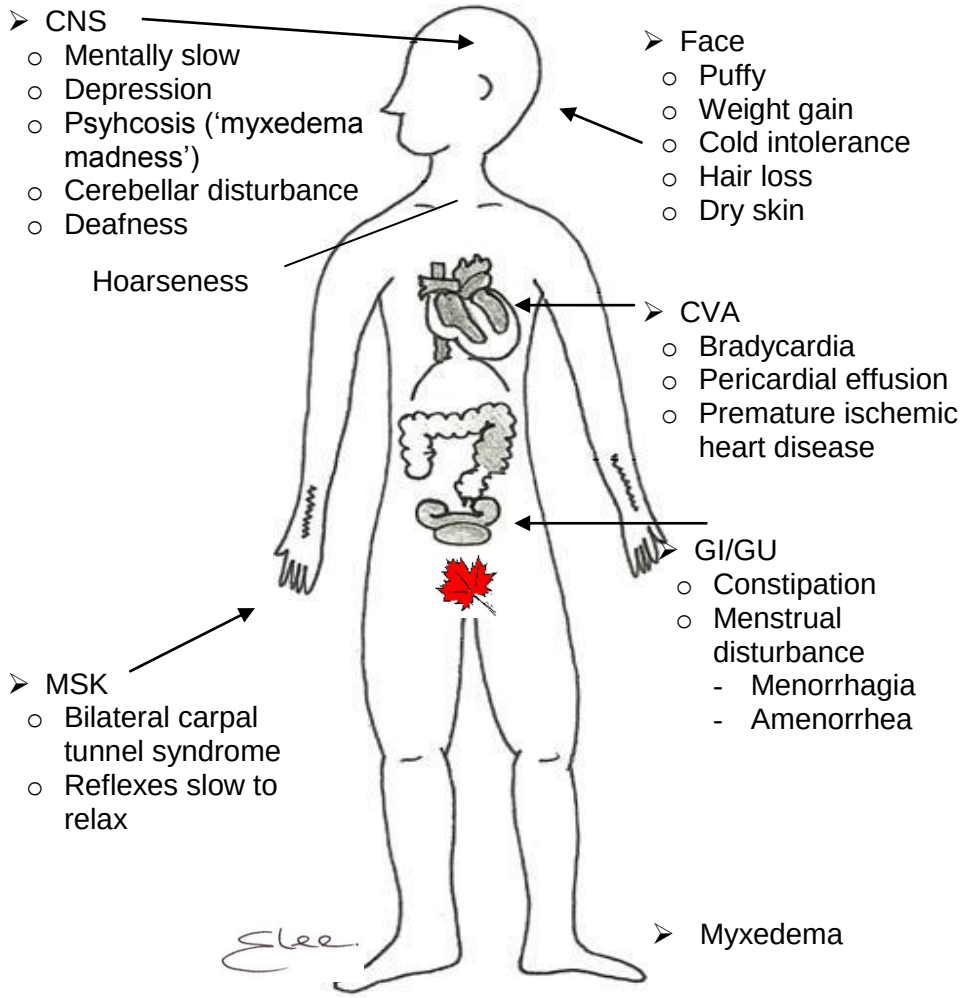
- Face
  - Weight gain
- Eyes
  - Periorbital and facial puffiness, lose of outer portion of eyebrows
- Skin/hair
  - Coarse, sandpaper like , dry, hair breaks easily
- Nails
  - Thick
- Hands
  - Doughy skin (glucosaminoglycan deposit)
- Mood
  - Lethargic, disinterested
- CNS
  - Slow reflex relaxation
  - Cerebellar syndrome
  - Psychosis
  - Coma
  - Unmasking of myasthenia gravis
  - Cerebrovascular disease
  - High cerebrovascular fluid protein
  - Nerve deafness
  - Peripheral neuropathy
- MSK
  - Entrapment, carpal tunnel, tarsal tunnel
  - Muscle cramps

- Proximal myopathy
- Hypokalemic periodic paralysis

- CVS
  - Bradycardia
  - CCF

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.5, page 318; Table 9.6, page 319; and Mangione S. *Hanley & Belfus* 2000, page 164.

Useful background: Physical examination for hypothyroidism.



Abbreviations: CNS, central nervous system; CVS, cardiovascular system; GI/GU, gastrointestinal/ genitourinary; MSK, musculoskeletal

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 234.

Useful background: Performance characteristics of physical findings for hypothyroidism

- Periorbital puffiness and slow movements (> 1 minute to fold a bed sheet) are not clinically significant physical findings for hypothyroidism.

Finding	PLR
➢ Skin	
o Cool and dry skin	4.7
o Coarse skin	3.4
o (Cold palms)	
o (Dry palms)	
o Puffiness of wrists	2.9
o Hair loss of eyebrows	1.9
o (Pretibial edema)	
➢ Speech - slow "Hypothyroid" speech	5.4
➢ Pulse <60 bpm	4.1
➢ Thyroid enlarged	2.8
➢ Neurologic	
o Delayed ankle reflexes	3.4

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

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 22.3, page 263.

Useful background: The causes of hypothyroidism

- Primary
  - Without a goitre (decreased or absent thyroid tissue)
    - Idiopathic atrophy
    - Treatment of thyrotoxicosis, e.g. iodine, surgery
    - Agenesis or a lingual thyroid
    - Unresponsiveness to TSH
    - Elderly people; inhibitory autoantibody to TSH
  - With a goiter (decreased thyroid hormone synthesis)
    - Chronic autoimmune diseases, e.g. Hashimoto's thyroiditis
    - Drugs, e.g. lithium, amiodarone
    - Inborn errors (enzyme deficiency)
    - Endemic iodine deficiency or iodine-induced hypothyroidism
    - Riedel's thyroiditis

- Secondary
  - Pituitary lesions

- Tertiary
  - Hypothalamic lesions

- Transient
  - Thyroid hormone treatment withdrawn
  - Subacute thyroiditis
  - Postpartum thyroiditis

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.5, page 318; Davey P. *Wiley-Blackwell* 2006, page 284.

Useful background: Billewicz diagnostic index for hypothyroidism

Finding	Points scored if finding is Present	Absent
SYMPTOMS		
Diminished sweating	+6	-2
Dry skin	+3	-6
Cold intolerance	+4	-5
Weight increase	+1	-1
Constipation	+2	-1
Hoarseness	+5	-6
Paresthesia	+5	-4
Deafness	+2	0
PHYSICAL SIGNS		
Slow movements	+11	-3
Coarse skin	+7	-7
Cold skin	+3	-2
Periorbital puffiness	+4	-6
Pulse rate <75/ min	+4	-4
Slow ankle jerk	+15	-6

Source: McGee SR. *Saunders/Elsevier* 2007, Table 22-1, page 264.

Finding	Sensitivity (%)	Specificity (%)	PLR	NLR
Billewicz score				
Less than –15 points	3-4	28-68	0.1	-
-15 to +29 points	35-39	…	NS	-
+30 points or more	57-61	90-99	18.8	-

Source: McGee SR. *Saunders/Elsevier* 2007, Box 22-3, page 263.

- Give a systematic approach to the causes of hypothyroidism.

- Thyroid
  - Primary failure
  - Hashimoto's disease (autoimmune thyroiditis)
- Pituitary
  - Primary failure, causing hypothyroidism
- Treatment/ surgery
  - Thyroidectomy
  - Treatment of hyperthyroidism
- Diet
  - Long-term iodine deficiency
- Hereditary
  - Autosomal recessive
  - Homozygote has thyromegaly and hypothyroidism

Hyperthyroidism

Useful background: Causes of hyperthyroid

Cause	Comments
➢ Grave's disease	○ Due to thyroid-stimulating immunoglobulins activating the TSH receptor; most common cause of hyperthyroidism ○ Patients frequently have eye disease and possibly pretibial myxedema. ○ RAIU is elevated and thyroid scan with pertechnetate or ^{123}I shows a diffuse pattern.
➢ Subacute thyroiditis	○ Scan poorly defines the gland ○ RAIU is very low
➢ Postpartum thyroiditis	○ Scan poorly defines the gland ○ RAIU is very low (not recommended if patient is lactating)
➢ Toxic nodule	○ Thyroid scan shows hot area
➢ Toxic multinodular goitre	○ Scan shows multiple hot areas. ○ RAIU is slightly elevated.

Cause	Comments
➢ Iodine excess	○ Usually in setting of multinodular goiter. ○ RAIU is low.
➢ Iatrogenic	○ Due to over-treatment with thyroid hormones; scan shows no thyroid; 0% RAIU
➢ Struma ovarii	○ Very rare ○ Thyroid hormone production in ectropic sites ○ RAIU is 0% ○ Body scan will show thyroid tissue in ovary.
➢ Metastatic thyroid cancer	○ With large tumor burden
➢ TSH-producing pituitary adenoma	○ TSH elevated
➢ Stimulation of TSH receptor by excessive human chorionic gonadotropin	○ Examples are – Hydatidiform mole – Hyperemesis gravidarum – Other tumors

Abbreviations: RAIU, radioactive iodine uptake; TSH, thyroid-stimulating hormone

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 368.

- Perform a focused physical examination to distinguish between Grave's disease from other causes of a diffuse enlargement of the thyroid gland and evidence of hyperthyroidism.
    - Pretibial myxedema
        - Local infiltration of the skin
        - May be pigmented or pruritic
    - Ophthalmopathy (exophthalmos)
        - Proptosis/ strabismus (involvement of medial and inferior rectus muscles)
        - Amblyopia
        - ↓ convergence
        - ↓ visual fields

- Thyroid bruit
- Signs of autoimmune disorders
  - Vitiligo
  - Premature graying
  - Hyperpigmentation
- Onycholysis (Plummer's nails: may be seen in other causes of hyperthyroidism)

- Perform a focused physical examination for hyperthyroidism.

➢ Face
- Anxious, nervous, restless, frightened faces, energetic

➢ Eyes
- Stare
- Wide palpebral fissures
- Lid lag
- Inability to wrinkle brow on upward gaze
- Opthalmopathy
- Exophthalmos (forward protrusion of eyeball >18 mm from the orbit)
- Conjunctivitis
- Conjunctival edema (chemosis)
- Periorbial edema
- Papilledema optic atrophy
- Extraocular defects
  - Muscle weakness
  - Amblyopia
  - Impaired upward gaze
  - Impaired convergence
  - Strabismus
  - Restricted gaze and visual acuity
  - Visual field competence defects

➢ Mood
- Apathy, depressed mood (especially in elderly)

➢ Skin/Hair
- Fine skin and hair
- Hyperpigmentation at pressure points
- Pretibial myxedema (non-pitting edema, pigmented, pruritic); note: myxedema of hypothyroidism is more general
- Warm, moist, velvety skin

- Nails
  - Broken
  - Onycholysis (Plummer's nails, IVth digit, separation of nail from nail bed)

- Hands
  - Palmar erythema
  - Fine tremor
  - Thyroid periostitis

- CNS
  - Hyperreflexia
  - Fine tremor

- GI/ GU
  - Diarrhea
  - Amenorrhea

- Muscle
  - Myopathy
  - Proximal muscle weakness

- Heart
  - Cardiomyopathy
  - CCF (high output)
  - Atrial fibrillation
  - Flow murmur
  - Tachycardia
  - Increased pulse pressure

- Lung
  - Means-Lerman scratch sound (high-pitch pulmonic sound similar to pericardial rub)
  - Primary
    - Graves' disease
    - Toxic multinodular goitre
    - Toxic uninodular goitre: (usually a toxic adenoma)
    - Hashimoto's thyroiditis (thyrotoxicosis early in its course; later H thyroiditis causes hypothyroidism)
    - Subacute thyroiditis (transient)
    - Postpartum thyroiditis (non-tender)
    - Iodine-induced ('Jod-Basedow' phenomenon – iodine given after a previously deficient diet)

- Secondary
  - Pituitary (very rare): TSH hypersecretion
  - Hydatidiform moles or choriocarcinomas: by HCG secretion (rare)
  - Struma ovarii (rare)
  - Drugs, e.g. excess thyroid hormone ingestion, amiodarone

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9-5, page 318; Table 9.6, page 319; and Mangione S. *Hanley & Belfus* 2000, page 163 and 164.

- Perform a focused physical examination for thyroid ophthalmopathy.

➢ Eyelid	○ Retraction ○ Upper eyelid lag on downward gaze ○ Tremor (closed eyelid) ○ ↓ blinking
➢ Conjunctiva	○ Edema ○ Hyperemia
➢ Cornea	○ Erosion / ulceration
➢ Orbit	○ Oxophthamos (aka proptosis)
➢ Optic nerve	○ Visual loss (optic nerve edema and compression)
➢ Extraocular motility	○ Impaired

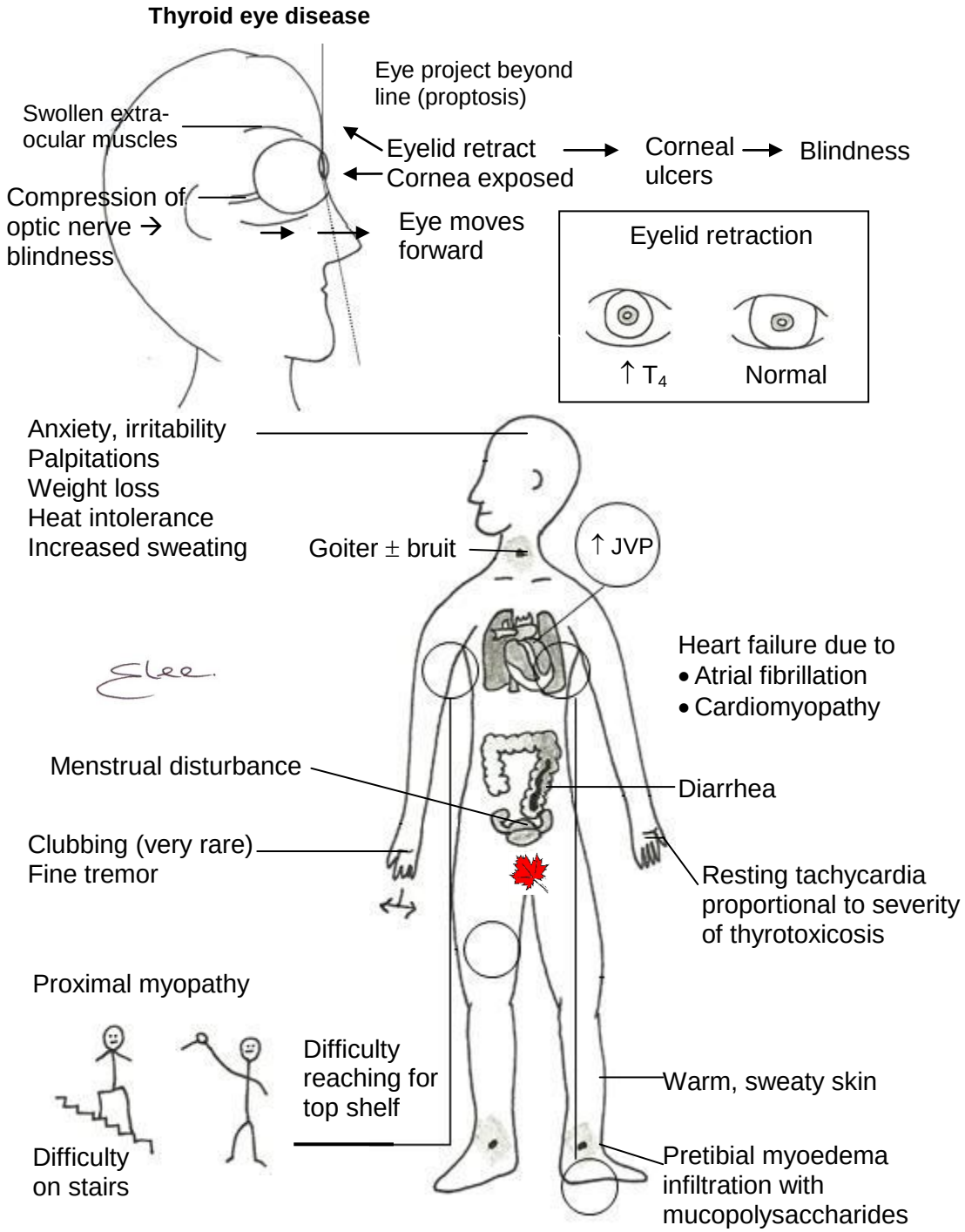
Source: Mangione S. *Hanley & Belfus* 2000, pages 81 and 82

Useful background: Performance characteristics of physical findings for hyperthyroidism

Finding		PLR
➢ Pulse	○ Pulse > 90 beats/min	4.4
➢ Skin	○ Moist and warm	6.7
➢ Thyroid	○ Enlarged thyroid	2.3
➢ Eyes	○ Eyelid retraction	31.5
	○ Eyelid	17.6
➢ Neurologic	Fine finger tremor	11.4

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 22-4, page 268.

Useful background: Complications of hyperthyroidism



Adapted from: Davey P. *Wiley-Blackwell* 2006, page 278.

Finding	Sensitivity (%)	Specificity (%)	PLR
➢ Wayne index			
○ <11 points	1-6	13-32	0.04
○ 11-19 points	12-30	…	NS
○ >20 points	66-88	92-99	18.2

Source: McGee SR. *Saunders/Elsevier* 2007, Box 22-4, page 268.

Useful background: Wayne diagnostic index for hyperthyroidism*

Symptoms of recent onset or increased severity	Present	Signs	Present	Absent
○ Dyspnea on effort	+1	○ Palpable thyroid	+3	-3
○ Palpitations	+2	○ Bruit over thyroid	+2	-2
○ Tiredness	+2	○ Exophthalmos	+2	
○ Preference for heat	-5	○ Lid retraction	+2	
○ Preference for cold	+5	○ Lid lag	+1	
○ Excessive sweating	+3	○ Hyperkinetic movements	+4	-2
○ Nervousness	+2			
○ Appetite increased	+3	○ Fine finger tremor	+1	
○ Appetite decreased	-3	○ Hands:		
○ Weight increased	-3	- Hot	+2	-2
○ Weight decreased	+3	- Moist	+1	-1
		○ Casual pulse rate:		
		- Atrial fibrillation	+4	
		- <80, regular	-3	
		- 80-90, regular	0	
		- >90, regular	+3	

Useful background: Causes of hyperthyroidism

➢ Graves' Disease

➢ Goiter
- Multinodular
- Uninodular (usually an adenoma)
- Toxic uninodular goiter (usually a toxic adenoma)

- Thyroiditis
  - Hashimoto's
  - Subacute
  - Postpartum

- Drugs
  - Iodine (after previous dietary deficiency)
  - Thyroxine excess
  - Amiodosone

- Tumor
  - Pituitary (TSH production)
  - Ovarian (struma ovarii; extrathyroidal T4)
  - Hydatid moles; choriocarcinoma (HCE secretion)

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.5, page 318.

Useful background: Causes of exophthalmos

- Bilateral
  - Graves' disease

- Unilateral
  - Cavernous sinus thrombosis
  - Tumors of the orbit, (e.g. dermoid, optic nerve glioma, neurofibroma, granuloma)
  - Pseudotumors of the orbit
  - Graves' disease

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.4, page 316.

- Perform a focused physical examination of the eye in a patient with thyrotoxicosis.

- Eyeball
  - Exophthalmos
  - When eyeball looking down, the eyelid stops moving down (Boston sign)
  - When looking up, upper lids move upwards faster than eyeball (Kocher sign)

- Eyelids
  - Retraction (Dalrymple sign) – sclera visible above the upper limbus of the cornea

- Lag – with movement, the lid lags behind the eyeball (von Graefe sign)
- ↓ blinking (Stellway sign)
- Tremor of closed eyelids (Rosen bach sign)
- ↑ pigmentation of eyelid margins (Jellink sign)
- Upper eyelid difficult to (Gifford sign)
- Upper eyelid difficult to move downward (Grove sign)
- ↑ fullness of eyelid (Enroth sign)
- Sclera - visible between the lower eyelid and lower limbs of cornea

- Muscle
  - ↓ movement of eyeball due to extraocular muscle involvement
  - ↓ convergence (Mobius sign)

- Cornea
  - ↓ strength of 1 or more extraocular muscles (Ballet sign)

- Optic nerve
  - ↓ vision
  - Paralysis (Jendrassik sign)
  - ↓ fixation on lateral gaze (Suker sign)

- Forehead muscle
  - ↓ wrinkling on quickly gazing upward (Joffroy sign)

- Pupils
  - Jerky contraction to consensual light (Cowen sign)
  - Unequal dilation (Knie sign)

Take a directed history for multinodular goiter

- Face – redness upper raising arms above head (Permberten's sign, suggesting a retrosternal goiter)

- Ears VIII involvement → deafness

- Larynx
  - Hoarseness → pressure on/ damage to recurrent laryngeal nerve

- Trachea
  - Stridor

- Esophagus
  - Dysphagia

- Thyroid
  - Multinodular goiter
  - May have painful enlargement
  - Symptoms of thyrotoxicosis (mention atrial fibillation)

Adrenal disease

- Take a directed history for the causes of hypoadrenalism (Addison's disease).

- Acute
  - Septicemia (especially meningococcal)
  - Adrenalectomy
  - Any stress in a patient with chronic hypoadrenalism or abrupt cessation of prolonged high-dose steroid therapy

- Chronic
  - Primary
    - Acute or chronic gland destruction
      - Idiopathic atrophy (Addison's disease)
      - Infection: TB, fungal
      - Infiltration: metastasis, amyloidosis, etc.
      - Hemorrhage (especially Waterhouse-Friderichsen syndrome)
      - Surgery
    - Metabolic failure
      - Virilizing hyperplasia, e.g. C21-hydroxylase deficiency
      - Enzyme inhibitors, e.g. metopirone
      - Drugs, e.g. OPDDD (cytotoxic)
      - Drugs (warfarin)
  - Secondary
    - Hypopituitarism
    - Suppression of hypothalamic-pituitary axis
      - Exogenous glucocorticoids
      - Endogenous glucocorticoids, e.g. Cushing's syndrome following tumor removal

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.10, page 327; Davey P. *Wiley-Blackwell* 2006, page 290; and Burton JL. *Churchill Livingstone* 1971, page 96.

- Perform a focused physical examination for Addison's disease

- General
  - Weight loss
  - Depression
- Skin
  - Pigmentation
    - Hands
    - Mouth & hips
    - Covered areas (e.g. collars, nipples, ring)
    - scars
  - Vitiligo
- Hair
  - ↓ pubic & axillary hair

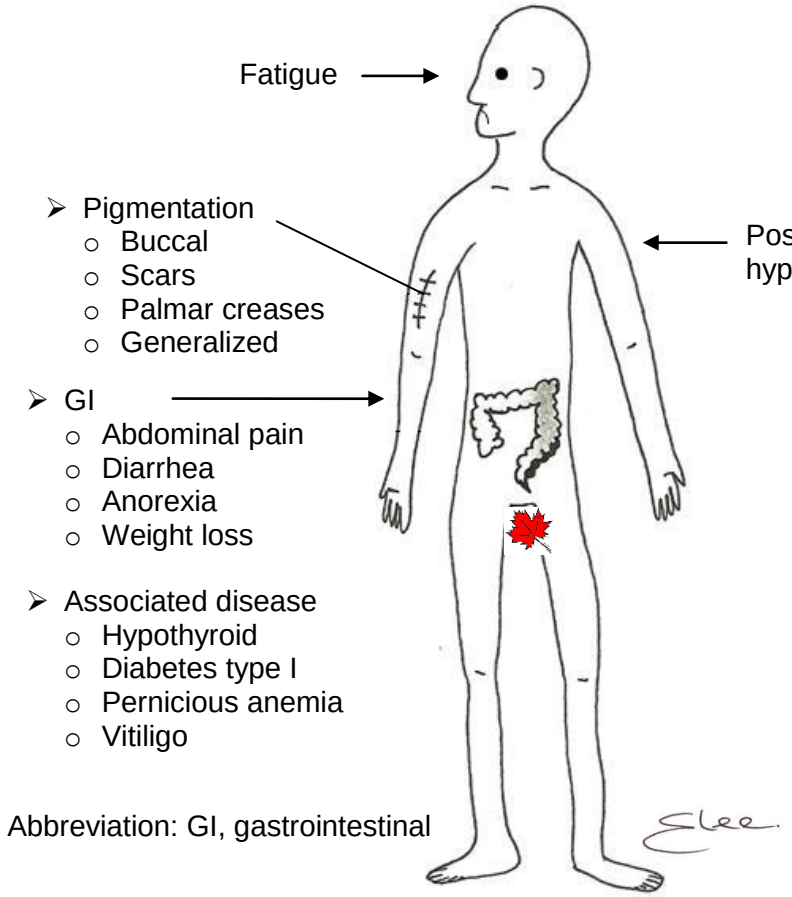
- CVS
  - ↓ BP, postured hypotension
  - Small heart
- Causes
  - TB
  - HIV
  - Metastases
- Associated autoimmune conditions (e.g. thyroiditis [Hashimoto], B12 deficiency [pernicious anemia])

- Perform a focused physical examination for disorders associated with hyperpigmentation.

- General
  - Hereditary (racial)
- Liver
  - PBC
  - Hemochromatosis
- Kidney
  - Uremia
- Intestinal/ nutritional
  - Malabsorption
  - Carotenemia
  - Protein-caloric malnutrition
  - Alcoholism
- Metabolic
  - Porphyria cutanea tarda
  - Ectobic ACTH

- Give a systematic approach to the causes of Addison's disease.
  - Idiopathic atrophy of adrenal cortical tissue
  - Sudden withdraw/ of therapeutic use of steroids
  - Infiltration
    - TB amyloid
    - Sarcoidosis
    - Hemorrhage
  - Infarction

- Perform a focused physical examination for hypoadrenalism (Addison's disease).



Adapted from: Davey P. *Wiley-Blackwell* 2006, page 290.

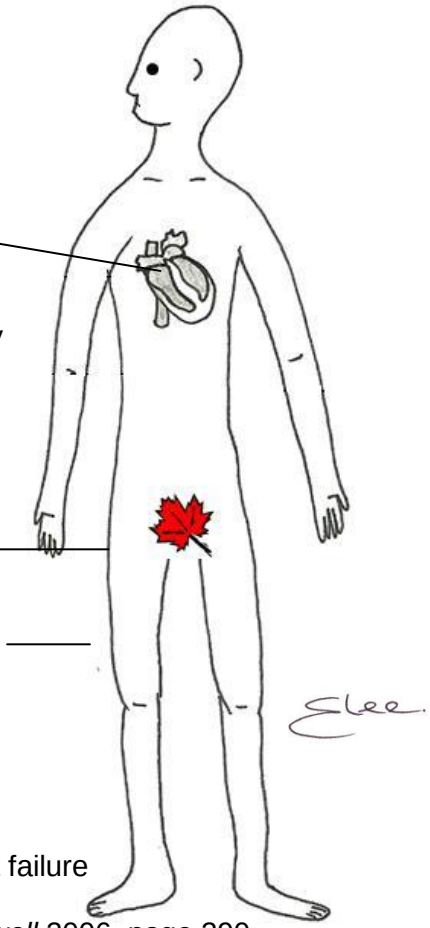
SO YOU WANT TO BE ENDOCRINOLOGIST!

Q. In the context of Addison's disease (AD), what are the Schmidt, polyglandular and all grove syndromes?

A.
- Schmidt syndrome
  - AD plus hypoparathyroidism
- Polyglandular (PGS), type I
  - AD, plus hypoparathyroidism, plus chronic mucocutaneous candidiasis
- Allgrove syndrome
  - AD* plus Achiolasia, plus alacrima, plus neurological disease

*AD; AD from loss of adrenal sensitivity to ACTH
Abbreviation: T_1DM, type I diabetes mellitus

- Perform a focused physical examination for pheochromocytoma (catecholamine-secreting tumor).



Abbreviations: CHF, congestive heart failure

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 290.

- Give a systematic approach to the causes of Cushing's syndrome.
  - Bilateral adrenal hyperplasia with or without increased pituitary ACTH
  - Benign adenoma of adrenal gland
  - Adrenal carcinoma
  - Carcinoma of bronchus, thymus

Useful background: Causes of Cushing's syndrome

- Adrenocorticotropic hormone (ACTA) dependent
- Exogenous administration of excess steroids or ACTH (most common)

- Adrenal hyperplasia
  - Secondary to increased pituitary ACTH production (Cushing's disease)
    - Microadenoma
    - Macroedema
    - Pituitary-hypothalamic dysfunction
  - Secondary to ACTH-producing tumors (e.g. small cell lung carcinoma)

- Adrenal neoplasia
  - Adenoma
  - Carcinoma (rare)

- Pituitary adenoma (Cushing's disease) (70%) F>M
  - Ectopic ACTH (14%)
  - Bronchial carcinoma
  - Carcinoid- lung, gastrointestinal tract, thymus

- ACTH independent
  - Adrenal adenoma (10%)
  - Adrenal carcinoma (5%)
  - Adrenal hyperplasia (1%)

- Differential diagnosis
  - Pseudo-Cushing's due to alcoholism or depression

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.9, page 324; Davey P. *Wiley-Blackwell* 2006, page 290.

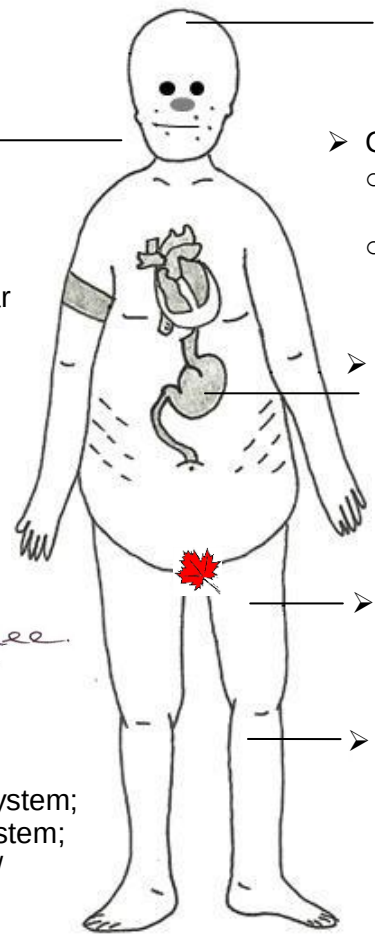
Useful background: Performance characteristics for physical examination for Cushing's syndrome

Although moon facies, generalized obesity, hirsutism (in women), striae, proximal muscle weakness, and peripheral edema have been suggested to be signs of Cushing's syndrome, these are in fact either non-significant or have positive likelihood ratios (PLR) < 2.

Finding		PLR
➢ Vital signs	○ Hypertension	2.3
➢ Body habitus	○ Central obesity	3.0
➢ Skin findings	○ Thin skinfold	115.6
	○ Plethora	2.7
	○ Ecchymoses	4.5
	○ Acne	2.2

Adapted from: McGee SR. *Saunders/Elsevier* 2007, page 114.

- Perform a focused physical examination for Cushing's syndrome.



- CNS
  - Depression
  - Psychosis
- Head and neck
  - Thin hair
  - 'Moon face'
  - Acne
  - Hirsutism
  - Supraclavicular fat pad
- CVS
  - Premature ischemic heart disease
  - Hypertension
- GI / GU
  - Peptic ulcer
  - Dysmenorrhea
  - Impotences
- MSK
  - Proximal hypopathy
- Skin
  - Central obesity
  - Striae
  - Thin
  - Easy bruising

Abbreviations:
CNS, central nervous system;
CVS, cardiovascular system;
GI/ GU, gastrointestinal/ genitourinary;
MSK, musculoskeletal

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 290; and McGee SR. *Saunders/Elsevier* 2007, Table 12-1, page 110.

"The difference between how a person treats the powerless versus the powerful is as good a measure of human character as I know."

Robert Sutton

If you know what is the distinction between Cushing's disease, Cushing's syndrome and pseudo-Cushing's syndrome then, YOU SHOULD BE AN ENDOCRINOLOGIST!

Q. Do you know the differences?

A.
- Cushing's disease is caused by pituitary adenoma, increased ACTH levels, and increased adrenal production of steroids

- Cushing's syndrome is caused by increased steroids from any cause:
  - Steroids, including adrenocorticotropic hormone (ACTH)
  - Pituitary adenoma (Cushing's disease)
  - Adrenal adenoma
  - Adrenal carcinoma
  - Ectopic ACTH (usually from small cell carcinoma of the lung)

- Pseudo-Cushing's syndrome
  - Chronic alcoholics or depressed persons
  - ↑ urinary steroids, no diurinal variation in steroids, positive over-night dexamethasone test, all of which return to normal when causative factors abate

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 386 and 387.

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q1. The prevalence of denial is of epidemic proportions in persons with increased body mass (aka "obesity"). When a patient claims "doctor, it's my glands", what endocrine causes do you consider?

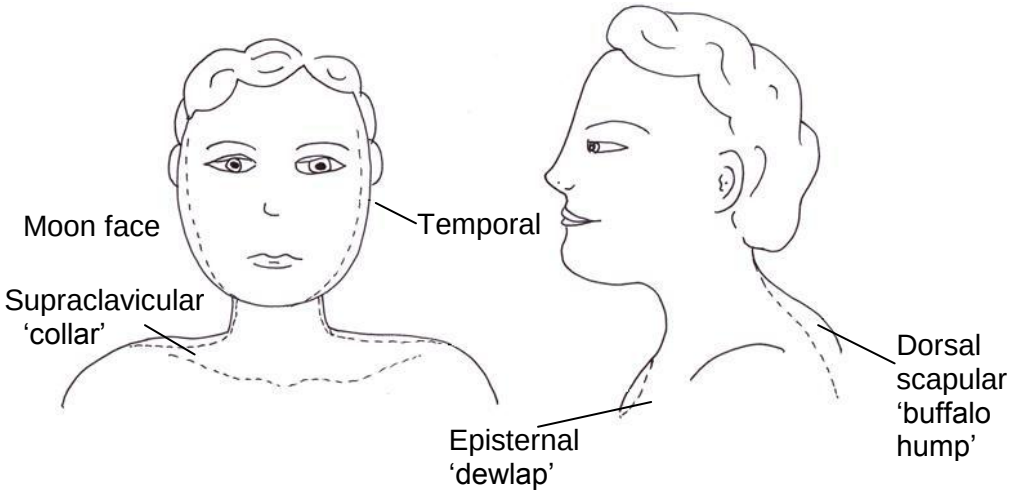
A1.
- Hypothyroidism
- Hypogonadism
- Cushing's syndrome
- Insulinoma
- Stein- Leventhal syndrome

Q2. In the same context, what is Nelson's syndrome?

A2.
- Bilateral adrenalectomy leading in 50% to increased ACTH levels, pituitary adenoma, hyperpigmentation

Source: Baliga RR. *Saunders/Elsevier* 2007, pages 386 and 387.

Useful background: Distribution of adipose tissue in Cushing's syndrome



- Rounding of cheeks and prominent bitemporal fat produces the characteristic 'moon facies'. Fat also may accumulate bilaterally above the clavicles ('supraclavicular collar'). In front of the sternum (episternal area, or 'dewlap'), and over the back of the neck (dorsal cervical fat pad, or 'buffalo hump'). In these drawings , the dotted line depicts normal contours of patients without Cushing's Syndrome.

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Figure 12-1, page 111.

Hyperlipidemia

- Take a directed history to determine the causes of secondary hyperlipidemia.

- Nutrition
  - Anorexia nervosa
  - Hypertriglyceridemia
  - Obesity
  - Hypothyroidism

- Endocrine
  - Diabetes mellitus
  - Hypothyroidism

- Immune
  - Dysglobulinemias
  - Systemic lupus erythematosus

- Liver
  - Cholestasis
  - Acute intermittent porphyria

- Kidney
  - Nephrotic syndrome
  - Renal insufficiency

- Drugs
  - Progestins
  - Anabolic steroids, glucocorticoid therapy
  - Estrogens
  - Thiazides, steroids
  - β- blockers

- Life style
  - Sedentary lifestyle
  - Alcohol
  - Cigarette smoking

- Miscellaneous

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 6-4, page 233.

Dyslipidemias

Q. In the context of cardiac risk reduction, take a directed history and perform a focused physical examination for risk factors for which screening of the lipid-profile is recommended:

A.
- Age
  - Children
    - Family history of hypercholesterolemia or chylomicronemia
  - Men
    - ≥ 40 years
  - Women
    - > 50 years, or postmenopausal
- Habit
  - Current cigarette smoking
- Signs
  - Xanthomes

	○ Xanthelasmas ○ Premature arcus conealis
➢ CVS	○ Hypertension ○ Artherosclerosis ○ CAD in first-degree relative < 60 years ○ Atherosclerosis
➢ Renal	○ eGFR < 60 mL/min/1.73 m^2 (chronic renal disease)
➢ Infection	○ HIV treated withHAART
➢ Inflammation, chronic e.g.	○ RA ○ SLE ○ Psoriasis

Adapted from: Roederer GO, et al. Chapter 34. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 432

- Take a directed history for causes of secondary hyperliperlipidemia.

➢ Endocrine	○ Diabetes ○ Metabolic syndrome ○ Obesity ○ Hypothyroidism
➢ Liver	○ Cholestatic liver disease ○ Alcohol excess
➢ Kidney	○ Nephrotic liver diseases ○ Alcohol excess
➢ Pregnancy	
➢ Medications	○ BB (beta blockers “without intrinsic sympathomimetric or alpha-blocking activity”) ○ Corticosteroids ○ Diuretics (thiazides) ○ HAART (highly active antiretroviral therapy) ○ HRT (hormone replacement therapy) ○ OCA (oral contraceptive agents)
➢ Post-transplantation	

Adapted from: Roederer GO, et al. Chapter 34. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 433.

Useful background: International Diabetes Federation Classification of the Metabolic Syndrome

Risk factor	Defining level
➢ Central obesity*	Waist circumference
o Europids	Men ≥ 94 cm; Women ≥ 80 cm
o South Asians	Men ≥ 94 cm; Women ≥ 80 cm
o Chinese	Men ≥ 94 cm; Women ≥ 80 cm
o Japanese	Men ≥ 94 cm; Women ≥ 80 cm
o Ethnic South and Central Americans, First Nations	Use South Asian recommendations until more specific data are available
o Eastern Mediterranean and Middle East (Arabic) populations, Sub-Saharan Africans	Use European data until more specific data are available
➢ Triglyceride level	≥ 1.7 mmol/L
➢ HDL-C level	
o Men	< 1.0 mmol/L
o Women	< 1.3 mmol/L
➢ Blood pressure	≥ 130/85 mm Hg
➢ Fasting glucose level	5.7-7.0 mmol/L

*Criteria: central obesity required, plus 2 or more other risk factors.

Abbreviations: HDL-C, high density lipoprotein cholesterol

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: Canadian Pharmacist Association 2012, Table 2, page 436.

Q. Persons at increased cardiovascular risk include these with the metabolic syndrome, diabetes, end-stage renal disease, renal transplantation patients, and these with family history. Various laboratory measures may be used to calculate a risk score, such as hsCRP, apolipoprotein B, cholesterol (LDL, HDL, non-HDL-C).

Give the conditions under which the serum triglyceride concentration may be associated with increased cardiovascular risk.

A. Insulin resistance
Diabetes
Chronic renal failure
Atherogenic dyslipidemias (e.g. familial combined hyperlipidemia)

Metabolic bone disease, parathyroid and calcium disorders

- Give a systematic approach to the causes of hypercalcemia and hypercalciuria.

- Hypercalcemia

➢ Hyperparathyroidism
  - Adenoma
  - Hyperplasia
  - Carcinoma (rare)

➢ Tumor
  - Malignancy (with or without metastases, eg breast cancer)
  - Myeloma
  - Reticulosis

➢ Vitamin D
  - Increased intake (eg milk-alkali syndrome)
  - Increased sensitivity to vitamin D (eg sarcoidosis)

➢ Increased release of Ca^{2+} from bone
  - Steroid withdrawal
  - Immobilization
  - Paget's disease

- Hypercaluria

➢ Hypercalcemia

➢ Idiopathic

➢ Osteoporosis
  - Renal tubular acidosis
  - Fanconi syndrome

- Take a directed history for the causes of hypo- and hypercalcemia.

	Hypocalcemia	Hypercalcemia
➢ Parathyroid	o Hypoparathyroidism o Pseudohypoparathyroidism	- Primary hyperparathyroidism
➢ Thyroid	o After thyroidectomy, idiopathic	- Thyrotoxicosis - Hypothyroidism in infants
➢ Gut	o Malabsorption o Deficiency of vitamin D o Magnesium deficiency	- Milk – alkali syndrome
➢ Pancreas	o Acute pancreatitis	
➢ Kidney	o Chronic renal failure	- Associated with renal failure (e.g. severe secondary hyperparathyroidism)
➢ Drugs		- Thiazide diuretics - Vitamin D excess - Milk-alkali syndrome - Steroid withdrawal syndrome
➢ Malignancy	o Hypocalcemia of malignant disease (with or without metastases)	- Carcinoma (bone metastases or humoral mediators) - Excessive intake production of vitamin D metabolites - Vitamin D sensitivity Sarcoidosis - Multiple myeloma - Reticulosis
➢ Inactivity		- Prolonged immobilization or space flight - “steroid withdrawal syndrome”
➢ Miscellaneous		- Paget’s disease - Infantile hypercalcemia

Note:

- Hypercalciuria occurs with all causes of hypercalcemia if renal function is normal.
- Causes of hypercalciuria without hypercalcemia include osteoporosis and renal tubular acidosis (RTA), idiopathic.

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003,Table 9.13, page 328; Table 9.14, page 329; Burton JL. *Churchill Livingstone* 1971, page 99.

Useful background: Causes of hypoparathyroidism

- Idiopathic
  - Dysembryogenesis (DiGeorge syndrome)
- Iatrogenic
  - Radioactive iodine therapy
  - External neck irradiation
  - Damage during thyroid or neck surgery
- Infiltration
  - Metastatic disease (breast, lung, lymphoproliferative disorder)
- Immune
  - Polyglandular autoimmune syndrome (PGA type 1) aka autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECD])
- Metabolic
  - Hemochromatosis and Wilson's deficiency

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 380.

Useful background: Causes of hypoparathyroidism

- Damage/ destruction of the parathyroid gland:
  - thyroid or neck surgery
  - Radioactive iodine therapy
  - External neck radiation
  - Hemochromatosis and Wilson's deficiency
  - Metastatic disease from the breast, lung, lymphoproliferative disorder
- Idiopathic
- Dysembryogenesis (DiGeorge syndrome)
- Polyglandular autoimmune syndrome (PGA type 1) which is also known as autoimmune polyendocrinopathy – candidiasis – ectodermal dystrophy (APECD)

Adapted from: Baliga RR. *Saunders/Elsevier* 2007, page 380.

Useful background: Causes of hyperparathyroidism

- Primary
  - Adenoma (80%)
  - Hyperplasia
  - Carcinoma (rare)
- Secondary
  - Hyperplasia associated with chronic renal failure
- Tertiary
  - Autonomous hyperparathyroidism is a complication of secondary hyperparathyroidism

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.12, page 328.

Useful background: Causes of radiographic punctate translucencies in skull

- Malignancy
  - Myelomatosis
  - Metastatic deposits
- Metabolic
  - Hyperparathyroidism
  - Cushing's
- Hematological
  - Sickle-cell anemia
  - Leukemia
  - Histiocytosis X

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 99.

Condition	Serum Calcium	Serum Phosphate	Parathyroid hormone Infusion, response
➢ Hypoparathyroidism	↓	↑	○ Marked
➢ Pseudo-hypoparathyroidism	↓	↑	○ None
➢ Pseudo- pseudo-hypoparathyroidism			○ None

Source: Burton JL. *Churchill Livingstone* 1971, page 100.

- Take a directed history to determine the cause of osteoporosis.

- Inherited
  - Osteogenesis imperfecta
- Ideopathic (young persons)
- Immobility, senile
- Immune
  - Rheumatoid arthritis
- Infiltration
  - Systemic mastocytosis
  - Multiple myeloma
- Endocrine
  - Deficiency of estrogen, androgen, protein, vitamin C or calcium
  - Hyperthyroidism
  - Diabetes mellitus
  - Acromegaly
  - Cushing's or glucocorticoid therapy
- Liver
  - Chronic cholestasis
  - Steroid use
- Kidney
  - Azotemic osteodystrophy
  - Liver
  - Glycogen storage disease
  - Cirrhosis in children

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 100.

- Give a systematic approach to the causes of osteoporosis and osteomalacia.

- Osteoporosis

- Idiopathic
- Senile
- Reduced activity (local, or generalized)

- Endocrine
  - Diabetes
  - Cushings
  - Acromegaly
  - Hyperthyroidism
  - Reduced estrogen/ progesterone

- Diet- reduced intake of
  - Protein
  - Calcium

- Tumor
  - Multiple myeloma
  - Systemic mastocytosis

- Liver
  - Cirrhosis (in children)
  - Glycogen storage disease

- Osteogenesis imperfect

- Osteomalacia

- Urine calcium ↓
  - ↓ intake/ absorption of calcium
  - Vitamin D deficiency
    - Renal acidosis
    - hyperparathyroidism
  - ↑ requirements
    - Prematurity
    - Multiple pregnancies
    - Breast feeding
    - ↓ UV light
    - Pigmented skin

- Urine – calcium, normal
    - Phosphate ↑
  - Renal tubular acidosis
  - Fanconi syndrome
  - Uremia

Useful background: Likelihood ratios for physical examination maneuvers suggesting presence of osteoporosis or spinal fracture

	PLR	NLR
➢ Weight < 51 kg	7.3	0.8
➢ Wall-occiput distance >0cm	3.8	0.6
➢ Rib- Pelvis distance <2 fingerbreadths	3.8	0.6
➢ Tooth count <20	3.4	0.8
➢ Height loss >3 cm	3.2	0.4
➢ Self reported humped back	3.0	0.85

Adapted from: Simel DL, et al. *McGraw-Hill Medical* 2009, table 36.5 and 36.6, page 483.

Useful background: Causes of metabolic bone disease

- Causes of osteomalacia and rickets

- Skin
  - pigmented skin
  - lack of UV light

- Pregnancy
  - multiple pregnancy
  - prolonged breast feeding

- GI
  - Malnutrition deficiency of vitamin D
  - Post-gastrectomy (probably dietary)
  - Malabsorption
- Renal
  - Chronic renal failure
  - Idiopathic hypercalcuria
  - Fanconi syndrome
  - Tubular acidosis
  - Hypo-phosphatasia

- Secondary to hyperparathyroidism.

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 98.

Useful background: Causes of secondary hyperuricemia

	Hyperuricemia	Hypouricemia
➢ Nutrition	○ Obesity ○ Increased purine ingestion	
➢ Tumor	○ Myeloproliferative disorders - Polycythemia, primary or secondary - Myeloid metaplasia - Chronic myelocytic leukemia ○ Lymphoproliferative disorders - Chronic lymphocytic leukemia ○ Plasma cell proliferative disorders - Multiple myeloma ○ Disseminated carcinoma and sarcoma	
➢ Anemia	○ Sickle cell anemia ○ Thalassemia ○ Chronic hemolytic anemia	
➢ Skin	○ Psoriasis ○	
➢ Infections	○ Infectious mononucleosis	
➢ Kidney		○ Intrinsic renal disease - Chronic renal insufficiency of diverse cause - Saturnine gout (lead nephropathy)
➢ Drugs / toxins	○ Cytotoxic drugs	○ Drug-induced - Thiazide diuretics - Furosemide - Ethacrynic acid - Ethambutol - Pyrazinamide - Low-dose aspirin - Cyclosporine - Nicotinic acid - Laxative abuse - Levodopa

Hyperuricemia	Hypouricemia
➢ Endocrine	○ Endocrine conditions - Adrenal insufficiency - Nephrogenic diabetes insipidus - Hyperparathyroidism - Hypoparathyroidism - Pseudohypoparathyroidism - Hypothyroidism - Diabetic ketoacidosis - Lactic acidosis - Starvation - Ethanolism - Glycogen storage disease type I - Bartter syndrome
➢ Genetic	○ Other - Sarcoidosis - Down syndrome - Beryllium disease

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 24-22, page 1004.

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q. On the basis of just the physical examination as well as the serum calcium (Ca) and phosphate (PO_4) concentrations, and their response to PTH, distinguish between the following three variations of hypoparathyroidism:

A.	Hypoparathyroidism	Pseudo-hypoparathyrodism*	Pseudo-pseudo-hypoparathyroidism
Ca	↓	↓	N
PO_4	↑	↑	N
Response to TSH	Yes	No	No
Skeletal changes		Yes **	Yes

*conceptualize as "end-organ non-responsiveness
** Typical skeletal changes
- ○ Short neck
- ○ Short fingers
- ○ Less than 5 fingers

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q. What is the neurological changes associated with hyperparathyroidism

A.
- Cataracts
- Papilloedema
- Basal ganglia defects
- Benign intracranial hypertension

Source: Burton JL. *Churchill Livingstone* 1971, page 81.

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Q1. Give 4 radiological signs for hyperparathyroidism

A1.
- Subperiosteal erosions
  - Femoral necks
  - Fingers, middle phalanges
  - Fragmental cortex of phalanges
- Multiple bone cysts
  - May project from surface of affected bone
  - Often affects the jaw) osteitis fibrosa cystic)
  - Aka von Reckling harsen's disease
- Loss of lamina dura around teeth
- Punctuate translucencies of the skull ("mottling" or "pepper-pot skull")

Source: Davies IJT. *Lloyd-Luke (medical books) LTD* 1972, pages 222 and 223.

Q2. What are the effects of renal osteodystrophy?

A2.
- Secondary hyperparathyroidism
- Osteoporosis
- Osteomalacia

Gynecomastia

Useful background:

- Causes of pathological gynecomastia*
- Increased estrogen production
  - Leydig cell tumor
  - Adrenal carcinoma
  - Bronchial carcinoma (human chorionic gonadotrophin)
  - Liver disease (increased conversion of androgens to estrogens)
  - Starvation

- Decreased androgen production (hypogonadal states)
  - Klinefelter's syndrome
  - Secondary testicular failure: orchitis, castration, trauma
- Testicular feminization syndrome
- Drugs
  - Estrogen receptor binders: estrogen, digoxin, marijuana
  - Antiandrogens: spironolactone, cimetidine

* Gynecomastia does not regress, but Mammaplasia (enlarged male breast) does regresses

- Take a directed history and perform a focused physical examination to determine the causes of gynecomastia.

- Hermaphroditism or pseudo- hermaphroditism
- Endocrine
  - Normal puberty and neonatal
  - Hypothyroidism
  - Thyrotoxicosis
  - Acromegaly
  - Testicular atrophy
  - Testicular and adrenal tumors
- Klinefelter's syndrome
- Cirrhosis
- Cancer of bronchus
- Malnutrition
- Paraplegia
- Generalized skin disease
- Drugs
  - Spironolactone
  - Amphetamine
  - Reserpine
  - Digitalis
  - Methyldopa

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 94; Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.16, page 334.

- Give the systematic approach to the causes of gynecomastia.

- Congenital
  - Hermaphrodite
  - Male pseudohermaphrodite
  - Kleinfelter's syndrome
- Physiological
  - Neonate
  - Puberty
  - Old age
- Endocrine
  - Diabetes
  - Hypo-/ hyperthyroidism
  - Acromegaly
  - Cushing's disease
  - Addison's disease
  - Tumors of testicle and adrenal glands
- Systemic disease
  - Failure
    - Heart, liver kidney
  - Tumor
    - Leukemia, lymphoma
    - Carcinoma of bronchus, kidney
  - Gut
    - Ulcerative colitis
    - Starvation
  - CNS
    - Paraplegia
  - MSK
    - Rheumatoid arthritis
- Drugs
  - Heart
    - Digitalis, methyldopa, reserpine, spironolactone
  - Hormones
    - Estrogens, androgens
  - GI
    - Prokinetics (metoclopramide, H2 blockers)
    - Steroids
  - Infections INH for TB

Amenorrhea

- Take a directed history and perform a focused physical examination to determine the cause of amenorrhea.

- Physiological
  - Pre-pubertal
  - Pregnancy
  - Infarction or pituitary appoplexy
  - Menopausal
  - "Functional"
    - change in environment
    - emotional upset
    - rapid change in weight
    - aggressive training
- Uterus
  - Uterine anomaly
  - Hysterectomy
- Ovary
  - Stein-Leventhal syndrome, tumors, e.g. arrhenoblastoma, hilus-cell
  - Oophorectomy
  - Follicular or lutein retention cyst
  - Granulosa cell tumor
  - Irradiation
- Endocrine
  - Thyrotoxicosis
  - Cong. Adrenogenital syndrome, acquired virilizing hyperplasia, adenoma or Ca.
- Head
  - Mid brain tumor
  - Trauma
  - Surgery radiation infection
    - Pelvic TB
    - Systemic infection
- Drugs
  - Estrogen, progesterone, testosterone
  - Glucocorticoids, spironolactone

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 97.

- Give a systematic approach to the causes of amenorrhea.

➢ Congenital
  - Intersexual states
    - Hermaphrodite: testicular plus ovarian elements in gonads
    - Male pseudohermaphrodite have tests, but are feminized because of end-organ non-responsiveness
    - Female pseudohermaphrodites: have ovaries, but are musculinized due to
      - Congenital adrenal hyperplasia
      - Virilizing condition in mother
      - Mother given androgens during pregnancy

➢ Physiological
  - Prepuberty
  - Menopause
  - Pregnancy

➢ Endocrine
  - Hyperthyroid
  - Hypopituitary
  - Mid brain tumor

➢ Systemic disease

➢ Malnourishment (e.g. anorexia nervosa, Crohn disease)

➢ Ovary/ uterus surgical removal

➢ Ovary/ adrenal - ↑ estrogen/ progesterone

Useful background: Absolute contraindications to estrogen and progestin therapy

➢ Estrogen therapy
  - Undiagnosed vaginal bleeding
  - Active liver disease
  - Active thromboembolic disease
  - Known or suspected carcinoma of the breast or other estrogen-sensitive tumors
  - Pregnancy
  - The risk of recurrence of breast cancer or thrombosis following estrogen therapy is unknown.
  - Caution is recommended in women with cardiovascular disease.

➢ Progestin therapy
  - Undiagnosed vaginal bleeding
  - Known or suspected carcinoma of the breast
  - Pregnancy

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 946.

Hirsutism

Useful background: Causes of hirsutism

- Ovarian
  - Tumor
  - Stein-Leventhal syndrome
  - Polycystic ovary syndrome (commonest cause)
- Endocrine
  - Adrenal
    - Cushing's syndrome
    - Congenital adrenal hyperplasia
    - Virilising tumor (more often a carcinoma than an adenoma)
    - Acromegaly
- Porphyria cutanea tarda
- Drugs
  - Phenytoin, diazoxide, streptomycin, minoxidil, anabolic steroids

Would you like to play (X's and O's? "Y" not "I"

- Turner's syndrome XO
- Kleinfelter's syndrome XXY
- Supermale XXY
- Superfemale XXX

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.15, page 333.

Pituitary disease

A curiosity: you are sitting on the beach at a nudist camp. A man walks towards you. As be approaches, what will you notice that will suggest that he has pituitary failure?

- Not obese
- Loss of body hair (including pubic hair)
- Fine, wrinkled skin (not greasy or thickened)

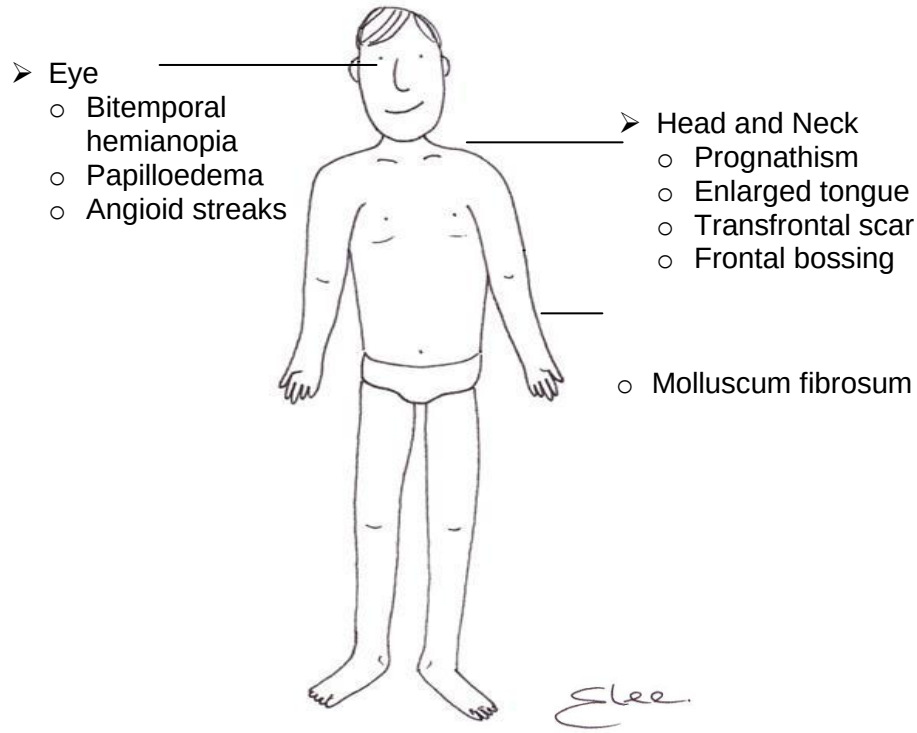
Useful background: Causes of hypopituitarism

- Infiltration
  - Pituitary tumor (non-secretory or secretory)
  - Other tumors
    - Craniopharyngioma
    - Metastatic carcinoma
    - Sarcoma

- Infection
  - Granulomata
    - e.g. Sarcoid, tuberculosis
- Idiopathic

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.7, page 320.

Useful background: Acromegaly



Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Figure 9.7, page 321.

- Perform a focused physical examination for acromegaly.

- General
  - Hyperhidrosis
- Eyes
  - Prominent supraorbital ridges
  - Bitemporal hemeanopia
  - Optic atrophy
- Nose & lips
  - Large

- Jaw/ teeth
  - Prognathia (large protruding lower jaw)
  - Macroglosia
- Neck
  - Goiter
- Axillae
  - Skin tags (molluscum fibrosum)
  - Acanthosis nigrans
- Hands
  - Large hands
  - Sweating
- Breasts
  - Gynecomastia
  - Galactorrhea
- Heart
  - Cardiomegaly
  - Hypertension
  - CHF
- Abdomen
  - Hypatosplenomegaly
- MSK
  - Kyphosis
  - Spinal stenosis
  - Osteoarthrosis (hands, hips, knees, feet) tight finger ring
  - Chondrocalcinosis
  - Carpal tunnel syndrome signs
- Spinal cord
  - Compression signs
- Endocrine
  - Signs of hypopituitarism
  - Signs of diabetes mellitus

Abbreviations: CHF, congestive heart failure

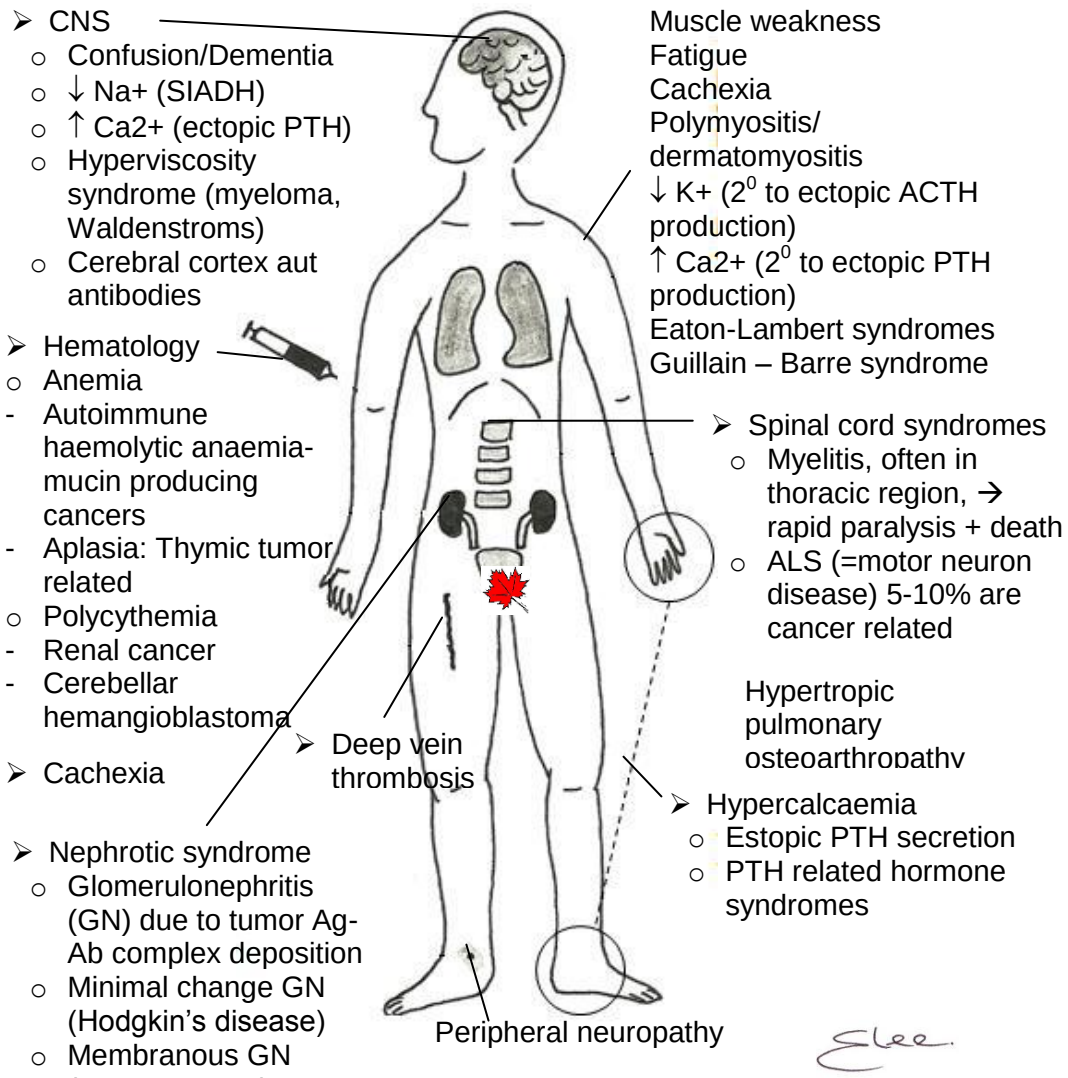
SO YOU WANT TO BE ENDOCRINOLOGIST!

Q. What are the typical X-ray changes in the hands and feet of a person with acromegaly?

A.
- "tufting" of terminal phalynx of fingers & toe
- ↑ thickness of heal pad

Paraneoplastic syndromes

- Perform a focused physical examination for paraneoplastic syndromes and hormone producing cancers.



Adapted from: Davey P. *Wiley-Blackwell* 2006, page 361; Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 9.16, page 339.

GASTROENTEROLOGY

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63. Give a systematic approach to the causes of chronic pancreatitis.
64. Give 8 clinical, diagnostic imaging and laboratory features that distinguish pseudocysts from cystic neoplasms of the pancreas.
65. There are literally hundreds of drugs which may cause pancreatitis. Give drugs commonly seen being used in GI patients which are considered to have a moderately strong association with the development of pancreatitis.
66. Perform a directed examination of an abdominal x ray (‘flat plate’).
67. Give 7 causes of calcification on abdominal X – ray.

68. Give 7 causes of radiological hepatic calcification.
69. Give the most common clinical presentations of the neuroendocrine tumors, VIPoma (Verner-Morrison syndrome), glucagonoma, and somatostatinoma and insulinoma. The approximate frequencies are given in brackets.
70. Give the clinical features that suggest Zollinger-Ellison Syndrome.
71. Give features which distinguish P-NET from other GI-NET.
72. Give the clinical features of glucagonoma.
73. Give the clinical and laboratory features of VIPoma syndrome.
74. Give 15 prognostic factors associated with decreased survival in patients with various pancreatic endocrine tumors.
75. Give 3 mechanisms explaining alterations in serum vitamin levels in obesity.
76. Give 7 symptoms/ signs of protein/ calorie malnutrition (PCM) which may occur in obesity.
77. Give 5 GI/ liver complications associated with stem cell transplantation, and give examples.
78. Give 10 gastrointestinal and /or hepatobiliary manifestations.
79. GI complications occur in > 80% of persons with PSS, and may affect all parts of the GI part. Give 20 examples.
80. Chronic renal disease associated with a plethera of GI complications, especially for these patients on hemodialysis (HD) or peritoneal dialysis (PD). Give 10 GI complications of chronic renal disease.
81. Give 8 conditions associated with NRH.
82. Give 3 complications of intraoperative endoscopy.

MOUTH

- Perform a focused examination of the mouth.

- Teeth
  - Carries
  - Brown molting of enamel
    - Fluorosis
    - Tetracycline

- Gums
  - Stippling
    - Poisoning; lead, bismuth
  - Bleeding
    - Gingivitis
    - Vitamin C deficiency (scurvy)
    - Amyloid
    - Dilantin

- Tongue
  - Furred
    - Fever
    - Acute abdomen
    - Uremia
  - Atrophic
    - Iron deficiency
    - Deficiency of riboflavin, nicotinic acid
    - Antibiotic reaction
  - Magenta colour, angular stomatitis, cheilosis (cracked lips)
    - Riboflavin deficiency
  - Red side and tip of tongue
    - Nicotinic acid deficiency
  - Macroglossia
    - Acromegaly
    - Myxedema
    - Amyloid
    - Down syndrome
  - "Scrotal"
    - Normal variant
    - Down syndrome

- Mucosa
  - Purpura, telangiectasia
  - Scleroderma (circumoral purpura)
  - Circumoral pigmentation- Peutz- Jeghers syndrome
  - "geographical tongue"
    - Patchy red depapillation
    - Normal variant

- Perform a focused physical examination to determine the causes of stomatitis.

- General
  - Malnutrition: protein, vitamins, minerals (esp. iron)
  - Smoking
  - Alcoholism
  - Infections
  - Drugs
    - Antibiotics
    - Atotoxic drugs
    - Phenytoin
    - Heavy metals
  - Trauma
    - Poorly fitting dentures
  - Tumor

- Systemic diseases
  - GI
  - Crohn
  - Ulerative colitis
  - Celiac disease
  - MSK
    - Behcet's
    - Reiter's
    - Lupus
  - Hematology
    - Leukemia and its treatment
    - Neutropenia
    - Iron deficiency

- Skin diseases (associated, including angular stomatitis)
  - Eczema
  - Erythema multiforme (Stevens-Johnson)
  - Pemphigus vulgaris
  - Pemphigoid
  - Benign pemphigoid of mucous membranes
  - Epidemolysis bullosa
  - Lichen planus
  - Dermatitis herpetiformis

- HIV/AIDS associated infections
  - Viral
    - Herpes simplex
    - Herpangina
    - Hand, foot and mouth disease

    - Exanthemata
  - Bacterial
    - Pyorrhea and alveolar abscess
    - Vincent's angina
    - TB
    - Syphilis
  - Fungal
    - Candidiasis
    - Actinomyocosis

Adapted from: Burton JL. *Churchill Livingstone* 1971, pages 36 and 37.

Halitosis

- Take a directed history to determine the causes of halitosis.

- Infection
  - Poor oral hygiene
  - Putrid (due to anaerobic chest infections with large amounts of sputum)

- Metabolic
  - Fetor hepaticus (a sweet smell)
  - Ketosis (diabetic ketoacidosis results in excretion of ketones in exhaled air, causing a sickly sweet smell)
  - Uremia (fish breath: an ammoniacal odour)

- Drugs
  - Alcohol (distinctive)
  - Paraldehyde
  - Cigarettes, tobacco

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 5.8, page 161.

- Give 6 non-dental causes of halitosis.

- Infection
  - Poor oral hygiene
  - Putrid (due to anaerobic chest infections with large amounts of sputum)

- Metabolic
  - Fetor hepaticus (a sweet smell)
  - Ketosis (diabetic ketoacidosis results in excretion of ketones in exhaled air, causing a sickly sweet smell)

- Drugs
  - Alcohol (distinctive)

- Paraldehyde
- Cigarettes, tobacco

Adapted from: Talley NJ, et al. 4th ed. *Blackwell Science* 2001.

Useful background: Causes of gum hypertrophy

- Gingivitis
  - from smoking
  - calculus
  - plaque
  - Vincent's angina (fusobacterial membranous tonsillitis)
- Drugs (Phenytoin)
- Pregnancy
- Scurvy (vitamin C deficiency: the gums become spongy, red, bleed easily and are swollen and irregular)
- Leukemia (usually monocytic)

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 5.6, page 161.

Useful background: Causes of pigmented lesions in the mouth, including tongue

- Drugs/Toxins
  - Heavy metals: lead or bismuth (blue-black line on the gingival margin), iron (hemochromatosis- blue-grey pigmentation of the hard palate)
  - Drugs
    - Anti-malarias
    - Oral contraceptive pill (brown or black areas of pigmentation anywhere in the mouth)
- Endocrine
  - Addison's disease (blotches of dark brown pigment anywhere in the mouth)
- Tumor
  - Malignant melanoma (raised, painless black lesions anywhere in the mouth)
- Genetic
  - Peutz- Jeghers syndrome (lips, buccal mucosa or palate)

Source: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 5.7, page 161.

Useful background: The tongue, gums and teeth

- Magenta-coloured tongue, angular stomatitis, cheilosis (cracked lips).
- Red side and tip of tongue (nicotinic acid deficiency)
- Dipapillating glossitis (antibiotic therapy).
- Large tongue-myxedema, acromegaly, amyloid, Down syndrome
- Jaundice (frequently appears first and disappears last from frenum of tongue)
- Scrotal tongue (normal or in Down syndrome)
- Geographical tongue-patchy redish depapillation surrounded by "fur" (of no importance)
- Brown mottling of enamel (Fluorosis)
- Stippling of gums (Pb, bismuth poisoning)
- Furred tongue-fever (acute abdomen, uremia, cholemia)

Source: Mangione S. *Hanley & Belfus* 2000, page 122 and pages130-133.

- Give 3 causes of an enlarged tongue (macroglossia).
  - Acromegaly
  - Hypothyroidism
  - Amyloidosis
  - Down syndrome

SO YOU WANT TO BE A GASTROENTEROLOGIST! – Coloured Mouth

Q. What lesions are seen in the mouth, which are pigmented (not white)?

A.
- Amalgam tattoo
- Peutz-Jeghers syndrome
- Smokers melanosis
- Hemochromatosis (15-25% of patients have a bluish-gray pigmentation of the hard palate with a lesser degree of pigmentation in the gingiva)
- Malignant melanoma (pigmented lesion with irregular borders, which may be palpable; often ulcerates)
- Addison's disease thus, the scattered melanotic spots
- Normal in African-Americans. This condition, termed "melanoplakia"

Source: Mangione S. *Hanley & Belfus* 2000, page 127.

SO YOU WANT TO BE A GASTROENTEROLOGIST! –White Spots in Mouth

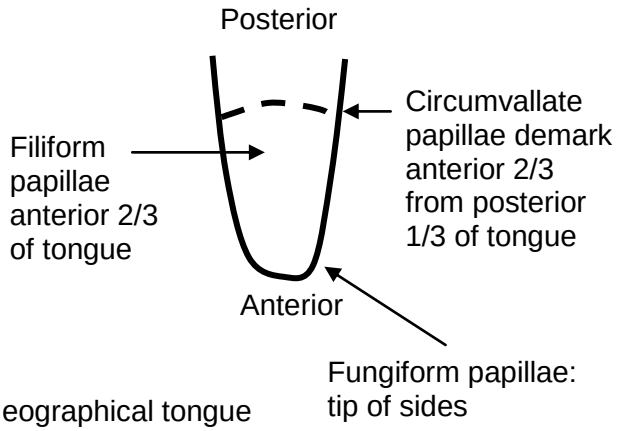
Q. What are the causes of white spots on the oral mucosa?

A.
- Thickened oral mucosa
  - Broken tooth
  - Poorly fitting dentures
- Squamous cell carcinoma
- Infection
  - Candidiasis
  - Rubeola, echovirus, adenovirus, (cluster of ting white macules on buccal mucosa or first and second molars, known as Koplik's spots)
  - HIV - hairy leukoplakia on lateral aspects of tongue and buccal mucosa
- Leucoplakia is a term which was used in the past to imply a malignant lesion, but don't use this term because as you see from above, not all white lesions are malignant, just like not all Koplik's spots are caused by Rubela

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 125.

"Tongues"

Papillae of tongue



Geographical tongue
Patchy red loss of papillae of tongue
Surrounding furred tongue

Causes of atrophic glossitis
Deficiency of iron, riboflavin or nicotinic acid
Loss of papillae from antibiotic therapy

Salivary gland

- Perform a focused physical examination to determine the causes of salivary gland swelling.

- Unilateral swelling
  - Ductal calculus, with staphylococcus or streptococcus viridians infection

- Bilateral swelling

- Connective tissue diseases
  - Sjogren's syndrome (kerato conjunctivitis sicca: xerothalmia and xerostomia)
  - Systemic lupus erythematosis (SLE)

- Infection
  - Staphylococcus
  - Streptococcus viridians
  - Tuberculosis
  - Sarcoidosis

- Infiltration
  - Lymphoma
  - Leukemic infiltrates

- Drugs and toxins
  - Alcohol (with or without chronic liver disease)
  - Sulfonamides
  - Propylthiouracil (PTU)

- Endocrine
  - Diabetes mellitus
  - Thyrotoxicosis

- Hematological
  - Waldenstrom's macroglobulinemia
  - Malnutrition; anorexia nervosa/ bulimia, starvation, Kwashiorkor
  - Alcoholism
  - Keratoconjunctivitis sicca (dry eyes and mouth)
    - Autoimmune (Sjögren's syndrome)
    - Mikulicz's syndrome (non-autoimmune keratoconjunctivitis sicca): TB, lupus, sarcoid, Waldenstrom's macroglobulinemia

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 144; Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 5.5, page 160.

- Perform a focused physical examination to determine the causes of parotid gland enlargement.

- Bilateral
  - Infection
    - Mumps (may be unilateral)
    - Sarcoidosis
  - Infiltration
    - lymphoma
  - Immune
    - Mikulicz syndrome (painless enlargement of all three salivary glands, probably an early stage of Sjogren's syndrome)
  - Drugs / toxin
    - Alcohol-associated parotitis
  - Malnutrition
- Severe dehydration
- Unilateral
  - Tumor
    - Mixed, parotid, occasionally bilateral
    - Infiltration (check for signs of VII nerve palsy)
  - Duct blockage, e.g. salivary calculus

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 5.5, page 160.

ESOPHAGUS

<u>Dysphagia</u>

- Take a directed history for dysphagia.

- Algorithm for symptomatic assessment
  - Solids
    - Suggests mechanical (e.g. stricture, ring, malignancy)
  - Liquids
    - Suggests motility problem (e.g. achalasia, diffuse esophageal spasm [DES], scleroderma)
  - Progressive
    - Stricture
  - Intermittent
    - DES
    - Lower esophageal ring
  - Painful
    - Esophagitis

- Painless
  - NERD (normal endoscopy reflux disease)
- Nasal/ ENT symptoms
  - Suggests oropharyngeal or CNS cause

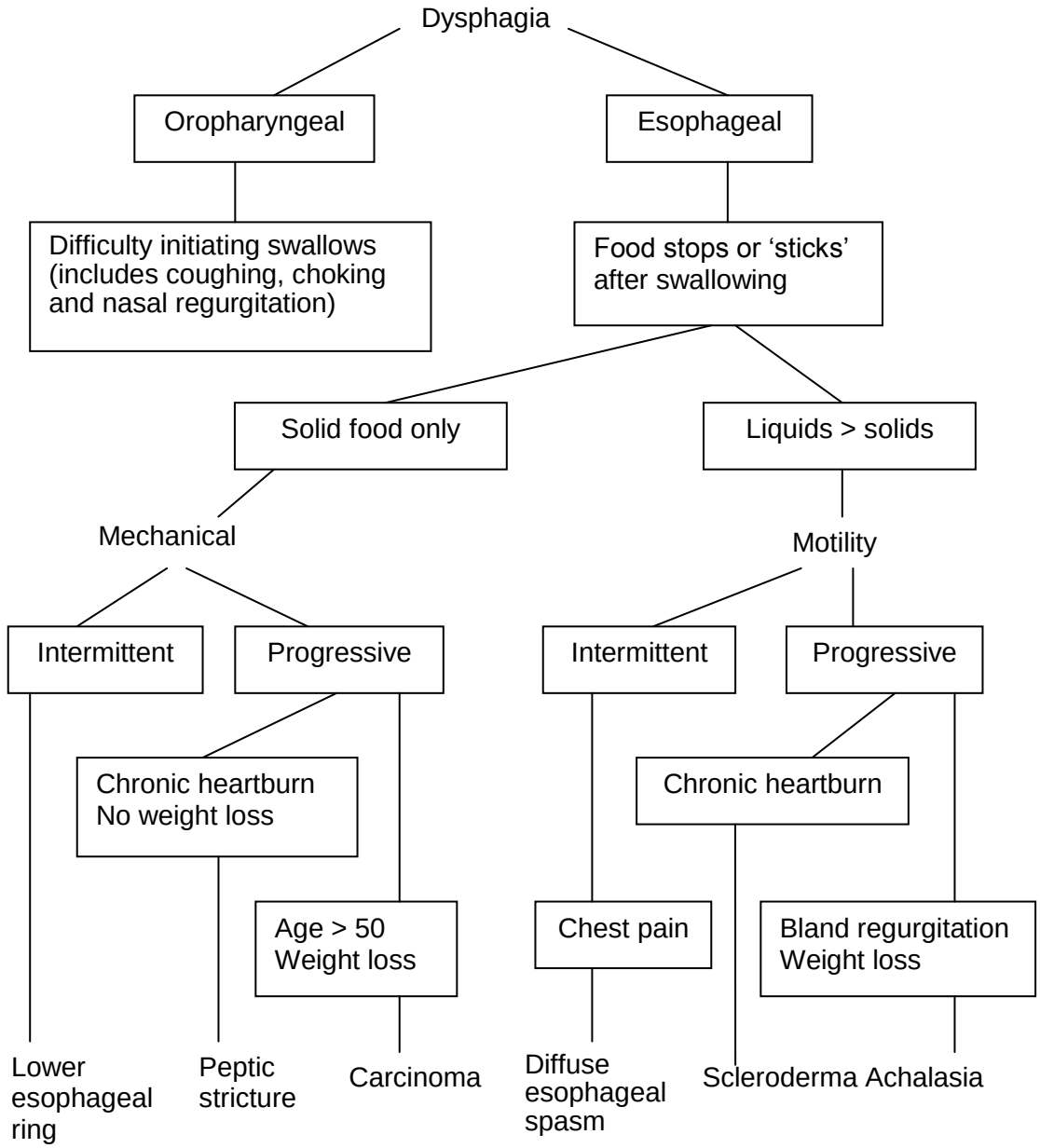
- Causes
  - CNS
    - E.g. CVA, Parkinsonisms
  - Lung
    - Compression
  - Stomach
    - Tumor
    - Gastric retention
  - Colon
    - Constipation (rare)
  - Drugs
  - Pregnancy
  - Diet
  - MSK
    - Scleroderma
    - Skeletal muscle disease

- Complications
  - Hemorrhage
  - Obstruction
  - Perforation
  - Malnutrition
  - ENT
    - Cough
    - Sinusitis
    - Dysphonia
  - Quality of life
  - Drug treatment
  - Lifestyle modifications

"Nothing helps more than experience"

Grandad

Useful background: Approach to the person with dysphagia



Adapted from: Cockeram, AW**.** Canadian Association of Gastroenterology Practice Guidelines: Evaluation of dysphagia. *Can J Gastroenterol* 1998,12(6):409-414.

Useful background: Causes of bilateral swelling of salivary glands.

SO YOU WANT TO BE A GASTROENTEROLOGIST! –GERD / NERD

Q1. In the person with heartburn but a normal EGD (esophagogastroduodenoscopy), what are the performance characteristics of the Bernstein test?

A1.
- Indication
  - Assess esophageal acid sensitivity in persons with NCCP or NERD.
  - Sensitivity 0-59%*
  - Specificity 59-94%

*Lack of association between symptoms induced by acid perfusion of esophagus compared with symptoms following spontaneous reflux in same individual, suggesting that heartburn following acid perfusion and spontaneous heartburn are induced by different stimuli.

Abbreviations: NCCP, non-cardiac chest pain; NERD, normal endoscopy reflux disease

Q2. When is a Virchow's node not a Virchow's node?

A2
- Virchow's node is a left supraclavicular node from metastasis from a gastric cancer
- When a left supraventricular node is metastatic from cancer of the esophagus, or an ipsilateral breast (L) or lung cancer, it is called a Troisier's node (!!)

Q3. What are the causes of an absent gastric air bubble?

A3.
- Large hiatus hernia
- Achalasia
- Stomach full of food/fluid
- Large, upper abdominal mass
- Splenomegaly

Useful background

- Some patients with oropharyngeal dysphagia may partially compensate for their swallowing dysfunction by turning their head when swallowing: "head turning can eliminate aspiration or pharyngeal residue by favouring the more functional side in pateints with hemiparesis" Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 700).

Neuromuscular Disorders Commonly Associated with Oropharyngeal Dysphagia

- Post-polio muscular atrophy
  - Atrophy / weakness of muscles of palate, pharynx and larynx
  - New symptoms of weakness 30 to 40 years after spinal or bulbar polio virus infection
  - Aspiration occurs in half of patients with post-polio muscular atrophy

- Amyotrophic lateral sclerosis (ALS)
  - Definition – "….. a progressive neurologic disease characterized by degeneration of motor neurons in the brain, brainstem, and spinal cord" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 688).
  - Cranial nerve involvement leads to progressive oropharyngeal dyspepsia
  - Death occurs from swallowing and respiratory dysfunction

- Parkinson disease
  - VFSS (video fluoroscopy swallowing study) abnormal in 95%, but oropharyngeal dysphagia in about 20%
  - Oropharyngeal dysphagia due to
    - ↓ pharyngeal contraction
    - ↓ relaxation of UES

- Myotonic dystrophy
  - VFSS abnormal in ~95%, but symptoms in only ~50%
  - Aspiration
    - During swallowing
      - ↑ weakness of muscles of pharynx and larynx
    - After swallowing
      - Laryngeal muscles open
      - Residue food / fluid in pharynx passes into airway → aspiration
  - Definition
    - Longer contraction and poor relaxation of affected skeletal muscles

- Myasthenia gravis (MG)
  - Definition - "…a progressive autoimmune disease, characterized by
    - High circulating levels of acetylcholine receptor antibody
    - Destruction of acetylcholine receptors at neuromuscular junction (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 688).
  - With repeated swallowing, there is amplitude of the pharyngeal contraction → oropharyngeal dysphagia
  - Oropharyngeal dysphagia in ~ 33%

Barrett epithelium (BE)

- Give the molecular biology (molecular events) in the progression of esophageal mucosa from normal to Barrett epithelium (BE) (metaplasia and dysplasia) to adeno' esophageal cancer (ECa).

Normal	----→	Metaplasia (globlet cells)	-------→	Dysplasia (globlet cells often depleted)	-----→	Eca

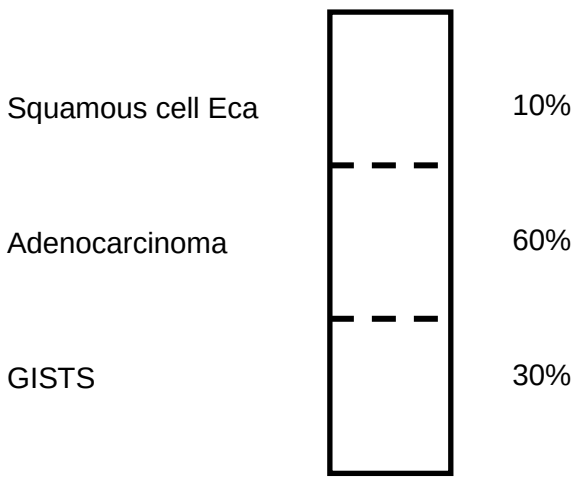
- ↑ proinflammatory cytokines, e.g. ↑ IL-1β, ↑ TNF-α
- ↑ homeobox proteins Cox-1 and Cox-2

- p16
- ↑ cyclin D1
- ↑ telomerase
- TP53

- ↑ IHC markers
  - PCNA
  - I67
  - Cyclin D1
  - TP53
  - AMACR (alpha-methyl acyl – CaA racemase), % positive
    - Metaplasia, 0%
    - LGD, 38%
    - HGD, 8%
    - BE-ECa, 72%

- ↓ E-cadherin
- ↓ B-catenin
- ↑ TNF-α
- ↑ Cox-2 expression

Abbreviations: HGD, high grade dysplasia; IHC, immunohistochemical markers; LGD, low grade dysplasia; PCNA, proliferating cell nuclear antigens; TNF-α, tumor necrosis factor-a;pha



SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1: BE (Barrett epithelium) occurs in about one in ten persons with GERD. Give the criteria for the definition of BE taking into account current controversies.

- Prague CM criteria
  - C, circumference
  - M, maximum extent (length)
- Long segment BE seen in 3% to 5% of GERD patients 10% to 20% short segment BE

A1:
- Country
  - USA
    - Endoscopic abnormality
    - "long" (> 3 cm) versus "short" (< 3 cm) segment

*Note: 5% of adults with non-GERD symptoms have BE

  - Europe
    - Biopsy abnormality (columnar epithelium, with goblet cells)

*Note: Dysplastic tissue may be patchy, and may appear normal on endoscopy)

- Biopsy
  - Metaplasia
    - intestinal metaplasia at the GE junction
    - metaplasia of gastric cardiac-type epithelium

Q2: Define "dysplasia", and give 5 changes in tissue architecture and cell morphology which are seen in this condition.

A2: The histological changes of dysplasia include:

- Architecture
  - Disorganized villiform surfaces
  - Crowded tubules
- Cell nucleus
  - Large nucleus
  - Pleomorphic hyperchromatic
  - Stratified
  - Atypical mitoses
- Cell cytoplasm
  - Loss of maturation

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q3: Give the approximate risk of BE metaplasia progressing to LGD (low grade dysplasia), HGD (high grade dysplasia), or ECa (esophageal adenocarcinoma) each year.

A3:

BE mataplasia	LCD	HGD	ECa

o----------→ 0.1% / year

o----------→ 4.3% / year

o----------→ 0.9% / year

o---------→ 4% to 6% /year

Q4: In symptomatic patients with GERD or BE, elimination of symptoms does not mean that the gastric % pH < 4 is less than 4% to 5%, or that the esophagitis has resolves. What is the physiological explanation for this disconnect?

A4: The data on PPI gastric acid suppression and targeting 24 hr pH < 4 to < 5% is for gastric and not for esophageal pH may be low (↑ H^+). Thus, the use of gastric pH as a surrogate marker for esophageal pH must be challenged.

Q5: Some authorities recommend endoscopic surveillance for BE, and discourage anti-reflux surgery for the prevention of development of esophageal adenocarcinoma. While EMR (endoscopic mucosal resection does provide a pathological specimen" …….to judge the depth of neoplastic invasion and the completeness of the ablation" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 731), this "suck and cut" or "band and snare" does have a significant risk of recurrent or metachronous cancer. Ablation methods for BE do not provide tissue samples for pathological assessment, and there is the risk that the ablation treatment may leave metaplastic tissue "buried" under healing squamous mucosa which looks endoscopically normal.
Give the risk of recurrent or metachronous esophageal adenomas in BE patients treated with these two different modalities.

A5:
- The risk of developing esophageal adenocarcinoma after therapy for BE
  - PPI alone, 29%
  - PPI plus PDT (photodynamic therapy), 15% to 21% in 5 years
  - EMR, 11% in 37 months, 21% in 5 years
- Consider ASA plus PPI for the prevention or ↓ recurrent cancers
- If BE extends to a large portion of the circumference of the esophagus, perform EMR over several sessions in order to ↓ risk of formation of stricture.

Q. There is progressively increased genetic instability of the normal esophageal mucosa progresses from metaplasia to dysplasia, and from dysplasia to esophageal adenocarcinoma. Give 5 "genetic and epigenetic alterations that endow the [esophageal squamous] cells with the physiological attributes of malignancy" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 729), including the mediators associated with each alteration.

A.

- Metaplasia
  - Self-sufficiency growth signals
    - ↑ oncogenes (cyclin D1)
    - ↑ growth factors (TGF-α), EGFR [epidermal growth factor receptor]
  - ↓ sensitivity to anti-growth signals
    - ↓ activation of tumor suppressor genes (TP_{53}, TP_{16})
  - ↑ angiogenesis
    - ↑ VEGF (vascular endothelial growth factor)
  - ↑ aneuploidy
  - ↑ abnormal cellular DNA content
- Dysplasia
  -
  - Evasion of apoptosis
    - ↓ activation of TP_{53}
  - ↑ replicative potential
    - ↑ activation of telomerase, ↑ telomeres for cell division
  - Tissue invasion and metastasis
    - ↓ cell adhesion (↓ cadherins, ↓ catenins)
    - ↑ extracellular matrix degeneration – (↑ MMPs [matrix metalloproteases]0
- Adenocarcinoma
  - Self-sufficiency in growth signals
    - ↑ oncogene (K-Ras)
  - self-sufficiency in growth signals
    - ↑ oncogenes

*Note that at least 10% of tissue with HGD (high grade dysplasia) will already contain in situ cancer

Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 729.

- **Pill Esophagitis**

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1: Some medications will injury the esophagus because of their inherent chemical properties (e.g. ASA, NSAIDs, bisphosphonates).
Give 6 non-medication related predispositions for "pill esophagitis".

A1:
- Esophageal conditions
  - ↓ motility
  - Dysmotility
  - Strictures
  - Diverticula
  - Trough zone (mid esophagus where the upper skeletal and lower esophageal muscle overlap)
- Esophageal compression
  - Left atrial enlargement
  - Aortic compression
  - Left bronchial impression

Achalasia

Incidence $1/10^5$ per year
Prevalence ~ $10/10^5$
Familial clustering

Genetic achalasia syndrome (6As)
- Achalasia
- Adrenal insufficiency
- Alacrima
- Autosomal recessive
- AAAS gene mutations
- ALADIN protein encoded by AAAS

- Manometry changes
  - Smooth muscle esophagus
    - A peristalsis
    - Non-peristaltic contractions (spastic [vigorous] achalasia)
  - LES
    - ↓ relaxation
    - ↑ pressure (in 60%)

- Pathophysiology
  - Latent HSV-1 infection (HSV-1 antibodies in 84%, and HSV-1 DNA in 63%)
  - Autoimmune process
    - ↑ active / inactive cytotoxic T cells
    - Clonal expansion in myenteric plexus of LES
  - Myenteric ganglia
    - IgM antibodies
    - Complement activation
  - Genetic predisposition
    - HLA DQA1* 0103 alleles
    - HLA DQB1* 0603 alleles
  - Loss of ganglion cells
    - In myenteric (Auerbach's) plexus
    - The longer the history of achalasia, the greater the loss of myenteric ganglion cells
    - ↓ inhibitory ganglion nerve function
      - LES relaxation (deglutitive inhibition)
      - ↓ sequenced propagation of esophageal peristalsis
  - The loss of myenteric ganglion cells → postganglionic excitation
    - ↓ NO synthase → ↓ NA, ↓ VIP effect

Achalasia associated with Chaga Disease

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q: Give 2 causes of postsurgical pseudoachalasia (secondary achalasia).

A:
- After fundoplication
  - Motility changes may be similar
  - Amyl nitrate markedly reduces LES in primary than in postsurgical achalasia
  - Ensure that post-fundoplication dysphagia and possibly associated achalasia-like symptoms are not due to a paraesophageal hernia.
- After laproscopic adjustable gastric banding (GB, bariatric surgery)
  - 14% of LAGB have postoperative dilation of esophagus > 3.5 cm
  - Mechanism unknown
  - Usually this form of secondary achalasia resolves with removal of the gastric band

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1: On HREP manometry, define the three esophageal segments, and give the method of calculation and the use of the CFV (contractile front velocity) for defining an esophageal spastic contraction.

A1:
- There is one proximal esophageal body segment (S_1), and the three distal esophageal segments (S_2, S_3, and S_4)
- The pressure minimum in the transition zone at the lower portion of the upper third of the esophagus represents S_1, resulting from skeletal muscle
- The lower two thirds of the esophageal body represents the distal esophageal segment formed from smooth muscle.
- Within the distal esophageal segment there are three pressure peaks, S_2, S_3, and S_4
- Connect the proximal margin of S_2 and the distal margin of S_3
- Calculate the slope of the line connecting the 30 cm Hg isobaric contour (IBC) line

Q2: Using HREP manometry terms, distinguish between the three subtypes of achalasia (both a peristalsis and impaired deglutitive EGJ relaxation are needed to diagnose achalasia)

Subtypes of achalasia	Pressurization of esophageal body	IRP (mm Hg)	CFV (cm / sec)	Overall treatment response
I classical (20%)	-	≥ 15	< 8	56%
II compression (50%) (panesophageal)*	+	≥ 15	> IRP**	96%
III spastic (30%)	-	≥ 15	> 8	29%

*
- Highly predictive of good response to treatment
- With compartmentalized esophageal pressurization, the 30 cm long and the 50 cm long IBC (isobaric contour) lines are not parallel to each other
- In type II, there is no esophageal dilation, as there is with type III

**
- In penesophageal compression achalasia, the ↑ IRP (integrated relaxation pressure, i.e., the causes the pressure in the body of the esophagus to be compartmentalized with high intrabolus pressure developing between the "contractile front of the distal esophageal contraction and the EGJ……" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 696).
- As a result of this intrabolus pressure compartmentalization, the slope of the 30 cm isobar contour line no longer represents the CFV, so "…the algorithm for computing CFV defaults to computing the slope of an isobaric contour line of magnitude greater than the EGJ relaxation pressure….so as to consistently represent the timing of the luminal closure.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. It is thought that the major pathophysiological defect in achalasia in dysfunction / loss of inhibitory ganglion nerve (IGN).
On the basis of the typical manometric changes in achalasia, give two pieces of evidence that this IGN dysfunction theory is correct.

A:
- Important in "deglutitive inhibition", i.e., swallow-associated LES, relaxation
- This impaired deglutitive inhibition leads to failure of relaxation of LES with swallowing which occurs in achalasia
- Important in "sequenced propagation" of esophageal peristalsis
  - This impaired sequence propagation leads to a peristalsis of smooth muscle of body of esophagus.

Q2. Achalasia may be associated with degenerative neurological disorders, such as Parkinson disease. The typical pathophysiological defect seen in biopsies of the esophagus of patients with achalasia is reduced (inhibitory) ganglion cells.
In persons with achalasia associated with Parkinsonism, what are the characteristics of the degenerating esophageal ganglion cells?

A2. The degenerating ganglion cells in persons with achalasia associated with Parkinsion disease show intracytocytoplasmic hyaline or spherical eosinophilic inclusions. These intracytoplasmic hyaline or spherical eosinophilic inclusions are called "Lewy bodies".

Q3. What is the normal effect of CCK on esophageal muscle, and what is its effect in achalasia.

A3. Normal - CCK → ↓ LES (i.e., ↑ LES contraction)
Achalasia - CCK paradoxically ↑ LES pressure (i.e. ↓ LES relaxation)
- this may explain why LES pressure may be increased in 60% of persons with achalasia

Q4: Pulmonary aspiration from food / fluid trapped in the esophagus from impaired relaxation of the LES is common in achalasia.
Give the significance of the development of stridor (large airway compromise) in achalasia.

A4: With failure of relaxation of the LES and a peristalsis in achalasia, the esophagus may dilate sufficient to compress the trachea

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q5: Patients with achalasia may experience regurgitation of food on fluid as the result of food and fluid not passing into the stomach. But when "heartburn" develop in an achalasia patient, what is the mechanism?

A5:
- Myotomy treatment used for or smooth muscle relaxing drugs
- Retained food in esophagus fermented to acidic short chain fatty acids (e.g., acetic, butyric, proprionic acids)

- Trypanosoma (T.) cruzi bits the host, and over a long interval (up to 20 years there is destruction of the autonomic ganglia cells of the GI tract (esophagus [with 90% destruction of ganglion cells]) and heart (cardiomyopathy → arrhythmias), urinary tract (megauretor) and respiratory tract.
- Intestine [50% destruction of ganglion cells, especially of duodenum or colon, leads to abnormal peristalsis and dilation of the affected organ]).
- Unlike HSV-1 associated "primary" (idiopathic") achalasia, dysfunction of the esophagus begins in the body and later involves the LES.
- Diagnosis
  - Acute: blood smear identification of T. cruzi
  - Chronic: complement fixation, or PCR (polymerase chain reaction)

Distal Esophageal Spasm

- The modern meaning of DES is "distal esophageal spasm", not diffuse esophageal spasm, since the defect is in the lower third of the esophagus which contains smooth muscle.
- Normally
  - There is a latency interval in which there is a lag period between neural stimulation and smooth contraction.
  - This lag period leads to proximal smooth muscle contraction which moves along the length of the esophagus.
- The defect in DES includes
  - "disordered balance between excitatory and inhibitory influences on the esophageal smooth muscle" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 691).
  - Abnormal latency (↓ inhibition)
    - ↓ deglutitive inhibition
    - ↓ sequenced propogation of esophageal peristalsis

- When, this latency interval is lost, there is no lag period, and the entire esophagus contracts at once, without the normal synchronized peristaltic action (instantaneous activity of esophageal smooth muscle).
- Normal latency
  - ↑ sensitivity to cholinergic agents (↑ excitation)
  - Contraction
    - ↑ amplitude
    - Longer

- It is possible That DES and achalasia are two conditions on a spectrum, in which there is first dysfunction (↓ inhibition, ↑ excitation), followed by detectable changes in the number of inhibitory ganglion cells, and the amount of NO synthase as well as release of NO and VIP.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q6. Chest pain distinct from heartburn-like retrosternal burning discomfort may occur in as many as two thirds of achalasia patients. What is the mechanism of this pain?

A6:
- Spasm of longitudinal smooth muscle of esophagus
- Dilation of esophagus (megaesophagus)

Q7: Which manometric feature helps to differentiate spastic achalasia from distal DES (diffuse esophageal spasm)?

A7: Both DES and spastic achalasia may have non peristaltic esophageal wave in the body of the esophagus, but only achalasia shows impaired relaxation of LES.

Q8: Why must the patient with oropharyngeal dysphagia always be assesses for a possible esophageal disease / disorder?

A8: The localization of the site esophageal disease is poor; half of patients with a disease in the lower esophagus may experience their symptom in the area of the upper esophagus, so that symptoms perceived to arise from the upper esophagus may in fact be from the upper of the lower esophagus.

Gastroesophageal Reflux Disorder (GERD)

- Esophageal biopsy
  - "things with holes in the middle"
    - Gland
    - Vessel
    - Duct
    - Esophagus has submucosal glands, so there are also ducts
    - Hyphae can be in the esophagus tissue rather than just the hyphae on the surface past, diastase – sensitive, glycogen; suspect glycogenic acanthosis
    - PAS – positive

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give 4 features on history which help to determine if the feeling of a lump in the throat represents globus, rather than dysphagia.

A. Globus
-- Present between meals, not with swallowing food as with dysphagia
-- Swallowing food/ liquids makes globus better, not worse
-- Emotional stress makes globus worse
-- Frequently associated psychiatric and somatization disorders

SO YOU WANT TO BE A GASTROENTEROLOGIST! – Esophageal bolus obstruction

- Esophageal Foreign Bodies

Incidence of Esophageal food bolus impaction, $16/10^5$ per year

Q. A patient with an esophageal food-associated obstruction is given glucagon. What is the success rate of glucagon, what is its mechanism of action, and why is EGD still necessary if the food bolus passes?

A.
- Success rate of glucagon ~ 50%
- Relaxation of LES pressure using glucagon ~50%
- Associated esophageal pathology, 75%
  - Peptic stricture
  - Schatzki's ring
  - Eosinophilic esophagitis

SO YOU WANT TO BE A GI JOE/ JILL!

Q1. What is the mechanism of cold – induced esophageal pain?

A1. Esophageal spasm. Nope – you're back in the last century!. Cold induced esophageal pain results from distention of the esophagus. In fact, cold produces lack of esophageal peristalsis, resulting in dilation of the esophagus.

Q2. A simple question: define "heartburn"

A2. "A burning feeling rising from the stomach or lower chest up toward the neck" (www.expertconsult.com)

Q3. What is the difference between "uninvestigated dyspepsia" and "functional dyspepsia"

A3.
- Uninvestigated dyspepsia" is pain a discomfort with upper abdomen, thought to be due to a disorder in the upper GI tract, "in persons in whom no diagnostic investigations have been performed and in when a specific diagnosis that explains the dyspeptic symptoms has not been determined"
- "functional dyspepsia" is dyspepsia occurring in a person who has had an EGD (esophagogastroduodenoscopy), and the EGD is normal.

Q4. Dyspepsia is a symptom complex, with large heterogeneity of symptoms. There are a number of pathophysiological changes seen in persons with functional dyspepsia. The Rome criteria are respected as definitions for and guidance of the management of translucence GI disorders. The Rome III committee recommended that functional dyspepsia be considered as two subgroups:
- PDS (meal – related dyspeptic symptoms)
- EPS (meal – unrelated dyspeptic symptoms)

Give the validity use of these terms, PDS and EPS, in persons with functional dyspepsia

A4. The validity of this classification and distinction is not evidence – based.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give the laboratory features of allergic gastroenteropathy

A.
- ↓ serum
  - Albumin and total protein
  - Immunoglobins
  - Transferrin
  - ↑ eosinophils in lamina propria of affected GI tissues
  - Stool samples contain Charcot-Leyden Crystal

Q1. Give the second most cause of esophagus-related chest pain.

A1. Esophageal peristaltic contraction > 180 mm Hg ("nutcracker esophagus")

Q2. Give the clinical and manometric differences between "nutcracker esophagus" and DES.

A2.

Finding	NE	DES
Chest pain	+	+
Dysphagia during bouts of pain	No	Yes
Wave propagation	Yes	No
Multi-peaked waves	-	+
Simultaneous, non-peristaltic wave	-	+

Q3. Give 4 neurological conditions associated with the development of globus and a cricopharyngeal bar.

A3.
- CVA (cerebrovascular accident)
- MS (multiple sclerosis)
- MG (myasthenia gravis)
- ALS (amyotrophic lateral sclerosis)
- Myopathies

Nausea(N) and Vomiting (V)

From the clinical history, what can you suspect to be the cause of N/V?

- Early morning or fasting N/V of micael material - Direct activation of vomiting centre in the medullar, a the CT2 (chemorecepter trigger zone) in the area postrema on the floor of the 4th ventricle
- Vomiting of semi-digested food in late postprandial period - Gastric outlet obstruction
- "vomiting" of indigested food, without prior nausea - Addison , Zerker diverticulum
- Feculent vomitus - Lengstanding cystric outlet obstruction, ileus, intestinal obstruction, colonic fistula

- Projectile vomiting without preceding retching/ nausea - Tumor, abscess or increased intravisceral pressure
- Vomiting without nausea or autonomic manifestations - Rumination syndrome

More details in Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 14.1, page 199 are listed hundreds of causes of nausea and nausea (N) and vomiting (V).

- Gastric Volvulus

- Define gastric volvulus, and give the pathogenesis based on the bisecting axis and the associated rotation.

- Definition
  - Trusting of the usually fixed portions of the stomach due to laxity of the normal ligamentous attachments, or fixation of the usually mobile portions of the stomach to adhesions on tumors.
  - 2/3 occur above the diaphragm in association with a paraesophageal (type 2 hiatus hernia), or a type 3 (mixed) diaphragmatic hernia (sliding plus paraesophageal hernia).

- Types of gastric volvulus

Name of volvulus	Bisection	Pathogenesis
o Mesenteroaxil (40%)	- Lesser and greater curves	- Anterior rotation of the antrum along the axis bisecting the lesser and greater curves
o Organoaxial (60%)	- Body of stomach	- Anterior-superior rotation of the antrum along the axis bisecting the body of the stomach - Often associated with a diaphragmatic hernia
o Organoaxial, passing through the GE junction and pylorus	- Body of stomach	- Anterior-superior rotation of the antrum, and posterior-inferior rotation of the fundus

SO YOU WANT TO BE A GASTROENTEROLOGIST! - Intraluminal duodenal diverticula

Q. In the context of duodenal diverticula, what is “windsox diverticula”.

A.
- Windsox or intraluminal duodenal diverticula are single sac-like strictures that arise from D_2 (the second portion of the diverticulum), and are attached to part or the entire circumference of the duodenal wall.
- Both sides of the diverticular are lined by mucosa
- If a diverticulum is inverted in an erect direction and is viewed by EGD, it will appear as a mass.

Useful background: Lower esophageal sphincter relaxation (LESR)

- ↑ tLESR
  - NO (nitric oxide)
  - CCK (cholecystokinin), acting through the CCK-A receptors
  - Muscarinic receptors

- ↓ tLESR
  - $GABA_s$ (γ-aminobutyric acid, or γ aminobutyric acid agonists)

- Esophageal sensation

Signaling (stimuli)	Sensory endings	Afferent nerves	Ganglia

- Mechanical
- Chemical
- Thermal
- Electrical
	- IGLEs
	  Tension sensitive
	- IMAs
	  Stretch sensitive
	- Respond to 5-HT, ATP, bile
		- Vagal
		  Upper 1/3 – superior laryngeal nerve
		  Lower 2/3 plus LES – branches of vagus
		- Spincal
		  Thoracic splanchnic
		  mGlaR5 (metabotropic glutamate receptor) antagonists inhibit tLESR
			- Jugular
			- Nodose
			- Cervical of thoracic dorsal root

Abbreviations:

- IGLEs
  - Intraganglionic laminar [free nerve] endings in the myenteric ganglia
  - In a "….laminar structure that encapsulates the myenteric ganglia" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 686).
  - Predominanatly tension-sensitive afferents
  - IGLEs in the proximal stomach mediate tLESR (IGLEs → medulla → vagal efferents and phrenic nerves)
- IMAs
  - Intramuscular arrays in the muscularis propria,
  - Mostly in the LES
  - Mostly stretch-sensitive
  - Forming a network with ICCs (interstitial cells of the Cajal)
- ASICs
  - GI-acid sensing ion channels involved in mechanotransduction and response to acid
  - Releases inflammatory substances and neuropeptides
- TRPV1
  - Transient receptor potential vanilloid – 1
- 5-HT, 5-hydroxytryptamine
- ATP, adenosine triphosphate

- Dilated (> 1.69 mm) (intercellular spaces) is the earliest sign of damage to the esophageal epithelial cells. The resulting ↑ paracellular permeability to hydrochloric acid, pepsin and bile acids stimulates receptors for the sensory neurons in the intercellular space, resulting in "heartburn".

- Gastropharyngeal reflux symptom severity falls after age 31 to 40 years, but the risk of associated esophagitis associated with symptoms necrosis.

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 708.

Comparison of LES vs tLESR

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1: About 10% of reflex episodes in health persons occurring when there is swallow-associated LESR, and the rest occur when there is incomplete peristalsis. Give 2 reasons why reflux during swallowing-induced LESR is so uncommon.

A1:
- LESR lasts only 5 to 10 seconds, so there is little time for reflux to occur.
- The crural diaphragm does not relax during swallowing, thereby acting as a barrier to reflux
- The approaching peristaltic waves push any refluxate body in to the stomach.

Q2: Give 6 means by which the presence of a sliding esophageal hiatus hernia (HH) contributes to GERD.

A2:
- In the presence of a HH, the EGJ has a lower compliance, so that the EGJ may open at pressure lower than the intragastric pressure.
- Esophagitis associated with an HH may release mediators which ↓ LESP.
- As LESP falls, there is an increased likelihood of reflux.
- The presence of the HH reduces the support of the crural diaphragm.
- Loss of the intra-abdominal high pressure zone
  - Proximal displacement of the LES, or
  - Shortening of the esophagus
- ↓ straining-associated ↑ LESP
- ↑ gastric-distention associated ↑ tLESRs
- ↓ esophageal acid clearance
- HH is commonly associated with esophagitis (> 50%)
- HH increases risk of esophagitis (not just GER)

Q3: Give the endoscopic definition of a nonreducable esophageal hernia.

A3:
- A non-reducable hiatus hernia is one in which "…. The gastric rugal folds remain above the diaphragm between swallows" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 710)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q4: Give the definition of esophageal peristaltic dysfunction (EPD).

A4:
- EPD increases with increasing degree of esophagitis, e.g. EPD in 25% of patients with mild GERD, to 50% with severe GERD.

Q5: Over half of GERD patients have sleep disturbances. Give the changes in esophageal function during sleep.

A5:
- During sleep in the supine position, there is
  - ↓ effect of gravity
  - ↓ salination
  - ↓ esophageal secondary peristalsis

Q6: The contents of the esophageal lumen are buffered by the alkaline, HCO_3^- rich submucosal glands of the esophagus. Give the chemicals which buffer the intracellular pH of the esophagus.

A6:
- The intracellular contents of the squamous mucosa of the esophagus are buffered by
  - HCO_3^-
  - Phosphates
  - Protein

Q7: Give the earliest cellular marker of GERD, and its dimensions.

A7:
- The normal intercellular spaces in the esophagus of normal persons is < 1.69 μm.
- Dilation beyond this value occurs by unknown mechanisms, and is the earliest sign of mucosal damage from H^+, pepsin, and bile acids

Q8: In the context of GERD, what is the "acid pocket"?

A8:
- At the LES, extending from the lower esophagus into the cardia, there is an acid pocket, which is not neutralized by the presence of food buffering the gastric acidity.
- In the LES area, the pH < 4 for about one quarter of the 24 hour day (a reflux episode is define as pH drop of < 4.
- Physiological reflux is limited to pH < 4 for 5.5% of the 24 hour day.
- This increased acid exposure may predispose to damage from GE reflux at this area.
- This has a sensitivity for esophagitis of 77% to 100%, and specificity of 85% to 100%.

Q9: TRPV1 (vanilloid receptor 1) is expressed on sensory neurons of the esophagus; what is its function.

A9:
- TRPV1 is activated by
  - Chemicals (H^+, bile acids)
  - Heat
  - Distention
- As such, TRPV1 may mediate the sensation, reported by patients as "heartburn"
- It is unknown why only ~ 20% of GE reflux episodes are associated with symptoms

Q10: You suspect that your patient's hoarseness is due to GERD. An EHT consultation agrees the patient has "reflux laryngitis". Give the laryngoscopic findings which would expect to have been seen.

A10:
- Reflux laryngitis is characterized endoscopically as
  - Redness of the medial arytenoid walls, in the interarytenoid areas
  - Red streaks on the posterior third of the vocal cord folds

Q11: Compare the performance characteristics of an empirical PPI trial for GERD versus NCPP (non-cardiac chest pain).

A11:
- For GERD, the PPI test represents standard dose PPI bid for 2 weeks, with 50% decrease in heartburn.
- For NCCP, the PPI test represents twice normal PPI dose in the AM and night time single standard dose (e.g. omeprazole 40 mg in AM and 20 mg pm)

	GERD	NCCP
○ Sensitivity	68% to 83%	78%

- RR of NCCP with PPIs versus placebo: 0.54 (NNT, 3)

Q12: Over half of persons with typical GERD symptoms have a normal EGD. These patients are said to have (normal endoscopy reflux disease, non-erosive reflux disease, aka functional dyspepsia). Give the role of esophageal pH testing in the subclassification of the 3 types of NERD.

A12:

Findings	Types 1	2	3
○ Abnormal esophageal pH testing	+	-	-
○ Response to PPI: correlation between symptoms and episodes of reflux	+	+	-

Q13: From the position of narrowing of the esophagus (stricture) seen on a barium esophagogram, give the likely cause.

A13:
- Mid – esophagus
  - Barrett's epithelium-associated adenocarcinoma
- Lower esophagus
  - Schatzki ring

Q14. Give the role of surgery in Zenker diverticulum.

A14. Over 80% of patient with a hypopharyngeal (Zenker) diverticulum and cricopharyngeal bar respond to diverticulectomy plus myotomy; neither of these is recommended by itself, except possibly simple myotomy for a small diverticulum.

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 708.

Q15: In the patient with symptoms of GERD, many treatment algorithm emphasize the importance of numerous "life-style-changes". Give the left style changes for which there is demonstrated efficacy in GERD.

A15: while the results from life-style changes may vary from one patient to another with symptoms of GERD, appropriately designed studies have provided evidence for benefit only for
- Elevation of the head of the bed
- Weight loss (if ↑ BMI)
- Lying down in the left lateral decubitus position space
- *Note that while the evidence for benefit from smoking cessation in GERD is not strong, physicians with often take the opportunity to advise GERD patients of the overall benefits of stopping the smoke.

Q16: In the context of ↑ tLESRs (transients lower esophageal sphincter relaxation) in persons with GERD, name four classes of drugs that reduce tLESRs.

A16: ↓ tLESRs may be achieved with
- Agonists $GABA_B$ (γ-amino butyric acid)
- CCK-1 receptor antagonists (CCKA)
- Anticholinergics (atropine)
- NO (nitric oxide) synthase inhibitors
- Morphine

Q17: Obesity is associated with an increased risk of GERD, BE and esophageal adenocarcinoma (ECa). Name 3 peptides which may be linked to this association.

A17:
- Obesity is associated with an ↑ risk of GERD, BE and Eca by way of
  - ↑ IGF-1 (insulin-like growth factor 1) (proliferative peptide)
  - ↑ leptin
  - ↓ adiponectin (anti-proliferative effect of adiponectin)

Higher-Resolution Esophageal Pressure (HREP) manometry

Q: Why do we need newer tests of esophageal function? Give 4 limitations of conventional (i.e., non-high-resolution esophageal) manometry.

A:
- LES
  - Lack of widely accepted definition of "incomplete deglutitive EGJ relaxation"
  - Lack of ability to access the radial nature of the asymmetrical LES
  - Hiatus hernia produces distortion
  - Body-confounding effects of deglutitive
    - Contraction of the crural diaphragm
    - Shortening of the esophagus
    - Movement of the recording sensors
- Diagnosis of achalasia, DES subtypes not possible
- Conventional manometry plus intraluminal Impedence measurement (ILM)
  - IIM
    - Bolus transit
      - Direction, content (liquid, air), completeness
      - Impedence
        - ↓ liquid passes
        - ↑ air passes
      - 50% ↓ II, bolus enters
      - 50% ↑ II towards baseline, bolus passes
  - Concordance of 97% with VFSS (video fluoroscopy swallowing study) to assess the transit of the bolus

- High-resolution esophageal pressure (HREP) manometry
  - Definition: "……. A sufficient number of pressure sensors [are used] within the esophagus such that intraluminal pressure can be monitored as a continuum along the length of the esophagus" (Feldman M., et al.

Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 694).

- HREP manometry "…….coupled with sophisticated algorithms to display the manometric data as pressure topography plots, [so that] esophageal contractility is visualized with isobaric conditions amonth sesers indicated by coloric regions on the pressure topography plots" " (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 694).
- The main advantage of high-resolution esophageal pressure topography HREPT are
  - Measure IRP (integral IRP (integrated relaxation pressure; normally IRP ≤ 15 mmHg) as the optimal assessment for "deglutitive relaxation" of the EGJ (esophageal-gastric junction)
  - Making the diagnosis of achalasia: HREPT for diagnosis of achalasia, using IRP:
    - Sensitivity, 98%
    - Specificity, 96%
  - Distinguishing the 3 types of achalasia
  - Characterization other forms of esophageal motility abnormalities, such as DES (distal [diffuse] esophageal spasm)
  - IRP is "….the average EGF pressure for the 4 seconds of greatest relaxation within the relaxation window" " (Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 695).

Oropharyngeal dysfunction (OPD) impaired neuromuscular function
Cricopharyngeal bar commonest structural cause of OPD.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. It is clinical important to distinguish between oropharyngeal versus esophageal causes of dysphagia. What is the use of the finding of a loss of the gag reflex to diagnose oropharyngeal dysfunction (OPD)?

A1. Since ~ one third of normal persons lack a gag reflex, this finding is neither sensitive nor specific for OPD.

Q2. Is a "Stroke" a stroke? Is a cortical stroke more likely to cause dysphagia and to be permanent than a brain stem stroke?

A2. Cortical stroke
- Less likely than brainstem stroke to cause oropharyngeal dysphagia
- Dysphagia more likely to improve

Q1: In the context of HREPT 9high resolution esophageal pressure topography), define DCI (distal contractile integrity), and give two examples of its use.

A2:
- Definition: "The DCI integrates the length, vigor and persistence of the two subsegments of the distal esophageal segment contraction" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 697).
- Nutcracker esophagus (by conventional manometry, pressure waves of esophageal body > 180 mm Hg)
  - DCI > 5000 mm Hg.s.cm
- "Spastic nutcracker" pattern
  - DCI > 8000 mm Hg.s.cm
- Hypertensive LES

Q2: Using HREPT, give the three components which are measured and use to create the Chicago classification of esophageal motility disorders (see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 42.2, page 699).

A2:
- IRP (integrated relaxation pressure, EGJ deglutitive relaxation)
- CFV (contraction front velocity)
- DCI (distal contractile interval)

Esophageal diverticulum

- Zenker diverticulum (ZD)

  - The incidence of development of squamous cell cancer in ZD of 1% per year does not justify surveillance, but does mean that if myotomy is planned, the diverticulum must be inspected to determine if it is also necessary to perform a diverticulectomy.
  - In persons with ZD having a thyroid scan, be aware that the radioactive iodine tracer may accumulate in the diverticulum and lead to the incorrect suspicion of metastatic thyroid cancer.

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- Epiphrenic diverticulum (ED)

Q1. What is the rational of performing myotomy plus fundoplication in persons with an ED?

A1.: ED may occur as a complication of bariatric surgery, but 80% of ED is associated with a motility disorder of the esophagus. Thus, the myotomy needs to be done at the time of the resection of the ED to reduce the high risk of recurrence. With the myotomy, there is risk of post-resection GERD, so a nondestructing fundoplication is performed.

- Esophageal Intramural Pseudodiverticular (EIP)

Q2. Define EIP, and list 4 of its complications.

A2. EIP are abnormally dilated ducts of the esophageal submucosal glands, leading to

- Periductal inflammation and fibrosis
- Atrictures
- Communication between adjacent pseudodiverticula
- Ulceration, hemorrhage
- Perforation → mediastinitis
- Misdiagnosis of esophageal cancer

Mallory Weiss Tear

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Q1: The MW (Mallory-Weiss) syndrome arises from a tear in the esophagus, usually within 2 cm of the EGJ (esophagogastric junction), along the lesser curve of the cordia. The bleeding arising from the tear is proceeded by vomiting in about two thirds of patients. Give the mechanism of the MW syndrome or tear.

A1: The MW tear is thought to arise from "…….shearing forces on the gastroesophageal junction and proximal stomach as it herniates through the diaphragm because of high intra-abdominal pressure due to forceful vomiting" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 740).

Infections

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1: Esophageal candidiasis is common in persons who are profoundly immune suppressed (e.g. HIV/AIDS, or post-transplantation). Give 7 additional conditions predisposing the patient to candida esophagitis.

A1: Conditions which predispose to the development of esophageal candidiasis include

- Esophageal stasis
  - Scleroderma
  - Achalasia
  - Stricture
  - Intramural pseudodiverticulosis
  - Eosinophilic esophagitis (possibly from treatment with topical steroids)
- Medications
  - PPIs
  - Topical steroids
- immunosuppression
  - Old age
  - Diabetes
  - Alcoholism

Q2: In the context of the immune-suppressed patient in the ICU who develop dysphagia and retrosternal pain, define the “black esophagus”.

A2:
- The “black esophagus” represents the endoscopic finding of acute esophageal necrosis
- This may arise from esophageal ischemia, or infections such as candidiasis or HSV.

Q3: HPV (human papillomavirus) is a DNA virus which infects squamous epithelium of normal, immune competent persons. HPV infection is often asymptomatic. Give the endoscopic findings of HPV esophagitis.

A3: Because HPV is often asymptomatic, the diagnosis may be missed. When EGD is performed, the following endoscopic changes are characteristic:

- Red macules
- White patches
- Nodules
- Frond-like lesions
- Associated esophageal squamous cell cancer in patients with APECED (autoimmune polyendocrinopathy-candidiasis-

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Q: A 60 year old patient with dyspepsia has EGD showing multiple white patches. Give ways to distinguish between candidiasis versus glycogenic acanthosis.

A:

Features	Candidiasis	Glycogenic acanthosis
➢ History, immunosuppression	+/-	-
➢ White patches wash away with EGD water infusion	+	-
➢ Brushing for, cytology hyphae on	+	-
➢ Biopsy	Hyphae	Large squamous cells because of ↑ glycogen in cytoplasm

Q: An immune suppressed patient with dyspepsia and odynophagia is found to have EGD. Give the endoscopic and biopsy changes which differentiate CMV versus HSV esophagitis.

A:

	CMV	HSV
Ulcers	o A few long, large, deep, serpiginous ulcers with undermined edges	o Numerous small, round, superficial “ulcer-like” ulcers
Location	o Mid and distal third	o Any part of esophagus
Biopsy	o Center of lesion o “Owl’s eyes” inclusion bodies	o Edge of lesion o Nuclei, “ground glass” o Multinucleated giant cells o Eosinophilic “Cowdry bodies”

Adapted from: Spiegel, BMR, et al. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time Resource. *Slack Incorporated* 2011, Table 147.1, page 180

Varices

Q:
- The risk of any patient with compensated cirrhosis having EV (esophageal varices) is high (50%),
- The risk of these EV bleeding is high (30% in next 2 years), and
- The risk of dying from this first EV bleeding is high (20%);
- It is important to identify all those cirrhotic patients who might have EV and therefore would benefit from EVBL (esophageal variceal band ligation).

If we were to accept that it is not cost-effective to perform EGD on all compensated cirrhotic to determine if EV are present, then indicate what factors predict the presence of EV in a patient with cirrhosis (↑ HVPG > 12 mm Hg), and which thereby be used to increase the pretest probability of finding EV on EGD.

A:
- Physical examination
  - Splenomegaly
- Laboratory
  - Platelets < 88,000 / mL
  - ↑ INR
- Diagnostic imaging (abdominal ultrasound)
  - Portal vein diameter > 13 mm

Abbreviations: EGD, esophagastroduodenoscopy; HVPG, hepatic vein pressure gradient

Q: Give the pathophysiological basis for EVBL being superior to β-blockers for primary (before first EV bleed) or secondary (after first EV bleed) prophylaxis of EV (esophageal variceal) bleeding (EVB).

A: B-blockers
- The risk of EVB is related to the HVPG
- The threshold for EVB is HVPG > 12 mm Hg
- B-blocker (BB) dosage is targeted to ↓ HVPG < 12 mm Hg, but it is not routinely possible to have HVPG measurements.
- Surrogate markers for BB ↓ HVPG < 12 mm Hg include
  - ↓ HR to 55-60 bpm
  - ↓ SBP by 25%
- Even with ↓ HR / ↓ SBP to these targets, the HVPG may still be > 12 mm Hg
- Also, the BB dosage may cause adverse effects and dose-escalation may need to be stopped before these HR / SBP endpoints are reached.
- Compliance with taking BB may be an issue if there HR / SBP endpoints are reached
- Risk reduction for EVB with BB, only 50%

- EVBL (endoscopic variceal band ligation)
  - Risk reduction, 66%
  - Less compliance issue
  - May still provide some benefit, even when HVPG > 12 mm Hg

Q: Varices may appear in the esophagus, at the junction of the esophagus and stomach (junctional varices), or as isolated gastric fundic varices. Fundic varices may occur in association with esophageal or junctional varices, when there is portal hypertension. When there are isolated fundic varices, the HVPG (hepatic venous pressure gradient) is normal (< 12 mm Hg).

- Give the anatomical basis for isolated fundic varices.

A:
- The splenic vein joins the superior mesenteric vein to form the portal vein (PV).
- The esophageal vein (EV) comes from the PV, so any obstruction which is proximal to the take-off of the EV from the PV causes left-sided portal hypertension, without esophageal or junctional varices.
- Thrombosis of the splenic vein leads to congestion of spleen and distention of the short gastric veins (SGV).
- Distention of the SGV leading from the spleen to the gastric fundus will cause isolated gastric fundal varices.
- The isolated gastric fundal varices.

Q: The usual treatment of isolated gastric fundal varices arising from splenic vein thrombosis (SVT) is splenectomy.

- Give the anatomical circumstances when a splenectomy may not be therapeutically successful to treat SVT and its associated left-sided portal hypertension.

A: Splenectomy for SVT would not be useful to treat left-sided portal hypertension if thrombosis of the splenic veins were also associated with thrombosis of the inferior and/or superior mesenteric veins.

Q: In a pregnant woman with cirrhosis, what are the risks of a splenic artery aneurysm (SAA).

A:
- Risk of rupture, 5%
- Mortality rate in – Mother, 75%
  - Fetus, 90%

- Risk of rupture increases when SAA > 2 cm

Q: In pregnancy, the portal pressure increases because of the physiological increase in plasma volume. In a pregnant woman with cirrhosis, give the risk of variceal bleeding.

A: o The risk of bleeding from esophageal varices during pregnancy depends on their size:
- Small varices, 25%
- Large varices, 75%

Q: In a pregnant cirrhotic woman, there is a high risk of bleeding. There are no trials of the efficacy or safety of EVC (esophageal variceal ligation) in pregnant cirrhotic patients. Beta-blockade is useful for primary and secondary prophylaxis of esophageal variceal bleeding in non-pregnant cirrhotics, and beta-blockers are FDA pregnancy class C.
 Give the reason why beta-blockers should not be used in the pregnant woman with cirrhosis.

A: o It is true that β-blockers are FDA pregnancy class C in T_1 (the first trimester of pregnancy), but in T_2 and T_3, β-blockers are FDA pregnancy class D.
o This class D rating in the second and third trimester is due to their adverse effect on the fetus at that time, due to fetal
- Growth retardation
- Bradycardia

Tumors

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 46.1, page 746

Malignant Esophageal Cancers (ECa)

 Incidence (per 10^5)
o USA
- Men 7.5
- Women 1.8
o "Asian esophageal cancer belt" (from Northern to North-Central China)
o Southeast Africa and South America, Northern France, Switzerland ~ 25
o Type
- In North America, adeno' ECa > squamous
- About 20% increase per year; especially among
  - Middle-aged Caucasian men
  - Long history of frequent, moderately sever GERD symptoms

Give 20 risk factors which predispose to the development of esophageal cancers (ECa), and 5 which may be protective.

- **Increase Risk**
- Food and drink
  - Contamination with soot (N-nitroso compounds)
  - Non-tap water
  - Fusarium fungi-contaminated corn
  - Smoked pickles
  - Hot beverages
  - Meat; red, salted, boiled
  - High intake of vitamin B12
  - Low intake of
    - Selenium
    - Zinc
    - Folate (MTHFR [5,A-methylenetetrahydrofolate reductase] 677 TT gene variant)
    - Fiber (adeno' but not squamous ECa)
    - Beta-carotene folate
    - Vitamins B6, C, E
- ↑ BMI / ↑ waist circumference
  - Obesity → ↑ GERD → ↑ GE → ↑ adeno ECa
- Alcohol and tobacco
  - Important in low incident areas (such as North America) Alcohol risk variability may be due to "…..specific polymorphism [specific variant alleles] in genes encoding for alcohol metabolizing enzymes" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 747).
  - Smoking; hazard ratios
    - Squamous, 9.3
    - Adenocarcinoma, gastric cardia (GC), 2.9
    - Non-GC, 2.0
- Pre-existing diseases
  - Esophagus
    - Achalasia
    - Strictures of esophagus associated with lye ingestion
    - Tylosis

- 50% lifetime risk of ECa
- LOH (loss of heterozygosity)
- TOC (tylosis esophageal cancer) gene

  - Non-esophageal
    - Celiac disease
    - Diabetes
    - Duodeno-gastroesophageal reflux (e.g. after cholecystectomy)

- Infections
  - HIV /AIDS
  - HPV
  - Chronic mucocutaneous candidiasis in APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy)

- Cancers of head and neck

- Radiation therapy

- Iron deficiency (Plummer-Vinson / Patter-Kelly syndrome)

- Family history and genetic factor
  - Squamous cell ECa
    - "consistent ribonucleic acid [RNA] expression patterns" " (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 749)
    - ESCC (esophageal squamous cell cancer) susceptibility gene
  - BE (Barrett epithelium)
    - 7% familial aggregation
  - Polymorphism (specific variant alleles) in genes affecting metabolism
    - Alcohol
    - Folate carcinogens
    - DNA repair
    - Control of cell cycle
    - Oncogenes

- (Decrease Risk) Protective factors
- Foods
  - Fiber (adeno' but not squamous ECa)
  - Beta-carotene folate
  - Vitamins B6, C, E

- H. pylori infection of stomach (in particular, cag A – positive strains)

- Drugs
  - ASA (aspirin)
  - NSAIDs

- Give the detailed molecular biology (molecular events) of Esophageal Cancers.

For full details of this complex topic, see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 749 to 751.

- Growth Factors

An excess of growth factors will lead to autonomous growth, and many of these have been identified for adeno' ECa:

- EGF (epidermal growth factor)
- TGF-α (transforming growth factor)
- CTGF (connective tissue growth factor)
- Endoglin
- HER2/NEU gene expression, coding for Cerb B2
- CCND1 gene expression, coding for cyclin D1
- Cyclin B

- Proliferation
  - LOH (loss of heterozygosity) of the antiproliferative protein of Rb (retinoblastoma),
  - Hypermethylation (functional repression) of
    - The tumor suppressor gene, p16
    - Allelic deletion of 5q where APC resides (↑ plasma level of hypermethylated APC DNA)

- Apoptosis

Disorder apoptosis reduces the effectiveness of this imporatant defense mechanism against the development of cancer. Such alterations include

- TP53 (seen in > 50% of ECas)
- Altered balance of bcl-2 family of genes
  - BCl-2
  - BCl-xl
  - BAX
- ↑ NF-kB (nuclear factor kappa B, an antiapoptotic factor, seen in 60% adeno' ECa)
- ↑ protein kinase Akt (serine-threonine kinase, aka protein kinase B)

- Replication*
  - ↑ telomerase → slowing of the usual shortening of the telomeres with each cell cycle → unlimited replication of cells

- Invasion
  - Metastasis results from
    - ↑ disruption of CAMs (cell-cell adhesion molecule):
      - ↓ E-cadherins, ↓ B-catenin
      - Integrins
      - CD44 tranmembrane glycoproteins
      - uPA (cysteine protease)
      - CTSB (capthepsin B)
      - MMP
      - TIMP

- Cyclooxygenase pathways**
  - ↑ Cox-2 expression
    - ↓ arachidonic acid (AA) in cells (thus, ↓ apoptosis)
    - ↓ PGE_2 (thus, ↑ angiogenesis)
  - Cox-2 inhibition
    - ↑ AA and PGE_2, ↑ apoptosis and ↓ angiogenesis
    - ↓ VEGF, ↓ bcl-2, ↓ AKT signaling, ↓ MMP, ↓ EGF receptor-mediated angiogenesis, ↓ IL-12

- Microsatellite instability (MSI)
  - Present in < 20% of adeno' ECa

- Chromosome abnormalities
  - ↑ aneuploidy, from defects in mitotic checkpoint genes

*Note: telomeres and telomerase

- Definition: "telomeres are composed of several thousand report of short six-base-pair sequence elements and are located at the ends of

chromosomes" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 750).

- With each replication of the cell cycle, the length of the telomeres become shorter
- Shorter telomeres lead to less replication
- At one point the telomers are so short that the cell moves from G_1 to G_0 phase of the cell cycle, and replication stops
- Telomerase is "….a ribonucleoprotein reverse transcriptase that counts shortening of telomeres" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 750).
- In cancer cells, there is ↑ telomerase which prevents the shortening of the telomeres, so replication continues ("unlimited replication")

** An alternate basis science question would be to ask the candidate to

"Give molecular biology of the anti-Cox-2 chemicals".

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Define "hamartoma".

A1: Hamartomas are "….benign developmental tumors consisting of disorganized and excessive focal growth of the mature normal cells" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 769).

 Give the therapeutic modalities available for early esophageal cancers.

 Endoscopic mucosal / submucosal resection (EMR / ESR). For early ECa)

- Polypectomy snare
- Lift-and-cut, with double channel endoscope
- Band-and-cut
- Cap assisted
- Space
- EMR plus EAT (endoscopic ablative therapy)
  - PDT (photodynamic therapy)
  - Laser / ablation (also used for tumor in-growth or overgrowth)
  - Radiofrequency ablation
    - APC (argon plasma coagulation)
    - Nd: YAG (neodymium : yttrium-aluminium-garnet)

        - KTP (potassium titanyl phosphate)
    - Palliation
        - Ablation (as above)
        - SEMS (self-expanding metal stents (covered for esophagorespiratory fistula)

- Radiotherapy
    - External beam
        - 3D-CRT (3-dimensional conformal radiotherapy)
        - IMRT (intensity modulated radiotherapy)
    - Brachy therapy (with or without concurrent chemotherapy)

- Chemoradiotherapy
    - Primary (by itself, no surgery)
    - With before surgery (neoadjuvant)
        - Concomitant
        - Sequential
    - Neoadjuvant chemoradiatherapy with surgery versus surgery alone: RR, allcause, mortality in adeno' or squam' ECa, 0.81

- Chemotherapy (metastatic disease)
    - Combination therapy:
        - Cisplatinum plus 5-fluorouracil (5-FU) plus epirubicin, or docitaxel
    - Biological agents (monoclonal antibody)
        - Cetuximab (anti-EGF receptor)
        - Erlotinib (nati tyrosine kinase)
        - Bevacizumab (anti VEGF)

- Nutrition
    - PEG, percutaneous endoscopic gastrostomy
    - PEJ, percutaneous endoscopic jejunostomy
    - NJ, naso-jejunal tube
    - Parenteral nutrition

- Pain control

- Team care, including palliative care

Abbreviations: EGF, epidermal growth factor; VEGF, vascular endothelial growth factor

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. If EUS is superior to CT for staging ECa as well as restaging nodal status of ECa after neoadjuvant preoperative chemoradiotherapy, give the role of FDG PET / CT in restaging ECa.

A: FDG PET CT is equivalent to EUS and superior to CT alone in evaluating post-chemoradiotherapy status of nodal ECa:

Useful background

Q-point values (overall joint sensitivity-specificity values
FDG PET, 85%
EUS, 86%
CT, 54%

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. In the context of esophageal dysphagia, what is the Howel-Evans syndrome?

A:
- Tylosis, or Howel-Evans syndrome
  - Autosomal dominant
  - GI associations
    - Oral leukoplakia
    - Squamous cell cancer of esophagus (SCCE)
  - Surveillance EGD (for SCCE) age 30, then q 2 years

CLINICAL VIGNETTE

- Case: A patient with a dysrhythmia develops fever and neurological symptoms 2 weeks after a cardiac radiofrequency ablation (RFA) procedure. Imaging shows multiple air bubbles in the left atrium. Give the mechanism by which the GI complication causes the neurological event.
- Answer: The RFA procedure has caused an atrial-esophageal fistula, with the development of an air embolus from the left atrium to the brain.

CLINICAL VIGNETTE

- Case: A patient with cough, fever, and weight loss is diagnosed with pulmonary TB. Give the complication which you suspect when the patient develops dysphagia, choking on swallowing chronic cough and recurrent pneumonia.
- Answer:
  - The development of dysphagia may be from mural compression from mediastinal nodes, or tuberculosis involvement of the esophagus, with ulcers and leaped up mucosa.
  - The choking on swallowing suggests that a fistula has developed between esophagus and the respiratory tract.
  - A fistula between the esophagus and the respiratory tree may also cause a chronic and recurrent pneumonia.

CLINICAL VIGNETTES

- Case: A 70 year old patient with weight loss, cough and dysphagia has a chest-X-ray before a barium esophagogram is performed. Give the change on chest-X-ray (CHX) which suggest esophageal cancer (ECa)
- Answer: Changes on CHX which suggest (ECa)

Trachea	Deviation Thick retrotracheal stripe
Esophagus	Dilated Esophagorespiratory fistula Air-fluid level
Mediastinum	Wide Air (pneumomediastinum) Abscess
Lung	Aspiration pneumonia Metastases Pleural effusion

CLINICAL VIGNETTE

- Case: Dysphagia, megaesophagus, megacolon, cardiomyopathy, sleeping in a hut with a thatched roof in Brazil with the reduviid bug defecating in your eye (!).
  - Answer: Trypanosome cruzi → Chagas disease

CLINICAL VIGNETTE

- Case: Sudden onset of dysphagia gastroparesis and constipation
  - Answer: Paraneoplastic syndrome

CLINICAL VIGNETTE

- Case: A 65 year old person is diagnosed with esophageal cancer (ECa). Give diagnostic imaging test recommended for staging.
  - Answer: First of all, consider the performance characteristics of CT and EUS for staging ECa:

	CT	EUS
Appropriate values	Sensitivity, 50% Specificity, 50% Accuracy, 50%	* 85%

  - Why – layers of esophageal wall are not seen as clearly on CT as on EUS.

*The use of EUS improved the survival of the patient, because the ECa was staged accurately, so that the correct treatment could be given, so difficult-to-detect more advanced disease would be correctly diagnosed, thereby improving mortality rate in the patients with earlier disease (stage migration)

- In restaging ECa after neoadjuvant chemoradiotherapy, EUS distinguishes ECa from fibrosis / scarring
- Ability to obtain FNA (fine needle aspiration for cytological diagnosis)

CLINICAL VIGNETTE

- Case: Pharyngeal dysphagia and untreated osteoarthritis (OA); difficult intubation at EGD
  - Answer: Cervical osteophyte (not pill esophagitis, since OA is not treated)

CLINICAL VIGNETTE

- Case:Dyspepsia and dysphagia in a young person; responds to dietary changes asthma and eczema; peripheral eosinophilia
  - Answer: Eosinophilic esophagitis

CLINICAL VIGNETTE

- Case: Dysphagia / globus, sensation of foreign body in mouth

Answer:
- Examine upper esophagus, threat and uvula for fibrovascular polyp on long stalk
- If polyp < 2 cm and EUS does not show penetrating blood vessels, remove endoscopically

CLINICAL VIGNETTE

- Case: Keratoderma of palms and hands and soles of feet, family history of esophageal cancer, personal history dysphagia.
  - Answer: Tylosis (aka tylosis palmaris)

Q1: Give the mechanism by which a small cell carcinoma of the lung can result in a paraneoplastic syndrome with sudden onset of dysphagia, gastroparesis, constipation, and on imaging the findings of megaesophagus, megacolon, ileus.

A1:
- The lung small cell cancer has an epitope similar to that on the myenteric plexus.
- The anti-Hw antibody forms against the lung tumor epitope.
- This antibody can also bind to the GI tract myenteric plexus, causing dysmotility.

STOMACH

Hypersecretion, Gastrin and ZES

Q1: In the context of the patient with dyspepsia, diarrhea and flushing, what is the Darier sign?

A1: Darier sign is the scratching of the skin causing visible urticarial, resulting from histamine release from mast cells in systemic mastocytosis.

Q2: Dyspepsia associated from hyperchlorhydria is usually treated most efficaciously with PPIs (proton pump inhibitors). Name the hypersecretory condition which responds as well to H2 receptor antagonists as to PPIs, and give the mechanism.

A2: The hyperchlorhydria associated from systemic matocytosis is due to the release of ↑ amounts of histamine from the mast cells. The histamine acts directly on the H2-receptor on the parietal cells, so blocking the H2-receptor with a H2-receptor antagonist is as effective as blocking the proton pumps, because the parietal cells would not be overstimulated by the Achor gastrin receptors.

SO YOU WANT TO BE A GASTRENTEROLOGIST!

Q. On the basis of the G cell, D cell and parietal cells, give the distinction between an H. pyroli infection of the gastric body (corpus predominant) versus the gastiic antrum (antral predominant).

A:
- Body predominant gastritis → gastric atrophy → ↓ H^+ → ↑ serum gastrin → ↑ PCM (parietal cell mass)
  Antrum predominant gastritis - ↓ D cells → ↓ somatostatin - ↓ inhibition of gastrin release from G cell → ↑ serum gastrin → ↑ HCl

Case: Dyspepsia diarrhea, renal colic, hypergastrinemia, positive secretin stimulation test.
A: ZES (MEN I)

Q2: Give the theoretical basis reflex hyperchlorhydria follwing withdrawal of ↓longterm PPI therapy.

A:
- PPI → ↓ HCl secretion - ↑ serum gastrin – EC cells hyperplasia and ↑ PCM (hypertrophy)
- When PPI stopped, PCM is hypertrophic, and more HCl may be secreted by unit stimulus

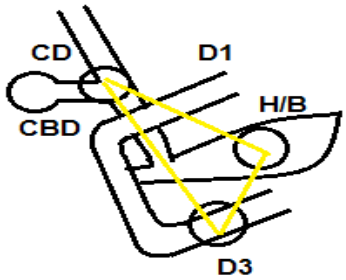
Understanding the physiology of gastrin: a trick – "start with the pathology"

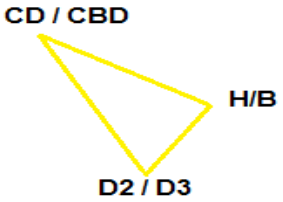
- ZES
  - Uncontrolled ↑ gastrin from gastrinoma
  - ↑ serum gastrin (usually > 1000)
  - ↑ HCl
  - Failure of ↑ HCl to inhibit further release of gastrin (and therefore of HCl) (loss of normal autoregulation)

Positive secretion stimulation test – serum gastrin increases by at least 200 U in response to IV infusion of a weight determined dose of secretin

Q: In the context of hypergastrinemia, hyperchlorhydria, parietal cell hypertrophy and a positive secretin stimulation test, define the "gastrinoma triangle".

A: The gastrinoma triangle is the anatomical area in which most gastrinomas occur





Abbreviation:

- Junction between CD (cystic duct) / CBD (common bile duct)
- Junction between D2 / D3 (2nd and 3rd portions of duodenum)
- Junction between H (head) / B (body) of pancreas

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. We are taught that treatment with proton pump inhibitors do not cause gastric carcinoid tumors, but what does the literature on the longterm follow-up of MEN-1-ZES patients treated with PPIs teach us?

A1. In MEN-1-ZES treated with longterm PPIs, half had ECL changes and 23% had gastric carcinoids.

Q2. Gastrin stimulates the growth of the colonic mucosa. What is the prevalence of colorectal carcinoma (CRC) in persons with ZES?

A2. Epimoilogic studies have not shown an increased risk of CRC in ZES.

SO YOU WANT TO BE A GASTROENTEROLOGIST OR HEMATOLOGIST!

Q. A 45 year old man presents with severe recurrent ulceration in the stomach and duodenum, occasionally with ulcers in the esopahgus and jejunum. While not on magnesium-containing antacids, he develops diarrhea which persists at night or when fasting, when his PPI is stopped or switched. The diarrhea Is worsened by alcohol, ASA and NSAIDs. The fasting serum gastrin is only modestly elucidated at 450 pg/ml. EGD demonstrates thickened gastric folds. CT of the abdomen shows hepatosplenomagaly, ascites, lymphadenopathy and a thick omentum, but no lesionsin the pancreas. EUS fails to show any lesion in the wall of the duodenum.

The patient is referred for a second opinion, and this consultant made the diagnosis when she asked the patient to remove his shirt , and by performing a colonoscopy.

Give the diagnosis made.

A.
- The reddish-brown freckle-like lesion on the patient's back were characteristic for urticaria pigmentosa.
- Colonoscopy showed purple coloured lesions.
- Small bowel biopsies showed infiltration of the lamina propria and muscularis mucosa with mast cells.
- The patient has systemic mastocytosis.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. There are numerous clinical features which suggest the Zollinger-Ellison Syndrome (ZES) (Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 32-6, page 502). About 99% of ZES patients have fasting hypergastrinemia.

- Name 2 circumstances where the fasting gastrin concentration may be normal in ZES.

A1.
- MEN-1 with hypercalcemia due to hyperparathyroidism
  - Hyperparathyroidectomy may normalize the previously elevated gastrin concentration
- Resection of a gastrinoma may allow the fasting gastrin concentration to normalize (there may still be the possibility that the tumor was not completely resected, and the hypersecretory syndrome may recur).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q2. In MEN-1-ZES associated hyperparathyroidism, what is the effect of parathyroidectomy on gastric physiology?

A2. Parathyroidectomy for hyperthyroidism in MEN-1-ZES has the following benefits:

- ↓ serum calcium
- ↓ fasting gastrin
- ↓ gastrin increase often secretin infusion
- ↓ basal acid output
- ↓ resistance of response to PPIs

Q3. The diagnosis of Zollinger-Ellison Syndrome requires the demonstration of gastric acid hypersecretion in the presence of hypergastrinemia. In ZES, 99% have a gastric pH < 2.

- What is the sensitivity of the measurement of BAO (basal acid output, mEq/hr) and the secretin provocative test to make the diagnosis of ZES?

A3.

- BAO (mEq/hr)

– No previous gastric surgery	>15	94% >10	90% >15	86% >18
– Previous gastric surgery	>5	100% >5		73% >14.4

- Secretin provocative test
  - Secretin infusion normally ↓ serum gastrin
  - When secretin infusion increases serum gastrin by ≥ 120 pg/ml, the test is positive/ a ZES (sensitivity, 94%; specificity, 100%)

Q4. ZES may be sporatic (S-ZES; 75%), or associated with MEN-1 (MEN-1-ZES; 25%). What clinical features suggest MEN-1-ZES rather than S-ZES?

A4.

- Renal stromas or colic (47% vs 4%)
- Younger age at presentation (34 years vs 43 years)
- Family or personal history of pituitary adenoma or hyperparathyroidism
- 70x greater risk of gastric carcinoids

Upper Gastrointestinal bleeding (UGIB)

- Checking for H. pylori infection during UGIB – blood reduces the sensitivity of RUT (rapid urease test; false negative test), but not of biopsy detection of H. pylori.
- In patients with an H. pylori ulcer complicated by bleeding, confirmation of eradications must be confirmed (no H. pylori, no ulcer, no rebleeding).
- If severe rebleeding occurs after EHT (endoscopic hemostatic therapy)/PPI for peptic ulcer disease, repeating EGD and EHY stops the bleeding in 73%, and thereby obviates the need for surgery.
- Systemic hypertension at the time of the initial presentation, and an ulcer > 2 cm predict failure of EHT to stop the bleeding.

- SRMI (stress-related mucosal injury)
  - Diffuse bleeding from erosions or superficial ulcers
  - Severely ill patients in ICU
  - Poor prognosis
    - High rebleeding rates
    - Multiple organ failure
    - ↓ wound healing
  - When to use anti-bleeding prophylaxis
    - Severe coagulopathy
    - Mechanical ventilator use for > 48 h
  - Injection (epinephrine) plus hemoclip superior to injection plus MPEC

- Dieulafoy lesion
  - usually seen in gastric fundus within 6 cm of GE junction
  - Protruding 1 mm to 3 mm submucosal artery
  - EHT is 90% effective, but banding is associated with high rate of rebleeding and perforation

- In patient with esophageal varices plus bleeding from Mallory-Weiss tear, focus on EBL (esophageal band ligation) of the varices
- APC (argon plasma coagulation) is 80% effective to achieve homeostasis from bleeding from GAVE (gastric antral vascular ectasia), even in patients with chronic renal failure.

SO YOU WANT TO BE A GASTROENTEROLOGIST! - EHT

Q. Give 3 examples of lesions causing UGIB in which EHT is not used.

EHT plays no role in the management of UGIB from portal hypertensive gastropathy (ectatic blood vessel), hemobilia, hemosuccus pancreaticus (rupture of splenic artery aneurysm into the pancreatic duct), or aortoenteric fistula.

SO YOU WANT TO BE A GASTROENTEROLOGIST! - UGIB

Q. Give the three patterns of portal hypertensive gastropathy (PHG) seen on EGD.

A.
- On EGD, PHG appears as
  - Diffuse, subepithelial bleeding giving a red, mosaic pattern to the mucosa (snakeskin appearance)
  - Fine red speckles on the mucosa
  - Red tips of the gastric rugae
- On biopsy of PHG, there are
  - Irregular, tortuous, dilated veins in the mucosa and submucosa
  - Intima thickened
  - No inflammation (no gastritis)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Give 4 examples of effective EHT.

A1.
- MPEC (multipolar electrocoagulation) probe
- Injection
- Hemoclips
- Band ligation
- Hemostatic spray
- Doppler probe ultrasound (cost-minimizing strategy)

Q2. What is the evidence for the use of pre-endoscopy and pre-EHT PPIs (proton pump inhibitors)?

A2.
- Theoretical
- Cost-effective modeling studies
- Hong Kong clinical study showing reduction in stigmata of recent bleeding (lower Forrest classification of bleeding source is associated with improved prognosis, i.e. Rebleeding, need for surgery, and mortality)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1: In a patient who presents with melena, a NG (nasogastric) tube is passes, and no blood is aspirated. Give the false-negative rate of a non-bleedy NG aspirate in a patient with upper GI bleeding (UGIB), proximal to the ligament of Treitz.

A1:	NG aspirate	No blood, but bile	No blood and no bile
	False negative for UGIB	< 5%	< 15%

Q2: Asked differently, of a NG aspirate is negative for blood, what is the likelihood of an upper GI cause of bleeding being the etiology.

A2: Answer differently.

- Clear but bilious NG aspirate in patient with melena is 95% specific for a source of bleeding below the ligament of Treitz.
- A clear but non-bilious NG aspirate in this setting is only 85% specific, so there is a 15% chance that the melena was caused by a source in the duodenum, stomach or esophagus.

Q: Give the distinction between a Mallory Weiss tear (MW) and Boerhaave syndrome.

A:
- Boerhaave syndrome
  - A MW tear with perforation
  - Retrosternal pain
  - Subcutaneous crepitus
  - Mediastinal air
  - L-sided pleural effusion
  - Surgical emergency

Incidence of hospitalizations for UGIB (upper GI bleeding), $170/10^5$

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. IV somatostatin/ octreotide reduces the risk of rebleeding from peptic ulcers, as compared with placebo or H_2 receptor blocker.

- Give the postulated mechanisms of this beneficial effect.

A.
- ↓ splanchnic/ gastroduodenal mucosal blood flow
- ↓ gastric acid (HCl) secretion
- ↓ GI motility

*Note – these drugs have not been shown to be effective as add- on to EHT (as is the case with PPIs), so they should only be used with UGIB which continues despite EHT plus PPI.

- Hereditary Hemorrhagic Telangiectasia (HHT), (aka Osler-Weber-Rendu disease)

- Define HHT, state the genetics, give the diagnostic criteria, and outline the distribution of lesions.

- Definition
  - A hereditary condition characterized by diffuse telangiectasias and large AV malformations.

- Genetics
  - Autosomal dominant traits with variable phenotypic expression
  - Mutations in 4 genes
    - ENG (gene which endoglin)
    - ALK-1 (activin receptor-like kinase 1)
    - MADHH, HIIT-3 (encode proteins which maintain the integrity of the vascular endothelium)

- Diagnostic criteria
  - Spontaneous and recurrent epistaxis
  - Multiple mucocutaneous telangiectasias
  - Visceral AVMs
  - A first-degree relative with HHT

Of interest, finding with ≥ 5 tekangiectasias found on upper endoscopy, this finding has a sensitivity of 75% and a PPV of 86% for the diagnosis of HHT.

- Distribution
  - 80% evenly distributed in small bowel
  - All actively bleeding HHT AVMs are found in duodenum and proximal jejunum
  - 1/3 of HHT patients have AVMs in lung, liver, brain

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 317.

What's new: Non-Variceal Upper GI Bleeding
- A methodology has been recommended for all the future RCTs in persons with non-variceal gastrointestinal bleeding (NVUGIB) (Laine et al, 2010).
- No scoring system has been validated to use to predict when rebleeding will occur after EHT (endoscopic hemostatic therapy) (El munzer et al, 2008). Thus, it is not recommended to routinely undertake a second-look EGD.

What's new: Enteroscopy

- The rate of complete enteroscopy is three times higher with double than with single-balloon enteroscopy (66% vs 22%) (May et al., 2010; 105: 575-81).

Useful background: Endoscopic treatment of varices

- EVL is the endoscopic method of choice to treat esophageal varices.
- No beneficial effects have been observed combining endoscopic sclerotherapy (EST) and EVL.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Suggest clinical endpoints when second-look EGD is indicated for rebleeding after EHT

A. Individualize such second-look EGD practice based on the unproven endpoints of
- Clinically apparent recurrent bleeding
- Unexplained low level of hemoglobin concentration after appropriate transfusion
- Hemodynamic instability
- Multiple patient morbidities
- High risk bleeding lesion seen at the index of EGD

- Proton pump inhibitors may enhance the safety of EVL
- Variceal bleeding is markedly reduced when the HVPG decreases to <12 mm Hg, or decreases by >20% from baseline
- EVL may reduce variceal size until variceal obliteration
- EVL has no effect on portal pressure
- Variceal obliternation with tissue adhesives (eg cyanoacrylates) is effective in the treatment of gastric varices

Abbreviations: EVL, endoscopic variceal ligation; EST, endoscopic sclerotherapy; HVPG, hepatic venous pressure gradient

Adapted from: Villanueva C, et al. *Best Practice & Research Clinical Gastroenterology* 2008;22(2): 263.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Give 3 methods to diagnose splenic vein thrombosis (SVT), which may lead to UGIB from gastric varices

A1.
- Doppler ultrasound
- MRI
- Angiography

Q2. Compare the efficacy of banding, gluing or injecting gastric varices from SVT.

A2. None of these choices is effective!
- The definitive treatment for bleeding gastric varices from SVT is splenectomy.

Q3. If the INR remains prolonged despite administration of FFP (fresh frozen plasma) in the cirrhotic patient who is bleeding from esophageal varices, what is the management?

A3. EHT (e.g. EBL) plus 80 μg/kg infusion of human recombinant factor VIIa, plus IV ciprofloxacin 400 mg bid.

Q4. A cirrhotic patient wishes to be informed about the efficacy of EBL for his bleeding esophageal varices and why he/she is not being offered sclerotherapy.

A4.
- Initial homeostasis from EBL of esophageal varices is about 80%, with a rebleeding rate of ~25%.
- EBV is superior to injection therapy in terms of lower rates of rebleeding, overall mortality, as well as mortality from bleeding.
- Just in case he/she asks, efficacy of octreotide for bleeding esophageal varices is similar to balloon tamponade (Sengstaken-Blakemore tube, Minnesota tube, or Linton-Nicholas tube): 90% initial control of bleeding,
- But there are 2 main problems with balloon tamponade
  - > 30% risk of rebleeding once balloon is deflated
  - 30% risk of serious complications

"Whoever said that old age was "The Golden Years"
was already demented."

Grandad

Q5. Bad examsmanship – never offer information which you cannot explain an obvious follow-up questions. You said it, so explain the differences between the 3 main types of balloon tamponade tubes used for bleeding esophageal varices!

A5.

		S-B	MINN	L-N
➢ Balloon	○ Esophagus	+	+	-
	○ Stomach	+	+	+
➢ Aspiration port	○ Esophagus	-	+	+
	○ Stomach	+	+	+

Abbreviations: L-N, Linton-Nicholas tube; S-B, MINN, Minnesota tube; Sengstaken-Blakemore tube

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give the "rule of two's" relating to Meckel Diverticulum.

A. Definition: "Congenital blind intestinal pouch that results from incomplete obliteration of the vitelline duct during gestation".

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 317.

- ○ Rules of 2's
  - Prevalence
  - Distance from ileocecal valve
  - Length, inches
  - Complications
  - Types of ectopic mucosa (gastric, pancreatic)
  - Age by which child usually presents age
  - Ratio of males to females

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 318.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give the clinical, etiological, pathological and complication differences in HHT (hereditary hemorrhagic telangiectasia, aka Osler-Weber-Rendu disease), and angiectasia.

A.

- Clinical unlike AEs, the lesions of HHT do involve the lips, mouth, nose, fingers. Curacao criteria need to be fulfilled to make a clinical diagnosis of HHT.
  - Telangiectasias
  - Epistaxis
  - Visceral lesions
  - Family history

- Etiology
  - Molecular genetic studies demontrate an autosomal dominant disorder in which there are two possible mutations of the HHT genes (genetypic heterogeneity).
    - ENG gene mutations
    - Encodes for endoglin, a TGF-β receptor
    - Type 2 : Activin receptor-like kinase-1 gene mutation
    - Encodes for ACVRL, protein, also a TGF-β receptor

- Pathology
  - Site
    - Stomach
    - Small bowel
    - Colon (AEs mostly in colon and small bowel)
  - Irregular, dilated, tortuous spaces
  - Single layer of endothelial cells
  - Vessels lack elastic lamina or muscular lissue
  - Arterioles
    - Thrombi (vascular stasis)
    - Proliferation of the intima
  - Venules
    - Thick wall (recall that the wall of venules in AE is thin)

- Complications
  - Involvement of lungs, brain and spinal cord, liver
  - High flow in vessels may lead to
    - High output congestive heart failure
    - Portal hypertension and liver failure

Useful background: Vital Signs and Acute Blood Loss

Physical Finding	Moderate Blood Loss Sensitivity (%)	Large Blood Loss Sensitivity (%)	Specificity (%)
Postural pulse increment ≥30/min or severe postural dizziness	7-57	98	99
Postural hypotension (≥ 20 mm Hg decrease in SBP)	9	...	90-98
Supine tachycardia (pulse >100/min)	1	10	99
Supine hypotension (SBP <95 mm Hg)	13	31	98

Source: McGee SR. *Saunders/Elsevier*, 2007, Table 15.2 page. 167.

Useful background: Performance characteristics of hypotension and its prognosis

Finding	PLR
Systolic blood pressure <90 mm Hg	
o Predicting mortality in intensive care unit	4.0
o Predicting mortality in patients with bacteremia	4.9
o Predicting mortality in patients with pneumonia	10.0
Systolic blood pressure ≤ 80 mm Hg	
o Predicting mortality in patients with acute myocardial infarcation	15.5

Source: McGee SR. *Saunders/Elsevier* 2007, Box 15.1 page 161.

- Perform a directed physical examination for hypovolemia (volume depletion).
  - Tilt test: (supine or standing) – postular ↑ HR by 30 bpm (sensitivity of 97%, specificity of 96% for blood loss >630 ml)
  - Supine SBP <95 mmHg, HR > 100 bpm
  - Poor skin turgor, seen as “tenting” of skin when pinched
  - Slow capillary refill time (2 sec for children and adult males, 3 sec for adult women, 4 sec for elderly) (sensitivity for hypovolemia only 11%, but specificity of 89%)
  - Drug mucous membranes and axilla
  - Sunken eyes
  - Longitudinal tongue furrows

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 3 and 4.

Bariatric Surgery

- Prepare a patient for informed consent prior to their having possible bariatric surgery, explain potential complications.
- Perioperative surgical complications
  - Surgery/ anesthesia
    - Anastomatic leaks
    - Hernia
  - Lung
    - Pulmonary embolism
    - Aspiration
  - Heart
    - Dysrhythmia
    - Cardiac arrest
  - GI
    - Hemorrhage
    - Incidental splenectomy
    - Small-bowel obstruction
    - Dumping syndrome
      - Flushing, palpitations, light-headedness, fatigue, diarrhea
    - Strictures
    - Cholelithiasis
  - Nutrition
    - Deficiencies Fe, B12, Ca, folate; vitamins A, D, E, K
    - Electrolyte disturbance
    - Protein deficiency
- Risks of not having obesity corrected

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 13-13, page 516.

Useful background: Mechanisms of benefit from bariatric surgery
- Restrictive
- Malabsorptive
- Combination of both
- Weight loss may be due to more than intake & absorption: there may be neuroendocrine changes such as reduced plasma ghrelin levels.

*Note that the rates of complications of bariatric surgery are proportional to the EWL (excess weight loss) achieved with the surgical procedure

BPD – DS >	Gastroplasty	=	Bypass >	Banding
(38%)	(18%)		(17%)	(7%)

- Esophagus
  - While these procedures generally improve pre-existing GERD symptoms, some patients will develop GERD after surgery (for example, about 50% with LAGB)
  - LAGB also is associated with esophageal dysmotility, including pseudoachalasia.

- Stomach
  - The rate of development of marginal ulcers varies (10%), and the risk is increased by smoking, and the use of NSAIDs or steroids

- Gallbladder
  - The increased incidence of post bariatric surgical cholelithiasis may be reduced with the use of UDCA for 6 mon. after surgery.

Abbreviation: UDCA, ursodeoxycholic acid; NHL, non-Hodgkin lymphoma; MM, multiple myeloma

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give the NIH consensus criteria for persons to qualify for bariatric surgery:

A. Without obesity – related co – morbidities: BMI > 40 kg/m^2
With obesity – related co – morbidities: BMI > 35 40 kg/m^2
Pre-operative weight loss is not part of the NIH criteria, but this is associated with shorter operative times, and greater weight loss at one year after surgery

"Your action with be judged by your pears"

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Give reasons why an EGD is recommended for all persons prior to bariatric surgery.

A1.

○ High risk of treatable lesion		%		%
- Esophagus	GERD			
	▪ LA A to D	3.7	▪ DU	0.7
	▪ BE	3.7	▪ Gastric carcinoid	0.3
	▪ GU	2.9	▪ Multiple lesions	1.1
- Stomach/ duodenum	▪ Erosive gastritis	1.8		

- ○ High risk of a symptomatic lesions - 1/3 of bariatric patients had a symptomatic pre-operative lesions
- ○ Difficult post-surgical investigation of upper GI tract with RNYGB

Abbreviation: BE, barrett epithelium; DU, duodenal ulcer; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; GU, gastric ulcer; RNYGB, Raux-on-Y gastric bypass

Q2. Draw the four most commonly performed gastric bypass procedures

A2.
- ➢ Malabsorptive
  - ○ BPD-DS (biliopancreatic diversion-duodenal switch)
- ➢ Restrictive
  - ○ LABG (laparoscopic adjustable banding gastroplasty)
  - ○ VBG (vertical banded gastroplasty)
- ➢ Restrictive and malabsorptive
  - ○ RNYGB (Roux-en-Y gastric bypass

For more details, see: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Figure 7.1, page 116

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. It is widely accepted that there is proven efficacy of bariatric surgery (RNYGB, VBG, LAGB and BPD-DS) in the areas of excess weight loss (EWL), mortality and resolution of comorbidities.

- Give the approximate rates of improvement in these categories overall, or by specific types of weight loss operations, in the mortality rates, resolution of co-morbidities.

A.
- % ↓ mortality from RNYGB
  - Coronary artery disease 56
  - Diabetes 92
  - Cancer, all types 60
  - Obesity – associated cancers
    - Esophagus 2
    - Colon 30
    - Breast 9
    - Uterus 78
    - NHL 46
    - MM 54

- % resolution of comorbidities (approximate)

	RNYGB	BPD-DS	Banding	Gastroplasty	Bypass
○ Hypertension	70	81	38	73	75
○ Diabetes	82	98	48	68	84
○ Hyperlipidemia	63	99	71	81	94

- Additional improvements
  - Q of L (SF 36 survey)
  - Resolution of GERD symptoms (may occur postoperatively)
  - NASH, % histological improvements
    - Steatosis 90
    - Hepatocellular ballooning 59
    - Centrilobular – perisinusoidal fibrosis 50

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 116-118

Abdominal pain and masses

- Take a directed history to determine the causes of RUQ pain.

- Heart
  - CHD
  - Pericarditis

- Lung
  - Pleurisy
  - Pneumonia
  - PE

- Aorta
  - Dissection /rupture

- Stomach/ duodenum
  - GU
  - DU

- Liver
  - Hepatitis

- Gallbladder
  - Cholecystitis
  - Choledocholithiasis

- Pancreas
  - Pancreatitis

- Kidney
  - Colic

Abbreviations: CAD, coronary artery disease; DU, duodenal ulcer; GU, gastric ulcer; PE, pulmonary embolism

Useful background: Location of pain in the abdomen and possible interpretation

*Note: Remember that disease of the heart and lungs, such as coronary artery disease and pneumonia, may present with upper abdominal pain

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. A sexually active woman of reproductive potential presents with acute abdominal pain three weeks after a missed menses. What are the most likely diagnoses?

A1.
- Ectopic pregnancy
- PID (pelvic inflammatory disease)
- Ovarian cyst or tortion

Adapted from: Filate W, et al.*The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 37.

Q2. How can you attempt to differentiate between involuntary or malingering pain?

A2. Try to distract patient by pretending to auscultate but pushing in the stethoscope, and watch the patient's face for signs of discomfort

Q3. Hyperalgesia and allodynia are both types of apin, but differ in the type of signal bringing on the pain; give the signal which causes the pain in each of these.

A3.

Word	↑ pain response to signal
○ Hyperalgesia	– Noxious
○ Allodynia	– Non-noxious

Q4. Which portions of the visceral pain transmission to the CNS are abnormal / dysfunctional in IBS?

A4.
- ACC (anterior cingulate cortex)
- PACC (perigenual anterior cingulate cortex)
- Dorsal ACC
- MCC (mid cingulate cortex)

Q5. Give the main mediators of the stress-immune response.

A5.
- CRF (corticotropin releasing factor)
- HPA (hypothalamic-pituitary-adrenal axis)
- Pro-inflammatory cytokines
- LC-NE (locus-coeruleus-norepinephrine) systems in CNS

Appendicitis and peritonitis

- Incidence $110/10^5$
- Lifetime risk F 6.4%
  M 8.6%
- CT signs
  - Diameter > 6 mm
  - Inflammation of periappendiceal fat
  - RLQ fluid
  - Non-filling of appendix with contract
- CT performance characteristics:
  - Diameter of appendix > 6 mm, PPV, NPV each 98%
  - False-negative rate F 10%
    M 6%
- Complication of appendectomy during pregnancy preterm delivery rate of 12%

The epiploic appendages are fat tags along the anti-mesenteric border of the colon, especially the transverse and sigmoid colon. Give the clinical, laboratory and diagnostic imaging differences between epiploic appendagitis versus appendicitis.

Clinical	Epiploic appendagitis	Appendicitis
o Acute abdominal pain	+, L-side	+, right side
o Peritoneal signs	-	+
o Fever, sweats	-	+
o CT scan of abdomen	- Focal, oval area of fat - Inflammatory stranding - Central, linear, attenuating line (from thrombosis of central vein)	- Obstructed lumen - Thick wall

Useful background: Terminology

- McBurney's point tenderness
  - Tenderness 1/3 along line from ASIS to umbilicus

- Rovsing's sign
  - LLQ palpation causes RLQ pain (indirect tenderness)

- Rectal tenderness
  - In patients with appendicitis whose inflammation is confined to the pelvis, rectal examination may reveal tenderness, especially on the right side, and some patients with perforation may have a rectal mass (i.e. pelvic abscess).

- Psoas sign
  - The patient lies down on their left side and the clinician hyperextends the right hip. Painful hip extension is a positive psoas signs, suggesting acute appendicitis.

- Obturator sign
  - Flex the patient's right hip and knee and then internally rotate the right hip; eliciting pain suggests acute appendicitis.

- Performance characteristics

  - The symptoms with the highest PLR for appendicitis are right lower quadrant (RLQ) pain (PLR, 7.3 to 8.5), migration of pain (3.2), and pain before vomiting (2.8).
  - The signs with the highest PLR are severe RLQ tenderness (7.3 to 8.5), rigidity (3.8), tenderness at Mcburneys point (3.4), rebound abdominal tenderness (1.1to 6.3), rectal tenderness (0.8 to 5.3), Rovsing's sign (2.5), and psoas sign (PLR, 2.0 to 2.4).

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

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Tables 48, page 577.

Useful background: Alvarado clinical decision rule (mnemonic "Mantrels") provides guidance to operate for suspected acute appendicitis.

- History
  - MAN – migration of pain (1), anorexia-acetone (1), nausea/vomiting (1)
  - TRE – tenderness in RLG (2), rebound (1), elevated temperature (fever) (1)
  - LS – leucocytosis (2), shift-to-the-left (1)

	PLR	NLR
Alvarado score ≥ 7	3.1	0.26

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

Source: Simel DL, et al. *JAMA* 2009, Table 5-5, page 62.

*Note that many historical points, symptoms and signs on physical examination have a PLR < 2 (and are not included here)

Useful background: Performance characteristics of physical findings that suggest the presence of peritonitis.

- Finding:
  - Guarding
  - Rigidity
  - Rebound tenderness
  - Percussion tenderness
  - Abnormal bowel sounds
  - Positive abdominal wall tenderness test
  - Positive cough test
  - Rectal tenderness

- None of the physical findings which have been taught to be clinically useful to diagnose peritonitis have a positive likelihood ration (PLR) greater than 3.9. the signs with a PLR > 2 include abdominal rigidity (3.9), guarding (2.6), percussion tenderness (2.4), and rebound tenderness (2.1).

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

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 48.1, page 576.

What is ”the best”? The “best” clinical tests for appendicitis in a person with RLQ pain are: McBurney’s point tenderness, Rovsing’s sign, and Psoas sign; the Alvarado score ≥ 7(is also useful).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. In the context of abdominal pain and tenderness, what are the Hover, Carnett and Jump signs?

A.
- Hover – the patient “hovers” their hand (s) over the abdomen during physical examination of the abdomen
- Carnet - ↑ tenderness of the abdominal call to palpation when the patient voluntarily tenses the muscles of the abdominal wall
- Jump – A negative reaction made by the patient when the abdominal wall is examined
  - The trigger point may be only the size of a finger tip

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. In the context of the patient with intra-abdominal pathology, what is the Kehr sign, and what is its mechanism?

A.
- With any cause of irritation of the diaphragm, for example from a subdiaphragmatic abscess or hematoma, or splenic rupture, the pain may be referred to the left shoulder.
- "Referred pain is ordinarily located in the cutaneous dermatomes that share the same spinal cord level as the affected visceral inputs" (Yarze JC & Friedman LS. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 163)
- First – order visceral afferent neuron from splenic rupture synapses With both first – order somatic afferent neuron as well as second – order spinal cord neuron.

Abdominal masses

- Perform a focused physical examination to determine the causes of abdominal masses.

- Upper abdomen
  - Retroperitoneal lymphadenopathy (e.g. lymphoma, teratoma)
  - Left lobe of the liver
  - Abdominal aortic aneurysm (expansile)
  - Carcinoma of the stomach
  - Pancreatic pseudocyst or tumor
  - Gastric dilatation (e.g. pyloric stenosis, acute dilatation in diabetic ketoacidosis or after surgery)
  - Carcinoma of the transverse colon
  - Omental mass (e.g. metastatic tumor)
  - Small bowel obstruction

- Right upper quadrant (palpable gallbladder)
  - With jaundice
    - Carcinoma of the head of pancreas
    - Carcinoma of the ampulla of Vater*
    - In-situ gallstone formation in the common bile duct
    - Mucocele of the gallbladder due to a stone in Hartmann's pouch and a stone in the common bile duct (very rare)
  - Without jaundice
    - Mucocele or empyema of the gallbladder
    - Carcinoma of the gallbladder (stone hard, irregular swelling)
    - Acute cholecystitis

- Right lower quadrant
  - Appendiceal abscess or mucocele of the appendix
  - Carcinoma of the cecum or cecal distension due to distal obstruction
  - Crohn disease (usually when complicated by an abscess)
  - Ovarian tumor or cyst
  - Carcinoid tumor
  - Amebiasis
  - Psoas abscess
  - Ileocecal tuberculosis
  - Hernia
  - Transplanted kidney
- Left lower quadrant
  - Feces
  - Carcinoma of sigmoid or descending colon
  - Diverticular abscess
  - Ovarian tumor or cyst
  - Psoas abscess
  - Hernia
  - Transplanted kidney
- Pelvis
  - Bladder
  - Ovarian tumor or cyst
  - Uterus (e.g. pregnancy, tumor, fibroids)
  - Small bowel obstruction
- Groin
  - Above the inguinal ligament
    - Inguinal hernia
    - Undescended testis
    - Cyst of the canal of Nuck
    - Encysted hydrocele or lipoma of the cord
    - Iliac node
    - Large femoral hernia (rare)
  - Below the inguinal ligament
    - Femoral hernia
    - Lymph node
    - Saphena varix (sensation of a 'jet of water' on palpation, disappears when supine)
    - Femoral aneurysm (pulsatile)
    - Psoas abscess (associated with fever, flank pain and flexion deformity)

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 5.14 page 174; Table 5.15, page 175, Table 5.17, page 179, Table 5.18, page 184 and Table 5.19, page 199.

What is “the best”? the “best four clinical tests for the presence of peritonitis are: rigidity, guarding, rebound and percussion tenderness.

Useful background: Causes of anterior abdominal wall masses

- Umbilicus
  - Malignant deposits – e.g. melanoma, carcinoma

- Rectus sheath
  - Umbilical, paraumbilical hernia, or epigastric hernia
  - Incisional hernia
  - Rectus sheath divarication
  - Rectus sheath hematoma

- Skin
  - Lipoma
  - Sebaceous cyst
  - Dermal fibroma
  - Epigastric hernia

Source: Talley NJ et al. *Maclennan & Petty Pty Limited* 2003, Table 5.15, page 193.

Useful background: Types of abdominal hernias

	Inguinal- indirect	Inguinal -direct	Femoral
Frequency	High	Medium	Low
Age and sex	All ages	Men >40	Women > men
Point of origin	Above inguinal ligament, through internal inguinal ring	Above inguinal ligament Through external inguinal ring	Below inguinal ligament
Course	Descends inguinal canal during straining, touching with examing finger in inguinal canal	Bulges anteriorly during straining	Inguinal canal is empty

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, Table 5, page 301.

Useful background: Causes of a palpable mass in the rectum

- In lumen
  - Feces
  - Foreign body

- In rectal wall
  - Hypertrophied anal papilla
  - Rectal or polyp carcinoma or rectal or sigmoid colon carcinoma prolapsed into the pouch of Douglas
  - Diverticular phlegmon (recent or old)

- Outside rectal wall
  - Metastatic deposits in the pelvis
  - Uterine or ovarian malignancy
  - Prostatic or cervical malignancy (direct extension)
  - Endometriosis
  - Pelvic abscess or sarcoma
  - Amebic granuloma

Adapted from: Talley NJ, et al. *Maclennan & Petty Pty Limited* 2003, Table 5.18, page 189.

Avoid A Common Mistake!

- Do not withhold analgesia in person with an “acute abdomen”, since several (6) studies have shown that giving such patients sufficient pain-relieving analgesia does not delay making the correct diagnosis of the cause of the pain.
- There is no reason to delay giving broad-spectrum antibiotics to an immunocompetent patient with peritonitis.

Useful background: Functional abdominal pain syndrome (FAPS)

- The explanation of FAPS arises from the biopsychosocial model of illness, the experiencing of pain arising from physiological, psychological (emotional) and cognitive (CNS – gut neuraxis) components

- There is
  - Upregulation of nociceptors in the mucosa
  - Sensitization of the visceral afferent nerves
  - Increased visceral efferent nerve signals in the brain (brain – gut dysregulation)

- Components may include
  - Dysregulation of CNS – ENS (central [C] and enteral [E] nervous systems)

- □ pain perception
- □ coping strategies
- □ social net works

Avoid Common Mistakes!

- Narcotics and "benzo's" (benzodiazepines) must be avoided in FAP/ IBS (irritable bowel syndrome)
  - □ pain sensitivity
  - □ pain threshold
  - □ dependency
  - Narcotic bowel syndrome
- Surgical lysis of adhesions – avoid laparoscopic adhesiolysis – not evidence – based

Management strategy in the prevention of recurrent SBP.

□ ***Recommended therapy***	o Oral norfloxacin 400mg p.o q.d (preferred) or o Oral ciprofloxacin 250-500 mg q.d* or o Oral levofloxacin 250 mg q.d*
□ Alternative therapy	o TMP-SMX 1 double strength tablet p.o q.d o (Patients who develop quinolone resistant organisms may also have resistance to TMP-SMX)
□ Duration	o Prophylaxis should be continued until the disappearance of ascites or until liver transplantation

* Empirical doses

Abbreviations: p.o, orally; q.d, once daily; SBP, spontaneous bacterial peritonitis; TMP-SMX, trimethoprim sulfamethoxazole

Source: Garcia T et al. *Am J Gastroenterol* 2009; 104: page 1812.

There are up-sides, down-sides and all kinds of sides (!)

Grandad

Intra-abdominal abscess (IAA)

- Give 10 bacterial adjuvant or host defense factors influencing the transition from bacterial contamination to infection.

- Bacterial Factors
  - Adherence capacity
  - Invasiveness
  - Metabolic systems
  - Resistance to antibiotics
- Adjuvant Factors
  - Barium
  - Blood
  - Fecal matter
  - Fibrin
  - Foreign material
  - Necrotic tissue
- Host Defense Factors
  - Fibrin sequestration
  - Lymphatic clearance
  - Neutrophil influx

Printed with permission: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 26-3, page 412.

- Give 5 causes of intra-abdominal abscesses (IAA), and 7 clinical risk factors.

- Causes of IAA
  - Stomach/ abdomen
    - Penetration / perforation
  - Small bowel
    - Crohn disease
  - Colon
    - Crohn disease
    - Diverticulitis
    - Neoplastic disease
  - Appendix
    - Appendicitis
  - Gallbladder
    - Cholecystectomy operations
  - Pancreas
    - Pancreatitis
  - General
    - Abdominal trauma
    - Perforated hollow viscus (e.g., duodenal or gastric ulcer)

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 26-1, page 412.

- Clinical Risk Factors for IAA
  - Systemic Factors

- Chronic glucocorticoid use
- Increasing age
- Malnutrition
- Preexisting organ dysfunction
- Transfusion
- Malignancy

o Local Factors
- Delay in performing surgery for underlying disease
- Formation of an ostomy
- Non-appendiceal source of infection
- Severe of illness, infection
- Severe of trauma

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 26-2, page 412.

 Give the abdominal diagnostic imaging findings suggestive of the presence of IAA.

 Plain films
- o Mass effect
- o Extraluminal gas
- o Localized ileus

 Ultrasound
- o Round/oval mass with
  - ↓central echogenicity (fluid, gas)
  - Thick wall
  - Internal debris

*Note: false negative findings may be due to overlying bowel gas blocking ultrasound waves

 Computed tomography (CT) scan
- o Extraluminal mass homogeneous fluid density, or heterogeneous solid density if IAA contains phlegmon
- o Extraluminal gas
- o Thick wall enhancement
- o Adjacent inflammatory changes

 Gallium 67 (^{67}Ga) or nuclear imaging scanning
- o Useful to follow-up CT scan

 Magnetic resonance imaging (MRI)
- o Limited use

Abdominal aorta

- Take a directed history and perform a focused physical examination for the cause of an abdominal bruit.
- Kidney
  - Renovascular disease
  - Unilateral renal hypertrophy
  - Bruit is rare in primary systemic hypertension
  - Normal variant (10% of normal persons)
- Liver
  - Hepatitis
  - Cirrhosis
  - Hepatoma (HCC)
  - AV fistula
- Pancreas
  - Neoplasia
- Spleen
  - AV fistula
  - Tortuous arteries
- Vessels
  - AAA (abdominal aortic aneurysm); aka “triple ‘A’”
  - Celiac artery compression, stenosis
  - Chronic intestinal ischemia
  - *An AB is rare in a person with essential hypertension. *In persons with renovascular hypertension, an AB is found in 77% with fibromascular disease, and 35% of those with atherosclerotic disease.

Adapted from: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 33.

Useful background: Performance characteristics of auscultation and palpation of abdomen for AAA*

- The value of the positive likelihood ratio (PLR) for AAA depends on the size of the lesion (see below), but overall the physical signs which have the highest PLR values include detecting renovascular hypertension (PLR, 38.9), palpating an AAA (8.0), and auscultating an abdominal bruit (5.6).

*sensitivity depends on size of AAA: > 3 cm, 29%; > 4 cm, 50%; >5 cm, 75%

Abbreviations: AAA, abdominal aortic aneurysm ; PLR, positive likelihood ratio

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 49-1, page 589; and Box 47-3, page 561.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. About 3 persons in 4 have the classic triad for ruptures of a "triple A" (AAA, abdominal aortic aneurysm).
Give the components of this triad:

A1.
- Abdominal pain
- Tender, pulsatile abdominal mass
- Hypotension

Q1. What are the names of the two signs of abdominal wall discolouration which suggest the presence of an ectopic pregnancy and ruptured AAA?

A1.
- Cullen's Sign: Purple-blue discoloration around umbilicus peritoneal hem caused by acute pancreatitis, ectopic pregnancy
- Grey-Turners Sign: Flank discolouration retroperitoneal hemorrhage; cau acute pancreatitis, ruptured abdominal aortic aneurysm (AAA), strangula

Adapted from: Filate W, et a. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 37.

NSAIDs

- Prepare a patient for informed consent for the use of non-steroidal anti-inflammatory drugs, explaining the potential adverse effects.
- Gastrointestinal
  - Constipation or diarrhea
  - Peptic ulcer disease; anemia, bleeding, perforation
  - Colitis
  - , bowel habit
  - Hemorrhage from diverticulae
  - Obstruction
    - "diaphragm" disease
- Renal
  - renal blood flow
  - glomerular filtration rate
  - creatinine clearance
  - Pyuria
  - Interstitial nephritis
  - Papillary necrosis
  - Nephrotic syndrome
  - Hyperkalemia
  - Type IV renal tubular acidosis

- Fluid retention

- Hematologic
  - Bone marrow suppression
    - Agranulocytposis
    - Aplastic anemia
  - Iron deficiency anemia
  - Platelet-aggregating defect

- Cardiac
  - Peripheral edema
  - Pulmonary hypertension

- Neurologic
  - Delirium/ confusion
  - Headache
  - Dizziness
  - Blurred vision
  - Mood swings
  - Aseptic meningitis

- Dermatologic
  - Urticaria
  - Erythema multiforme
  - Exfoliative syndromes (toxic epidermal necrolysis)
  - Stevens Johnson syndrome
  - Oral ulcers
  - Dermatitis

- Pulmonary
  - Nasal polyps
  - Pulmonary infiltrates
  - Non-cardiac pulmonary edema (aspirin toxicity)
  - Anaphylaxis
  - Bronchospasm

- Drug interactions
  - effect of warfarin
  - antihypertensive effect of diuretics, beta -blockers, angiotensin-converting enzyme inhibitors
  - Influence drug metabolism
    - Methotrexate (high doses only)
    - Lithium
    - Oral hypoglycemic agents

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 24-21, page 999.

Useful background: Risk factors for development of upper GI adverse effects with NSAIDs – need for c0-therapy (PPI or PEG_2)

- Age ≥ 65
- Comorbid medical conditions, e.g.
  - Cardiovascular disease
  - Alcoholic liver disease
  - Rheumatoid arthritis
- High doses of NSAID
- Use of
  - Anticoagulants (including low dose ASA)
  - Oral glucocorticoids
- History of upper GI bleeding
- Presence of H. pylori infection
- Multiple NSAID use (including low-dose ASA)

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: Canadian Pharmacist Association 2012, Table 1, page 1028.

Tumors and Polyps

- Gastrointestinal Lymphomas
- Hodgkin lymphoma is very rare in Gi tract, but non-Hodgkin lymphoma (NHL) has an incidence of $1/10^5$ per year

- Gastric Maltoma (mucosa associated lymphoid tissue)
  - Contains B and T cells at various stages of differentiation
  - B cells that have encountered antigen crossing the intestinal mucosa reside in the germinal centre of the MALT.
  - These germinal centre B cells or antibody-producing plasma cells.
  - B cells that have not encountered antigen remain in the mantle zone.
  - The memory B cells enter the systemic circulation, and return to the MALT marginal zone.
  - Most lymphomas of the GI tract arise from malignant transformation of the marginal B cells
  - Some GI tract lymphomas arise from germinal centre (follicular lymphoma) or from the mantle zone (mantle cell lymphoma).
  - Gastric lymphomas represent about 60% of lymphomas of the GI tract (marginal zone B cell lymphoma of the MALT type, or diffuse large B cell lymphoma)
  - Most gastric MALT lymphomas are associated with an H. pylori infection (98% serological and 90% histological association).

- When the H. pylori infection is eradicated, the gastric MALT lymphoma may regress; of considerable interest, small intestinal and rectal lymphoma may also respond to the eradication of associated gastric lymphoma (75%).

- Gastric Lymphomas
  - B cell
    - Marginal zone B cell lymphoma of MALT type
    - Diffuse large B cell lymphoma
  - Uncommon types

Useful background: EUS layers of gastric wall

Source: Spiegel BMR, et al. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time Resource. *Slack Incorporated* 2011, Figure 94.2, page 128

	Layer	Colour / echoic nature	Layer	
erosion ↑	1	Light, hyperchoic	Superficial epithelial layer	Mucosa
	2	Dark, hyperechoic	Deep epithelial layer	Muscularis mucosa
↓ ulcer	3	Light	Submucosa	Lamina propria
→ GCa arises	4	Light	Muscularis propria	
	5	Light	Serosa	

Abbreviation: GCa, gastric cancer

Useful background: GIST (gastrointestinal stromal tumor)

- Arise from interstitial cells of Cajal
- Usually EUS 4 and 2
- Positive immunohistochemical staining for CD 117 (c-kit positive; C-kit is a tyrosine kinase receptor)
- ~ 20% may be malignant

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. In the 25% of gastric MALT which show non - response to H. pylori eradication, what are the explanations?

A1. May be due to

- One of the chromosomal translocations [t (11, 18)], as suggested by IHC staining for nuclear BCL-10.
- Possibly due to expression of Cag A protein.
- High grade and/or extensive disease.

- Gastric H. Pylori infection causes chronic gastritis, an immune response which attracts T and B cells to the gastric mucosa. The T cells and the B cells proliferate during this T cell-dependent B-cell response to the H. Pylori.
- B cell monoclonality develops.
- These lymphomas cells invade the lamina propria, grow around reactive follicles, and invade the germinal centres (follicular colonization); MALT lymphoma results.

Q2. Half of gastric lymphoma are MALT and the remainder are DLBCL (diffuse large B cell lymphomas, aka :DLBCL with areas of marginal zone-MALT-type lymphoma). What is the use of PET scans to distinguish between the diffuse superficial gastric infiltration of MALT lymphoma, versus the masses seen in diffuse large B cell (DLBCL) lymphoma?

A2. Very little of fluorodeoxyglucose (^{18}F-FDG) used for PET scanning is taken up by gastric lymphomas, so better do EGD plus biopsy, EUS or CT scan.

- Incontrast to the > 90% association with MALT lymphoma with H. pylori, with DLBCL the association is only absent one third, even if MALT and DLBCL co-exist.

Q3. Give the history of PETs.

A3.

- Sheets of homogeneous, small round cells
- Uniform nuclei and cytoplasm
- High vascularity
- Few mitotoc figures

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give the 4 types of inherited F-NETs, for which family screening may be appropriate.

A.
- MEN-1 (Werner syndrome)
- Von Hippel-Lindau disease
- Tuberous sclerosis
- Neurofibromatosis-1 (Von Hippel-Lindau disease)

 Give the differences on EUS of benign versus malignant GIST in mid-stomach

Characteristics	Benign	Malignant
Echo texture	Homogeneous	Heterogeneous
Margins	Regular	Irregular
Cystic spaces	-	+
Size	< 3 cm	> 4 cm
Associated lymph node	-	+

Q: Give the differences on EUS of 4 gastric submucosal tumors.

A:	GIST	Leioyoma	ECL cell carcinoid tumors	Glomus tumor	Lipoma	Schwannoma
IHC						
o CD 117	+	-	-	-	-	-
o Actin	-	+	-	-	-	-
o Vimenten	-	-	-	+	-	-
o S-100	-	-	-	-	-	+
EUS						
o Layer	4, 2	4	2, 3	4	3	4
o Hypoechoic	+	+	+	+	-	+

Useful background: “pillow sign”
- Definition: pressure on a lesion causes an indentation which lasts for a short interval after the forceps is removed.
- A positive pillow signs suggests a lipoma

Q: A duplication cyst (DC) may cause a spherical, anechoic, subepithelial gastric mass. Give 2 pathological association of DC.

A:
- Carcinoid tumors
- Gastric cancer

 EUS and Submucosal Gastric Tumors

Layer	Tumor
1	
2	o Carcinoids o (GIST)
3	o Lipomas o Carcinoids
4	o GIST o Leimyoma o Glomus tumor o Schwannoma
5	

 Give 4 treatable premalignant gastric conditions.
- H. pylori adenocarcinoma
- MALT (mucosa associated lymphoid tissue)
- Lymphocytic gastritis
  - May progress to atrophy, metaplasia, CA
  - > 25 CD8 positive T lymphocytes per 100 epithelial cells
- Adenoma
- Pernicious anemia (unknown if early diagnosis and treatment with vit B_{12} will present development of gastric carcinoid tumors or adenocarcinoma)

Q: A patient with chronic dyspepsia on PPI therapy has a family history of colonic polyps. Your patient has a normal colonoscopy, but shows multiple fundic gland polyps (FGP). Biopsy of these polyps shows
- Cystic dilations of oxyntic gland mucosa
- Reduced numbers of parietal, chief and mucous neck cells

 Give the immunological staining that should be performed to distinguished sporatic from familial FGPs.

A: Sporatic
- Mutations of B-catenin gene
- Enhanced growth with PPIs
- May be associated with APC gene alterations when there is associated dysplasia (3%)

 Familial
- APC gene alterations on chromosome 5
- Colonic polyps do not necessarily develop (i.e. characteristic FAP)
- Dysplasia in 25%

Q. Give the mechanism for the development of hypernatremia, hypokalemia, hypochloremic, metabolic alkalosis (↑ Na^+, ↓ K^+, ↑ Cl^-, ↑ HCO_3^-) which occur with gastric outlet obstruction.

A.
- Gastric outlet obstruction → vomiting HCl
- HCO_3^- secreted by pancreas and by parietal cell basolateral membrane ("alkaline tide")
- The HCO_3^- is not nebulized by HCl, since HCl was lost by vomiting.
- The resulting metabolic causes H^+ reabsorption and K^+ loss by the renal NHE (Na^+ / H^+ exchanger).
- Vomiting causes dehydration, which leads to Na^+ and more K^+ loss through the Na^+ / K^+ exchanger
- Dehydration causes ↑BUN

Q: A patient with dyspepsia, chronic diarrhea and perianal disease ONEGD multiple reddish areas seen in the gastric body, and biopsy shows "focal gastritis".
 Give the 2 commonest causes of focal gastritis.

A:
- H. pylori
- Crohn disease

Thick gastric folds, protein losing enteropathy – Ménétrier's disease

Corkscrew foveolar hyperplasia of gastric body – Ménétrier's disease

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Name 4 cell types of endocrine tumors of the stomach.

A.
- ECL (histamine-producing enterochromaffin-like) cells in the gastric body and fundus
- G (gastrin producing) cells in the antrum
- D (somatostatin-producing) cells (a subset may contain calcitonin, PP and ACTH
- P (ghrelin-producing) cells
- EC (serotonin-producing enterochromaffin) cells

Mentrier disease

Mentrier disease
- Associated with ↑EGF receptors
- "corkscrew" foveolar hyperplasia of gastric body
- Protein-losing enteropathy
- Premalignant may lead to gastric
  - Lymphoma
  - Adenocarcinoma
- May be associated with H. pylori or CMV infection
- Treatment cetuximab (anti-EGF [epidermal growth factor] receptor antibody)

CLINICAL VIGNETTE

- Case: Dyspepsia, ↑ serum gastrin; ↑ gastric H^+; secretin stimulation test negative
  - Answer: Antral gastritis (usually H. pylori infection)

CLINICAL VIGNETTE

- Case: Dyspepsia, age 70, weight loss with anemia; acanthosis nigricans in axilla
  - Answer: Gastric cancer

CLINICAL VIGNETTE

- Case: Dyspepsia, numerous “sheets” of T cells in gastric mucosal biopsy, blunted mucosa and crypt pyperplasia on small bowel biopsy
  - Answer: Lymphacytic gastritis

CLINICAL VIGNETTE

- Case: Recurrent dyspepsia after gastric surgery for peptic ulcer disease; intermittent elevation of serum gastrin concentration; bloating, heartburn; secretin stimulation test negative.
  - Answer: Billroth II surgery, Retained Antrum Syndrome

CLINICAL VIGNETTE

- Case: Upper GI bleeding, recurrent abdominal pain, reddish lesions on lips and tongue
  - Answer: Cavernous hemangioma associated with BRBN (blue rubber blue nevus) syndrome

CLINICAL VIGNETTE

- Case: Gastric nodule; EUS shows lesion is spherical, extramural, with no echo
  - Answer: Duplication cyst

CLINICAL VIGNETTE

- Case: Abdominal pain, diarrhea, bleeding in a “vasculopath” (extensive atherosclerosis), ↑ ESR and eosinophilia, rectal or gastric yellow nodule on endoscopy; give the likely mucosal pathology?
  - Answer: “Needle-shaped clefts” on mucosa biopsy from cholesterol embolization

SMALL BOWEL

Bowel obstruction

- Take a directed history for bowel obstruction.
- Abdominal pain – where, when, what, why, how
- Associated symptoms
  - Appetite
  - Weight change
  - Nausea, vomiting (bilious, feculent, bloods)
  - Jaundice, dark urine
  - Recent weight
  - Pale stools
  - Bloating
  - Borborigmi
- Changes in bowel movements
  - Constipation/ obstipation/ no flatus
  - Diarrhea
  - Tenesmus
  - Calibre of stool
  - Melena
  - Hematochezia
  - Flatus
- Medical history
  - Previous surgeries
  - Abdominal hernia
  - Gallstones
  - Colorectal cancer
  - Drugs (opiates, anticholinergics, antipsychotics)
  - Diagnoses – inflammatory bowel disease, colorectal cancer, diverticulitis, gallstones, abdominal hernia, vascular ischemia, endometriosis
- Causes/Associations
  - Small bowel
    - Adhesions
    - Hernias
    - Strictures from IBD
    - Gallstone ileus
    - Mesenteric artery syndrome
    - Small bowel tumors
    - Metastatic cancer
    - Cystic fibrosis
    - Volvulus

- Crohn disease
- o Large bowel
  - Cancer
  - Volvulus
  - Diverticulitis
  - Ileus
  - Narcotics ileus
  - Mesenteric ischemia
  - IIBD with stricture
  - Ogilvie's syndrome
  - Adhesions
  - Intussusception
  - Endometriosis

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 58 and 59.

- Performance characteristics for a focused physical examination for bowel obstruction.
  - o While there may be numerous abnormal physical findings which have been traditionally thought to be useful to diagnose a bowel obstruction, the four best tests in terms of the value of the value of their positive likelihood ration (PLR) are the findings on inspection of visible peristalsis (PLR, 18.8) and distended abdomen (9.6) and on auscultation hearing hyperactive (5.0) or abnormal bowel sounds (3.2)

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

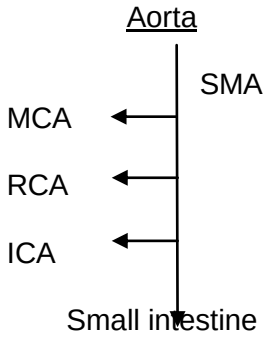
Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 48.4, page 579.

Mesenteric Ischemia

Q: SMAE (superior mesenteric artery embolism) causes half of all cases of AMI (acute mesenteric ischemia). A patient has severe abdominal pain out of keeping with the mildness of abdominal finding on physical examination, metabolic (lactic) acidosis, and leucocytosis with bandemia (shift to the left).

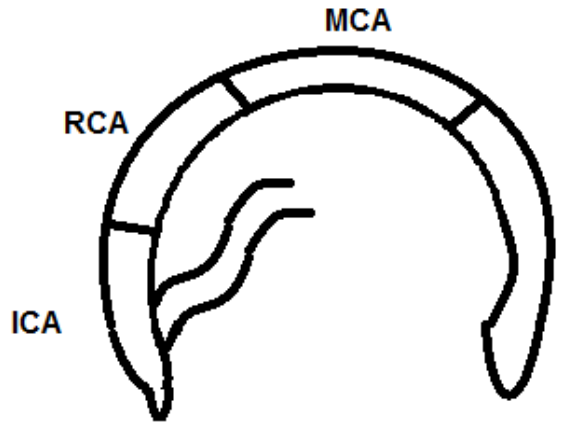
Give 3 reasons for performing an emergent angiographic study rather than a CT scan of the abdomen.

A: Angiography is



- More sensitive, showing distal splanchnic vessels
- Demonstrates vasoconstriction, which might benefit from a vasodilation (e.g. papaverine)
- Provides prognostication: major embolization proximal to the ileocolic artery (ICA), versus minor lesion distal to ICA
-- Avoids potentially negative CT scan, with worsening clinical picture and only late consideration of performing angiography, potentially missing the ~ 6 hour preinfarction window

Abbreviation: SMA, superior mesenteric artery; MCA, middle colic artery (to transverse colon); RCA, right colic artery (to distal ascending colon); ICL, ileocolic artery (to proximal ascending colon)



Potential Clinical Error

When you suspect SAME, doesn't waste time / resources – do the right test first-do angiography

*Note: RUQ pain and tenderness with or without diarrhea may occur with appendicitis, active Crohn disease, or ischemic bowel disease, as well as by infections such as C. difficile, campylobacter, tuberculosis.

Crohn Disease

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give 6 prognostic indicators of successful spontaneous fistula closure.

A. Parameter	Spontaneous Closure Likely
➢ Output (mL/day)	o <500
➢ Age (yr)	o <40
➢ Site	o Proximal small bowel
➢ Nutritional status	o Well nourished
➢ Cause	o Anastomotic breakdown
	o No malignancy, inflammatory or infectious disease, or complete anastomotic dehiscence
➢ Anatomic characteristics	o Long fistulous tract
	o No eversion of mucosa
➢ Duration	o Acute

➢ Gastrointestinal Fistulas

*Note
- o The successful use of octreotide to closeintestinal fistulas has not been confirmed by RPC DB (randomized, placebo-controlled, double-blind) studies in terms of
  - Closure of fistula
  - Rate of complications
  - Mortality rate

➢ Fistula Classification

- o Anatomic
  - Internal (e.g., ileocolic, colovesical)
  - External (e.g., enterocutaneous)

- o Physiologic
  - High output (>500 mL/day)
  - Moderate output (200-500 mL/day)
  - Low output (<200 mL/day)

- Site, High
  - Intestinal > 500 ml/ day
  - Pancreas > 200 ml/ day

source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 26-5, page 419.

- Conditions Associated with Non-healing Fistulas (acronym, "FRIEND")
  - **F**oreign body within the fistula tract
  - **R**adiation enteritis involving the affected bowel
  - **I**nfection or inflammation at the fistula origin
  - **E**pithelialization of the fistula tract
  - **N**eoplasm at the fistula origin
  - **D**istal obstruction of intestine

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 26-6, page 420.

 Give the benefits of strituroplasty in CD, besides the relief of a partial small bowel obstruction.

- regression
- recurrence
- mucosal healing

 Prepare a patient for informed consent for the use of steroids (GCS, glucocorticosteroids) in a patient with IBD, explaining the adverse effects.

- Psychological
  - Depression
  - Hallucinations
  - Psychosis, insomnia
  - Aggravation of pre - existing mood
  - Instability
  - Psychotic tendencies

- Neurological
  - Transient worsening of myasthenia gravis
  - Syncope
  - Seizures
  - Pseudotumor cerebri (with GCS withdrawal)
  - Neuritis
  - Paresthesias

- Eyes
  - Cataracts (posterior subcapsular)
  - Glaucoma
  - Activation of ocular herpes simplex
  - May enhance establishment of secondary ocular infections due to fungi or viruses

- Face
  - Puffiness

- Dermatological
  - Buffalo hump striae
  - Necrotizing angiitis
  - Impaired wound healing
  - Petechiae, ecchymoses
  - Facial erythema
  - Hirsutism
  - Acne
  - Allergic dermatitis, urticaria, angioneurotic edema
  - Perianal burning
  - Hypo/ hyper pigmentation
  - Scarring, induration
  - Sterile abscesses
  - Cutaneous/ subcutaneous atrophy

- MSK
  - Muscle wasting (steroid myopathy)

- Cardiovascular
  - Hypertension
  - Thromboembolism, fat embolism
  - Hypercholesterolemia
  - Accelerated atherosclerosis
  - K^+ deficiency →cardiac arrhythmias
  - Cardiac rupture after MI

- GI
  - Interaction with peptic ulcer disease
  - Cautions concurrent use of steroids with ASA/NSAIDs to increase INR
  - Anorexia/ nausea/ vomiting
  - Increased/ decreased appetite- change in body weight
  - Increased/ decreased BMs
  - Ulcerative esophagitis
  - Perforation of small bowel/ colon (especially in IBD)

- Adrenal glands
  - Risk of adrenal insufficiency (if GCS is quickly withdrawn)

- Kidney
  - In the presence of a fixed or decreased GFR, edema may develop
  - May worsen renal insufficiency (especially with acute glomerulonephritis and chronic nephritis)
  - Sodium and water retention- edema
  - Aggravation of CHF
  - Hypokalemic alkalosis
  - Hypocalcemia

- Bone
  - Osteoporosis
  - Fractures
  - Avascular (aspectic) necrosis (more likely in rheumatoid arthritis or lupus)

- Endocrine
  - Pancreas
  - Type II diabetes, adipose cells
  - Obesity
  - Increased requirement for insulin or oral
  - Hypoglycemic in diabetics
  - Secondary adrenocortical and pituitary responsiveness in stress situations
  - Menstrual irregularities
  - Increased sweating
  - Protein catabolism

- Infections
  - Activation of amebiasis, TB
  - Suppression of patch tests

- Enhanced risk of steroid AEs with cirrhosis or hypothyroidism

- Children
  - Suppression of growth

- Drug interactions look up numerous drug interactions in CPS

- Hematology
  - ↑WBC, ↓ lymphs, ↓ platelets
  - Thrombophlebitis

- Pregnancy
  - Possible increase of oral cleft in fetus
  - Possible hypercortisolism effects in fetus of pregnant mothers on high dose steroids

Q: Distinguish between hereditary angioedema (HA), familial Mediterranean fever (FMF), and MR (Melkersson-Rosenthal) syndrome*

A:

Clinical	HA	FMF	MRS
Severe, recurrent abdominal pain	+	+	+
Edema of lips and periphery	+	-	-*
Familial	+	+	+
Tongue swelling	+	-	+
Facial paralysis	-	-	+

*Melkersson-Rosenthal syndrome is facial Crohn diseases with
- Recurrent tongue swelling
- Fissured tongue
- Granulomas on tongue biopsy
- Facial paralysis

- Crohn disease, on azathioprine (AZA), what causes AZA – associated liver pathology

  - Dx – Hepatotoxicity from 6 –MMP; VOD/SOS (veno – occlusive disease, aka sinusoidal obstruction syndrome); peliosis hepatis

Spiegel, BMR, et al. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time Resource. *Slack Incorporated* 2011, Figure 60.1, page 96

Azathioprine dosing and metabolism

	6-TG	6-MMP
1. Understand, or poor compliance	↓	↓
Overdose	↑	↑
2. TPMT activity ↓/o inheritance low / low (9%)	↑	↓
↑ high / high (1%)	↓	↑

- What are these metabolites in heterozygous TPNT high / low inheritance – this is the normal person
- Give the implication of ↑ 6-MMP (> 5700) due to overdosing, or highlight TPMT.

A: ↑ 6-MMP - ↑ hepatotoxicity

Infections

Useful background: Small bowel infection

- Cryptosporidium
  - Immunocompetent & immunocompromised
  - Recreational water exposure
  - Site
    - Day care
    - Nursing home
    - Fecal – oral (poor hand sanitation)
  - Complication
    - Viable oocytes ingested
    - Acalalous cholecystitis
    - Ascending cholangitis
    - Pancreatitis
  - Diagnosis
    - Acid-fast stain of stool, duodenal aspirate, biopsy for trophozoites, cysts
    - Antigen detection
    - Direct immunofluorescence (DFA)
    - Molecular methods (PCR)
    - No reliable treatment
- Diagnosis of giardia
  - Enzyme immunoassay (EIA) for giardia detects antigen with a sensitivity of 65-100%, and a specificity of 90-100%
  - Microscopy still needed to exclude other pathogens which may cause diarrhea, since the patient may be an asymptomatic cyst excretor

Q1: In the patient with unexplained chronic diarrhea, you resort to the measurement of the osmotic gap determined on a spot collection of stool. Show how to calculate the stool osmotic gap (SOG). In the patient with SOG > 50 mOSm/kg, you return to the history: give substances which can cause chronic diarrhea when SAG > 50.

A1:
- Stool osmotic gap (SOG) = 290 – 2 ($Na_s^+ + K_s^+$)
  Na_s^+, stool Na_s^+; K_s^+, stool K^+
  - Abnormal SOG ≥ 50 mOsm/kg
- Commonly ingested substances causing chronic (osmotic) diarrhea with SAG > 50
  - Carbohydrates
    - Lactose – milk
    - Sucrose ┐ pop, sweeteners
    - Fructose ┘

- o Magnesium-laxatives
  - Sorbitol – chewing gum, diabetic candy
  - Lactulose – laxative
  - Trehalose - mushrooms

*Note: It is not understood why Mg causes an ↑ SAG

Q2: In the context of chronic diarrhea and SOG > 50 mOsm/kg, indicate how to distinguish patient use of sorbitol versus magnesium.

A2:

Measurements	Sorbitol	Magnesium
Stool pH < 5	+	-
↑ Stool Mg^{2+} (!)	-	+

More details: Important reference tables in Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010

Table 15.2 Diarrhea in Well-defined patient groups or settings
Table 15.3 Differential diagnosis of causes of diarrhea
Table 15.4 Infections cause diarrhea
Table 15.5 medications and toxins associated with diarrhea (216)
Table 15.6 Nonspecific drug therapy for chronic diarrhea (227)
Table 15.7 Groups of patients predisposed to laxative abuse (230)

Small Intestinal Bacterial Overgrowth (SIBO)

Q1: In the context of SIBO (small bowel bacterial overgrowth), the jejunal aspirate (JA) is accepted as the "gold standard".
 Give 3 reasons why this needs to be rethought.

A1: The problems leading to

- False negative JA
  - o SIBA distal to end of aspirating tube
  - o Recent use of antibiotics
  - o Species of bacterial aspirated which is not described or cultivated (? Use DNA fingerprinting)
- False positive JA
  - o Contamination by oral or gastric organisms

Q2: In the context of a positive lactulose hydrogen breath test, give the pathogenesis of a “double peak”.

A2:
- The single peak of H_2 > 20 ppm by 180 mm is diagnostic for SIBO by one population of organisms.
- A double peak of H_2 suggests a proximal and a separate distal population

Q3: In the context breath testing, give the likely symptom of which the patient complains if the gas detected is H_2, CH_4 or H_2S.

A3:
- H_2, diarrhea
- CH_4, constipation
- H_2S, foul flatus

Small Intestinal Lymphoma

- Small Intestinal Lymphomas
  - B cell
    - Non-IPSID
      - Marginal zone B cell lymphoma of MALT type
      - Diffuse large B cell lymphoma
      - Mantle cell lymphoma (multiple lymphomatous polyposis)
      - Follicular lymphoma
      - Burkitt's lymphoma
    - IPSID
  - T cell
    - Enteropathy-type intestinal T cell lymphoma
    - Other types not associated with enteropathy

- Immunodeficiency-Related Lymphoma
  - Post-transplantation
  - HIV-associated

Abbreviations: HIV, human immunodeficiency virus; IPSID, immunoproliferative small intestinal disease; MALT, mucosa-associated lymphoid tissue.

Adapted from: Feldman M, et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 29-1, page 445.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. A small bowel barium study reports a curious bull's eye lesion. MR enteroscopy demonstrates a small bowel tumor. The diagnostic imager suggests the lesion may be a metastasis.

- Give the primary cancers which spead directly, by seeding or by lymphatic spread to the GI tract.

A.

- Esophagus
  - Stomach
  - Lung
- Stomach
  - Breast
- Pancreas
  - Lung
  - Kidney
  - Luminal GI
- Small bowel
  - Stomach
  - Pancreas
  - Biliary tree
  - Kidney
  - Retroperitoneum
  - Melanoma

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. A middle-aged male smoker presents with symptoms suggestive of motility disorders of the esophagus, stomach, small bowel and colon. Give 3 serum biochemical measurements which would help the diagnosis and indicate in which organ the underlying defect may reside.

A. This man likely has a paraneoplastic lung tumor, with cross-reacting autoantibodies from the tumor causing an inflammatory infiltrate and neuronal degeneration of the myenteric plexus. The circulating autoantibodies to be assessed include:

- ANNA-1 (anti-neuronal nuclear antibodies)
- Anti-Hw
- PCA-1 (type 1 Purkinje cell antibodies)
- N-type (calcium channel binding antibodies)

- Classify small intestinal lymphomas, based on their morphology and clinical response to chemotherapy.

- B cell
  - Indolent
    - Marginal zone
    - Follicular zone
  - Aggressive
    - DLBCL
    - Mantle cell
    - Burkitt
    - IPSID (immuno-proliferative small intestinal disease)
    - Lymphoproliferative disorders
    - HIV – associated non-Hodgkin lymphoma
    - Primary effusion lymphoma

- Immunoproliferative small intestinal disease (IPSID)
  - Aka 2 heavy-chain disease, or as Mediterranean lymphoma
  - Plasma cells cecrete an abnormal IgA heavy chain protein which corresponds to the Fc portion of the alpha subunit of IgA.
  - Antigen stimulation, for example by Campylobacter jejuni, may stimulate lymphocytes in the small intestine, resulting initially in a monoclonal response.

- The therapy for immunoproliferative small intestinal disease (IPSID).
  - Stage the disease
  - For early stage
    - Nutritional care
    - Antibiotics
      - Tetracycline, or
      - Metrodinazole and ampicillin
  - For lack of response to 6 months of the above
    - Chemotherapy

- Enteropathy-type intestinal cell lymphoma (EITL)
  - The normal polyclonal $CD3^+$/ $CD8^+$ intraepithelial (IE) T cells underdo malignant transformation by way of T cell receptor gene rearrangements of the IE T cells to a monoclonal abnormal phenotype ($CD3^+$, $CD7^+$, $CD4^-$, $CD5^-$).
  - The response to a gluten-free diet is lost.
  - There results
    - Refractory celiac disease, type I and II
    - Ulcerative jejunitis (may progress to EITL
    - EITL (enteropathy-type intestinal T cell lymphoma)
  - Monoclonal T cells may be seen adjacent non-involved mucosa

- Large, highly pleomorphic cells with numerous, bizarae, multinucleated forms.
- Singor multiple sites, ulcerating or circumferential.
- Unlike gastric MALT or DLBCLs, EITLs are demonstrated in ^{18}F-FDG

- Post-transplantation Lymphoproliferative Disorder (PTLD)
  - Associated with organ transplantation, particularily heart-lung, and T cell depleted allogeneic bone marrow transplantations.
  - Result from B cell clones (monoclonal, polyclonal, or oligoclonal) transformed from poliferation of Epstein-Barr Virus (EBV).
  - Treatment approaches
    - Where possible, reduce or withdraw immunosuppression
    - Treat the associated EBV infection with acyclovir or gancyclovir
    - Interferon-α
    - Ritaximab (monoclonal antibody to T cells)
    - Donor leucocyte infusions (PTLD following allogeneic bone marrow transplantation)

Gastrointestinal stroma tumors (GIST)

- GISTs have some histological features and common precursor cell to ICCs (interstitial cells of Cajal)
- Increased expression of cell efflux pumps
  - P-glycoprotein (product of the MDR-1 gene)
  - Multidrug resistance protein
- Expression of KIT receptor tyrosine kinase (RTK) seen in > 95% of GISTs.
- CD117 by IHC (immunohistochemical) assay in > 95% of GISTs (*Note: normal ICCs and mast cells express CD117).
- CD34 positive (CD43-positive stem cells in the wall of the intestine) in 2/3.
- The prognosis of a GIST is not determined by its histology, but rather by its size and number of mitosis.
- Histologically
  - Spindle cell, 20%
  - Epithelioid or round cell, 30%
- On EUS, the features of GIST which suggest a benign prognosis include
  - Regular margins
  - ≤ 3 cm or ≤ 4 cm
  - Homogeneous echogenicity (lack of cystic spaces < 4 mm)
- High affinity of GISTs for ^{18}F-FPG PET scanning.
- Because of GIST expression of MDR-1 gene, the increased levels of P-glycoprotein and multidrug resistance protein (pumping some drugs out of cells), these tumors are resistant to chemotherapy).
- Inhibitors of KIT, RTK and PDGFR (Imatinib mesylate; Gleevec ®, Glivec ®), or other kinase inhibitors (Sunitinib).

- Treatment of pain or focal bleeding (from bleeding in the bulky vascular tumor using IMRT (intensity modulated radiotherapy) or proton beam radiation.
- Surgery for early-stage localized GISTs, followed by adjuvant (postsurgical resection) Imatinib.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. What IHC stains help to distinguish GISTs, leiomyosarcomas and schwannomas?

A1.
- Leiomyosarcomas positive for both SMA (smooth muscle actin) and desmin, negative for CD117
- Schwannomas, positive for S100 (a neural antigen), CD117 negative
- Recall that GISTs are usually (>95%) CD117 positive

Q2. About 5% of GISTs are KIT-negative. What is the non-KIT signal for these GISTs?

A2. Mutational activation and aberrant signaling from PDGFRA (platelet-derived growth factor receptor-alpha)

- GIST (Gastrointestinal Stromal Tumors)
  - Prevalence $1/10^5$
  - Precursors to cells of Cajal are similar to the cells which form GISTs
  - GISTs are the most common form of sarcoma in the GI tract
  - Great diversity in the molecular pattern of GISTs (family of molecular subtype disease)
  - Often in muscularis mucosa
  - Stomach (60%), small bowel (30%), duodenum (5%), colon (<5%)
  - Colonic GISTs are most aggressive: colon > small bowel > stomach
  - Malignancy diagnosed on size > 2 cm
    # of mitoses, > 5/hpf
  - KIT mutation in 85%
    - Small bowel, exon 9
    - Stomach, colon, exon 9
  - The KIT-negative GISTs are $PDGFRA^+$
  - Tyrosine kinase inhibitors (TKI) greatly improve prognosis, (exon 11 mutations), except in those who are KIT^-, $PDGFRA^-$.
  - Response to imatinib (TKI) is best shown on PET scan, not on CT
  - Bleeding from GIST occurs only when tumor is bulky (5%)

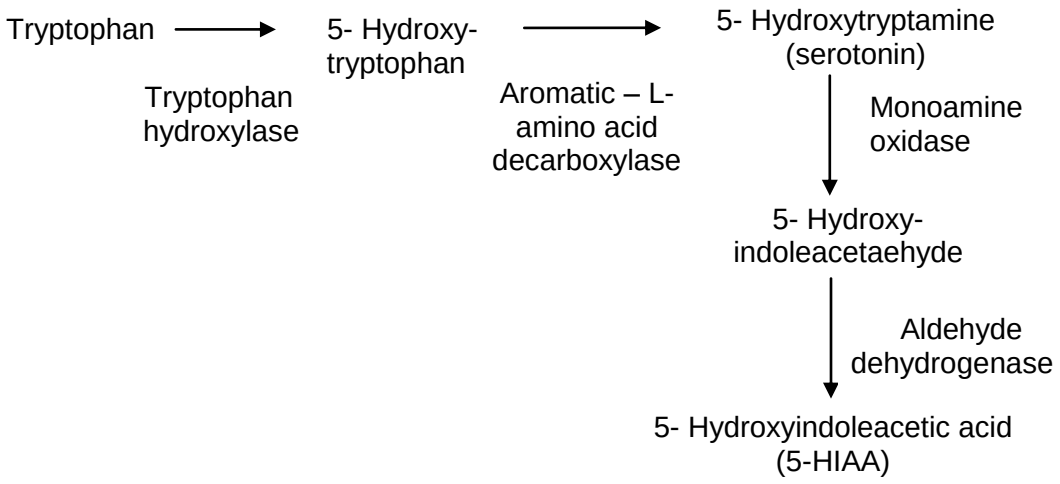
- AEs of TKI: dyspepsia, rash, diarrhea, pain
- Causes of non-response to imatinib
  - Primary KIT^-, $PDGFRA^-$
  - Secondary emergence of new secondary mutations
- Non-response to imatinib, use sunitnib, nilotnib, nilotnib or rigorafinib

The mixed connective tissue disorders may be associated with microangiopathic antiphospholipid-associated syndromes, such as systemic lupus erythematosis (SLE).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Tryptophan is metabolized to 5-HIAA. The finding of increased urinary 5-HIAA suggests the possible diagnosis of carcinoid tumor. Give the metabolism of tryptophan to 5-HIAA.

A. Synthesis of serotonin (5-hydroxytryptamine [5-HT]). 5-HT synthesis involves enzymatic steps for its production from tryptophan and for its degradation to 5-hydroxyindoleacetic acid (5-HIAA), which is then excreted into the urine.



Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Figure 31-7, page483.

- Gastrointestinal Carcinoid Tumors (Gastrointestinal Neuroendocrine Tumors, GI NETs)

  - GI-NETs are related to medullary carcinoma of the thyroid, pheochromocytoma or the adrenal gland, and pancreatic neuroendocrine tumors (P-NETs).

  - Incidence, $5/10^5$ per year; prevalence $35/10^5$

  - Site of carcinoid tumors
    - GI tract, 67%
    - Lung, 25%
    - Other sites: hepatobiliary, pancreas, testes, ovaries

- Pathology
  - Obstruction from mesenteric fibrosis, 50%
  - Ischemia from thickening of wall of intestinal blood vessels (vascular elastosis)
  - Carcinoid syndrome 10%
  - Synchronous or metachronous association with other tumors
  - Scleroderma-like fibrosis of lower extremities
  - 1/3 are multicentric
  - Small intestine = rectum > stomach > appendix
  - Moderate atypia, low mitotic rate, little tumor necrosis
  - Growth patterns
    - Nodular / insular (common in small intestinal)
    - Trabecular
    - Acinar/tubular
    - Atypical solid
    - Mixed
  - Definition of EC (enterochromafin) cell carcinoid.
    - Staining: silver (argentaffin)
    - Production: serotonin
  - Markers positive for EC cell carcinoids
    - Chromogranin A
    - Synaptophysin
    - Leu 7
    - NSE (neurospecific endolase)
    - VMAT-1/-2 (vascular monoamine transporters 1 and 2)
  - Positive for EC cells carcinods
    - Cytokeratins 8 and 18
    - CEA (carcinoembryonic antigen)
    - PAP (prostatic acid phosphatase)
    - CDX2 (an intestinal transcription factor)

- Peptides secreted by GI-NETs
  - Bioactive peptides
    - Chromogranin A
    - 5-HT (5-hydroxytryptamine, aka serotonin)
    - 5-HTP (5-hydroxytryptophan)
    - NSE (neuron-specific enolase)
  - Peptides
    - Calcitonin
    - CCK
    - Gastrin
    - Insulin
    - Neurotensin
    - PP (pancreatic polypeptide)
    - Somatostatin
  - Tachykinins
    - Neurokinin A
    - SP (substance P)
  - Growth factors
    - EGF (endocrine growth factor)
    - FGF (fibroblast growth factor)
    - PDGF (platelet-derived growth factor)
    - TGF-β (transforming growth factor-beta)
    - VEGF (vascular endothelial growth factor)

- Perform a focused physical examination for carcinoid syndrome.

- Face
  - Telangiectasia
  - Flushing
  - Tearing
  - Periorbital edema

- Lung
  - Wheezing (bronchial carcinoid)

- Heart
  - Tricuspid/ pulmonary regurgitation/ stenosis
  - Aortic/ mitral stenosis/ regurgitation
  - CHF
  - Endocardial fibrosis

- Liver
  - Hepatomegaly
    - CHF
    - Metastases
  - Pulsation, bruit
    - TR

Abbreviation: CHF, congestive heart failure; TR, tricuspid regurgitation

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. What is the three most common NET (carcinoid tumors) in the duodenum?

A1.
- Gastrin, 70%
- Somatostatin, 25%
- Gangliocytic paraganglioma, 5% (a benign humartoma)

Q2. Give 3 cytosolic markers for poorly differentiated GI-NET.

A2.
- NSE
- PEP 9.5
- Synaptophysin (marker for synaptic-like vesicles)

Q3. There are 3 types of gastric carcinoid tumors (NET), type I, II, and III. For type I and II, there is a slow rate of metastasis to the liver and lymph nodes, so the survival rate is very good; the cell of the origin is ECL (rather than EC for the type III); there may be more than one tumor; the tumors are usually < 1 cm in size and there is hypergastrinemia.

- Give 3 pathological features which help to distinguish the type III sporatic tumors from the type I and II gastric NETs.

A3.

Pathological Feature	I	II	III
Associated gastric pathology	AMAG	HG	N/NS
Antral G-cell hyperplasia	+	-	-
ECL hyperplasia	+	+	-

Abbreviations: AMAG, autoimmune metaplastic atrophic gastritis; HG, hypertrophic gastropathy; N/NS, normal or non-specific changes

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 31-2, page 479.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q4. GI NETs are associated with gene point mutations, deletions, methylation, as well as chromosomal gains and losses.

- Give 3 examples.

A4.
- Fore-gut (stomach)
  - MENIN gene (tumor suppressor gene), common in MEN-1 syndrome
  - MENIN intracts with numerous factors such as the AP1 transcription factor, JUN D and NF-κβ
  - Loss of heterozygosity on chromosome II in MEN-1 gene
- Mid-gut (small intestine)
  - Deletions on chromosome 18
- Hind-gut (colon)
  - TGF-α
  - EGF
- Others
  - NAPILI
  - MAGE D2
  - MTA1

Carcinoid Crisis

- Definition
  - A worsening of carcinoid syndrome of
    - Hypo- or hypertension
    - Tachyarythmias
    - Bronchospasm
    - Flushing
    - Hyperglycemia
- Usually precipitated by surgical or anesthetic stress
- Give the management of the patient with known carcinoid syndrome to avoid carcinoid crisis.
- Management
  - IV fluids
  - Octreotide (IV for treatment or during surgery, SC as pre- and post-op care)
  - Glucocorticosteroids
  - BEWARE – avoid pressors which may worsen crisis by further releasing serotonin and other peptides

- Give 3 markers of NET which suggest possible poor prognosis (high-grade tumors with poor differentiation).

- Granins
  - Chromogranin A (Cg A), Cg B, Cg C (aka secretogranin II)
  - Secretogranin III, IV, V and VI
  - Cg A is correlated with mass of NET
  - Cg A may be falsely positive
    - Stomach – CAG
    - Bowel – IBD
    - Liver – hepatic dysfunction
    - Kidney – CRF

- NSE (neurospecific endolase)

- HCG alpha (NSE and HCG alpha correlated with poor differentiation)

Abreviations: CAG, chronic atropic gastritis; IBD, inflammatory bowel disease; CRF, chronic renal failure; HCG, human chorionic gonadotropin; SRS (somatostatin receptor scintigraphy), PET (positron emission tomography, using ^{18}F-FDG or ^{18}F- L-Dopa), MIBG (metaiodobenzylguanidine), EGF, EUS, CT, MDCT (multidetector CT), MRI and CE (capsule endoscopy) have been found to be useful to localize a carcinoid tumor primary or metastases.

- Treatment of NET (carcinoid tumor)

- Surgery
  - Resection
  - Hepatic resection
  - Liver transplantation
- Chemotherapy
  - Systemic
  - TACE (transcathetor arterial chemoembolization)
- Somatostatin analogs (to improve symptoms)
- Interferon-α (may be combined with somatostatin analogs)
- New agents
  - Biologics
    - VEGF inhibitor (Bevacizumab)
    - mToR inhibitor (RAD 001)
  - PRR T (peptide receptor radionucleotide therapy)
    - 90 Y – DOTA octreotate,
    - 177 Lu- DOTA octreotate

Small bowel transplantation

Persons with an intestinal transplantation undergo intense immunosuppression, which is associated with an increased risk of malignancy.

- Give the 2 types of malignancies which are more common with intestinal transplantation.
  - EBV-LPD (Epstein-Barr lymphoproliferative disease)
  - De novo cancer of non-lymphomatous origin

Diarrhea and Malabsorption

SO YOU WANT TO BE AN GASTROENTEROLOGIST OR ENDOCRINOLOGIST!

Q1. Medullary carcinoma of the thyroid (MCT) is often associated with diarhea.

- Give 4 causes of diarrhea in MCT which are related to this condition.

A1.
- ↑ calcitonin
- ↑ VIP
- ↑ prostaglandins
- ↑ rate of colonic transit (etiology not yet known)
- Men II
  - A. hyperparathyroidism (usually causes constipation, rather than diarrhea)
  - Pheochromocytomas

Q2. Apolipoprotein B is contained in chylomicrons, LDL (low density lipoprotein) and VLDL (very low density lipoproteins). Lack of apoprotein B results in recessive disorder, abetalipoproteinemia. Abetalipiproteinemia is characterized by steatorrhea, ataxia, atypical acanthosis pigmentosa, acanthotic red blood cells, and absence in the serum of chylomicrons, LDL and VLDL. Give the histological features of abetalipoproteinemia seen on small bowel biopsy.

A2.
- Mucosal cells
  - Abundant lipid droplets
- Submucosa and lamina propria
  - Little lipid

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Give 3 factors associated with the ↑ risk of pneumatosis intestinalis in SOT.

A1.
- Infection
  - CMV
  - C. difficile
- Drug / toxins
  - Steroids

Q2. EBV does not usually form mucosal ulcers and cause GI tract bleeding. What is the exxception to this "rule"?

A2. When EBV-LPD (lymphoproliferative disease) develops, ulceration and bleeding may occur. This is the cause of PTLD (post-transplant lymphoprolifertive disorder, A B or T cell lymphoma, and may require reduction of immunosuppression, rituximab.

Useful background: Intestinal lymphangiectasias

- Cause
  - o Child - Autosomal dominant
    - Primary lymphangiectasias
  - o Adult - Secondary to
    - CHF (congestive heart failure)
    - Abdominal – lymphoma
      - Other malignancies
    - Tuberculosis
    - Sarcoidosis
    - Whipple disease
    - Miscellaneous fibrotic conditions e.g. retroperitoneal fibrosis
  - o Endoscopy - white spots (fat-filled dilated lacteals)
  - o Small bowel biopsy - Fat globules in enterocytes and in villi
    - Lymphocytic infiltration

Q: Give the location of Isospora and Cryptococcus on small bowel biopsy.

A:	Isospora	Cryptococcus
o Brush border membrane	+	+
o Intracytoplasmic vacuoles	+	-

Q: A patient with acute Crohn disease (CD) requires therapy with steroids (glucocorticosteroids), immunosuppressants and/or anti-TNF therapy. She is an HBV positive carrier. Give the therapeutic management of the CD and HBV.

A:
- o These therapies can cause a flare of disease activity and hepatic decompensation in 50% of patients, regardless of HBV DNA level.
- o Hopefully the HBV status was diagnosed before treatment for the active CD began.
- o Ideally then the therapy for HBV is started before prednisolone, immunosuppressants or anti-TNF therapy (or before chemotherapy, if that were a relevant consideration in a different patient).
- o Nucleoside / nucleotide therapy is given for the duration of the CD therapy, plus 6 months longer.
- o *Note that it is the interval when the dose of prednisolone is being tapered when the HBV carrier is at risk for a flare.

Whipple disease

 Name 3 conditions which are PAS positive, and indicate how they can be distinguished by special histological stains.

Organism	Diastase resistant	AFB stain
Tropheryma whipplei	+	-
MAC	-	+
A_1AT deficiency	-	-

Abbreviations: A_1AT, alpha-1 antitrypsin deficiency; AFB, acid fast bacilli; MAC, mycobacterium intracellular

Lymphoma

Give the features which distinguish IPSID (immunoproliferative small intestinal disease) from MALT lymphoma (marginal T-cell lymphoma).

Feature	IPSID	MALT
Males	+	-
Middle east	+	-
Onset, years	> 25	> 30 to 40s
Alpha heavy chain paraproteins	+	-
Association with Campylobacter jejuni	+	-
Associated with "poor sanitation"	+	+/-

*Note: MALT may be associated with an H. pylori infection, which itself may be associated with a lower socioeconomic status

CLINICAL VIGNETTE

- Case: Small gastric tumor, right-sided congestive heart failure; flushing; ↑ serum chromogranin A
  - Answer: Carcinoid syndrome

CLINICAL VIGNETTE

- Case: Chronic diarrhea, giardiasis
  - Answer:
    - Plasma cells in lamina propria (LP) bowel biopsy (SBBx)
    - No plasma cells in LP on SBBx
      - MAL (median arcuate ligament) syndrome
      - CVID (common variable immunodeficiency, ↓ B cell function, ↓ IgG
      - Multiple lymphoid nodules

CLINICAL VIGNETTE

- Case: Diarrhea, exposure to Beavers, sprue-like biopsy, “eyelike” nuclei in flagellated trophozoites
  - Answer: Giardiasis

CLINICAL VIGNETTE

- Case: Diarrhea on a cruise ship
  - Answer: Norwalk virus

CLINICAL VIGNETTE

- Case: Bloody diarrhea, HIV+, “saddle distribution paresthsia
  - Answer: HSV proctitis

CLINICAL VIGNETTE

- Case: Diarrhea plus anemia with ↑ MCV, Puerto Rica
  - Answer: Tropical sprue

CLINICAL VIGNETTE

- Case: Recurrent crampy abdominal pain and small bowel obstruction; hypercalcemia; dyspepsia with hypergastrinemia; flushing
  - Answer: Carcinoid tumor associated with MEN-1 (gastrinoma → ↑ gastrin; parathyroid adenoma → ↑ Ca^{2+})

CLINICAL VIGNETTE

- Case: 3 D’s: diarrhea, dermatitis, dementia
  - Answer: Niacin deficiency

CLINICAL VIGNETTE

- Case: More 3 D's: diarrhea, dysmotility, autonomic dysfunction; CHF (congestive heart failure)
  - Answer: Amyloid of GI tract and heart

CLINICAL VIGNETTE

- Case: Diarrhea, ↓ K^+; pancreatic mass; gastric achlohydria
  - Answer: VIPoma

CLINICAL VIGNETTE

- Case: Diarrhea and recurrent abdominal pain; asthma
  - Answer: Churg-Strauss syndrome

CLINICAL VIGNETTE

- Case: Diarrhea / steatorrhea with weight loss and diabetes; pancreatic mass; gallstones
  - Answer: Somatostatinoma

CLINICAL VIGNETTE

- Case: Chronic diarrhea with abdominal pain and dyspepsia; ↑ WBC, platelets, CRP and ↓ hemoglobin; colonoscopy normal; EGD shows red particles which on biopsy reveal H. pylori negative focal gastritis
  - Answer: Crohn disease of small bowel (proximal to "reach" of colonoscope) and EGR

CLINICAL VIGNETTE

- Case: Small gastric tumor, right-sided congestive heart failure; flushing; ↑ serum chromogranin A
  - Answer: Carcinoid syndrome

CLINICAL VIGNETTE

- Case: A patient presents with diarrhea, endoscopic and biopsy changes suggestive of celiac disease, but does not respond to a gluten free diet. Give three features which would suggest tropical sprue.

Answer:
- Acute symptoms (fatigue, abdominal discomfort, but not always with diarrhea) occurring any time after moving to the "sprue belt", or malabsorption after living for two or more years in the "sprue belt"
- Macrocytic, megaloblastic anemia (from folate deficiency)
- Rod-like organisms seen on EM (electron microscopy) of small bowel biopsies
- Response to tetracycline and folic acid, not to gluten free diet

CLINICAL VIGNETTE

- Case: Give the circumstances that a macrocytic, megaloblastic anemia may develop in gluten sensitive enteropathy.

Answer:
- Folate deficiency
- B12 deficiency
  - Severe maldigestion / absorption,
    - Associated atrophic gastritis (pernicious anemia)
    - Associated SIBO (small intestinal bacterial overgrowth)

CLINICAL VIGNETTE

- Case: Diarrhea oral ulcers, anterior uveritis, genital ulcers, terminal ileal ulcers; it's not Crohn disease – what is it?
- Answer: Bachet disease

CLINICAL VIGNETTE

- Case: Female with butterfly rash, abdominal pain, red plaque skin lesions with follicular plugging. Give the likely diagnosis.
- Answer: SLE affecting pancreas

CLINICAL VIGNETTE

- Case: Diarrhea, weight loss, beer drinker; red, scaly, vesticopustular plaques on face and legs. Give the likely nutritional deficiency.
  - Answer: Dermatitis enterohepatica from zinc deficiency

CLINICAL VIGNETTE

- Case: GI bleeding, fragile skin, hypermodile joints, aortic root and splanchnic artery aneurysms. Give the likely diagnosis.
  - Answer: Ehler-Donlose syndrome

CLINICAL VIGNETTE

- Case: Small gastric tumor, right-sided congestive heart failure; flushing; ↑ serum chromogranin A
  - Answer: Carcinoid syndrome

CLINICAL VIGNETTE

- Case: Diarrhea glossitis, angular stomatitis, dystrophic wails, marked weight loss, red patches on skin in buttocks, thighs, groin. Give the likely diagnosis.
  - Answer: Necrolytic migratory erythema from NET tumor (glucagonoma) of pancreatic head

CLINICAL VIGNETTE

- Case: GI symptoms, fundoscopy shows “angioid streaks”. Give the two most likely diagnosis.
  - Answer: PXE (pseudoxanthoma elasticum)
    Paget disease

COLON

Lower GI Bleeding (LGIB)

- Diverticular occur in about half pf persons over 50 yr, and bleeding occurs in about 5% of persons with diverticular.
- Diverticular bleeding occurs from the base or the neck of the diverticulum in about similar ratios.
- Most diverticular are on the left side of the colon, but 2/3 of bleeding from diverticular at or proximal to the splenic flexure.
- "Definitive" diverticular bleeding occurs when "stigmata of recent hemorrhage (e.g., active bleeding, visible vessel, adherent clot) are seen on colonoscopy or acute bleeding is demonstrated on angiography or nuclear red blood cell scanning, with later confirmation of a diverticulum in that location as the souce of bleeding by colonoscopy or surgery. "Presumptive" diverticular hemorrhage is diagnosed when colonoscopy reveals diverticulosis is used "when another lesion is identified as the cause of hematochezia and colonic diverticulosis is evident" (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, page 311).
- The ratio of these three types of diverticular bleeding are definitive (52%), presumptive (31%) and definite (17%)
- In persons with definite or presumptive diverticular bleeding, over a four year-period. 9% had recurrent diverticular bleeding and 9% bleed from other GI sources cliniccal point; do not presume the LGIB after a previous diverticular bleed is from the same source.
- Multi-detector CT is more accurate than technetium-tagged RBC in LGIB
- Colonoscopy is of limited use in LGIB, visualizing presumed or definite causes in only about 2/3's
- Ischemic colitis
  - Incidence approximately $25/10^5$ per year
- Postpolypectomy bleeding (PPB)
  - Occurs after ~1% of polypectomies, from 1 to 14 days after polypectomy (usually days 5 to 7), and half require blood transfusions.
  - Colonoscopy at the time of a delayed PRB often shows an ulcer.
- Predictors of in-hospital mortality rate (MR) from LGIB
  - The MR from LGIB may be predicted from the assessment of the above total rate points
  - Multivariate analysis
    - > 70 yr

- Intestinal ischemia
- 2 comorbid illness
- In hospital bleeding for a different condition
- Coagulopathy
- Hypovolemia
- P=RBC transfusion

*Note: The MR from LGIB is lower if the source is hemorrhoids or colonic polyps

- Risk factors predicting severe LGIB
  - Use of ASA (aspirin)
  - > 20 comorbidities
  - HR ≥ 100 bpm
  - SBP ≤ 115 mmHg
  - No tenderness on abdominal examination
  - Rectal bleeding within 4 hr of evaluation
  - Syncope

Abbreviations: HR, heart rate; SBP, systolic blood pressure

- Risk (%) of severe bleeding (SB), need for surgery (surg), mortality rate (MR), hospital days (HD), and mean number of units of packed red blood cells used (P-RBC)

	Total Risk Points		
	0	1-3	≥ 4
SB	6	43	79
Surg	0	1.5	77
MR*	0	2.9	9.6
HD	2.8	3.1	4.6
PRBC	0	1	3

*overall MR is 3.9%, a blend from the MR from the total risk points of 0 (6% of all severe UGIB), 1-3 (15%), and ≥ 4 (19%)

Source: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 19.10, page 309.

Useful background: Angiorectasias lesion

- It is speculated that repeated obstruction of submucosal veins leads to dilated, tortuous and thin-walled submucosal veins, the capillary ring becomes dilated, and the precapillary sphincters become leaky / incompetent, and a small AV (arteriovenous) lesion develops.

- The AV itself is comprised of venules, capillaries, and arterioles, and is thus an arteriolar-capillary-venular unit, an AV fistula. VEGF (vascular endothelial growth factor) and VEGF receptor 1 may also play a role in the pathogenesis of angioectasia.
- These angioectasia (AE) involve the colon and small intestine, and do not involve other organs or the skin.
- The proximal and distal colon are affected equally by AEs. Bleeding AEs are not as common a cause of severe lower GI bleeding (LGIB) as is diverticulosis (10% vs 30%, respectively).
- Because up to half of people over 60 years have AEs, then in a patient withLGIB, seeing AEs does not prove the AEs were the cause of bleeding, any more than seeing diverticula by itself does not prove that these tics are the cause of ALGIB. The AEs are no more common in persons with chronic renal failure, but they bleed more frequently.
- Colonoscopy is useful to demonstrate AEs, but angiography is also useful, as long as the rate of bleeding is at least 0.5 ml / min.
- Colonoscopy at the time of a delayed PRB often shows an ulcer

- Performance characteristics of radiologic imaging for GI bleeding

	Sensitivity	Specificity
o Angiography, (> 0.5 mL blood/ min)	30% to 50%	100%
o Radionuclide scan (> 0.04 mL blood/ min; technetium sulfur colloid, or technetium-pertechnetate-labeled autologous RBCs – latter has higher Sens. & Spec)	45%	78%
o Meckel's scan	>25 year	< 50%
	< 25 year	90%

- Diet and diverticular disease
  - o Low fiber diets are no larger recommended for persons with diverticular disease
  - o The recurrence of symptoms of diverticulitis is lower in persons treated prophylactically with 5-ASA plus probiotic lactobacillus CAE, than when either is given alone

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Give 4 disadvantages of angiography preferred for LGIB

A1.
- Positive results in only ~ half of patients (bleeding may intermittent, or too slow [requires arterial bleeding rate of > 0.5 ml/min])
- Complication rate 3% to 10%
  - Bowel
    - Ischemia
    - Hematoma
  - Femoral artery thrombosis
  - Reactions to contrast dye
    - Acute renal damage
  - TIAs (transient [cerebral] ischemic attacks)

Q2. Why are colonic diverticular misnamed?

A2. Colonic diverticular are "…..herniations of colonic mucosa and submucosa through the muscular layer of colon…at points of entry of the small arteries (Vasa Recta)." (Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 311). Because these "diverticular" do not contain all layers of the colonic wall, they are actually pseudodiverticular.

Q3. Give 4 risk factors for PPB (post polypectomy bleeding).

A3.
- polyp
  - > 2 cm
  - Thick stalk
  - Sessile
  - Right colon
- Patient
  - Use of ASA, NSAID, anticoagulant

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 313.

Q4. Give the blood supply of rectal varices.

A4. "Ectopic varices may develop in the rectal mucosa between the superior hemorrhoidal veins (portal circulation) in persons with portal hypertension"

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 314.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Define severe LGIB, give the predictors of severe LGIB, and the predictors of in hospital mortality.

A1. ➢ Definition
- Continued bleeding within the first 24 hours of hospitalization
  - Transfusion of ≥ 2 units PRBC, ±
  - ≥ 20% ↓ hematocrit, ±
- Recurrent bleeding after 24 hours of stability
  - Need for additional transfusions
  - ≥ 20% further ↓ hematocrit, or
  - Readmission to hospital for LGIB within 1 week of discharge

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevie* 2010, page 309.

Q2. Give 4 angiographic signs of AEs (angioectasias).

A2. The important angiographic signs of AEs include:
- Dilated, tortuous vains, which are slow to empty the angiographic dye
- Vascular tuft
- Early filling vein
- Extravasation of contrast material

SO YOU WANT TO BE A GASROENTEROLOGIST!

Q. In the context of lower gastrointestinal intestinal bleeding (LGIB), what is Heyde syndrome?

A. Heyde syndrome is LGIB from colonic angiodysplasia in the patient with aortic sclerosis, thought to be due to 'proteolysis of the largest multimers of the Von Willebrand factor' (Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 584).

Fecal Incontinence

	Pelvic dyssynergia	Hirschprung disease
Rectal balloon inflation, failure of muscle relaxation	EAS	IAS
Increased pressure on straining to defecate	EAS	IAS

Abbreviations: EAS, external anal sphincter; IAS, internal anal sphincter

- All you need to know about rectal manometry
  - Urge to purge
  - Voluntarily pushing down (in) of abdominal muscles (valsalva maneuver)
  - ↑ rectal pressure
  - ↑ relaxation of puborectalis
  - ↓ anorectal muscles
  - ↓ internal anal sphincter (IAS) pressure causing relaxation

- Failure of relaxation of IAS
  - Pelvic dyssynergia (functional anorectal outlet obstruction)
  - Hirschsprung disease

Constipation

- Definition
  - Medical 3 BMs/wk
  - Public terms used to describe constipation
    - Straining (52%)
    - Hard stools (44%)
    - Inability to have a BM (34%)
  - Colonic function
    - Absorption
      - Fluid, 1000 to 1500 mL/day
  - Motility
    - Delays, stores, propels colonic contents
    - Mean colonic transit time, 35h
    - Types of colonic propulsions
      - LAPC - low-amplitude propagated contractions
      - HAPC - high – amplitude propagated contractions may be in STC (slow transit constipation)

SO YOU WANT TO BE A GASROENTEROLOGIST!

Q1. Give a clinical classification of the mechanisms of functional constipation.

A1.
- Normal – transit constipation
- Slow-transit constipation (STC)
  - Colonic retention of > 20% of radiopaque markers at day 5 post ingestion
- Defecatory disorders
  - Abnormal balloon expulsion test, ±
  - Abnormal rectal manometry

Q2. Give 4 abnormalities of colonic function in patients with STC (slow-transit constipation).

A2.
- ↓ HAPCs (high – amplitude propagated contractions)
- ↓ SP (substance P, an excitatory transmitter)
- ↑ VIP (vasoactive intestinal polypeptide) and NO (nitric oxide) (inhibitory transmitters)
- ↓ number & abnormalities of ICCs (interstitial cells of Cajal)
- ↓ number of myenteric ganglion cells

Intractable constipation. In persons with non-responsive defecatory disorders, the STARR (stapled transanal rectal resection) surgical procedure may need to be considered.

- Enteric nerves
  - Hirschsprung's disease
    - Absence or reduction of ganglion cells in distal colon
    - Associated with genetic defects (mutations)
      - RET proto - oncogene
      - Endothelin B receptor
  - Intestinal neuronal dysplasia (congenital hyperganglionosis)
  - Acquired neuropathies
    - Infection with Trypanosoma Cruzi (Chaga disease)
    - Paraneoplastic visceral neuropathy

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. From the lateral view of the rectum on barium enema examination, what are the features that suggest the descending perineum syndrome?

A1.
- Rectum is more vertical than is normal
- The anorectal angle is wide
- Perineal discent is > 3 cm

Q2. What is thought to be the pathophysiology of the solitary rectal ulcer syndrome (SRUS)?

A2. SRUS is thought be caused by paroxysmal contraction of the puborectalis muscle from excessive straining during defecation.

Q3. What is the pathophysiology of constipation occurring in hypothyroidism?

A3.
- Myxedematous infiltration in the wall of the colon
- Reduced peristalsis

Q4. The colon transit time (CTT) is ~12 hours. What does the measurement of CTT indicate about the pathophysiology of constipation?

A4. CTT is delayed in transit disorders, whereas in defecatory disorders of the rectoanal inhibitory reflex, or pelvic floor dysfunction (anismus), there will be a hold-up of fecal marks in the rectal area.

Defecatory disorders

- Definition
  - Impaired effective emptying of the rectum

- Synonyms
  - Pelvic floor dyssynergia (or just dyssynergia)
  - Spastic pelvic floor (syndrome)
  - Outlet obstruction
  - Obstructive defecation
  - Anismus

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010 (Table 18.6 Rome III criteria for functional defecation disorder).

- Give 4 examples of disorders of the CNS, spinal cord, smooth muscle and enteric neurons which are associated with constipation, and for each give the mechanism (s) responsible for the development of the constipation.

- CNS
- Parkinson's disease
  - dopamine – containing neurons in CNS and myenteric plexuses
  - relaxation of skeletal (striated) muscles of pelvic floor which are involved with defecation

- Multiple sclerosis
  - Visceral neuropathy leading to loss of the normal postprandial colonic motor activity
  - Dysfunction of anal sphincter
  - Dysfunction of muscles of pelvic floor
  - Immobility
  - Medications

- Spinal cord
- UMN spinal cord disorders (1)
  - rectal sensation to distention
  - rectosigmoid transit
  - colonic compliance
  - usual postprandial motor activity
  - anal relaxation on rectal distention
  - rectal pressure on rectal distention (high-pressure contractions)
  - rectal pressure on straining
  - control of EAS
  - relaxation of EAS on straining

(1) UMN (upper motor neuron) spinal cord lesions above the sacral segments

- LMN spinal cord disorders
  - left colonic contractions
  - colonic compliance
  - caliber of distal colon/ rectum (distention)
  - pressure in anal canal
  - sensation of rectum, anus, perianal skin

- Smooth muscle
  - Congenital or acquired myopathy, hereditary IAS myopathy
  - PSS (progressive systemic sclerosis) – smooth muscle atrophy
  - Muscular dystrophies – visceral smooth muscle may accompany dystrophy of skeletal (striated) muscle

Laxatives

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Give a mechanistic classification of laxatives, and for each give an example.

A1.

○ Osmotic	- Magnesium, sulfate, phosphate - Lactulose, sorbital, mannitol, PEG (polyethylene glycol)
○ Stimulant	- Anthraquinones: senna, cascara - Ricinoleic acid: castor oil - Diphenylmethanes: phenolphthalein, bisacodyl, sodium picosulfate
○ Prokinetics	- Cisapride, tegaserod
○ Softeners	- Sodium docusate
○ Lubricants	- Mineral oil
○ Locally acting	- Suppositories, glycerin, bisacodyl - Enemas tap water, soap suds, phosphate, mineral oil
○ Chloride channel activator	- Lubiprostone

*Note: in extreme circumstances laparoscopic open subtotal colectomy with ileorectal anastomosis may be necessary for severe constipation

Q2. There are many laxatives which are available to treat chronic constipation. For which of these is their used based on two or more randomized controlled trials (RCTs) with adequate sample sizes and appropriate methodology?

A2. Lactulose, PEG, Tegaserod®.

Diarrhea

- Take a directed history for diarrhea.

- Stools
  - Timing (duration, onset, and course)
  - Frequency
  - Aggravating/alleviating factors (milk, coffee, drugs)
  - Blood
  - Fat droplets
  - Food particles
  - Floating stools
  - Foul odour
  - Difficult to flush
  - Excess flatus

- Associated symptoms
  - Fever
  - Weight loss
  - Change in appetite and diet
  - Vomiting, nausea
  - Urination changes
  - Tenesmus
  - Extraintestinal symptoms of inflammatory bowel disease
  - Arthritis: Ulcerative colitis, Crohn disease, Whipple disease, *Yersinia* infection, malabsorption, inflammatory bowel disease, cancer, thyrotoxicosis
  - Lymphadenopathy: Lymphoma, Whipple disease
  - Neuropathy: Diabetic diarrhea, amyloidosis
  - Postural hypotension: Diabetic diarrhea, Addison disease, idiopathic orthostatic hypotension, autonomic dysfunction
  - Flushing: Malignant carcinoid syndrome
  - Hyperpigmentation: Whipple disease, celiac disease, Addison disease, pancreatic cholera, eosinophilic gastroenteritis
  - Dyspepsia: peptic ulcer disease, Zollinger-Ellison syndrome, MEN I

- Risk factors
  - Travel history
  - Outbreak (friends/family)
  - Seafood (food poisoning)
  - Extraintestinal symptoms (eye, skin, and joint)
  - Diet changes
  - Laxative use
  - Steatorrhea
  - Celiac disease
  - Immunosuppression, including HIV/AIDs
  - Medications and allergies

- Anal intercourse
- Family history (inflammatory bowel disease (IBD), bowel cancer,celiac disease, lactose intolerance)
- Personal history of IBD, celiac disease, pancreatic or hepatobiliary disease, bowel surgery
- Medications

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 25-27.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give five clinical and/or laboratory features which increase the pretest probability that a patient's chronic diarrhea is factitious and caused by surreptitious laxative abuse

A.

o Demographic groups	- Female - Health care worker - Secondary gain - History of bulimia - Munchausen syndrome - Polle syndrome (Munchausen syndrome by proxy (dependent child or adult poisoned with laxatives by parent or caregiver)
o Serum	- Hypokalemia (senna)
o Stool	- ↑ fecal osmotic gap - ↑/ ↓ osmolality (addition of hypertonic urine, or of water)
o Sigmoid mucosa	- Pseudomelanosis coli (anthracene)

What's new: Celiac disease

- Growth failure may occur in children with undiagnosed celiac disease, and catch-up growth may be incomplete after introducing a gluten-free diet. Anti-pituitary antibodies (APA) suggestive of autoimmune hypopituitorism (based on lymphocytic hypophysitis) occur in 42% of newly diagnosed celiac youths (30% high and 70% low titer of APA), and may also be associated with low level of IGF-1 (Devecchio et al, AJG 2010; 105: 691-6).
- In Europe, the standard mortality rate of persons with symptomatic celiac disease is increased and varies from 1.26 in Finland to 3.6 in Sicily (Biagi & Corazza, 2010).

Ischemia

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. When ischemic changes are seen in the wall of the colon, what are the histopathological features which suggest a microangiopathic antiphospholipid – associated disorder?

A1.
- Vasculitis
- Deposits of immune complexes
- C3 complement
- Fibrinogen

Inflammatory bowel disease

- Take a directed history to determine the cause of infertility in men with inflammatory bowel disease.
- Medications
- Active inflammatory bowel disease
- Poor nutritional status
- Tobacco use
- Alcohol use
- Postsurgical states

Source: Feagins LA, et al. Sexual and Reproductive issues for men with IBD. *Am J Gastroenterol 2009;* 104(3):773.

Useful background: IBS

- Terms
  - Allodynia – non-noxious stimulus causes pain
  - Hypersensitivity – noxious stimulus causes excess pain
  - Distention – mobile fullness
  - Bloating – subjective sensation of abdominal fullness/ gas

- Pathophysiology
  - Bio psychosocial disorder (“brain – gut dysregulation”)
  - cytokines & chemokines (in blood, but not in colonic tissue maladaptive cognition)

Q. The timing of the use of anti-TNF drugs chronic inflammatory CD is moving towards early introduction for persons suspected as being at risk for future severe disease.

 Give 5 risk factors for severe CD.

A. The patient
  - Age of onset <35 years
  - NOD positive
  - Smoking
  - Early need for steroid treatment

 The disease
  - Ileum
  - Fistulizing
  - Deep ulcers

Useful background: Diagnostic criteria for irritable bowel syndrome (Rome III)

 Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with change in form (appearance) of stool
  - Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
  - Supportive symptoms that are not part of the diagnostic criteria include abnormal stool frequency (a) < 3 bowel movements per week or (b) > 3 bowel movements per day; abnormal stool form (c) lumpy/hard stool or (d) loose/watery stool; € defecation straining; (f) urgency or also feeling of incomplete bowel movement, passing mucus and bloating.
  - In the absence of structural or metabolic abnormalities to explain the symptoms.
  - “Discomfort” means an uncomfortable sensation not described as pain.

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Useful background: Alarm symptoms that cannot be explained by irritable bowel syndrome

 Fever

 Anemia

 Bleeding from the gut

 Significant weight loss

 Family history
  - Cancer
  - Inflammatory bowel disease

- Celiac disease

- Recent consistent change in bowel habit
- Persistent, daily diarrhea or constipation
- Abnormal physical findings, for example, abdominal mass or malnutrition

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: Canadian Pharmacist Association 2012, Table 2, page 857.

Useful background: Immunosuppression

- Prediction of azathioprine (AZA) toxicity
  - Consult http://www.immunize.org/reports041.asp
  - Genotype – TPMT only predicts early development (< 1 month) of leucopenia
  - Phenotype – 6-TGN therapeutic benefit
  - 6- MMP risk of hepatotoxicity
  - If AZA od is causing elevated hepatic transaminases, try halving the dose but giving AZA bid (same total daily dose e.g. 100 mg p.o. o.d. 50 mg b.i.d.), rather than reducing the total daily dose.
- Vaccination while on azathioprine (AZA)
  - Vaccination (inactivated) does not exasperate disease activity in multiple sclerosis or in SLE (lupus); we need more long-term studies in IBD
  - Vaccinate for HPV young males, not just females
  - Vaccinate family members of IBD patient protect your IBD patient – doc, get vaccinated!
  - Risk of MD with active viremia to immune suppressed IBD patient is unknown, just in case.
  - Response to inactivated vaccines is normal when on AZA, but is reduced when on infliximab (IFX) or IFX + AZA
- Rotavirus immunization uses a live virus. Do not immunize a child for rotavirus if they are already on anti-TNF medications, or if the mother was on anti-TNF therapy during the 3rd trimester of pregnancy.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. In the IBD patient who fails to respond to adequate doses of AZA/6-MP, give 3 possible reasons to measure the metabolites of these drugs:

A.
- 70% - ↓ 6-TG: too low a dose
- 25% - ↓ 6-TG + ↑ 6 MMP: predominant metabolism by TPMT
- 5% - ↓ 6-TG + ↓6-MMP; poor adherence

Useful background: Yin & Yang of Concomitant immunomodulators

- Benefit
  - Shorter duration of response (with episodic therapy)
  - Positive benefit in steroid-dependent patient (SONIC)
- No benefit
  - Antibodies (at least to infliximab)
  - No difference in short- or long-term responses to induction + maintenance therapy in refractory CD
    - ACCENT, CHARM, PRECISE
  - Associated with acute/delayed infusion reactions
  - No benefit with steroid-induction (COMMIT)
- Harm
  - Immunomodulators reduce immunogenecity across all trials
  - Increase long-term toxicity
    - Serious infections
    - Risk of infections

Adapted from: Hanauer SB. *ACG Annual Scientific Meeting Symposia Sessions 2009*, page16-18.

Useful background: Mesalazine for IBS

- Observational data suggests benefits of mesalazine for IBS[1]
- Randomized, placebo controlled pilot study in IBS patients from Italy[2]
- Compared to placebo, mesalazine reduced mast cell infiltration ($p<0.0001$)
  - Reduced mast cell histamine release ($p<0.001$)
  - Reduced abdominal pain intensity scores ($p=0.0026$)
  - Improved general well-being ($p=0.0007$)

Source: Andrews and Barbara et al, DDW 08
GEMS, Pearls and interesting Trivia

Useful background

- In the woman with IBD who wishes to breast-feed her baby, the mother needs to avoid the use of cipro', cyclosporine or methotrexate.

Useful background: Probiotics

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. How are your 10^{14} cells today?

A1. They are fine, but I am experiencing destructive interference from my 10^{15} gut microbiotica cells!

Q2. Funny! We all know what are probiotics, prebiotics and symbiotics. What are bacteriocins?

A2. Bacteriocins are substances that are produced by some bacteria which modify the growth of other bacteria.

- The commensual bacterium faecalibacterium prausnitzii has an anti-inflammatory action, and Crohn disease (CD) recurrence after surgery.

The placebo response rate (PRR) in IBS varies over time, rising to a PRR of 70% after 8 weeks of placebo therapy, and falling to 10% to 20% PRR at 24 wks.

- Little known fact: IBS is associated with a risk of the development of ischemic colitis, $1.1/10^3$ cases per year.

Useful background: Colonic infections

- Amebiasis
  - 90% of E. histolytica are asymptomatic, but should be Rx because
    - May become symptomatic
    - May be passed on to others (food-handlers, infectious-!)
  - Colon
    - Flask-shaped ulcer
    - Ameboma
  - Liver
    - Abscess
    - Usually R. lobe of liver
  - Metastatic amebiasis
    - Usually direct/ hematogenous spread
    - CNS, lung, pericardium, skin

Infections

CLINICAL VIGNETTE

➢ Male traveler, single low-attenuating lesion on CT with enhancement of rim, elevated right hemidiaphragm on chest X-ray, "anchovy paste" substance on aspiration of abscess	o Amebic abscess
➢ Mild diarrhea illness, bright red blood per rectum traveler or lives in Southern USA (e.g., Texas), ulcerative colitis-like appearance of mucosa sigmoidoscopy, "flask-shaped ulcers" on biopsy	o Amebic colitis

Q: Give the antibiotic recommended for the treatment of hemorrhagic colitis due to E. coli O157:H7 infection.

A: There is none; in fact, antibiotic treatment of E. coli O157:H7 may precipitate HUS-TTS (hemorrhagic uremic syndrome and thrombotic thrombocytopenic purpura).

Sorry to trick (i.e. mislead you, but…….)
"The GI tract is one Hugh Immune Organ" (Spiegel, BMR, et al. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time Resource. *Slack Incorporated* 2011, page 114)

Obstruction / Pseudo-obstruction

Q: Define "Ogilvie Syndrome", and give 4 of its commonly associated causative conditions.

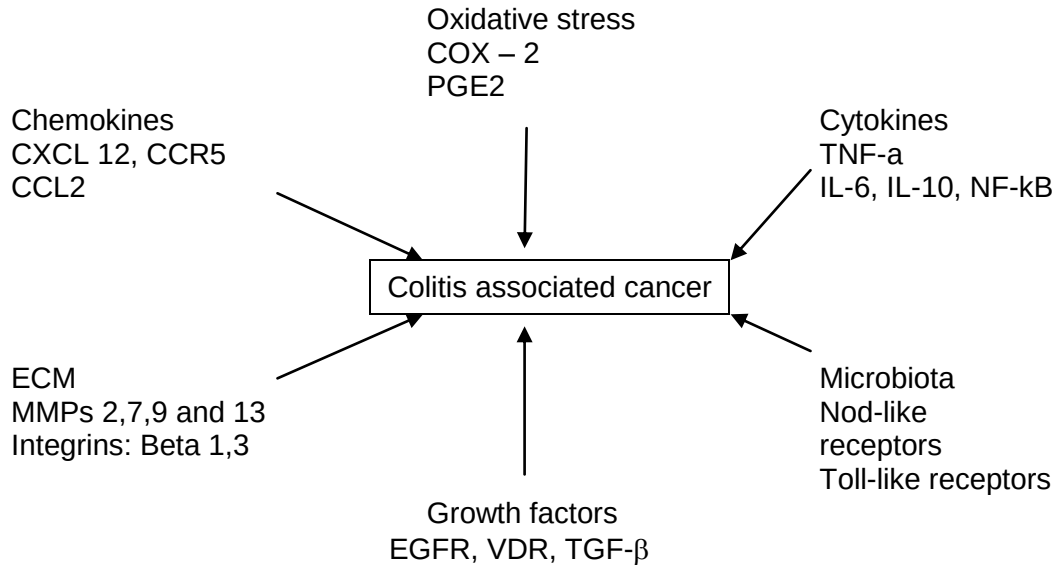
A: Definition: Ogilvie Syndrome is acute colonic pseudo-obstruction.
"……characterized by marked dilation of the cecum [> 10 cm] and ascending colon in the absence of mechanical obstruction" (Spiegel, BMR, et al. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time Resource. *Slack Incorporated* 2011, page 110).

- o Common associations
  - ICU patients
  - Sepsis
  - Recent surgery
  - Electrolyte abnormalities
  - Trauma
  - Drugs
  - Immobilization

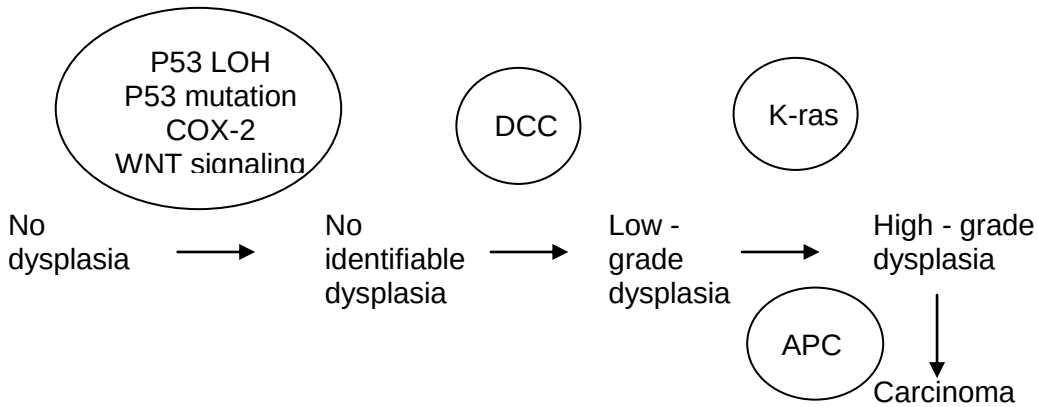
Ulcerative Colitis

Pathology Tip: Branching colonic crypts – the "trouser" or pyjamas" sign, a sign for an event that has occurred in the post (i.e. chronic disease)

- Postulated mechanisms of IBD-associated colorectal cancer
- Mediators



- Genetics



Abbreviations: APC, adenomatous polyposis coli; COX-2, cyclooxygenase-2; DCC, deleted in colorectal cancer; K-ras, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LOH, loss of hetterozygosity; WNT, wingless and INT; CCL2, chemokine (C-C motif) ligand 2; CCR5, C-C chemokine receptor type 5; COX-2, cyclooxygenase-2; CXCL12, chemokine (C-X-C motif) ligand 12; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; IL-6, interleukin-6; MMP, matrix metalloproteinase; NF-kB, nuclear factor-kB; PGE2, prostaglandin E2; TGF-β, transforming growth factor-β; TNF-a, tumor necrosis factor-a; VDR, vitamin D receptor

Source: Goel GA, et al. *Am J Gastroenterol* 2011;106: page 721.

SO YOU WANT TO BE AN GASTROENTEROLOGIST OR ENDOCRINOLOGIST!

Q1. What endocrine disease may co-exist with ulcerative colitis (UC), worsen the symptoms, and reduce the response of the UC to therapy.

A1. Hyperthyroidism may occur in UC.

Proctitis

Q1: Give the 4 most common infectious causes of proctitis in MSM (men who have sex with men).

A1:
- HSV (herpes simplex virus)
- Chlamydia
- T. pallidum (syphilis)

Q2: Give the most common infectious organisms in AIDS / HIV which lead to fulminant colitis.

A2:

- MAC (CD4 ≤ 50)
  - Deep ulcers
  - High risk of perforation
  - Intra-abdominal lymphadenopathy
  - Acid-fast MAC in "foamy macrophages"
- CMV CD4 ≤ 100)
  - Vasculitis thrombosis of intraluminal arterioles
  - Ischemia
  - Discrete / seropignous ulcers
  - Ulcers often in right colon
  - CMV seen in centre ulcer: biopsy base
- E. histolytica
  - High risk of perforation
  - Stricture formation
  - Liver abscesses

Q3: In a patient with colonic ulceration from suspected viral infection, from what location of the ulcer, are mucosal biopsies taken?

A1:
- CMV – centre of ulcer, as well as from normal tissue
- HSV – rim of ulcer

Diverticulitis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Outline the treatment of acute diverticulitis, based on the Hinchey grading system of abdominal CT.

A. Hinchey CT grade		Treatment
0	Perforation and no comorbidity	- Outpatient oral antibiotics
I	Abscess pericolic/ pericolic inflammation	- IV antibiotics
II	Abscess (pelvis, abdomen, retroperitoneal)	- IV antibiotics -- CT – guided drainage of abscess
II IV	Generalized purulent peritonitis Generalized fecal peritonitis	- Surgery

Polyps

- Name the Colonic Polyp Syndrome.

- Adenomatous
- Non-GI associations
  - o CHRPE (congenital hypertrophy of the retinal pigmentation epithelium)
  - o Desmoid tumors
  - o Lipomas
  - o Fibromas
  - o Epithelloid cysts
  - o Sebaceous cysts
  - o Osteoma jaw
  - o Mesenteric fibromatosis
  - o Supernumerary teeth

Answer: Gargner syndrome (FAP plus extraintestinal associations)

- Extracolonic associations (tumor)
  - o GI (Muir-Torre Variant)
  - o GI
    - Stomach
    - Small intestine
    - Biliary tree

- o Non-GI
  - Endometrium
  - Ovary
  - Kidney
  - Ureter

Answer: HNPCC

- o GI
  - CNS
    - Mental challenge
    - Epilepsy
  - Bone
    - Cysts
  - Heart
    - Rhabdomyoma
  - kidney
    - Cysts
- Medulloblastoma

Answer: Turcot Syndrome (FAP plus brain tumor)

- Non-colonic associations
  - o Biliary tract disease
  - o Gastric cancer
  - o Small intestinal cancer

Answer: HNPCC (Muir-Torre Variant)

- Hematomatous

- Tuberous sclerosis (autosomal dominant; hamartomas)

- Non GI
  - o Testicular tumor (Sertoli)
  - o Ovarian tumor (Sex-cord)

Answer: Non-colonic associations

Cronkhite – Canada Syndrome

- o Etiology unknown (not inherited)
- o GI manifestations
  - Malabsorption
  - Protein-losing enteropathy
  - Hamartomatous polyps
    - Stomach
    - Small bowel
    - Colon

Q: Give the differential of hamartomatous syndromes which affect the GI tract, and indicate which one is not autosomal dominant.

A: Cronkhite-Canada syndrome

- o Differential of GI hamartomatous
  - Pentz-Jegher
  - Juvenile polyposis
  - Tuberous sclerosis
  - Cronkhite-Canada
- o Cronkhite-Canada
  - Etiology unknown (not inherited)
- o GI manifestations
  - Malabsorption
  - Protein-losing enteropathy
  - Hamartomatous polyps
    - Stomach
    - Small bowel
    - Colon
- o Skin changes
  - Alopecia
  - Dystrophy of mails

Q: Give the differential of hamartomatous syndromes which affect the GI tract, and indicate which one is not autosomal dominant.

A:
- Pentz-Jegher
- Juvenile polyposis
- Tuberous sclerosis
- Cronkhite-Canada
- Cowden syndrome

Colon Irritable Bowel Syndrome (IBS)

- Definition: “The irritable bowel syndrome (IBS) is a collection of symptoms attributed to the intestine, related to defecation and unpredictable habit……recognized by its characteristic pattern of abdominal pain and discomfort, which is relieved by defecation or associated with a change in bowel habit [in which]…there is no known pathology or pathophysiology”

Thompson WG, et al. Chapter 64. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 856.

Endometriosis

Definition: “Endometrisis [is] diagnosed by finding tissue that histologically resembles endometrium at sites outside the uterine cavity” (Gilliland GB, et al. Chapter 70. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 927).

Note: “there is no direct correlation between the volume of endometriatic tissue and……the severity of symptoms”.

Colorectal cancer (CRC)

SO YOU WANT TO BE AN GASTROENTEROLOGIST OR ENDOCRINOLOGIST!

Q. Give reasons why the risk of colorectal cancer is increased two-fold in acromegaly.

A.
- ↑ incidence of colonic adenomatous polyps
- These adenomatous polyps are often
  - Large
  - Multiple
  - Right-sided (possibly more difficult to see on colonoscopy)

☐ Take a directed history for colon cancer screening, and surveillance.

Screening	Surveillance
☐ Age	☐ When polyps found
☐ Gender	☐ Size > site
☐ Race	☐ Number
☐ GI symptoms	☐ Histology
☐ Family history o Colon polyps o Cancer - Bowel - Abdomen - Brain	☐ Removal
☐ Previous screening - Stool - Imaging - Colonoscopy	☐ Who did colonoscopy
☐ Diet - Alcohol - Obesity - Fresh fruit - Vegetables - Fiber	
☐ Smoking	
☐ Rx, ASA, NSAIDs, Coxibs	

CLINICAL VIGNETTE

- Case: Hamartomatous polyps of stomach, small intestine or colon; weight loss and edema, balding; negative family history
  - Answer: Cronkhite – Canada Syndrome

CLINICAL VIGNETTE

- Case: Colonic “polyp” in a female which appears when abdominal pain is present, then disappears.
  - Answer: Endometriosis

CLINICAL VIGNETTE

- Case: Screen colonoscopy, larger polypoid lesion which disappears with a “pop” on mucosal biopsy patient has COPD.
  - Answer: PCI (pneumatosis cystoides intestinalis)

CLINICAL VIGNETTE

- Case: Recovering from hospitalization for treatment of endocarditis due to Streptococcus bovis; weight loss and altered bowel habit polypoid lesion on colonoscopy
  - Answer: CRC (colorectal cancer)

“Consent is a dialogue, not a signature”

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

LIVER

Alcohol abuse

- At risk drinking- drinking more than the recommended levels of alcohol (no more than 2 standard drinks per day to a maximum of 9 standard drinks a week for females and 14 standard drinks for males) but no apparent physical or social problems related to alcohol.
- Problem drinking- same as at risk drinking but with one or more alcohol related social or physical problems and no clinical features of dependency.
- Alcohol dependency- a maladaptive pattern of alcohol use leading to clinically significant impairment or distress with 3 or more of the following criteria in the past 12 months:
  - Tolerance
  - Use of larger amounts of alcohol for longer periods of time
  - Presence of withdrawal
  - Symptoms, excessive amount of time spent in obtaining alcohol
  - Important activities missed or reduced due to alcohol use
  - Persistent desire but unsuccessful efforts to cut down alcohol

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 103 and 106.

- Take a directed history of alcohol abuse.

- Alcohol
  - Drinking behavior – where, when, what, who, why
  - CAGE questionnaire
    - Have you ever felt the need to **C**ut down on your drinking?
    - Have you ever felt **A**nnoyed by criticism of your drinking?
    - Have you ever had **G**uilty feelings about drinking?
    - Have you ever had an **E**ye opener (a drink first thing in the morning?)
  - Medical complications and associations
  - Fatigue
  - Seizures
  - Blackouts
  - Sleep disturbances
- Alcohol withdrawal
  - Shakes, seizures, hallucinations, DTs

- Liver – cirrhosis, hepatitis
- Cardiac – hypertension, cardiomyopathy
- GI- esophagitis, gastritis, hepatitis, fatty liver, liver cirrhosis, pancreatitis, peptic ulcers, esophageal or rectal varices, oral and esophageal cancers, malabsorption, UGIB
- Cardiac- alcoholic cardiomyopathy, arrhythmias
- Peptic ulcer disease, variceal or non-variceal upper GI bleeding
- Neurologic- Wernicke's syndrome, Korsakoff's syndrome, cerebellar degeneration, peripheral neuropathy, myopathy
- Hematologic- iron or folate anemia, thrombocytopenia, coagulopathies
- Endocrine- impotence, hyperlipidemia
- Immunologic- immune system impairment
- Electrolytes- symptoms of low serum calcium, magnesium, or phosphate; ketosis
- Mental
    - Depression
    - Attempted suicide
    - Family Hx of alcoholism
    - Other substance abuse
    - Stressors
        - Family
        - Spouse
        - Friends
        - Stress
        - Money
    - Social consequences
        - Occupation
        - Family
        - Leisure
        - Financial problems
        - Legal problems
        - Accidents and fights
        - Driving intoxicated

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 103 and 105.

SO YOU WANT TO BE GASTROENTEROLOGIST!

Q. In the context of alcohol abuse, what is Zieve syndrome?

A. Zieve syndrome is jaundice, hemolytic anemia and hyperlipidemia/ hypercholesterolemia.

 Perform a directed physical examination for alcohol withdrawal (SSH-DTs: shake, seize, hallucinate, DTs).

Time after stopping alcohol	Name of withdrawal syndrome	Clinical picture
- 6-8 hours	Shake	- Tremor - Nausea/vomiting - Insomnia, agitation - Tachycardia (autonomic hyperactivity), fever
- 8 hours to 2 days	Seizures	- Multiple tonic-clonic seizures
- 1-2 days	Hallucinations	- Visual hallucinations
- 3-5 days	DTs	- Fluctuating LOC, coma, agitation/anxiety, death

- o Autonomic hyperactivity (tachycardia, pyrexia, sweating, tremor, irritability)
- o Depressed mood
- o Nausea, vomiting
- o Insomnia
- o Anxiety
- o Seizures
- o Delirium tremens
- o Hallucinations (usually visual, but auditory and tactile are possible).

GI liver alcohol

Q1: In the context of substance withdrawal, take a directed history and perform a focused physical examination for alcohol and benzodiazepine withdrawal syndromes.

A1: History
- Alcohol / benzodiazepine use, and discontinuation
- Specific assessment tools
  - CIWA-AR (Clinical Institute Withdrawal Assessment for Alcohol)
  - CIWA-Bezo (Clinical Institute Withdrawal Assessment for Benzodiazepines)
- Anxiety
- Depression (with alcohol but not benzodiazepine cessation)
- Nausea / vomiting

 Physical
- Autonomic hyperactivity
  - Pulse > 100 bpm
  - Hypertension
  - Fever (including hyperthermia)
  - Dehydration
  - ↑ hand tremor
  - Psychomotor agitation
- Psychosis
  - Delusions
  - Hallucinations, transient
    - Visual
    - Tactile
    - Auditory
- CNS disorders
  - Grand mal seizures
- Liver disease
  - Cirrhosis
  - Bleeding disorders
  - Wernicke encephalopathy
- CVS
  - Arrhythmias
  - Cardiac death

Adapted from: Grey J, Therapeutic Choices. 6th Edition, *Canadian Pharmacists Association* 2012, Table 1, page 141.

Liver transplantation

Useful background

- Indications for liver transplantation, a rule of thumb
  - Hepatic encephalopathy
  - Jaundice
  - Varices
  - Ascites

- Contraindications
  - Sepsis
  - Cancer
  - Hemodynamic instability

- Survival after liver transplantation

1 year	90%
5 years	80%

Beyond 5 years, the mortality rate is not influenced by the liver transplantation itself, but rather by coronary artery disease, cancer or infection.

  - 5 to 7% of compensated cirrhotic patients become decompensated every year

- The MELD score predicts the three month mortality rate after liver transplantation. Remember the factors which make up the MELD score: AA-B-CC-HE-Na^+
  - Ascites
  - albumin
  - Bilirubin
  - Creatinine
  - coagulation (INR)
  - hepatic Encephalopathy
  - Na^+ (risk for central pontine myelinolysis)
    - The MELD – Na^+ score is better than the original MELD score to predict the death of the patient on the liver transplantation list.

- The transplantation of livers from brain-death donors is superior to heart-dead donors.

SOT (solid organ transplantation) / HCT (hematopoietic cell transplantation)

Useful background:

- About 1/3 of patients with a SOT (e.g., liver) will develop postoperative complains, which are usually due to
  - Graft dysfunction
  - Medications (Rx) causing adverse effects (AEs)
  - Infections
    - CMV, HSV, EBV, V2V, HAV-6
    - Opportunistic
  - Malignancy
    - Acquired
      - Prior to surgery
      - A complication of surgery, or
      - Transmitted with the allograft

Abbreviations: EBV, Epstein-Barr virus; HHV-6, human herpesvirus-6; VZV, varicella-zoster virus

Intestinal adverse effects are common after solid organ transplantation, but some respects of these AEs are different in SOT of kidney transplant (KT).

- Give 15 common hepatobiliary complications of SOT /HCT.
- Liver
- DILI (drug-induced liver injury)
  - Azathioprine
    - ↑ transaminases
    - Mainly cholestatic
    - Centrilobular hepatocyte damage
    - Veno-occlusive disease (sinusoidal obstruction syndrome) → PHT
  - Cyclosporin, tacrolimus
    - Cholestasis
  - Sirolimus
    - Dose-dependent ↑ ALT/AST
- Infection
  - Bacterial sepsis (cholangitis lenta syndrome)
  - CMV, V2V, HSV, EBV
    - Hepatitis
    - Acute liver failure (V2V, HSV)
  - HBV, HCV
    - Primary disease, or recurrence
  - Fungal abscess

- Vascular
  - Post KT
    - NRH (nodular regenerative hyperplasia)
    - Peliosis hepatitis
  - Ischemic liver injury
  - Veno-occlusive disease (aka sinusoidal obstructive syndrome [SOS])
- Infiltration
  - HCC
  - PTLD
- Immune
  - GVHD
- Biliary tree
  - Acalculous cholelithiasis
  - Cholelithiasis → cholecystitis
    - Mortality rate for acute cholecystitis is 29%
    - Use UDCA prophylaxis

Abbreviations: GVHD, graft-versus-host disease; HCC, hepatocellular cancer; HCT, hematopoietic cell transplantation; NRH, nodular regenerative hyperplasia; PHT, portal hypertension; PTLD, post transplant lymphoproliferative disease; UDCA, ursodeoxycholic acid

Veno occlusive disease (VOD) /Sinusoidal obstructive syndrome (SOS)

Useful background: VOD (veno occlusive disease; aka SOS [sinusoidal obstruction syndrome])

- Narrowing of central portal venules
- Non-thrombotic occlusion
- Dilation of sinusoids
- RBC accumulation (congestion)
- RBC accumulation (congestion)
- Painful hepatomegaly
- Abnormal LE's (liver enzymes)
- Associated with
  - Bone marrow transplantation (BMT; up to 21 days post BMT)
  - Chemotherapy
  - Therapy with azathioprine

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Unfortunately, the liver disease which led to the need for a liver transplantation (LT) may recur in the transplanted liver.

Q. Give 5 types of liver disease which may recur after LT (liver transplantation)

A.
- Infection
  - HBV*
  - HCV
- Immune
  - PBC
  - PSC
  - AIH
- Metabolic
  - NASH
- Toxins
  - ALD

*Acquisition of HBV after LT does not alter 5 year survival rate , 25% redeveloping cirrhosis

Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus (99^{+} % recurrence); NASH, non-alcoholic lsteatohepatitis; PBC, primary biliary cirrhosis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Veno-occlusive disease (aka sinusoidal obstruction syndrome [SOS]) occurs in up to 20% of HST patients, depending on the myloid-ablative conditioning used, and the presence of pre-existing liver disease. A clinical diagnosis may be made in the first three weeks after HCT. In difficult cases, WHVPG (wedge hepatic venous pressure gradient and liver biopsy may be necessary.

- Give the histological features of SOS.

A.
- Sinusoids
  - Dilated, disrupted
  - Fibrosis
  - Late collagenization
- Space of Disse
  - Extravasation of RBCs
- Hepatocytes
  - Zone 3 necrosis
  - Drop out
- Central vein (CV)
  - Subendothelial edema (CV remains potent)
  - Late colagenization

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. What is the clinical course of C. difficile in SOT (solid organ transplantation)?

A1.
- Common
- May be clinically mild
- Severe
  - Megacolon
  - Death
- Poor response to antibiotics (only ~ 70%)

Q2. What is the benefit of probiotics for C. difficile infection in the immunosuppressed SOT patient?

A2. None. In fact beware, there may be an ↑ risk of yeast infection and dissemination!

Q3. Pancreatitis is common in the SOT setting (liver –Tx, 5%, KT, ~2%).

- Give 7 common causes of this post-SOT pancreatitis.

A3.
- Infiltration
  - Malignancy
- Drug / toxins
  - Alcohol
  - Azathioprine
  - Steroids
  - Cyclosporin
  - Tacrolimus
- Cholelithiasis (perhaps because of precipitation of cyclosporin in bile, formimg the nidus for crystalization and stone formation)
- Surgical manipulation of pancreas

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Liver transplantation may improve the clinical course of some patients with cystic fibrosis (CF). These LT-CF patients may develop some of the above GI complications, but may also develop complications which are unique to LT-CF.

- Give 2 unique GI complications of LT in CF

A
- Secondary biliary cirrhosis → ↓ absorption of fat-soluble drugs; such as cyclosporin
- Distal intestinal obstruction syndrome (20%)

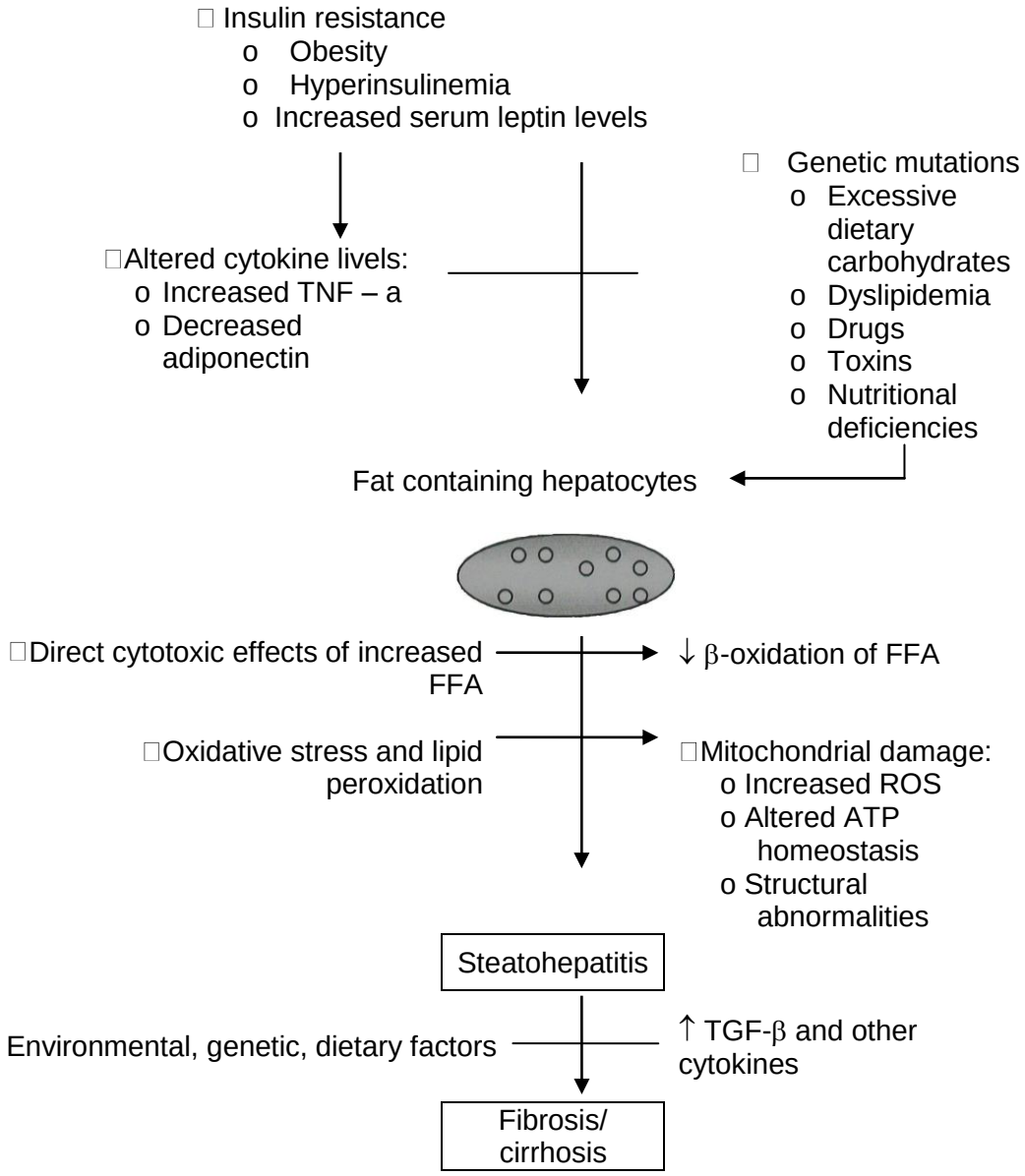
Cystic Fibrosis

- Give 20 GI/Hepatobiliary clinical manifestations of cystic fibrosis.
- Esophagus
  - Gastroesophageal reflux disease
- Stomach
  - Peptic ulcer disease
- Small bowel
  - Fat malabsorption
  - Mecomium ileus
  - Ileal atresia
  - Intussusception
- Colon
  - Volvulus
  - Distal intestinal obstruction syndrome (meconium equivalent)
  - Fecal masses
  - Constipation
  - Impaction
  - Rectal prolapse
  - Hemorrhoids
- Peritoneum
  - Peritonitis
- Pancreas
  - Nutritional failure caused by pancreatic insufficiency
  - Diabetes
  - Calcification
  - Maldigestion
  - Fat soluble vitamin deficiencies
  - Steatorrhea and azotorrhea
- Gallbladder
  - Gallstones, atrophic gallbladder
- Liver
  - Focal biliary cirrhosis
  - Cirrhosis
  - Portal hypertension
  - NAFLD
  - Hepatomegaly
  - Premature death

Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 8th Edition. *Saunders/Elsevier* 2006, page 1214 and1322.

NAFLD /NASH

Pathogenesis of nonalcoholic fatty liver disease (NAFLD)



Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Figure 85-1, page 1404.

 Give the 10 benefits and AEs (adverse effects) of TZD (pioglitazone).

Benefit	AEs
o adipokinins	BMI
o adiponection (a protector of the liver)	CV event
o oxidation	osteoporosis
o TG, VLDL	bladder cancer
o Converts “bad” into “good” fat	
o insulin resistance	

SO YOU WANT TO BE A HEPATOLOGIST!

Q. Patients with NAFLD may have elevated serum levels of ALT and AST. What level of these liver enzymes should signal the need to refer the patient for a liver transplantation (L-Tx)?

A. No level! The decision to refer the NAFLD patient for L-Tx is based on the risk factors for progressing to NASH, and not on the level of their ALT or AST. In fact, ~ 60% of persons with NASH-cirrhosis have normal transaminases.

SO YOU WANT TO BE A HEPATOLOGIST!

Q1. Bariatric surgery may improve NASH; how useful is dieting for persons with NASH?

A1. There is an inverse linear relationship between increasing weight loss and a decline in NAS (NAFLD activity score; even just a 5% loss of body weight has a clinically meaningful decline in NAS)

Q2. Does weight loss in NAFLD reduce mortality of this liver disease?

A2. Person with NAFLD treated with weight loss have a reduced mortality rate from both cardiovascular as well as hepatic causes of death.

Q3. The pathogenesis of the progression of NAFLD to NASH involves insulin resistance, as well as oxidative stress. There is evidence that VE (alpha tocopherol may benefit NASH. Accepting that the treatment of insulin resistance, with TZD for example, is not sufficient by itself, give 5 benefits and 3 adverse events (AEs) of the use of a TZD, such as pioglitazone,

A3. ↑ blood insulin suggests the presence of insulin resistance, and is as good a measure as more complicated end points such as HOMA, to predict the presence or degree of insulin resistance.

Hepatosplenomegaly

- Dermatitis herpetiformis
  - Definition
    - Bilateral, symmetrical, gry and itchy vesicles or urticarial plagues on extensor surfaces, neck, back, buttocks, elbows, knees
  - Associations
    - Celiac disease
    - GI lymphoma
    - Hypothyroidism

Useful background: Causes of hepatomegaly

- Raised venous pressure
  - Congestive cardiac failure
  - Constrictive pericarditis
  - Tricuspid stenosis
  - Hepatic vein thrombosis
- Degenerative conditions
  - Fatty infiltration and early cirrhosis
- Storage disorders
  - Amyloidosis
  - Gaucher's
  - Niemann-Pick's
  - Histiocytosis X
  - Glycogen storage disease
  - Haemochromatosis
  - Hurler's (Gargoylism)
- Infections
  - Viral
    - Infective and serum hepatitis
    - Infectious mononucleosis
  - Bacterial
    - Hepatic abscess
    - TB
    - Syphilis
    - Weil's disease
  - Protozoal
    - Amoebic abscess
    - Malaria
    - Toxoplasmosis
    - Kala-azar
  - Fungal

    - Histoplasmosis
  - Parasitic
    - Hydatid cyst

Source: Burton JL. *Churchill Livingstone* 1971, pages 43 and 44.

- Perform a focused physical examination for hepatosplenomegaly.

- Liver
  - Palpable liver in patients with chronic liver disease
  - Palpable liver in epigastrium in patients with chronic liver disease
  - Liver edge firm to palpation in patients with chronic liver disease
  - Palpable liver in patients with jaundice, detecting hepatocellular disease
  - Palpable liver in patients with lymphadenopathy, detecting serious disease
  - Liver tenderness in patients with jaundice, detecting hepatocellular disease non-obstructive jaundice

- Spleen
  - 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

- Because of the wide values of the reported sensitivity and specificity for detecting hepatosplenomegaly, none of the values of the positive likelihood ratios (PLR) are much greater than 2: palpation of a firm liver edge in a person with chronic liver disease (PLR, 2.7), palpable liver in the epigastric area in a person with chronic liver disease (2.6), or any palpable liver again in a person with chronic liver disease (2.0).

  - A palpable liver is not necessarily enlarged, but increases the likelihood of hepatomegaly (LR if present, 2.5 [95% CI, 2.2-2.8]). A non-palpable liver edge does not rule out hepatomegaly, but reduces its likelihood (LR is absent, 0.45 [95% CI, 0.38-0.52]).

- The likelihood of a high PLR for splenomegaly depends on the clinical setting for example, in a returning traveler and fever where there is splenomegaly from malaria (PLR, 6.6), with much lower values to detect hepatocellular disease in a person with non-obstructive jaundice (2.9), or detecting cirrhosis in the person with chronic liver disease (2.3).

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 47.2, pages 556 to 559.

- Give 4 causes of a hard knobbly liver.
  - Carcinoma metastases
  - Post-necrotic cirrhosis
  - Congenital cystic liver
  - Hydatid cysts
  - Hepar lobatum (syphilis)

Useful background: Causes of hepatosplenomegaly
- Infective e.g. infectious mononucleosis
- Myeloproliferative e.g. myelofibrosis, chronic myeloid leukaemia
- Some causes of portal hypertension e.g. Budd-Chiari syndrome
- Reticuloses
- Storage diseases e.g. Gaucher's disease, amyloidosis
- Anemia e.g. PA, sickle cell anemia in children

Source: Burton JL. *Churchill Livingstone* 1971, page 44.

- Tenderness in Hepato / Splenomegaly for viral hepatitis

	HBV/ HCV	EBV
Liver	+	(-)
Spleen	(-)	+

Useful background:

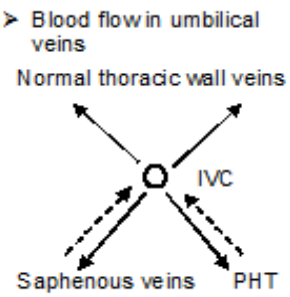
- Hemolytic anemia is not associated with pruritus or bradycardia.

- Examination of abdomen
  - Pancreatic cysts may be palpable, but cancer is usually not
  - Ovarian tumors may be palpated in midline
  - A distended bladder
    - is usually palpated in the midline
    - is usually symmetrical, unless the bladder has a diverticulum
  - Unlike an enlarged spleen, an enlarged kidney may have an anterior band of resonance
  - In the patient with hematemesis, the common cause is a bleeding peptic ulcer; in the patient with hematemesis and splenomegaly/ hepatomegaly/ ascites, or skin changes of portal hypertension, the commonest cause is still bleeding from a duodenal or gastric ulcer, followed closely in frequency bleeding esophageal varices.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. What are the uses of examining the "belly button"? Or, Perform a focused examination of the abdominal veins to distinguish between obstruction of the inferior vena cava (VC), and portal hypertension (PHT).

A.
- The normal irection of flow of blood in veins of abdominal wall-flow below umbilicus is down into saphenous veins, above umbilicus is upwards into veins of thoracic wall. In portal hypertension, dilated veins show normal direction of flow.
- In IVC obstruction, flow in veins below umbilicus is reversed, i.e. Flows upward.



- In obstruction of inferior vena cava (IVC), blood does not flow away from the umbilicus towards the saphenous veins
- In PHT, the enhanced blood flow is still through the normal route, upwards to veins of the thoracic wall, and downwards to the saphenous veins

Umbilicus is common site of infiltration by cancer metastases (Sister Mary Joseph's nodule)
Protuberance from ascites (an "out-ie")

Acute and Chronic liver disease

- Give 5 functions of the liver.
- Synthesis
  - Albumin
  - Glycogen
  - Urea
- Storage
  - Fat
  - Vitamins A, D, B12
- Detoxification
  - Hormones
  - Drugs
- Secretion
  - Bilirubin
  - Bile salts
  - Cholesterol

- Perform a focused physical examination to determine the cause of pruritus.

- Various skin diseases
  - Infection
  - Eczema
  - Urticaria
  - Lichen simples
  - Dermatitis herpetiformis

- Systemic
  - Hepatic
    - Obstructive jaundice
    - Recurrent pruritus of pregnancy
  - Blood disorders
    - Reticuloses
    - Leukemia
    - Polycythaemia
    - Fe-deficiency
    - Mastocytosis
  - Endocrine
    - Diabetes mellitus
    - Diabetes insipidus
    - Myxoedema
    - Hyperthyroidism
    - Gout
    - Carcinoid
  - Neurological
    - Tabes
    - GPI
    - Thalamic tumor
  - Carcinoma (especially lung, stomach, colon, breast, prostate)
  - Chronic renal failure (probably due to secondary hyperparathyroidism)
  - Psychogenic
  - Drugs
    - Cocaine
    - Morphine
    - Allergic drug reactions

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 122.

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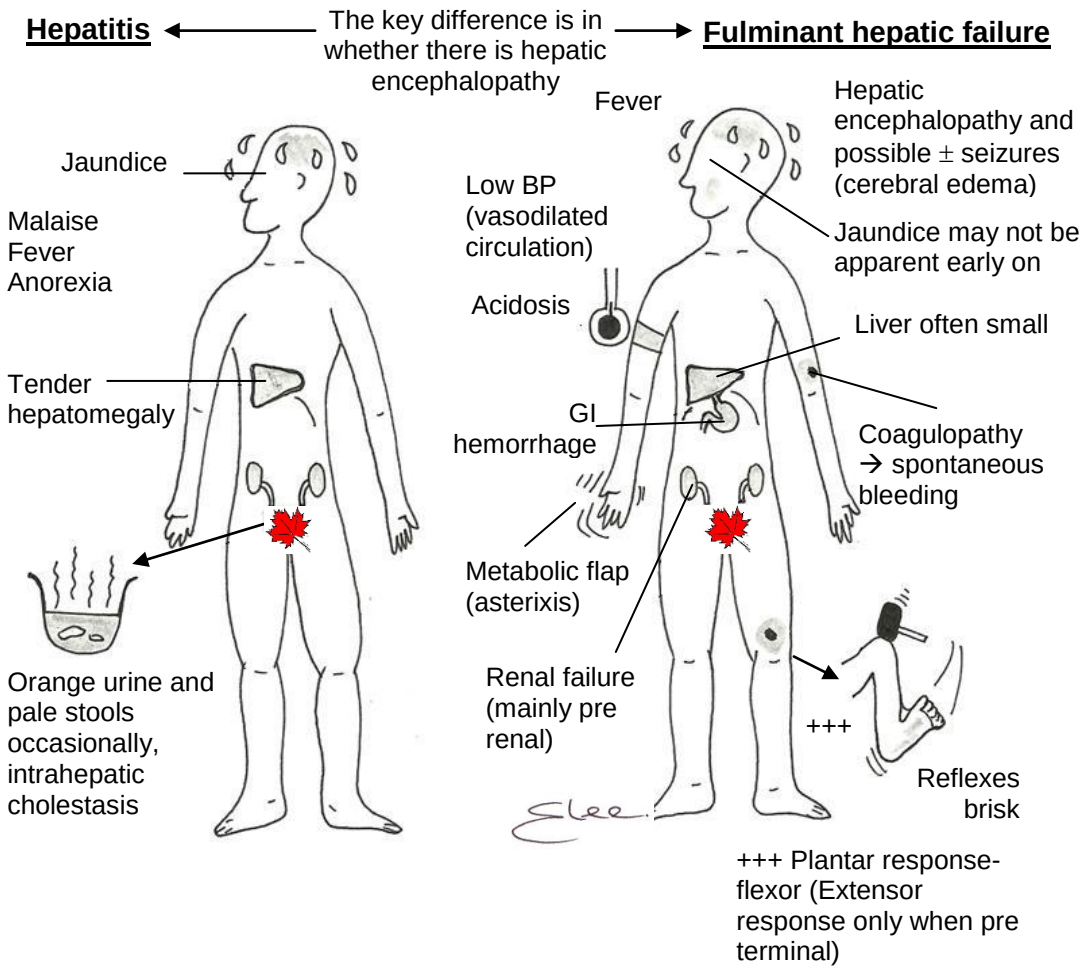
- Perform a physical examination for acute liver disease (acute hepatitis and fulminant liver failure).



Adapted from: Davey P. *Wiley-Blackwell* 2006, page 234.
Useful background: Interferon

- The use of interferon (INF) in HCV is associated with an early anti-viral effect (type I, measured in days), and a later immune effect (step II, measured in weeks).
- The type II (immune response) to INF type depends on IL-28B polymorphisms.
- The response to INF mHCV depends on INF-sensitive genes (ISG).
- Genome wide association studies suggest that there may be a genetic basis for the sustained viral response (SVR) to INF mHCV.

- This genetic variation in the SVR to INF mHCV relate to variations in the host gene on chromosome 19, and to IL-28B gene polymorphisms.
- The CC “cure” haplotype in the IL-28B gene is associated with high SVR to INF mHCV; the TT “terrible” haplotype is associated with slow SVR.
- Low levels of the CC IL-28B in African Americans is associated with a 20% SVR to INF for HCC, whereas the high levels of CC in Asians is associated with a SVR of 80%, with intermediate SVR in Caucasians and Hispanics.
- The response of HCV to telaprevir or boceprevir may be predicted from the response to INF, and heterofere to the CC IL-28 genotype.
- In CC genotype, INF plus ribavirin plus boceprevir give SVR of 96%.

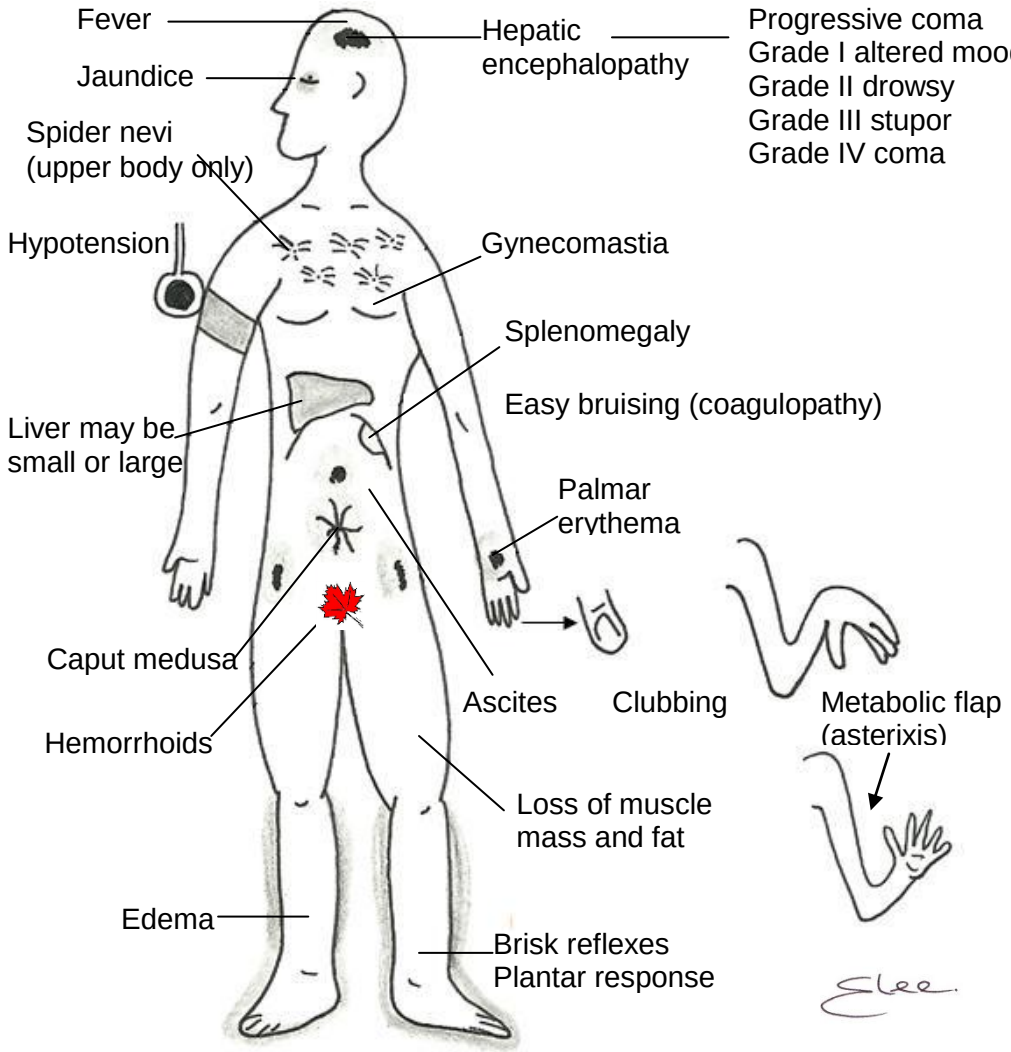
SO YOU WANT TO BE GASTROENTEROLOGIST!

Q. What locations/ parts of the nervous system are affected by hepatic encephalopathy (HE)?

A.
- Cortex
- Cerebellums
- Basal ganglia
- Spinal cord
- Peripheral nerves
- Muscles
- Hepatic histology shows
  - Normal histology, or
  - NAFLD
  - Mild portal cirrhosis

“Is there an upper age limit as to who should be offered a liver transplantation? “Remember that the patient’s physiology is more important than chronology when making the selection decision.”

□□□Perform a focused physical examination for signs of chronic liver disease (portal hypertension).



Causes of acute deterioration in known chronic liver disease

- Drugs (including alcohol)
- Electrolyte disturbance
- Sepsis (especially spontaneous bacterial peritonitis)
- GI bleed
- Hepatoma

*Note that the signs of hepatic encephalopathy (HE), hypotension, fever, acidosis and coagulopathy may occur in acute liver failure. The liver may normal size or small early on. Jaundice may be present. The patient may also experience seizures, which is not a feature of HE.

□□Spider nevi are telangiectasias

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 234.

Occult GI bleeding (O-GIB)
- Vascular lesions of SB account for 75% of SB bleeding

- Incidence
  - U-GIB $40/10^5$/yr
  - L-GIB $25/10^5$/yr
  - 16% of Meckel's have ectopic gastric tissue, from which they bleed

- TIPS

- Definition:
  - TIPS (transjugular intrahepatic portosystemic shunt) "……is an interventioned radiologic procedure in which an expandable metal stent is placed via percutaneous insertion between the hepatic and portal veins, thereby creating an intrahepatic portosystemic shunt" (Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 208.)

- Junctions
  - Bridge to LT (liver transplantation)
  - Reduces portal pressure, and may be useful for short-term control of bleeding esophageal varices

Cirrhosis

SO YOU WANT TO BE GASTROENTEROLOGIST!

Q. The patient with portal hypertension is examined, and does not have splenomegaly. Please give the possible explanations.

A.
- Asplenism
  - Congenital
  - Surgical removal
- Dextrocardia
- Multiple splenic infarcts (eg. Sickle cell disease)
- Splenic vein thrombosis

Perform a focused physical examination for cirrhosis in patients with chronic liver disease.

There are numerous findings on physical examination of a patient with chronic liver disease which give a positive likelihood ration in the 2's or 3's (spider angiomata, 3.7; peripheral edema, 3.0; liver edge firm to palpation, 2.7, or just palpable in the epigastrium, 2.6; palmar erythema, 2.6;

splenomegaly (2.3 or hepatomegaly, 2.0), but it is the presence of encephalopathy, ascites, and dilated abdominal wall veins (PLR of 8.8, 6.6 and 5.4, respectively), which have the best performance characteristics.

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

Adapted from: McGee SR. *Saunders/Elsevier* 2007, page 80.

Remember

- Persons with hemolytic anemia do not have pruritus or bradycardia
- Spider nevi are telangiectasias
- Leukonychia may be normal, although they are often found in patients with chronic liver disease, give two other causes of leukonychia.
  - Arsenic poisoning
  - Vasomotor disorders of the digits
  - Leprosy (!)
- The mechanisms causing a hyperdynamic circulation include
  - blood volume
  - cardiac out put
    - Vasodilation
    - Shunts
    - Anemia
    - Fever
- All parts of the nervous system are affected by hepatic encephalopathy
  - Cortex
  - Cerebellum
  - Basal ganglia
  - Cord
  - Motor nerves
  - Muscles

"Resources may influence the community standard of care"

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

Ascites

- Take a directed history and perform a focused physical examination for ascites.

Item	PLR	NLR
History		
o Increased girth	4.2	0.2
o Recent weight gain	3.2	0.4
o Hepatitis	3.2	0.8
o Ankle swelling	2.8	0.1
o Heart failure	2.0	0.7
Physical		
o Bulging flanks	2.0	0.2
o Flank dullness	2.0	0.3
o Shifting dullness	2.7	0.3
o Fluid wave	5.0	0.4

*Note that a history of alcoholism or carcinoma, and the Puddle sign and auscultatory percussion have a PLR < 2, and are not included here.

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

Adapted from: Simel DL, et al. *McGraw-Hill Medical* 2009, Table 6-2, page 68 and Table 6-5, page 69.

What is "the best" test? Only the finding of a fluid wave and shifting dullness have a LR>2 for the detection of ascites, but the history of increased girth, recent weight gain and hepatitis are useful with PLR of 4.2, 3.2 and 3.2, respectively.

Useful background: Pre-existing diseases which increase the pretest probability of finding ascites. (Existing Disease);

- Heart
  - o CHF
  - o Pericarditis

- Liver – cirrhosis

- Kidney – nephrotic syndrome

- GI
  - Protein losing enteropathy
  - Malabsorption
  - Malnutrition

- Cause
  - Systemic infection
  - Blunt abdominal trauma

Useful background: Management strategy for refractory ascites

Definitions	o Ascites that is not eliminated even with maximum diuretic therapy o Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic induced complications
Recommended therapy	o Salt restriction and diuretic therapy as tolerated o Total paracentesis +I.V. albumin (6-8 g/l of ascites removed) o If <5 L of ascites is removed, a synthetic plasma volume expander may be used instead of albumin o
Alternative therapy	o TIPS for patients who require paracenteses (every 1-2 weeks) and whose CTP score is <11 o PVS for patients who are not TIPS or liver transplant candidates o Liver transplantation

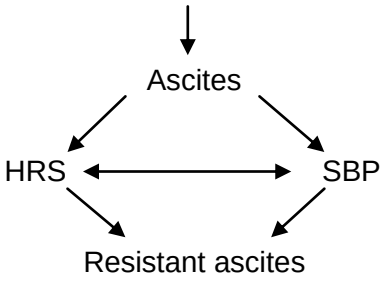
Abbreviations: CTP, Child Turcotte Pugh; I.V., intravenous; TIPS, transjugular intrahepatic portosystemic shunt; PVS, peritoneovenous shunt

Printed with permission: Garcia T, et al. *Am J Gastroenterol* 2009; 104:1802-1829 (Table 7).

Useful background:

- PICD (paracentesis induced circulatory disorder) & HRS (hepatorenal syndrome)
  - PHT/ ascites may develop as the result of an inappropriate signal to the kidney to reabsorb Na^+/ H_2O
  - The intravascular volume is normal/ in cirrhotics with ascites
  - Loop diuretics, but not paracentesis, cause mild (14%) depletion of intravascular volume

PHT



PICD – parecentesis → circulatory dysfunction → ↓ RBF to cortex → HRS

Abbreviation: HRS, hepatorenal syndrome; PHT, portal hypertension; RBF, renal blood flow; SBP, spontaneous bacterial peritonitis

- TIPS
- 5 RCTs show that TIPs is superior to LVP (large volume paracentesis) for
  - Control of ascites
  - Need for repeat paracentesis
  - Mortality rate
- Vasopressin
- Give the mechanism of action of vasopressin (ADH) in distal renal tubule (DRT).
  - ADH binds to V2 receptor on blood side of DRT   AC, cAMP, PKA   AQP2 H_2O reabsorption

Abbreviation: AC, adenyl cyclase; AQP2, aquaporin 2; PKA, protein kinase A

Useful background:

- Hyponatremia and vasopressin $(V)_2$ blocker
  - If hyponatremia in the presence of cirrhosis persists despite Na^+ intake & diuretics, consider using a V_2 blocker:
    - iv, conivaptan
    - po, tolvaptan
  - V_2 blocker for hyponatremia – associated ascites results in more rapid correction of ascites, but no change in the mortality rate from the associated cirrhosis
  - Na^+ retention in PHT
    - Early systemic arterial vasodilation
    - Late renal vasoconstriction
    - Development of HRS, SBP, resistant ascites

- Perform a focused physical examination for the HELLP syndrome.
  - Hypertension
  - Hyperreflexia
  - Petechiae

Jaundice

Useful background: Findings predicting hepatocellular cause in patients with jaundice

- The peripheral findings on physical examination of dilated abdominal wall veins (17.5), palmar erythema (9.8) and spider angiomata (4.7) have the highest values for positive likelihood ratios (PLR) for predicting a hepatocellular cause of jaundice. The PLRs for the presence of ascites and palpable spleen are much lower, 4.4 and 2.9, respectively. All other findings have PLR less than 2.0.

Abbreviation: LR, likelihood ratio; if finding present = positive LR: PLR

Adapted from: McGee SR. *Saunders/Elsevier* 2007, page 79.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Which is the better test to assess the size of the liver in a patient with suggested cirrhosis, abdominal ultrasound with doppler, or transient elastography.

A1.
- Meta-analysis supports transient elastography to diagnose cirrhosis with a high diagnostic accuracy independent from the underlying liver disease (Friedrich-Rust, et al. *GE* 2008;134:960-974), and is not used to assess liver size.

Q2. In most patients with viral hepatic, the liver is usually enlarged and tender whereas the spleen is enlarged and none tender. Which hepatic infection instead causes a large, tender spleen and non-tender hepatomegaly?

A2. EPV (Epstein Barr virus)

Q3. Dupuytren contracture (DC) is caused by thickening and flexure contraction of the palmar tendons, usually of the 4th and 5th digit (never the 1st digit, i.e. thrumb). We all know that DC is associated with alcoholism (~40%) or alcoholic liver disease (~40%). Give 4 other GI or non-GI conditions are commonly associated with DC?

A3.
- Other GI conditions
  - Peptic ulcer disease
  - Cholecystitis
- Non GI conditions
  - Lung – tuberculosis
    - smokers
  - CNS – epilepsy
  - Endocrine – diabetic retinopathy

Hepatocellular Cancer (HCC)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. What is the clinical use if auscultating and hepatic bruit or friction rub?

A.
- o Hepatic arterial bruit
  - Alcoholic hepatitis
  - HCC (hepatocellular cancer)
  - Metastases
- o Venous hum
  - Portal hypertension(PHT, usually from cirrhosis, aka Cruveilhier-Bamgarten syndrome)
- o Venous hum plus hepatic arterial bruit (PHT+ alcoholic hepatitis, or PHT + HCC)
- o HCC
  - o Rub + bruit
- o Rub and bruit + venous hum
  - Cirrhosis and HCC
- o Friction rub
  - Infection in and around liver (e.g. gonococcal perihepatitis [Fitz-Hugh-Curtis syndrome])

 Give 10 paraneoplastic syndromes associated with HCC.

 CNS
- o Neuropathy

 Endocrine
- o Sexual changes- isosexual precocity, gynecomastia, feminization

 MSK
- o Carcinoid syndrome
- o Hypercalcemia
- o Hypertrophic osteoarthropathy
- o Hypoglycemia
- o Osteoporosis
- o Polymyositis
- o Thyrotoxicosis
- o Thrombophlebitis migrans

 CVS
- o Systemic arterial hypertension

 Skin
- o Porphyria

 GI
- o Watery diarrhea syndrome

 Hematology
- o Polycythemia (erythrocytosis)

Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 94.2, page 1571.

Useful background: Hepatocellular cancer (HCC)

- Risk factors
  - 70-90% of HCC occur against the background of hepatic fibrosis grades 3 to 4, or cirrhosis, 1-4% per year (El-Serag HB, et al. *Gastroenterology* 2007:2557-2576); the remainder are associated with HBV and hemochromatosis (HCV in Japan)
  - M:F 2:1-4:1; increased BMI, androgenic hormones

- Give 7 risk factors for HCC in HBV.

- Patient
  - Presence of cirrhosis
  - Young age of acquisition
  - Asian or African race
  - Male gender
  - Oler age
  - Family history of HCC
  - Exposure to aflatoxin, alcohol, and tobacco
- Infection
  - Co-infection with HCV, HDV, and possibly HIV
  - Active replication of HBV
  - Genotype C

- Give 7 risk factors for HCC in HCV.

- Patient
  - Alcohol drinking (heavy > 50 gm/d)
  - Male gender
  - Larger BMI
- Liver
  - Degree of hepatic fibrosis
- Infection
  - HBV coinfection
  - Older age of HCV onset and diagnosis
  - HIV co infection
  - Absence of previous HCV treatment
  - Long duration of active disease

Adapted from: El-serag HB. 2009 *ACG Annual Postgraduate Course*: 39-43.

- Give 7 patient groups requiring screening for HCC.

- Hepatitis B carriers
  - Asian males >40
  - Asian females >50
  - Family history of HCC
  - African >20 years
  - All cirrhosis
- Non hepatitis B cirrhosis
  - Hepatitis C
  - Alcoholic cirrhosis
  - Hereditary hemochromatosis
  - Primary biliary cirrhosis
  - Possibly: alpha 1 antitrypsin, NASH, autoimmune

Source: El-serag HB. *2009 ACG Annual Postgraduate Course*: 39-43.

- Screening
  - Risk stratification, including HBV and HCV

- 96 months AFP (alpha-fetoprotein) and abdominal ultrasound over 5 years improves survival from HCC in HBV-positive patients in China (42-5). Most of the detected HCC in the screened group were detected at an early stage; with 3 year survival rates after HCC resection of 53% in the screened group versus none in the non-screened group
- Improved survival from HCC screening depends of course on the availability of effective therapy for the early detected lesions
- HCC screening in persons awaiting liver transplantation is cost-effective

Abbreviation: AFP, alpha-fetoprotein; HCC, hepatocellular cancer

Useful background: HCC screening and diagnosis

- Abdominal ultrasound sensitivity, > 60%, specificity, > 90% (Bolondi L, et al. *Gut* 2001251-259.; Singal A, et al. *Aliment Pharmacol Ther* 2009)

- Only 1/3 of HCC patients have AFP > 100 mg/ml, but values > 200 mg/ml are highly specific for HCC, 10.9 mg/ml, sensitivity 66% (Marrero JA, et al. *Gastroenterology* 2009.)

- AFP
  - Performance depends on cutoff value: 20 mg/ml, sensitivity 25-65%
  - AFP in a person with a high rate of hepatocyte regeneration (e.g., HCV) can be eluded without presence of HCC (El-Serag HB, 2009)

- CT
  - Arterial enhancement (hypervascular, supplied by hepatic artery) and washout, for HCC, sensitivity is 90% and specificity is 95%

- MRI
  - Similar performance characteristics as CT, but size of HCC is a factor, with accuracy of > 90% for > 20 mm lesion seen on MRI, but 30% for lesion < 20 mm
  - Biopsy under radiological guidance

	Sensitivity	Specificity
US	90%	91%
CT	92%	98%

  - For hyper-enhanced nodule > 1 cm, suspect HCC

a) Imaging criteria applied for confirming HCC in patients with cirrhosis and a nodule detected by ultrasound.

- Lesion has nodular configuration

- Lesion is at least 1 cm in longest diameter*
- Lesion shows arterial hypervascularization:
  - Hyper enhanced nodule in the arterial phase by two imaging techniques**
  - Hyper enhanced nodule in the arterial phase and as hypo enhanced nodule in the portal venous or delayed phase by one imaging technique**

*apply to lesions emerged during Us surveillance. For lesions detected at first imaging examination, lesion diameter should be at least 2 cm to allow non-invasive diagnosis of HCC.

**imaging techniques include: contrast-enhanced US, contrast-enhanced spiral CT, and gadolinium enhanced MRI.

Source: El-serag HB. *2009 ACG Annual Postgraduate Course*: 39-43.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. In the context of Hodgkin lymphoma (HL), what is the ideopathic intrahepatic cholestasis (IIC) syndrome.

A1. The IIC syndrome is cholestasis in HL, with exclusion of all other causes of liver involvement. The HL tumor load and the level of cholestasis are not correlated. The mechanism of the cholestasis is unknown, since in only a small proportion of patients. There is loss of small intrahepatic bile ducts.

Q2. At autopsy, about half of patients with Hodgkin lymphoma (HL) have hepatic involvement, including extrahepatic involvement (nodes in the porta hepatis, or compressing the bile ducts), but only about 10% of HL patients have histological hepatic abnormalities.

- Give intrahepatic lesions seen in HL.

A2.
- Portal infiltration with lymphocytes (32%)
- Granulomas (9-25%)
- Steatosis (11%)
- Hemosiderosis (9%)
- Reed-Sternberg cells (8%)

* In brackets is given the frequency, as quoted from Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.2, page 565.

Nodular Regenerative Hyperplasia (NRH)

- Give 8 conditions associated with NRH.

- Drugs
  - Azathioprine
- After orthotopic liver transplantation
- Early stages of PBC
- Connective tissue disorders
  - SLE (systemic lupus erythematosus)
  - RSS (progressive systemic sclerosis)
  - PMR (polymyalgia rheumatica)
  - Sarcoidosis
  - Feltyès syndrome
  - Primary hypogammaglobulinemia
- Hematological disorders
  - PCV (polycythemia vera)
  - AMH (agnogenic myeloid hyperplasia)

Finger nails

Useful background: Conditions alternating the normal appearance of the fingernails

- Terry's nails: characterized by whitening of the proximal 80% of the nail, leaving a small rim of peripheral reddening. They are seen in older people or patients with heart failure, cirrhosis, or non-insulin dependent diabetes.

- Red half-moons in nail beds (variety of Terry's nails, also described by Terry): characterized by a lunula that is not white but red. They also are called the nails of cardiac failure.

- Azure half-moons in nail beds: the nails of Wilson's disease (hepatolenticular degeneration). The lunulae are not white but light blue.

- Muehrcke's lines (from the American nephrologist who first described them in 1956): two arcuate white lines parallel to the lunula and separated by normal nail. Because they are located in the nail bed (not the nail plate). Muehrcke's lines do not progress with the growth of the nail. They are seen in patients with hypoalbuminemia (<2 gm/100 ml) and disappear with its resolution.

- Beau's lines: transverse grooves on the fingernails of patients recovering from a serious illness such as myocardial infarction.

- Mees lines (also called Reynolds or Aldrich lines): transverse white lines distal to the cuticle. They are seen in arsenical or thallium poisoning, cancer chemotherapy, Hodgkin's lymphoma, and other systemic disorders, such as severe cardiac or renal disease.

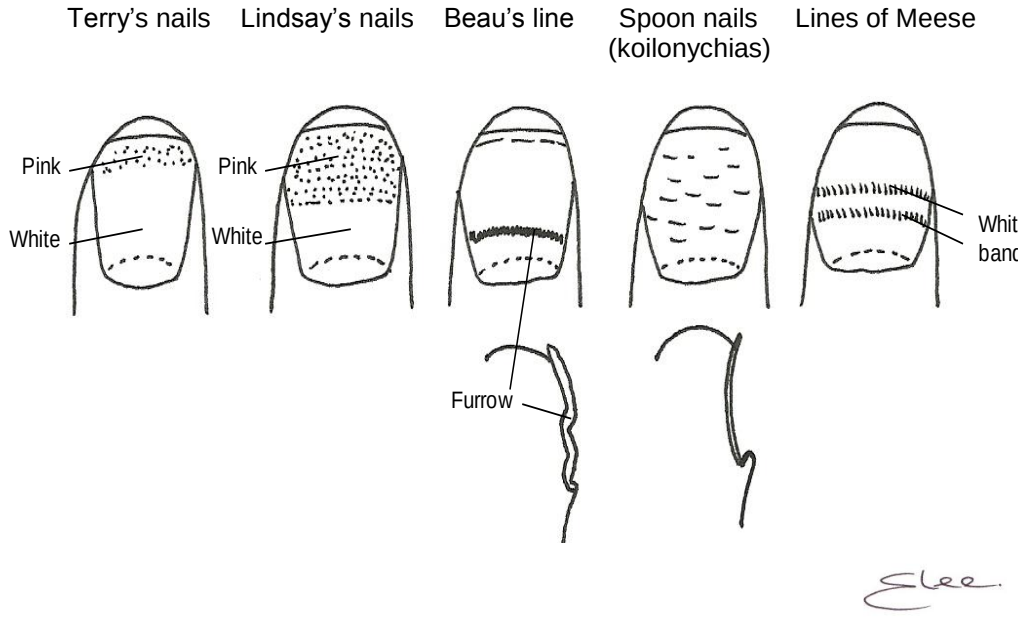
- Nail pitting: an early (but non-specific) sign of psoriasis.

- Yellow nail syndrome: characterized by a yellowish colour of the plates due to abnormal lymphatic circulation.

- Brittle nails: seen in various dysmetabolic states such as hyperthyroidism, malnutrition, and iron or calcium deficiency. They are characterized by irregular, frayed, and torn nail borders.

- Splinter hemorrhages: linear red hemorrhages, extending from the free margin of the nail bed toward the proximal margin; typical finding of subacute bacterial endocarditis, or trichinosis, trauma.

- Leukonychia-white nails, beginning at the lunula-may be normal; seen in cirrhosis, leprosy, arsenic poisoning, vasomotor disturbance of fingers



Adapted from; Mangione S. *Hanley & Belfus* 2000, page 412.

Pruritus

- Perform a focused physical examination to determine the cause of pruritus.

- Various skin diseases
  - Infection
  - Eczema
  - Urticaria
  - Lichen simples
  - Dermatitis herpetiformis

- Systemic
  - Hepatic
    - Obstructive jaundice
    - Recurrent pruritus of pregnancy
  - Blood disorders
    - Reticuloses
    - Leukaemia
    - Polycythaemia
    - Fe-deficiency
    - Mastocytosis
  - Endocrine
    - Diabetes mellitus
    - Diabetes insipidus
    - Myxoedema
    - Hyperthyroidism
    - Gout
    - Carcinoid
  - Neurological
    - Tabes
    - GPI
    - Thalamic tumour
  - Carcinoma (especially lung, stomach, colon, breast, prostate)
  - Chronic renal failure (probably due to secondary hyperparathyroidism)
  - Psychogenic
  - Drugs
    - Cocaine
    - Morphine
    - Allergic drug reactions

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 122.

Jaundice and Hyperbilirubinemia

For a list of factors contributing to postoperative jaundice, please see Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.7, page 583.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give the typical histological changes seen on liver biopsy of a jaundiced post-operative patient.

A. the typical histological changes seen on liver biopsy in the perioperative setting include:

- Intrahepatic cholestasis
- Kupffer cell erythrophagocytosis
- Centrilobular congestion

Q3. The commonest cause of death in adult-onset Still disease (A-OSD) (the adult form of juvenile RA) is liver failure. In the milder cases with hepatitis, the clinical presentation includes fever, sorethroath, weight loss, abdominal pain, jaundice, hepatosplenomegaly, ↑ ALT / AST. Give the hepatic histological changes in A-OSD.

A3.

- Hepatitis
  - Interface
  - Lobular
- Lymphoplastic infiltration

List 4 possible causes for failure to achieve pain relief after biliary sphincterotomy for presumed sphincter of Oddi dysfunction (SOD).

Sphincter

- Inadequate initial sphincterotomy (remaining SOD pressure)
- Restenosis

Pancreatitis

- Chronic pancreatitis with a normal pancreatogram
- Nonpancreaticobiliary pain (beware functional gastrointestinal disease)

Source*:* Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 8th Edition. *Saunders/Elsevier* 2006, page 1365*.*

Jaundice / Cholestasis

SO YOU WANT TO BE A GASTROENTEROLOGY!

Q1. What proportion of patients having a bone marrow transplant (BMT); (hematopoietic cell transplant) develop jaundice due to GVHD (graft-versus-host disease)?

A1. 20%; implication – don't assume that jaundice in BMT patients is related to GVHD.

Q2. In the context of cholestasis, what is Stauffer-syndrome?

A2. Stauffer syndrome is intrahepatic cholestasis and hepatosplenomegaly occurring as a paraneoplastic syndrome arising from lymphoma or renal cell carcinoma.

SO YOU WANT TO BE A GASTROENTEROLOGY!

Q. Give the molecular defect(s) causing benign recurrent cholestasis (BRC), sepsis-associated cholestasis (SAC), cholestatic jaundice in pregnancy (CJP), and estrogen-associated cholestasis (EAC).

A.
- BRC
  - FIC1, ATP8B1 (P-type ATPase "flippase")
  - BSEP, ABC B11
- SAC
  - TNF-α and IL-1β associated down regulation of NTCP and MRP_2
  - IL-1β – dependent down regulation of BSEP
- CJP
  - Polymorphism in genes encoding hepatocyte canalicular membrane phospholipid transporters, e. g., MDR_3, MRD_2, BSEP, FIC1.
- EAC
  - ↓ NTCP (SLC10A1, sinusoidal bile salt uptake transporter protein sodium taurocholate cotransporting peptide)
  - ↓ BSEP

SO YOU WANT TO BE A GASTROENTEROLOGY!

Q1. Give the performance characteristics for diagnostic imaging studies in cholestasis.

A1.

- Ultrasound
  - Gallbladder – sensitivity (sens) ~ 80%, specificity (spec) ~90%
  - Bile ducts, low sens/spec

	Sens	Spec
– CT	80%	95%
– MRCP	90%	95%
– ERCP	90%	95%
– PTC	99%	95%
– EUS	95%	95%

Q2. Give 5 conditions in which UDCA (ursodeoxycholic acid) is therapeutically beneficial.

A2.

- PBC
- Intrahepatic cholestasis
- TPN-associated cholestasis
- CF-associated cholestasis
- Bone marrow-associated cholestasis
- Prevention/reduction of formation of gallstones in persons undergoing bariatric surgery

*Note: Deduct marks for suggesting use of UDCA in PSC

"Medicine is not a popularity contest"

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

Hepatitis B virus (HBV)

GEMS, Pearls and interesting Trivia

Useful background: HBV

- Development of chronicity: adults, 5%
  children, 85%
- Mechanism of liver damage
  - HBV: host cellular immune response causing lysis of hepatocytes
  - HCV: cytotoxic liver damage
- Mutations in HBV core may lead to immune clearance of HBe Ag
- Typical pathological changes in HBV
  - Ground glass inclusions (HBs Ag) in hepatocytes
  - Mononuclear cells in portal tracts
  - Interface hepatitis
  - Steatosis (rare)
- What is the interpretation of IgM anti-HBc
  - Acute HBV infection
  - Flare of chronic HBV
- Prognosis of HBV cirrhosis, in 5 years
  decompensation 15%
  development of HCC 15%
- Genotypes – HBV letters
  - HCV numbers
- If liver transplantation is done for HBV, 20% develop recurrent HBV liver disease
- Progression of HBV acute chronic
  - Horizontal 5%
  - Vertical 95%

Hepatitis C virus (HCV)

Useful background: HCV

- In blood free or , bound to
  - Lipoproteins
  - Immunoglobulins

- Mechanism of HCV liver damage
  - Direct cytotoxicity
  - Possible humorally – mediated T cell response
- Having jaundice during acute HCV infection is good less common to progress to chronic HCV
- Compensated HCV cirrhosis becomes decompensated or HCC develops at a rate of 3%/ year
- Anti-HCV is not a neutralizing antibody and does not clear
- Remember there is also a fibrosing cholestatic form of HCV

	HAV	HBV	HCV	HDV[a]	HEV
Virus type	RNA	DNA	RNA	RNA	RNA
Incubation (days)	15-45	30-180	15-60	21-140	15-65
Transmission	Fecal-oral	Percutaneous, sexual, perinatal	Percutaneous, perinatal (uncommon)	Percutaneous, sexual, preinatal	Fecal-oral
Acute hepatitis progressing to chronic disease	No	Adults 2-7%, pre-schoolers 25%, neonates 90%	70-80%	In superinfection; rare in co-infection	No
Prevention	Pre/post-exposure immunization	Pre/post-exposure immunization	Blood donor screening, risk behaviour modification	HBV immunization prevents HDV infection	Ensure safe drinking water

[a] Requires coexisting HBV infection; HDV may infect a chronic HBV carrier (superinfection) or may infect a subject at the same time as HBV (co-infection)

Abbreviations: HAV, hepatitis A; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 782.

Hepatatic mass

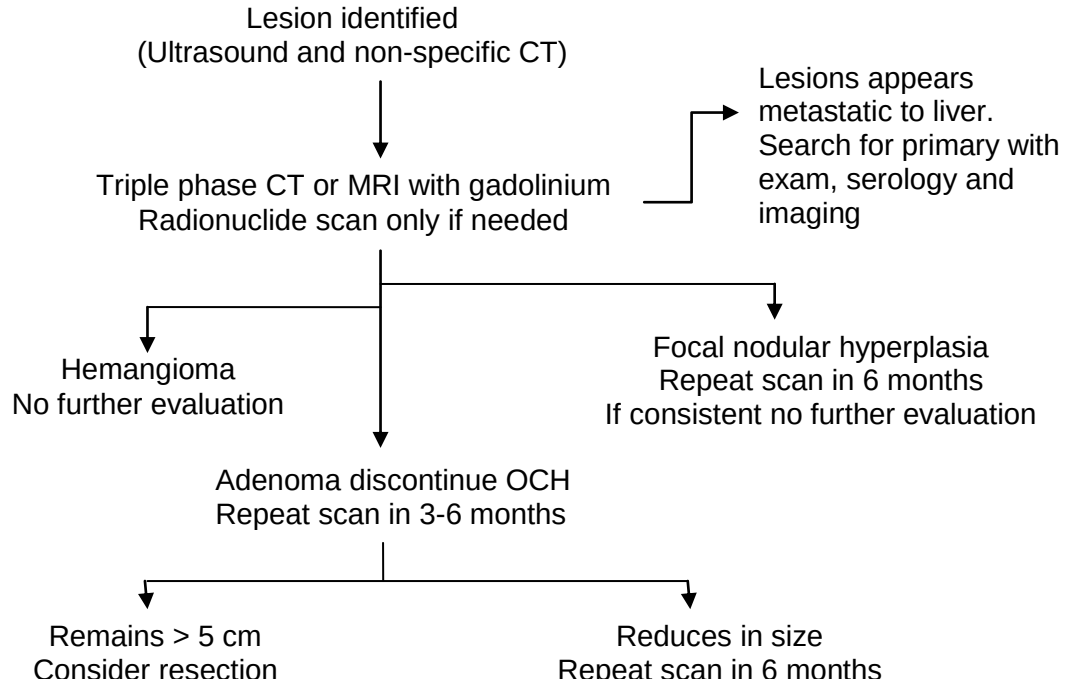
Useful background: Evaluation of hepatic mass

a) Imaging features of common benign liver mass lesions

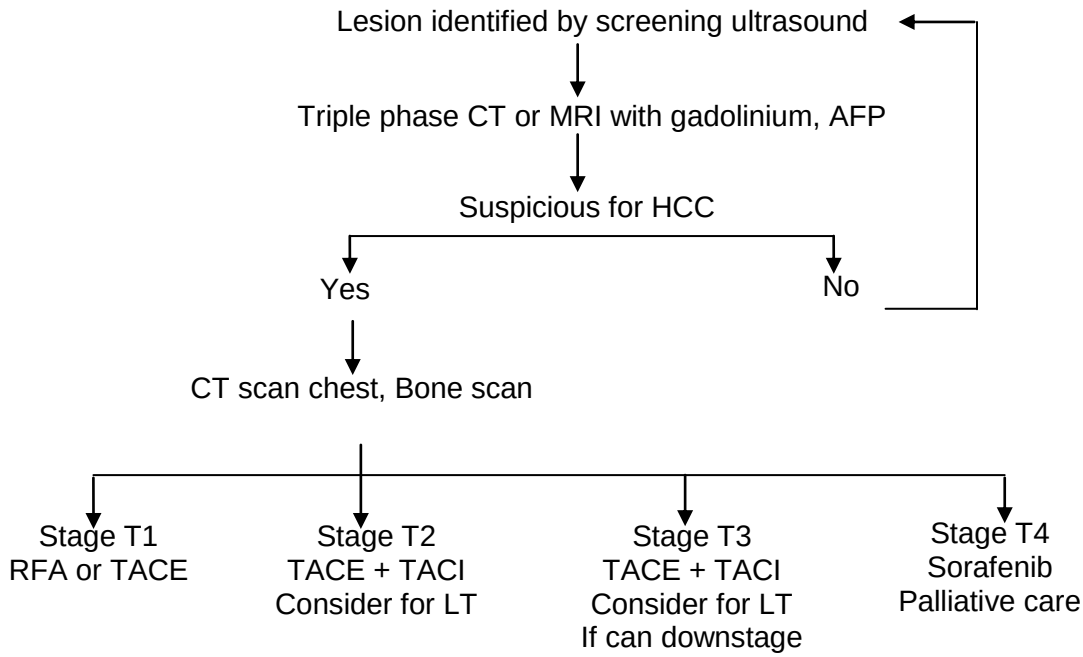
	Hemangioma	Focal nodular hyperplasia	Adenoma
Ultrasound	o Hyperechoic o Well defined borders	o Variable appearance well defined borders	o Non diagnostic
Triple phase CT	o Pre contrast: hypodense o Centripital globular enhancement o Retained contrast in delayed images	o Pre contrast: Hypo or isodense o Homogenous arterial enhancement with hypodense central scar o Isodense in delayed imaging	o Pre contrast: Hypo or isodense o Irregular enhancement o Delayed peripheral arterial enhancement during venous phase
MRI	o T1: well circumscribed low signal o T2: Hyperintense signal	o T1: low signal o T2: Hyperintense signal with central scar	o T1: Low signal intensity with well-defined capsule on o T2: Heterogenous enhancement
Gadolinium enhanced MRI	o Progressive enhancement with delayed washout on venous phase	o Homogenous arterial enhancement o Hypodense central scar o Contrast accumulates in scar on delayed T1	o Irregular enhancement with delayed washout
Radionuclide scan	o Tagged red cell study: Increased uptake during venous phase and delayed emptying	o Equal or increased uptake compared to surrounding liver	o Reduced uptake compared to surrounding

Source: Shiffman ML. *2009 ACG Annual Postgraduate Course*, page167-171.

b) Evaluation of mass in patient <u>without</u> chronic liver disease



c) Evaluation of mass in patient <u>with</u> cirrhosis



Source: Shiffman ML. *2009 ACG Annual Postgraduate Course*, page167-171.

- When a mass is identified in the liver of a person with or without chronic liver disease, a triple phase CT or MRI with gadolinium is performed

- Nuclear scintigraphy with sulfur colloid is taken up by the Kupffer cells; uptake is increased with metastatic lesions (thyroid, breast, lung, pancreas, colon), hemangioma or cysts, and is reduced with hepatic adenomas and HCC
- Radionucelotide scanning with RBC identifies an hepatic mass as an hemangioma
- Hepatic hemangioma
  - Common congenital malformation of the liver vasculature, with ectactic blood vessels with no malignant potential and not affected by oral contraceptive hormones. Because of tortuous vessels and stasis, thrombosis and pain may occur
- Focal nodular hyperplasia (FNH)
  - Common congenital malformation of the liver vasculature, with hyperplasia of hepatocytes around the vascular abnormality, leading to a central scan
- Hepatic adenomas
  - Usually seen in 1/ 10^6 women in their childbearing years, and especially if they are on OCA (3 x increased risk)
  - Premalignant, with risk of malignancy increasing with size
  - Features on triphasic CT or gadolinium enhanced MRI may be difficult to distinguish from HCC, so a technicium sulfur colloid scan may be needed to show the typical cold lesions (no sulfur colloid uptake); AFP may become positive when hepatic adenomas becomes malignant

Abbreviation: FNH, focal nodular hyperplasia

Liver granulomas

- Causes of Hepatic Granulomas

Infectious	Medications
Bacterial Diseases	
o Tuberculosis	o Allopurinol
o Disseminated *Mycobacterium avium* complex	o Carbamazepine
o Brucellosis	o Chlorpropamide
o Tularemia	o Diltiazem
o Listeriosis	o Gold
o Lepromatous leprosy	o Halothane
o Disseminated BCG	o Hydralazine
o Syphilis (secondary)	o Methyldopa

Infectious	Medications
Rickettsiosis	o Nitrofurantoin

- o Q fever

- Viruses
  - o Cytomegalovirus
  - o Epstein-Barr virus

- Fungal Diseases
  - o Histoplasmosis
  - o Coccidioidomycosis
  - o Cryptococcosis

- Parasitic Diseases
  - o Toxoplasmosis
  - o Schistosomiasis
  - o Visceral larva migrans
  - o Fascioliasis
  - o Hepatic capillariasis
  - o Ascariasis

- Neoplastic
  - Hodgkin's lymphoma
  - Non-Hodgkin's lymphoma
  - Renal cell carcinoma

- Miscellaneous
  - Sarcoidosis
  - Primary biliary cirrhosis
  - Berylliosis
  - Talc
  - Whipple's disease
  - Inflammatory bowel disease
  - Wegener's granulomatosis
  - Lymphomatoid granulomatosis
  - Idiopathic

- o Penicillin
- o Phenylbutazone
- o Phenytoin
- o Procainamide
- o Quinidine
- o Quinine
- o Sulfonamides

Abbreviation: BCG, bacille Calmette-Guérin.

Printed with permission: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.10, page 589.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Lesions form and obliterate small portal veins and hepatic veins. This leads to ischemia, atrophy and then to nodular regenerative hyperplasia (NRH) comprised of:

A.
- Multiple, monoacinar nodules resulting in nodular proliferation of hepatocytes (nodular transformation)
- The nodular proliferation of hepatocytes may compress the liver plates at the periphery of the nodules.
- No fibrous septa

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. NRH is associated with all the usual complications of portal hypertension.

- What are the biochemical tests which reflect the functions of the liver, and outline the changes in the liver function test which occur in NRH.

A. the functions of the liver are to synthesize proteins such as albumin and coagulation factors, and to excrete chemicals such as bilirubin and bile acids. Because of the regenerative hyperplasia if the hepatocyte, these hepatic functions are presumed despite the associated portal hypertension.

 Give 5 complications of hepatic granulomas in sarcoidosis.

- Incidental (in active pulmonary, cutaneous or ocular disease)
- Sympatomatic (fever, and weight loss with or without extrahepatic disease)
- Severe intrahepatic cholestasis
- Portal hypertension secondary to
  - Cirrhosis
  - Extensive granulomas
  - Nodular hyperplasia

Source: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.11, page 589.

- Sarcoidosis does not usually affect the luminal GI tract. However, when sarcoidosis does affect the liver, it is usually near portal triads, or in the lobule.
- Curoiusly, intrahepatic and extrahepatic sarcoidosis may recur after liver transplantation.

 Give 10 features of sarcoidosis seen on liver biopsy.

A: In sarcoidosis, there are the pathological changes relating to granulomas; vascular, and fibrotic changes in those with cirrhosis and hypertension, as well as cholestatic changes which may have some passing resemblence to PBC or PSC.

- Granulomas
  - Site
    - Diffuse, or
    - In portal tracts and periportal areas
  - Composition
    - Epitheliod cells
    - Multinucleated giant cells
    - Lymphocytes, macrophage
  - Necrosis
    - Central, granular (not caseating)
- Kupffer cell hyperplasia
- Portal tracts, hepatic lobules
  - Infiltration of mononuclear cells
- Portal of hepatic veins
  - Granulomatous phlebitis
- NRA
  - Nodular regenerative hyperplasia
- Periductal
  - Onion skin fibrosis (like PSC)
  - Ductopenia
- Cholestasis
  - Bile duct lesions (like PBC)
- Cirrhosis

Abbreviations: PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis

CLINICAL VIGNETTE

- Case: Cholestatic liver disease, "florid duct lesion", plus
  - Granulomas – PBC (primary biliary cirrhosis)
  - Onion skinning – PSC (primary sclerosing cholangitis)

CLINICAL VIGNETTE

- Case: Hepatitis, ↑ IgG interface hepatitis plus plasma cells
  - Answer: AIH (autoimmune hepatitis)

CLINICAL VIGNETTE

- Case: HIV /AIDS, jaundice; culture positive for Batonella henslae
  - Answer: Peliosis hepatis

CLINICAL VIGNETTE

- Case: Third trimester jaundice; hypoglycemia and drowsiness; ↑ bilirubin and INR
  - Answer: AFLP (acute fatty liver of pregnancy)

CLINICAL VIGNETTE

- Case: Constipation with normal DRE (digital rectal examination); dilated sigmoid colon; abnormal rectal manometry; failure of relaxation of IAS (internal anal sphincter) on Valsava maneuver
  - Answer: Hirschprung's disease

CLINICAL VIGNETTE

- Case: ↑↑ ALP with normal aminotransferases and "LFT's" (liver function tests); bone pain
  - Answer: Paget disease

CLINICAL VIGNETTE

- Case: ALF (acute liver failure), ↑ ALT and AST but ↓ ALP; hemolytic anemia; neuropsychiatric changes; Fanconi syndrome
  - Answer: Wilson disease

CLINICAL VIGNETTE

- Case: Stellate cells on liver biopsy filled with fat; normal serum cholesterol and triglycerides; first nations person
  - Answer: Overconsumption of vitamin A

CLINICAL VIGNETTE

- Case:Chronic hepatitis with itchy purple lesions on lower legs
  - Answer: Lichen planus associated with HCV

CLINICAL VIGNETTE

- Case:↑ aminotransferase with arthritis in MCP joints; glucose intolerance; family history of liver cancer; benefit form “leaches” (phlebotomy)
  - Answer: Hereditary hemochromatosis

CLINICAL VIGNETTE

- Case:NRH (nodular regenerative hyperplasia), splenomegaly and portal hypertension; neutropenia; morning stiffness and subcutaneous nodules; positive rheumatoid factor
  - Answer: Rheumatoid arthritis and Felty syndrome

CLINICAL VIGNETTE

- Case:3 A’s: alcohol use, ataxia, acidosis; tachycardia
  - Answer: Thiamine deficiency

CLINICAL VIGNETTE

- Case: ↑ ALP and GGT with thrombocytosis; no use of OCA (oral contraceptive agents); CT abdomen does not show subcapsular mas; CT shows multiple hypodense hepatic nodules
  - Answer: NRH (nodular regenerative hyperplasia)

CLINICAL VIGNETTE

- Case: Acute hepatitis, hyperbilirubinemia, fever, temperature-pulse dissociation, conjunctival redness and jaundice, lymphadenopathy, cough, rhabdomyolysis, renal insufficiency. Give the likely diagnosis.
  - Answer: Leptospirosis

GALLBLADDER

Useful background: Terminology

- Murphy's sign
  - Breathing in suddenly stops with RUQ palpation, suggesting cholecystitis
- Courvoisier's sign
  - Painless, palpable distended gallbladder, suggesting pancreatic cancer
- Cullen's sign
  - Bruising of periumbilical area from retroperitoneal due to acute hemorrhagic pancreatitis or ectopic pregnancy
- Gray-Turner's sign
  - Bruising of the abdomen and flanks due to acute hemorrhagic pancreatitis, ruptured abdominal aortic aneurysm or strangulated bowel
- Rebound tenderness
  - Pain on quick withdrawal of palpation, suggesting peritonitis

Useful background: Performance characteristics for the palpation of gallbladder.

Finding	PLR	NLR
Palpable gallbladder		
o Detecting obstructed bile ducts in patients with jaundice	26.0	0.7
o Detecting malignant obstruction in patients with obstructive jaundice	2.6	0.7

*Note that Murphy's sign and back tenderness have a PLR <2, and are not included here as signs for cholecystitis.

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

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 47.3, page 561.

Q1: Give 3 causes of pneumobilia

A1:
- Sphicterotomy
- Gallstone ileus
- Chlostridium perfringens infection (gas-forming organism)

Q2: Give the likely sites of obstruction in gallstone ileus, depending on the size of gallstone.

A2:
- Ileocecal valve, > 2 cm
- Sigmoid colon, > 2.5 cm
- "rolling obstruction" – the site of the mechanical obstruction moves ("rolls") distally as the gallstone passes along the small and large intestines.

Q: About 10% of pregnant woman develop gallstones, and 1% have symptomatic cholelithiasis. State when should cholecystectomy be performed in a pregnant woman for symptomatic biliary colic or gallstone pancreatitis?

A:
- It is recommended that a woman with symptomatic gallstones should have a laparoscopic cholecystectomy, and not be followed "expectantly".
- This "do-surgery-now" approach is rationalized by the high morbidity for the mother and the fetus if there is a recurrent episode of cholecystitis / pancreatitis.
- Ideally perform cholecystectomy in T_2, because surgery in T_1 may lead to fetal mortality, and during T_3 surgery may lead to premature delivery.

Acute Cholecystitis

- Suggestive
  - The demonstration of gallstones on abdominal ultrasound is only suggestive
- Diagnostic
  - Clinical
    - RUQ tenderness
    - Guarding
    - Murphy sign (stopping inspiration with palpation of RUQ)
  - Ultrasound
    - Cholelithiasis
    - Thickening of gallbladder (GB) wall
    - Fluid around GB
    - Sonographic Murphy sign
  - HIDA scan
    - Non – filling of gallbladder
- Clinical
  - Cholecystectomy (laparoscopic or open) during pregnancy preterm delivery rate of 11%

'Sweet Nothings'

- Gall bladder (GB) may be often enlarged without a palpable liver; feel GB better with patient on left side.
- Obstructive jaundice plus palpable GB-unlikely to be due to stones (unless stones in cystic duct or Hartmann's pouch).
- Finger clubbing with portal cirrhosis. Dupuytren's contracture in alcoholic cirrhosis
- Patients with hemolytic jaundice do not have pruritus or bradycardia
- Biliary cirrhosis-1°, 2°-GB disease, methyltestosterone, chlorpromazine; very occasionally due to severe infection, hepatitis
- Parotid enlargement is common in liver disease, as is fever, even in absence of infection (look for spontaneous bacterial peritonitis)
- Knobbly liver with umbilication – is pathognomonic of hepatic metastases (2°); jaundice with hepatic 2° is usually due to lesions at hepatic fissure; ascites due to portal vein obstruction by glands, or peritoneal deposits
- Impossible to insert a finger between kidney and erector spinae muscle; there is a band of resonance anteriorly over an enlarged kidney
- Pancreatic cysts may be palpable, but tumors rarely are
- Ovarian tumors may be palpated in the midline, including at the umbilicus
- Distended bladder is symmetrical, unless a diverticulum is present

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. In the presence of obstructive jaundice, a palpable gallbladder is not due to cholelithiasis. What are the exceptions to this clinical "rule"?

A. Stones in the cystic duct, or Hartmann's pouch.

Gallbladder Polyps

Useful background: Gallbladder polyps

- Premalignant
- Symptoms
- May be asymptomatic

- Abdominal ultrasound surveillance
- Cholecystectomy
- ≥ 1 cm - cholecystectomy
- < 1 cm + stones- cholescystectomy
- No stones → ultrasound (or EUS) surveillance until polyp ≥ 1 cm or stones develop → cholescystectomy

PANCREAS

Pancreatitis

Q. Pancreas divisium and annular pancreas are two common congenital abnormalities of the pancreas. Compare and contrast the two.

A:	Annular pancreas	Pancreas divisum
Frequency	o Second most common	o Most common
Embryology	o Failure of the left pancreatic bud to complete rotate	o Incomplete fusion of the dorsal and ventral pancreatic buds
Clinical symptoms	o Recurrent obstruction of stomach or duodenum from the pancreas wrappy around D2 (second part of duodenum)	o Recurrent pancreatitis (often asymptomatic)
Diagnostic imaging	o "double bubble" sign o "ring like" aberrant pancreatic duct surrounding the duodenum o Normal pancreatic duct	o No pancreas encircling the duodenum o Two separate drainage systems pancreatic ductular
Treatment	o Surgical bypass of the encircling pancreas	o Sphincterotomy of minor duct

Q: In the context of a possible cholangiocarcinoma seen on diagnostic imaging, what is the Mirizzi syndrome.

A: The Mirizzi syndrome is a stone in the cystic duct, which externally compresses the common bile duct (CBD), and looks like a CBD filing defect which could be easily confused to be a CBD tumor, such as cholangiocarcinoma.

Q: If the CT scan shows thickening of the bowel wall of the appendix, terminal ileum or cecum, typhlitis may be suspected. Give the clinical and laboratory abnormalities which should alert you to this diagnostic possibility, and state why this diagnosis must not be missed.

A:
- Typhlitis is also known as neutropenic enterocolitis with most of the conditions in the differential, the WBC would be increased or at least normal. If the neutrophil count is low, then consider this diagnosis.
- Typhlitis is highly prone to perforate (mortality rate, 50%) because of the necrotizing nature of the process. Because of this, colonoscopy or barium enema studies should be avoided.

 Give the Ranson prognostic criteria for acute pancreatitis.
 On admission

o Age (years)	>55	>70
o White blood cell count (cells/mm^3)	>16, 000	>18, 000
o Blood glucose (mg/dL)	>200	>220
o Lactate dehydrogenase (IU/L)	>350	>400
o Aspartate aminotransferase (IU/L)	>250	>250

 During Initial 48 hours

o Decrease in hematocrit (%)	>10	>10
o Increase in blood urea nitrogen (mg/dL)	>5	>2
o Calcium (mg/dL)	<8	<8
o pO_2 (mm Hg)	<60	NA
o Base deficit (mEq/L)	>4	>5
o Estimated fluid sequestration (L)	>6	>4

Source:Quoted from original paper in Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 8th Edition. *Saunders/Elsevier* 2006, page 1241-1270.

 Give a systematic approach to the causes of chronic pancreatitis.
- Idiopathic
- Immune
- Infection
  - Mumps
  - Sepsis
  - Syphilis
  - H.pylori- peptic ulcer disease
- Infiltration
  - hemochromatosis
- Iatrogenic
  - Drug

- Alcohol
- o Inherited
  - Cystic fibrosis
- o Ischemic
  - Atheroma
- o Endocrine
  - Hypercalcemia
  - Hypertriglyceridemia

 Give 8 clinical, diagnostic imaging and laboratory features that distinguish pseudocysts from cystic neoplasms of the pancreas.

Feature	Pseudocyst	Cystic neoplasm
Clinical		
o Gender	- More commonly male	- Usually female
o Age	- 30-40 years	- 60-70 years
o Alcohol abuse	- Common	- Uncommon
o History of acute or chronic pancreatitis	- Common	- Uncommon
o Diagnostic imaging (ultrasonography [US], endoscopic US [EUS], or computed tomography [CT])	- Unilocular - No solid component - Associated gland calcification	- Unilocular or multiocular - Solid component - Rim calcification of cyst - Mural nodules of wall
o Communication between cyst and pancreatic duct on ERCP	- 70%	- Rare (except for IPMN)
Cyst fluid		
o Amylase	- High	- Low
o Carcinoembryonic antigen	- Low	- High
o Cytology	- Inflammatory cells	- Glycogen - Mucin-containing cells - Malignant cells

Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 8th Edition. *Saunders/Elsevier* 2006, page1297.

- o Pancreatitis plus ↑ ALT > 4x ULN (150 IU/L), PPV is 95% for gallstone pancreatitis

- In gallstone pancreatitis, first there is ↑ ALT and ↑ AST, then ↑ ALP and bilirubin

Q: In gallstone pancreatitis, give the explanation why there is first an elevation in serum ALT or AST, followed by ALP.

A:
- Aminotransferases (ALT, AST) are released early from damaged hepatocytes.
- ALP is produced from the gallstone obstruction inducing the synthesis of this enzyme from the bile duct cells, so the process takes longer and ALP peaks later.

- There are literally hundreds of drugs which may cause pancreatitis. Give drugs commonly seen being used in GI patients which are considered to have a moderately strong association with the development of pancreatitis.

PUD	Cimetidine ASA NSAIDs (e.g. sulindac)
Ascites	Furosemide Thiazides
IBD	Azathioprine, 6-MP Sulfasalazine Metronidazole
Tropical sprue	Tetracycline

"I answer questions – with a question"

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

Abdominal X-ray

SO YOU WANT TO BE A PULMONOLOGIST! OR A GASTROENTEROLOGIST?

Q1. Metastases to the lung are usually seen as a few large deposits. From what primary tumors are the metastases to the lung usually multiple and small?

A1. Lung metastasis from primary cancers of
- Bronchus
- Stomach

Q2. What is the difference between mottling and military mottling on a chest X-ray?

A2.
- Mottling is multiple, discrete semi-confluent shadows, < 5 mm.
- Military mottling is multiple, discrete, bilateral shadows, < 2 mm.

 Perform a directed examination of an abdominal x ray ('flat plate').

 General
- Patient demographics (age, sex)
- Type of study, study date and time
- Patient's clinical history, if any provided
- Obtain previous films for comparison
- Critique quality of film

 Supraphrenic structures
- Pleural effusions
- Consolidation
- Rib fractures

 Bones
- Lower thoracic spine, hips, pelvis
- Lumbosacral vertebrae
  - Lytic or sclerotic lesions
  - Degenerative changes

 Soft tissue
- Fat stripe
- Flank stripe
- Psoas muscles

- Gas pattern
  - Intestinal dilation (Small bowel, <3 cm; large bowel [transverse colon] <5 cm), cecum < 7 cm)
  - Air fluid levels
  - Mucosal thickening
  - Intramural gas
  - Extraintestinal
    - Pneumoperitoneum
    - Pneumobilia
    - Portovenous gas
    - Abscess

Adapted from: Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 191 and 192.

- Give 7 causes of calcification on abdominal X – ray.
- Lumen of bowel - Fecoliths
- UEIN - Phleboliths
- Nodes - Calcified lymph nodes
- Stones - Calculi-renal, gall bladder, prostatic
- Glands - Calcified pancreas, adrenal, liver (see below), kidney, aorta, psoas muscle, costal cartilage
- Tumor - Calcified tumor-dermoid, fibroid
- Fetus
- Abdominal wall - Calcification in abdominal wall, e.g. cysticerci
- Foreign body on abdominal wall

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 49.

- Give 7 causes of radiological hepatic calcification.
- Infection
  - Hydatid cysts
  - Amoebic abscess
  - TB
  - Histoplasmosis
  - Gumma
  - Brucellosis
- Tumor
  - Hepatoma (HCC)
- Veins
  - Hemangioma

- Intrahepatic bile ducts
  - Calculi

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 49.

Pancreatic tumor

- Give the most common clinical presentations of the neuroendocrine tumors, VIPoma (Verner-Morrison syndrome), glucagonoma, and somatostatinoma and insulinoma. The approximate frequencies are given in brackets.
  - Watery diarrhea and dehydration (100%)
  - Hypokalemia (95%)
  - Achlorhydria (30%)
- Glucagonoma
- Skin
  - Migratory necrolytic erythema (85%) (red macules-bullae- bullae with central necrosis, scaly eczematoid lesions, central clearing, scaling: face, hands, exposed areas)
- GI
  - Weight loss (85%)
  - Chelitis (15%)
  - Diarrhea (15%)
- GU
  - Hypoaminoacidemia (85%)
- Metabolic
  - Diabetes (85%)
- Lung
  - Thromboembolic pneumonia (20%)
- Blood
  - Anemia (85%)
- Psychiatric symptoms (10%)
- Somatostatinoma
- GI
  - Diarrhea (95%)
  - Gallstones (95%)
  - Weight loss (90%)
  - Hypochlorhydria (85%)
  - Steatorrhea (80%)
- Metabolic
  - Diabetes (95%)

Adapted from: Cancer risks in BRCA2 mutation carriers.The Breast Cancer Linkage Consortium. *J Natl Cancer Inst.* 1999;91(15):1310-6 and Metz DC., et al. *Gastroenterology* 2008;135:1469-1492.

- Gastrinomas
  - ½ in pancreas (head-body-tail, 1:1:2)

- ½ in duodenm (D1, 56%; D2, 32%; D3, 6%; D4, 6%)
- Rarely gastrinomas are found in ovary, liver, biliary tree, pylorus,
- Jejunum, mesentery, omentum, renal capsule, lymph nodes
- Metastases to liver, bone, lymph nodes

 Give the clinical features that suggest Zollinger-Ellison Syndrome.

PUD

- Multiple
- Unusual sites
  - D_2 to D_4, small bowel
- Severe ulcer disease
  - Complications
  - GERD, stricture
- Refractory to treatment
- Frequent recurrence or persistent symptoms
- Maybe H.pylori negative
- Not associated with use of ASA / NSAIDs
- Family history of PUD
- Thick gastric folds, or
- Endocrinopathy

 Associations

- Diarrhea
- Weight loss
- Endocrinopathy
  - Pancreas
  - Parathyroid

Abbreviations: GERD, gastroesophageal reflux disease; PUD, peptic ulcer disease; UGI, upper gastrointestinal; ZES, Zollinger-Ellison syndrome.

Pancreatic endocrine tumors (PETs)

- The terms PET and carcinoid tumor should be replaced by neuroendocrine tumor.
- Origin from
  - Pancreatic-islet cells
  - Ducts
- PET may be called “functional” when tumor releases a hormone which causes a clinical syndrome, a may be called “non-functional PETs (NF-PETs) because either a hormone is released but there is no clinical syndrome (eg., release of pancreatic polypeptide, ghrelin, neurotensin) or no hormone is released.

 Pancreatic NETs (P-NET)

 Give features which distinguish P-NET from other GI-NET.

 P-NETs are

- Larger (mean, > 7 cm)
- Higher rate of metastasis
- Lower rate of survival (5 year, 29% vs 82%)
- Higher incidence of carcinoid syndrome (29% vs ~ 10%)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. In the context of glucagonoma, what other conditions cause necrolytic migratory erythema (NME) and hyperglucagonemia

A.

- Conditions associated with NME
  - Small intestine
    - IBD
    - Celiac disease
    - Short bowel syndrome
    - Nutritional deficiency
  - Liver
    - Cirrhosis
    - HBV infection
  - Stomach
    - ZES
- Conditions associated with hyperglucagonemia
  - Small bowel
    - Celiac disease
  - Liver
    - Cirrhosis
  - Pancreas
    - Acute pancreatitis
  - Kidney
    - Chronic renal failure
  - Endocrine
    - Diabetic ketoacidosis
    - Starvation
    - Acromegaly
    - Hypercorticism
  - Trauma
    - Burns
    - Sepsis
  - Drugs
    - Danazol
  - Familial

- Give the clinical features of glucagonoma.

- GI
  - Weight loss
  - Glossitis, stomatitis, cheilitis
  - Diarrhea
  - Abdominal pain
  - Anemia
- Endocrine
  - Diabetes mellitus, glucose intolerance
  - Hypocholesterolemia
  - Renal glycosuria
- Skin
  - Dermatitis
  - Migratory necrolytic erythema
    - Periorofacial
    - Intertrignous argas
- Thromboembolic disease
  - Venous thrombosis
  - Pulmonary emboli
- Psychiatric disturbance
- CNS
  - Depression
- DVT/PE

Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, , Table 32-7, page 506.

Cysts

Q1: IPMN (intraductal papillary mucinous neoplasm) may occur in the MD (main pancreatic duct; MD-IPMN) or BD (branch duct; BD-IPMN). Give the Sendi guidelines which help to distinguish low from high risk of malignancy developing in IPMN, and therefore the criteria for surgical resection.

A1: Resect
- All MD-IPMN
- BD-IPMN
  - > 3 cm
  - Symptoms ("…pain is a predictor of underlying malignancy" [from IPMN] (Spiegel, BMR, et al. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time

Resource. Slack Incorporated. Thorofare, NJ, 2011, page 145).

- MD- / BD-IPMN with nodules or thickening on EUS CEA > 192

Q2: A high amylase concentration in the aspirated mucus from an IPMN does not fit with Sendi guidelines / or resection of the tumor. Please explain why.

A2:
- An ↑ amylase in the aspirated fluid in IPMN means that the duct communicates with the main pancreatic duct, but the lesion could be BD or MD.
- MD-IPMN must be resected because of its high malignant potential, but finding ↑ amylase in fluid means this could be MD- or BD-IPMN.
- If the IPMN < 3 cm, no symptoms, no nodules or thickening, and CEA < 192, then surveillance could be offered q 6-12 months (CT, MRI / MRCP, EUS)

VIPoma

- Give the clinical and laboratory features of VIPoma syndrome.
  - Diarrhea
    - Secretory
    - Volume depletion
  - Weight loss
  - Abdominal pain
  - Flushing
  - Laboratory Findings
    - ↓ K^+, Cl^-
    - ↑ Ca^{2+}, blood sugar

Abbreviations: VIPoma, vasoactive intestinal peptide secreting pancreatic endocrine tumor.

Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 32-8, page 509.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q The VIPoma syndrome is characterized by secretory diarrhea, hypochlorhydria and hypokalemia. About half of patients will also have hyperglycemia and hypercalemia and a third will have flushing. This syndrome is associated with elevated levels of VIP as well as in some persons PNM-27 (peptide histidine methionine), PP, glucagon, insulin and somatostatin.

- Give the pathophysiological basis of the clinical features, based on the action of VIP.

A.
- Diarrhea
  - ↑ actuates adenylate cyclase, ↑ cAMP → secretory diarrhea
- Hypochlorhydria
  - ↓ gastric acid secretion
- Hypokalemia
  - ↑ release of renin, leading to second hyperaldosteronism
- Hyperglycemia
  - ↑ hepatic glycogenolytic activity
- Hypercalcemia
  - ↑ bone osteolytic activity
- Flashing
  - VIP is a vasodilator

Somatostatinoma

 Approximate sensitivities (%) of diagnostic imaging methods for localization of primary pancreatic NET.

Test	%
Abdominal ultrasonography	22
CT	42
MRI	27
Arteriography	70
Somatostatin receptor scintigraphy	70
Endoscopic ultrasonography	70

Abbreviations: NA, not applicable

Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 32-10, page 516.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. The Somatostatinoma Syndrome is complished by diarrhea, weight loss, diabetes, and gallstones; hypochlorhydria may also be a feature. Give the pathophysiological basis of the clinical features, based on the actions of somatostatin (SS-14 and SS-28)

A.

- Diarrhea
  - ↓ pancreatic secretion
  - ↓ lipid digestion
  - ↓ lipid absorption
- Weight loss
  - Steatorrhea (see above)
- Diabetes
  - ↓ insulin release
- Gallbladder disease
  - ↓ gallbladder motility → ↑ biliary sludge / stones
- Hypochlorhydria
  - ↓ gastric acid secretion

*Note:

- The sensitivity of these tests to detect insulinoma is generally 10% to 20% lower
- The sensitivity of these to detect hepatic metastases arising from pancreatic endocrine tumors is generally > 20% higher

 Give 15 prognostic factors associated with decreased survival in patients with various pancreatic endocrine tumors.

- Female gender
- Absence of MEN-I syndrome
- Liver metastases
  - Extent
  - Growth
- Lymph node metastases
- Bone metastases
- Incomplete tumor resection
- Nonfunctional tumor
- Ectopic Cushing's syndrome (gastrinomas)
- Depth of tumor invasion
- Tumor size
- Histologic features
  - High nuclear atypia
  - Poor tumor differentiation

- High growth indices (Ki-67 index > 2%, PCNA expression)
- Capsular invasion
- Vascular or perineural invasion
- Necrosis

o Flow cytometric features (i.e., aneuploidy)
o Laboratory findings
- Elevated serum chromogranin A (in some studies)
- Elevated serum gastrin level (gastrinomas)
- Lack of progesterone receptors

o *Ha-Ras* oncogene or *p53* overexpression
o Molecular biological features
- High *HER2/neu* gene expression (gastrinomas)
- High 1q loss of heterozygosity (gastrinomas)
- Increased EGF or IGF receptor expression (gastrinomas)
- Chromosomal instability
- CGH findings (loss = 1p, 3p, 3q, 6q, 9q, 12q; gains = 7q, 17q, 17p, 20q)

Abbreviations: EGF, epidermal growth factor; IGF, insulin-like growth factor; MEN-I, multiple endocrine neoplasia type I; PCNA, proliferating cell nuclear antigen; PET, pancreatic endocrine tumor.

Printed with permission: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 32-11, page 520.

- Therapy of PETs
  - o Chemotherapy
    - Streptozotocin plus doxorubicin; etoposide plus ciplatin
    - Hepatic artery emboization +/- postocclusion chemotherapy
  - o RTA radiofrequency ablation
  - o Somatostatin analogs (all PETs except insulinoma)
  - o Interferon –α
    - ↓ symptoms
    - ↑ bcl-2 expression (? Tumorostatic)
    - May be combined with somatostatin analogs
  - o Surgery
    - Debulking
    - Liver transplantation (strict selection process)

- Leukemia

- Leukemic Invasion of the Bowel and Related Structures
  - o Intussusception
  - o Adynamic ileus
  - o Mucosal ulceration
    - Perforation, hemorrhage
  - o Hepatosplenomegaly
    - Splenic infarction, rupture

- o Portal hypertension
  - Ascites, variceal hemorrhage, encephalopathy
- o Biliary and pancreatic duct obstruction
- o Protein-losing enteropathy
- o Pneumatosis intestinalis
- o Watermelon rectum

- Immunodeficiency
  - o Necrotizing enterocolitis (typhlitis)
  - o Increased susceptibility to common infections
    - Appendicitis, wound infections, perirectal abscess, sepsis
  - o Opportunistic infections
    - Esophageal or hepatic candidiasis, mucositis
    - Herpes infections (HSV < CMV); protozoa
    - Pseudomembranous colitis

- Coagulation Defects
  - o Intramural hemorrhage
    - Hemorrhagic necrosis, obstruction
    - Gastrointestinal hemorrhage

- Drug Toxicity
  - o Mucositis
  - o Nausea and vomiting
  - o Ileus, megacolon
  - o Bowel necrosis
  - o Pancreatitis

SO YOU WANT TO BE A GASTROENTEROLOGIST OR HEMATOLOGIST!

Q. About 10% of patients with leukemia have involvement of GI tract, relating to infiltration of leukemia cells into the GI tract, associated immunodeficiency, coagulation defects, drug toxicity, and complications associated with bone marrow transplantation (see Sleisenger and Fordtran's Gastrointestinal and Liver Disease, Table 35.3, page 566, Ninth Edition, 2010

- In the patient with acute or chronic leukemia who present with an acute abdomen. Give 4 of the most common causes, which are related to the leukemia.

A.
- o Acute appendicits
- o Intra-abdominal abscess
- o Perforation
- o Necrotizing enterocolitis (ileum and cecum)
- o Typhlitis (inflammation of cecum, often in the presence of neutropenia)

CLINICAL VIGNETTE

- Case: Recurrent abdominal pain, ↑ serum lipase and ↑ IgG-4
  - Answer: Autoimmune pancreatitis

CLINICAL VIGNETTE

- Case: Abdominal pain, mass in head of pancreas; cough, fever; bilateral lymph adenopathy; erythema nodosum; female
  - Answer: Saciodosis of pancreas, lung

CLINICAL VIGNETTE

- Case: Abdominal pain, progressive weight loss in an alcoholic; glucose intolerance; mental depression; skin rash (superficial migratory thrombophlebitis; abnormal ultrasound)
  - Answer: Pancreatic cancer

CLINICAL VIGNETTE

- Case: Diarrhea, glucose intolerance; neurolytic migratory erythema
  - Answer: Glucagonoma

CLINICAL VIGNETTE

- Case: Isolated gastric fundic varices; chronic pancreatitis
  - Answer: Splenic vein thrombosis

BILIARY TREE

Q: Define “Choledochal cyst”, and give examples of the common types.

A: Definition: Choledochal cyst are congenital “segmental dilations of the biliary tree that can lead to ….complications, including structures, recurrent pancreatitis, and … cholangiocarcinoma” [30%] (Spiegel, BMR, et al. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time Resource. *Slack Incorporated* 2011, page 67).

- Types I CBD diffusely enlarged, with tapered ends (“fusiform”)
- Type II CBD diverticula
- Type III Dilation of intraduodenal portion of CBD (aka “choledochcele”)
- Type IV Multiple intra- and extra-hepatic cysts of the bile ducts
- Type V Diffuse intrahepatic cysts

- Usual treatment
  - Surgery – I, II
  - Sphincterotomy – III

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. In the context of cholangiohepatitis, give the Reynold’s Pentad modification of Charcot’s Triad.

A:
- Charcot’s Triad (CT)
  - RUQ pain
  - Jaundice
  - Fever
- Reynold’s Pentad: CT plus
  - Hypotension
  - Altered mental status

CLINICAL VIGNETTE

- Case: RUQ / RLQ pain, fever, diarrhea, CD4 count < 180

Answer:
- Cryptosporidium of
  - Biliary tree
  - Terminal ileum

CLINICAL VIGNETTE

- Case: Intermittent abdominal pain, on ERCP
  Bulb-like dilation of ampulla
  - Answer: Choledochal cyst, type III (aka choledochocele)
  Mucinous discharge from papilla
  - Answer: IPMN, main duct (MD-IPNN)
  Blood from ampulla

Answer: Hemosuccus pancreaticus

CLINICAL VIGNETTE

- Case: Recurrent RUQ pain, with ↑ AST, ↑ serum amylase; abdominal ultrasound shows dilated CBD (common bile duct) without lithiasis
  - Answer: SOD (sphincter of Oddi) spasm, type I (moderate benefit from sphincterotomy)

NUTRITION

Malnutrition

Useful background

- Likelihood ratios of malnutrition screening tool for adult malnutrition, as compared with subjective global assessment

Combination of findings	PLR	NLR
Serum albumin < 3.0 g/dL	3.3	0.88
LAW criteria	6.1	0.10
Malnutrition screening tool (score ≥2)	13	0.27

	Item score
Have you lost weight without trying?	
No	0
Unsure	2
Yes	Use question.2 instead
If No.1 is 'yes', use the question, How much weight (kg) have you lost?	
None	0
1-5	1
6-10	2
11-15	3
>15	4
Unsure	2
Have you been eating poorly because of a decreased appetite?	
No	0
Yes	1
Malnutrition screening score	Sum of above

*Note that many historical points, symptoms and signs on physical examination have a PLR < 2 (and are not included here)
Abbreviations: **LAW** criteria: discriminant function using **L**ymphocyte count, **A**lbumin, percentage **W**eight loss; NLR, negative likelihood ratio; PLR, positive likelihood ratio

Source: Simel DL, et al. *McGraw-Hill Medical* 2009, Table 28-5 and 28-6 page 380.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Define the "refeeding syndrome", and outline its pathophysiological basis.
A1.

- If glucose is fed rapidly, insulin is released, phosphate is rapidly taken up into cells, and the serum PO_4^- falls
  - the complications which develop include:
    - Neurological (seizures, paresthesias, hyperosmolar coma) and cardiovascular (CCF, death)
    - GI – diarrhea
    - RBC fail to release O_2 normally → VT (ventricular trachycardia)
    - Acute thiamine deficiency (wet beriberi) may develop on the initiation of peripheral as well as total parenteral nutrition
- The cells in PEM are depleted of K^+ & Mg^{2+}, and refeeding with glucose/ AAs shifts these back into cells, and may lead to serious cardiovascular adverse effects
- In order for hypocalcemia to be corrected, it is necessary to correct any associated body depletion of Mg^{2+} (best assessed from urinary levels after IV infusion rather than from serum concentrations)
- Predigested monomeric or oligomeric elemental or semi-elemental diets are not superior to polymeric diets or whole food

Q2. In the context of gastrointestinal diseases, give the major complications arising from deficiencies of 6 of the following micronutrients and vitamins:

A2.

- Copper – anemia, altered taste
- Iodine – hypothyroidism
- Manganese – thin, light hair
- Selenium – myositis, cardiomyopathy, collagen vascular disease
- Zinc – acrodermatitis enterohepatica, impaired taste, glucose intolerance healing, alopecia, depression, diarrhea
- Chromium – glucose intolerance
- Thiamine (B1) – beriberi, wernicke encephalopathy, polyneuritis, anorexi ataxia
- Riboflavin – sore mouth & lips, swollen tongue, photophobia
- Niacin – pellagra – glossitis, dermatitis, mental confusion
- Pantothenic acid – poor wound healing

Useful background

- Increased pretest probability for presence of malnutrition
  - Intake
    - appetite
    - Psychiatric illness
    - Conditions requiring a change to a suboptimal solid diet (eg liquid diets, tube diets)
    - Elderly patients
  - digestion/ absorption
    - Gastrointestinal tract illness
  - requirements
    - Malignancy
    - Disorders affecting metabolism
  - looses
    - Patients with unintentional weight loss of more than 5%, a major category of individuals for whom additional testing is warranted.

Adapted from: Simel DL, et al. *McGraw-Hill Medical* 2009, page 381.

Gating Disorders

Definitions:

- Anorexia nervosa
  - Disturbed perception of body image and weight
  - Fear weight gain
  - Deliberate loss of weight
  - Fear of weight gain
  - Amenorrhea
  - In contract to restricting anorexia nervosa (AN), the binge-eating / purging form of AN is associated with binge eating with or without purging
- Purging bulimia nervosa (BN)
  - Disturbed perception of body image and weight
  - Repeated binge
    - Eating followed by-self-induced vomiting, or
    - Misuse of laxatives
  - Non purging BN
  - Repeated binge-eating, with excessive
    - Fating
    - Exercise

CN VII

Obesity

- Definition:
  - "Obesity is a complex heterogeneous disorder that places individuals at increased risk for adverse mental and/or physical health consequences from excess body fat.

- The current definition of obesity is based on body mass index (Sharma AM, et al. Chapter 32. In: Therapeutic Choices. Grey J, Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 412).

- Give 3 mechanisms explaining alterations in serum vitamin levels in obesity.
  - intake
  - transport proteins (chronic inflammation in obesity proinflammatory cytokines
  - turnover
  - Shift in tissue distribution

- Give 7 symptoms/ signs of protein/ calorie malnutrition (PCM) which may occur in obesity.

- General
  - Fatigue
  - Weakness
- Hair
  - Brittle
  - Loss of hair
  - Altered colour
- Skin
  - Edema
  - Pressure sores
  - Dry/ scaly skin
  - Slow healing
- CVS
  - Tachycardia

MISCELLANEOUS

HIV

- HIV infection and the GI tract in the HAART era

- HAART
  - Highly active antiretroviral therapy may lower HIV viral load to undetectable levels, making opportunistic infections (0%) much less common.
  - Curiously, in some HAART-treated persons, the HIV viral load may be zero, but the CD4 count is < 200 mm^3 (level below which person has AIDS.
  - A symptom-based diagnostic approach remains reasonable.

- Differential Diagnosis of Dysphagia and Odynophagia in Patients with AIDS
  - *Candida albicans*
  - Cytomegalovirus
  - Idiopathic ulcerations
  - *Herpes simplex*
  - *Histoplasma capsulatum*
  - *Mycobacterium avium* complex
  - *Cryptosporidium* spp.
  - Neoplasm: Kaposi's sarcoma, lymphoma, squamous cell carcinoma, adenocarcinoma
  - Gastroesophageal reflux disease
  - Pill-induced esophagitis

Abbreviation: AIDS, acquired immunodeficiency syndrome.
Printed with permission: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 33-1, page 525

- For the differential diagnosis of diarrhea in patients with AIDS, please see: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 33-2, page 526.

For differential diagnose of abdominal pain in patients with AIDS, please see: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 33-5, page 530.

- HIV-AIDS, involvement of esophagus
  - Idiopathic esophageal ulceration
    - Multiple
    - Well-circumscribed
    - Punched-cut
    - Normal intervening mucosa

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. About 90% of AIDS patients are infected with HBV. What is the nature of the infection between HIV and HBV?

A1.
- HBsAg
  - Reapprearance of previously cleared HBsAg
  - Reinfection or reactivation of HBV
  - Chronic carrier state has less HBV-related liver injury, and only mild changes in serum hepatic biochemistry and liver histology
- HBeAg
  - ↑ expression of HBeAg
  - ↑ DNA polymerase
  - ↑ HBeAg
- Carrier
  - ↑ prevalence of highly infectious chronic carrier state
- Acute HBV flares
  - Fulminant hepatic failure following immune reconstitution from HAART
- Development of escape mutants
  - Associated with use of lamivudine
  - Clinical acute hepatitis
  - Seroconversion to anti-HBe and/or HBs Ag
- HBV does not cause progression of HIV disease

Useful background: Dermatological conditions in GI disorders

- Acanthosis nicricans
  - Definition
    - Black, velvety skin growth, especially in axilla
  - Causes
    - Benign
      - T2DM
      - Cushing syndrome
      - Acromegaly
      - Polycystic ovary disease (Stein-Leventhal syndrome)
    - Malignant
      - Adenocarcinoma, specially of stomach or other parts of GI tract; uterus or ovary; lung, breast, prostate
      - Lymphoma

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. What is the nature of the interation between HCV and HIV?

A1.
- Prevalence of HCV in HIV is common drug users, hemophiliacs, about ¾ non-drug users, MSM, about 1/20
- ↑ HCV RNA
- ↑ ALT / AST
- ↑ risk of cirrhosis
- ↑ HCC

HCV does not cause progression of HIV disease

Q2. Give 4 risk factors for the clinical worsening of HCV in HIV.

A2.
- ↑ age at infection
- ↑ ALT
- ↑ inflammatory activity
- ↑ alcohol (>50 g/day)
- ↓ CD (< 500 cell/mm)
- Steatohepatitis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. What is the most common infections cause of diarrhea in HIV/AIDS patients with HAART era?

A1.
- C. Difficile
- "punishment marks if you said Giardia lamblia or Entamoeba histolytica

Q2. Infections by enteric bacteria such as Salmonella, Shigella and Campylobacter are common and virulent in HIV/AIDS. Give their characteristics in this setting.

A2.
- High rates of bacteremia
- High rates of antibiotic resistance
- May need to be treated with IV ciprofloxacin

Q3. What is the commonest cause of drug-induced diarrhea in HIV/AIDS?

A3. The commonest cause of drug-induced diarrhea in HIV/AIDS is HAART therapy (protease inhibitors), the most common of which for diarrhea as an adverse effect is Nelfinavir.

Q4. An HIV/AIDS patient develops bloody diarrhea, fever and a raised serum LDH concentration. What is the most likely infections cause?

A4. Histoplasmosis, causing diffuse colitis with ulceration.

Q5. What are the infectious agents which are most commonly induced in the immune reconstitution syndrome following the introduction of HAART therapy?

A5.
- Myobacteria, e.g. MAC lymphadenitis
- CMV, e.g. CMV uveitis

Q6. What is the viral infection associated with condyloma acumnatum and squamous cell carcinoid of the anorectal area in HIV/AIDS?

A6. HPV (human papilloma virus)

Q7. What is the screening method to detect this infection, and what do they predict?

A7. Cytological specimens of the anal canal are used to screen for HPV (type 16 and 18), and have a high predictive valve for dysplasia.

Q8. What general group of causes of upper GI blood (UGIB) is most frequently involved in HIV/AIDS patients in the HAART era?

A8: Causes of UGIB not related to HIV/AIDS are the comment cause in the HAART-treated patient.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. What is the commonest cause of lower GI bleeding in HIV/AIDS patients in the HAART era?

A1. CMV colitis

Q2. Name three infections which do not cause colitis and rectal bleeding in HIV/AIDS?

A2. Pathogens which do not cause mucosal ulceration (such as MAC, microsporidia and cryptosporidia) do not cause bleeding.

Q3. Drug-induced liver injury (DILI) is common in HIV/AIDS treatment HAART (ritonavir is the most common). A hepatocellular biochemical pattern is seen. Indirect hyperbilirubinemia is uncommon except for indinavir. In this context, what is the lactic acidosis syndrome?

A3. The lactic acidosis syndrome

- The nucleoside reverse transcriptase inhibitors (eg., zidovudine, dideoxy inosine [ddI] and stavudine) reduce mitochondrial DNA synthesis.
- The reduced mitochondrial DNA synthesis leads to damage in
  - Liver
    - Hepatomegaly
    - Fatty liver
    - Liver failure
  - Pancreas
    - Pancreatitis
  - Muscle
    - Myopathy
  - Nerve
    - Peripheral neuropathy

Q4. What is the nature of the interaction between HAV and HIV?

A4.

- ↑ HAV RNA titers
- Longer viremia
- ↑ AST / ALT
- Clinical outcome of HAV unchanged
- HAV vaccination is safe, but less immunogenic

Q5. In the context of HIV/AIDS, which infection agents cause Kaposi sarcoma, and bacillary peliosis hepatitis?

A5.

- Kaposi sarcoma – HHV-8 (human herpes virus-8)
- Bacillary peliosis hepatitis

- For the differential diagnosis of anorectal disease in patients with AIDS, please see: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadephia, 2010, Table 33-8, page 532.

- For the differential diagnosis of hepatomegaly and abnormal biochemical liver tests in patients with AIDS, please see: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadephia, 2010, Table 33-9, page 533.

Solid organ transplant

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. About half of all persons having a transplantation of the heart (HT), lung (LT), or heart plus lung (HLT) will develop GI symptoms. Give 7 complains which develop after HT, LT or HLT.

A.
- Esophagus
  - GERD
  - Severe necrotizing fungal esophagitis, complicated with esophageal perforation
  - Increase the risk of obliterative bronchiolitis
- Stomach
  - Gastroparesis (possibly due to CMV V2V)
  - Giant (>3 cm) gastric ulcers (no ↑ risk of H. pylori infection)
- Bowel
  - Diverticulitis
  - Ischemic colitis
  - Infectious colitis
    - CMV
    - C. difficile
- Pancreas
  - Pancreatitis
- Galbladder
  - Cholelithiasis
- GVHD (graft-versus-host disease)
  - Fever, skin rash, GI symptoms
  - Non infectious diarrhea may increase the incidence and the fatal outcome

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Give 4 unusual features of the postoperative course of kidney transplant, or kidney/pancreas transplant.

A.
- GERD-develops in ~ 50%
  - Associated with ↑ kidney graft loss and death
- ↑ risk of HBV or HCV (~50%)
- Interferon α and ribavirin cannaot be used to treat HCV in KT (↑ risk of allograft rejection)
- ↑ risk of GI bleeding, with ↑ mortality rate
- ↑ risk of intestinal ischemia (especially KT for polycystic kidney disease)

GI complications of hematopoietic stem cell transplantation

- Give 5 GI/ liver complications associated with stem cell transplantation, and give examples.

- Liver - space occupying lesion
  - Portal hypertension - ascites, encephalopathy, hepatic failure
  - Cholestatic liver disease

- Small bowel: Graft-vs-host disease
  - Hemorrhage, malabsorption, strictures, webs, protein-losing enteropathy
  - Lymphoproliferative syndromes - EBV-associated B-cell lymphoma

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. In the context of hematopoietic cell tranplantation (HCT), what is the Typhlitis Syndrome?

A1.
- Typhlitis
  - Characterized by cecal inflammation, friability, ulceration and edema in persons who are neutropenic
  - Usually caused by C. septicum
  - Often results in polymicrobial sepsin

Q2. Give methods to diagnose hepatic fungal infection in HCT.

A2.
- Diagnostic imaging
  - Ct, MRI
- Serum fungal biomarker assays
  - Galactomannan
  - Glucan
- Liver biopsy
  - PCR
  - Culture

Gastrointestinal manifestations of systemic disease

- **Rheumatologic Disease**
- Give 10 gastrointestinal and /or hepatobiliary manifestations.

Rheumatoid arthritis	o Temporomandibular arthritis	-	Impaired mastication
	o Esophageal dysmotility	-	Dysphagia, GERD
	o Visceral vasculitis	-	Abdominal pain, cholecystitis, intestinal ulceration and infarction
	o Amyloidosis	-	Pseudo-obstruction, malabsorption, protein-losing enteropathy, intestinal ulceration and infarction, gastric outlet obstruction
	o Portal hypertension (Felty's syndrome)	-	Variceal hemorrhage
	o Gold enterocolitis	-	Enteritis, diarrhea, fever, eosinophilia, megacolon

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. About 15% of patients with rheumatoid arthritis (RA) have positive biochemical markers for liver disease. Give 6 histological changes in the liver seen in RA.

A.
- Fatty liver
- Kupffer cell hyperplasia
- Portal tract infiltration of mononuclear cells
- Hepatic necrosis
- Periportal fibrosis
- ↑ incidence (associated) AIH, PBC
- HCV patients
  - 75% become rheumatoid –factor positive, some of whom develop mixed cryoglobulinemia
  - These persons raarely have antibodies to CCP (anticyclic citralinated peptide, so do not have true RA)
- RA plus HBV, treated with anti-TNF therapy → severe flares of HBV
- Fatty syndrome (splenomegaly and neutropenia)
  - ↑ incidence of hepatomegaly and abnormal Les
- DILI
  - Anti-TNF therapy associated hepatic toxicity

- Scleroderma (aka progressive systemic sclerosis [PSS])

- GI complications occur in > 80% of persons with PSS, and may affect all parts of the GI part. Give 20 examples.

- Mouth
  - Perioral skin
  - Xerostoma
- Esophagus
  - ↓ LES pressure
  - ↓ motility → ↓ acid clearance
  - GERD (- 100% in those with severe cutaneous PSS)
  - Strictures Barrett epithelium (BE)
  - ↑ risk of candidiasis
  - ↑ risk of esophageal adenocarcinoma
- Stomach
  - Gastroparesis
  - GAVE (gastric antral vascular ectasia)
- Small bowel (SB)
  - ↓ motility (↓ IMCC [înterdigestive migrating motor complex])
  - Duodenum – dilated
  - Pseudo-obstruction, malabsorption, intussusception, volvulus, pneumatosis intestinalis
- Jejunum
  - Dilated
  - Shortened
  - Accordion-like
  - POI (pneumatosis cystoides intestinalis)
  - Pseudo-obstruction
  - Pseudo-diverticula
  - Sacculations
  - SB volvulus
  - SIBO (small intestinal bacterial overgrowth)
  - Arteritis (rare)
    - Mesenteric thrombosis
    - Infarction
- Colon
  - Constipation
  - Wide-mouthed diverticula (actually, pseudodiverticulae on the antimesenteric side, transverse and descending colon)
  - Telangiectasis –bleeding
  - Stricture, volvulus obstruction
  - Rectal prolapse
  - Fecal incontinence

- Pancreas
  - Pancreatitis
  - Exocrine insufficiency
  - Calcification
  - Ischemic necrosis (vasculitis)

*Note: penalty for suggesting gallbladder motility changes in PSS

Systemic lupus erythematosus (SLE)

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. Vasculitis leading to ischemic changes in the GI tract are common in SLE. Visceral angiography is not usually helpful in this setting. CT diagnostic imaging may help to make this diagnosis of ischemia in SLE. Give the typical features of CT which help to make the diagnosis of bowel ischemia in SLE.

A.
- Bowel wall thickened ± target sign
- Target sign (bowel wall thickening plus
  - Peripheral rim enhancement (hyperattenuation)
  - Inner and outer rim enhanced, with the centre not enhanced (hy
- Intestinal segments – dilation
- Mesenteric vessels – engaged
- Mesenteric fat – hyperattenuation

- Sjögren's syndrome
  - Desiccation of membranes - Oral fissures, oropharyngeal dysphagia
  - Esophageal webs - Dysphagia
  - Gastric lymphoid infiltrates
  - Pancreatitis - Abdominal pain, pancreatic exocrine insufficiency
  - Primary biliary cirrhosis - Jaundice, hepatic failure, variceal hemorrhage

Polymyositis-dermatomyositis	o Skeletal muscle dysfunction	- Aspiration, impaired glutition
	o Dysmotility	- Dysphagia, GERD, gastroparesis, constipation, diverticula
	o Mesenteric vasculitis (rare)	- GI ulceration, perforation, pneumatosis intestinalis

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. Give 10 GI complications of SLE

A.

- Mouth
  - Oral ulcer
- Esophagus
  - ↓ motility
  - GERD
- Stomach
  - Hypertrophic gastropathy
  - Gastritis
- Small bowel
  - Protein-losing enteropathy
  - Steatorrhea
  - PCI (pneumatosis cystoides inntestinalis)
- Colon
  - NEC (necrotizing enterocolitis)
  - Vasculitis – small vessels
- Pancreas
  - Pancreatitis
- Liver
  - Lobular hepatitis
  - Antinuclear antibodies (but not AIH [autoimmune hepatitis])
  - NRH (nodular regenerative hyperplasia)
  - Budd-Chiari syndrome
    - Lupus anticoagulants
    - Anticordiolipin antibodies
  - Fatty liver

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q1. Polymyosistis and dermatomyositis have been traditionally considered to represent an inflammatory myopathy of skeletal muscle. This would explain transfer dysphagia and nasal regurgitation, but how is it explained that these patients may have other GI complications such as disorders of the motility of the lower esophagus, gastroporesis, and hypomotility of the small ntestine, pneumoitosis intestinalis, as well as colonic dilation and pseudodiverticula.
What is the explanation of the GI symptoms which develops in these parts of the GI tract which do not contain skeletal muscleÉ

A1. Involvement in polymyositis and dermatomyositis extents to GI tract smooth muscle, as well as the skeletal muscle in the upper third of the esophagus.

Q2. Polymyositis, PSS and SLE may overlap in a syndrome known as MCTD (mixed connective tissue damage).
What is the unusual therapeutic feature of the esophageal motility complication which occur in MCTD?

A2. In MCTD, the esophageal motility disorder responds to glucocorticosteroids.

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. Churg-Strauss Syndrome (CSS, aka allergic granulomatous angitis) is characterized by sinusitis, rhititis, asthma and peripheral eosinophilia. The level of the esosinophilia may be " 1500 eosinophils/mm^3 in these CSS patients who have GI complications. Give 5 complications of CSS.

A.
- Abdominal pain (nausea, vomiting, bleeding)
  - Eosinophilic gastroenteritis (diarrhea)
  - Ulcerations
  - Perforations
- Pancreas
  - Pancreatis
- Gallbladder
  - Cholecystitis
- Colon
  - Ulceration
- Peritoneum
  - Ascites

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. o In SLE, the vasculitis is usually in the small vessels, and visceral angiography is not very useful diagnostically.
o In contrast, the vasculitis which occurs in polyarteritis nodosa (PAN) is a necrotizing vasculitis which involves both the small as well as the medium-sized arteries.
o In fact, about 80% of PAN patients will have aneurysmal dilations especially if the superior mesenteric artery.
o Thus, bowel ischemia is common.
Give 4 GI associations of PAN in addition to bowel ischemia, with its complications of infarction and perforation.

A. ➢ Gall bladder / BT
- o Acalculous cholecystitis
- o Hemobilia
- o Biliary strictures

➢ Pancreas
- o Pancreatis

➢ Liver
- o Hepatic infarcts
- o HBV infection

MCTD	o Dysmotility	- Dysphagia, GERD, stricture, gastroparesis, bezoars, pseudo-obstruction
PAN	o Mesenteric vasculitis (rare)	- Ulceration, perforation, pancreatitis
	o Mesenteric vasculitis	- Cholecystitis, appendicitis, intestinal infarction, pancreatitis, perforation, strictures, mucosal hemorrhage, submucosal hematomas
CSS	o Mesenteric vasculitis	- Hemorrhage, ulceration, intestinal infarction, perforation
	o Eosinophilic gastritis	- Gastric masses
Henoch-Schönlein purpura	o Mesenteric vasculitis	- Intussusception, ulcers, cholecystitis, hemorrhage, intestinal infarction, appendicitis, perforation

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. Henoch-Schonlein Purpura (HSP) is characterized by abdominal pain, renal disease, arthralgias and non-thrombocytopenic purpura arising from a systemic vasculitis. GI bleeding is also common. Give 6 GI complications of HSP, other than the abdominal pain and GI bleeding.

A.
- Small bowel
  - Aphthous ulcers
  - Walll thickening
  - Dilation
  - Protein-losing enteropathy
  - Strictures
  - Intramural hematoma
  - Intussusceptions
- Colon
  - Ischemic perforations
- Appendix
  - Appendicitis
- Pancreas
  - Pancreatits
- Gallbladder
  - Cholecystitis

□ Kohlmeier-Degos disease	o Mesenteric vasculitis	- Hemorrhage, ulceration, intestinal infarction, malabsorption
□ Cogan's syndrome	o Mesenteric vasculitis (infrequent)	- Hemorrhage, ulceration, intestinal infarction, intussusception
	o Crohn's disease	- Bloody diarrhea, abdominal pain, fissures, fistulas
□ Wegener's granulomatosis	o Mesenteric vasculitis	- Cholecystitis, appendicitis, ileocolitis, intestinal infarction
□ Reactive arthritis	o Ileocolonic inflammation	- Usually asymptomatic
□ Familial Mediterranean fever	o Serositis/peritonitis, amyloidosis, PAN, Henoch-Schönlein purpura	- Abdominal pain, fever, dysmotility

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. Wegener's granulomatosis (WG) is characterized by vasculitis involving sinuses, lung and kidney. When WG involves the GI tract, why may it be confused with Crohn disease (CD)?

A. The GI complications of WG include

➢ Stomach	o Granulomatous
➢ Small bowel	o Ileocolitis, with granulomas* - may mimic CD
➢ Gallbladder	o Gangrenous cholecystitis
➢ Cryoglobulinemia	o Mesenteric vasculitis (rare)

□□Mixed cryoglobulinemia

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. Mixed cryoglobulinemia (raised serum concentration of IgG plus IgM) is characterized by arthralgia, purpura, and asthenia.
Give 5 GI associations of cryoglobulinemia

A.
- o HCV infection
- o IBD
- o Celiac disease
- o Postintestinal bypass syndrome
- o Small intestinal
  - − Colonic vasculitis
  - − Ischemia
  - − Diarrhea
  - − Perforation

□ Behçet's disease o Mucosal ulcerations
- Hemorrhage, perforation, pyloric stenosis
- Complications as in rheumatoid arthritis

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q. Behcet disease (BD) is characterized by uvetis, aphthous ulcers of the mouth, skin lesions, and genital ulcers. About half of BD patients have GI complications which may mimic Crohn disease (CD). Give GI complications of BD which reflect why BD needs to be differentiated from CD.

A.
- Esophagus
  - Aphthous ulcer
  - Perforation
  - Varices
- Stomach
  - Aphthous ulcers
- Small bowel
  - Ulcers (punch-out)
  - Fistulas enteroenteric
- Colon
  - Punched-out ulcers
  - Fistulas
    - Perianal
    - Rectovaginal
- Liver
  - Budd-Chiari Syndrome (thrombosis of hepatic vein)
  - Portal vein thrombosis

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Q1. A middle-aged man who moved to canada 20 years ago develop acute abdominal pain, fever, arthralgias. The relapsing and remitting nature of the symptoms led to the consideration of porphyria as the diagnosis, but laboratory investigations for porphyria negative. CT scan of the abdomen suggested small bowel obstruction. Give the renal conditions which may develop.

A1.
- Nephrotic syndrome
- Amyloidosis
- Chronic renal failure

Q2. I still do not know the diagnosis!

A2.
- The diagnosis is familial mediterranean fever (FMF), an autosomal recessive disease due to a disorder in the gene MEFV, leading to an abnormal protein, pyrin (aka marenostrin).
- With many of his attacks he would have developed sterile peritonitis, leading to the symptoms of small bowel obstruct from adhesions.
- Treatment is with colchicine.

Hematologic malignancies and Hepatic involvement

Lesion	Approximate Hepatic Involvement from Clinical Evaluation (%)	Histologic Abnormalities (approximate Frequency)
o Hodgkin's lymphoma	10	- Portal lymphocytic infiltrates (32%) - Granulomas (9%-25%) - Steatosis (11%) - Hemosiderosis (9%) - Idiopathic cholestasis (<5%)
o Non-Hodgkin's lymphoma	40	- Portal lymphocytic infiltrates (20%-25%), steatosis (7%)
o Multiple myeloma	40	- Amyloidosis (10%) - Light-chain deposition - Extramedullary hematopoiesis
o Hepatosplenic γδ T cell lymphoma	80	- Sinusoidal infiltrates
o Leukemias		
- ALL	—	—
- AML	—	—
- CLL	—	—
- HCL	100	- Angiomatous lesions (64%)

-

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; HCL, hairy cell leukemia; LGLL, large granular lymphocyte leukemia.

Adapted from: Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.2, page 565.

SO YOU WANT TO BE A GASTROENTEROLOGIST OR HEMATOLOGIST!

Q1. A 25 year old man was admitted to the ER in a hospital in St. Thomas, ON, complaining of diffuse abdominal pain, chest pain and discomfort in his arms and legs. He was febrile. Bolld testing showed mild unconjugated hyperbilirubinemia, elevated LDA, mild anemia yet increased serum ferritin concentration. Serology was negative for HBV and HCV, and testing for ANNA and SMA were negative. Abdominal ultrasound was normal. Liver biopsy was performed.

- Give the likely findings on this man's liver biopsy.

A1.
- Sinusoids
  - Dilated
  - Adjacent ischemic necrosis
  - Peri-sinusoidal fibrosis
- Kupffer cells
  - Erythrophagocytosis
  - Increase iron staining
- Central zones
  - Atrophy of liver cells
- Space of Disse
  - Accumulation of
    - Collagen
    - Thin basement mambrane
- Cirrhosis

Q2. Ah, still don't have the diagnosis? Why was the erythrophagocytosis in a Kupffer cell in a hepatic sinusoid and important clue? And what is so special about St. Thomas?

A2.
- Sickle red blood cells were seen in the Kupffer cells
- St. Thomas was one of the communities which in 1861-1865 were terminals for the Underground Railroad from the Southern (confederate) states.

□□□□For a list of the causes of intramural hematomas in the GI tract, please see Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.4, page 569.

Diabetes of gut

SO YOU WANT TO BE AN GASTROENTEROLOGIST OR ENDOCRINOLOGIST!

Q. Give the role of EMG studies in the diabetic patient with unexplained upper abdominal pain.

A. An abnormal EMG of the anterior abdominal wall muscles, as compared with an EMG of Thoracic paraspinal muscles, supports the diagnosis of diabetic radiculopathy (neuropathy of thoracic nerve roots)

Neuromuscular diseases affecting GI tract

□□□□For the GI manifestations of Neuromuscular Diseases, please see Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.6, page 579.

SO YOU WANT TO BE AN GASTROENTEROLOGIST OR NEUROLOGIST!

Q. GI symptoms are common (70%) in persons with multiple sclerosis (MS), such as oropharyngeal dysphagia.

- Give causes of constipation related to MS.

A. Causes of constipation in patients with MS that are related to the MS include
  - ↓ activity
  - Rectal intussusception
  - Rectal outlet obstruction
  - Stercoral ulcers
  - Incoordinated relaxation of muscles
    - Puborectalis
    - IAS (internal anal sphincter)

Useful background: Neuromuscular disorders (such as Charcot-Marie-Tooth syndrome, myasthenia gravis, muscular dystrophies, amyotrophic lateral sclerosis) may be associated with motility disorders.

□ Esophagus	o Cervical (oropharyngeal) dysphagia o Achalasia (in MNGIE (mitochondrial neurogastrointestinal encephalomyopathy)
□ Stomach	o Gastroparasis
□ Small intestine	o Pseudo-obstruction
□ Colon	o Fecal incontinence

SO YOU WANT TO BE AN GASTROENTEROLOGIST OR NEUROLOGIST!

Q1. GI complications are common often a cardiovascular accident (CVA), or injury to the head or spinal column.

- Give 3 of the most common lesions.

A1. The numbers in brackets indicate the percentage of patients with these lesions seen on EGD.

- CVA, Head Injury
  - Esophagus
    - Esophagitis (11%)
  - Stomach
    - Gastritis (69%)
    - Gastric ulcer (23%)
  - Duodenum
    - Duodentis (8%)

Source: Feldman, M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 579.

- Spinal cord
  - Esophagus
    - GERD
  - Stomach
    - Gastroparasis
      - ↓ availability of drugs for absorption
    - Ulceration (GU)
  - Duodenum
    - Ulceration (DU)
      - ↑ risk of
        - Bleeding
        - Asymptomatic perforation
  - Small intestine
    - Amyloidosis (secondary)
  - Pancreas
    - Pancreatitis
  - Colon
    - Constipation
      - Sensation ↓ rectaal fullness
      - Motor ↓ control of defecation

Q2. Why is the defecation reflex usually intact in a person with spinal cord injury?

A2. The defecation reflex is usually intact in spinal cord injury patients because the lower motor neurons of the S_2, S_3 and S_4 sacral nerve roots.

Q3. Idiopathic autonomic neuropathy affecting the sympathetic and/or parasympathetic systems often (70%) affects the GI tract. Give the symptoms which suggest autonomic (parasympathetic) neuropathy.

A3.
- Diarrhea
  - Hypersalvation
  - hyperhydrosis
- *Note
  - Small intestinal bacterial overgrowth is uncommon, despite the common manometric demonstration of motility disorders associated with some neurological disorders such as CVA

Amyloidosis

For a list of the clinical manifestations of amyloides along the GI tract, please see Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 35.9, page 585.

- Give the typical changes of amyloidosis seen on diagnostic imaging of the GI tract, and biopsy of the liver.
- Esophagus
  - Dysmotility
- Stomach
  - ↓ gastric rugal folds
  - Stiff rugal folds
- Small intestine
  - Vavulae conniventes – thickened
  - Ulcers
  - Intramural bleeding
- Colon
  - Ischemic ulcers
  - Thickened wall
  - Narrowing
  - Rigid wall
- Liver
  - Hepatomegaly
- Liver
- Walls of arteries, arterioles, portal and hepatic veins
  - Extracellular, amorphous, hyaline deposits
- Three patterns of deposits:
  - Globular deposition space of Disse
  - Parenchyma and sinusoidal intralobular deposit
  - Mixture of parenchyma and periportal vascular

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. The liver commonly involved in primary amyloidosis, and the GI tract in secondary amyloidosis (classification systems now stress the different types of fibrillar proteins in the amyloid deposits, rather than the primary and secondary designations). The GI tract can be included from the mouth to the anus, as well as the liver, pancreas and spleen. Depending upon where the amyloid is deposited in the GI tract will determine the nature of the symptoms:

A.
- Muscularis mucosa
  - ↓ absorption
- Muscle layer
  - Dysmotility
- Vessel walls
  - Ischemia
  - Infarction
- Direct pressure damage to myenteric plexus and visceral nerve trunks

Chronic renal disease

- Chronic renal disease associated with a plethera of GI complications, especially for these patients on hemodialysis (HD) or peritoneal dialysis (PD). Give 10 GI complications of chronic renal disease.

- Esophagus
  - Esophagitis
    - Possibly related to
      - ↑ abdominal pressure from PD
      - Amyloidosis (secondary)
- Stomach
  - Gastric folds-thickened
  - Ulcers (GU, DU)
    - ↑ bleeding (but not ↑ prevalence of peptic ulcers, i.e. only more likely to bleed
- Duodenum
  - Duodenitis (nodular)
  - Brunnee gland hyperplasia
- Small bowel
  - Angiodysplasia
    - ↑ risk of bleeding
    - Risk of bleeding related to
      - Duration of renal failure
      - Need for HD
  - Ulcers
  - Ischemia (non-occlusive)
  - Ileus
  - SIBO
  - Cholerrhetic diarrhea
- Colon
  - ↑ rupture of diverticulae
  - Ileus
  - Intussusception
  - Cecal ulcers
  - Fecalomas
    - ↓ motility
    - Use of barium, aluminium-containing antacids
- Pancreas
  - Pancreatitis

ICU – Type patient

- The need of a patient for mechanical ventilation in the ICU or post-operative setting is associated with numerous GI complications. Give GI complications in the ICU setting, including patients who are in the ICU after major surgery.

- GI complications in the ICU setting include

- o Esophagus - GERD, including severe esophagitis
- o Stomach
  - Gastroparasis
  - Stress ulceration
    - Usually seen in the ICU patients who are ventilated, or who have coagulopathies
- o Small intestine - Diarrhea in half of the hospitalized patients with severe acute respiratory syndrome (SARS)
- o Colon - Ischemic colitis
- o Gallbladder - Acalculous cholecystitis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Hepatic dysfunction is common in patients with systemic infections arising from diverticulitis, appendicitis, lobar pneumonia, or pyelonephritis. The biochemical profile usually reflects underlying cholestasis which is associated with sepsis or extrahepatic infection.

A. The changes on liver biopsy of a patient with systemic infection include:

- ➢ Hepatocytes
  - o Little changes, no necrosis
  - o Portal area
    - – Mild portal infiltrate of mononuclear cells
  - o Some parenchymal dropot
- ➢ Zone 2 and 3
  - o Bile stasis
- ➢ Cholanitis lenta
  - o Dlated
  - o Bile thrombi
  - o Surrounded by neutrophils
- ➢ Mild steatosis

Endoscopy

- Give 3 complications of intraoperative endoscopy.

- Gut
  - Tear/ perforation
  - Avulsion of superior mesenteric artery

- Patient
  - CHF (congestive heart failure)
  - CRF (chronic renal failure)
  - Ileus

- Capsule endoscopy (CE)

- Enteroscopy
  - Push (peds colonoscope)
  - Balloon
    - Single balloon (SBE)
    - Double balloon (DBE)

- CT scan
  - Regular
  - CT angiogram
  - CT enterography/ enteroclysis

- MRI
  - Regular
  - MR enterography/ enteroclysis
  - Problems with MR enterography
    - Patient must sit still for 10 min
    - SB peristalsis
    - Claustrophobia

"In the end, it's not going to matter how many breaths you took, but how many moments took your breath away"

Shing Xiong

HCT

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. In the context of HCT, give early causes of anorexia, and vomiting other than medications (calcineurin inhibitors Septra®).

A1.
- GI
  - Mucositis
  - Drug adverse effects opiods myeloablation therapy
  - Gastroduodenal GVHD
    - Patchy condition, so may be missed on biopsy
    - EGD
      - Gastric retention
      - Patchy erythema
    - Biopsy
      - Edema
      - Apoptosis of epithelial cells
      - Lymphoid infiltrate
  - Infection
    - CMV (may be just in mucosa and not in blood stream)
    - HSV
  - Gastric retention
  - TPN
- Non-GI
  - CNS disease
  - Adrenal insufficiency

We get too soon old
And too late smart
Grandad

Suggested practice case scenarios for OSCE examinations

Primary Stem	Secondary Stem	Diagnosis
□ Abdominal pain	o Is an alcoholic	- Pancreatitis
	o With jaundice and R upper quadrant pain	- Acute cholelithiasis
	o With jaundice and fever in a diabetic	- Ascending cholangitis
	o Acute epigastric with guarding	- Perforated DU
	o Chronic epigastric	- DU and H-pylori
	o Acute epigastric with hypotension in elderly male	- Rupture AAA
	o Diffuse pain with atrial fibrillation & diarrhea	- Intestinal ischemia
	o Lower abdominal pain & fever in older person	- Diverticulitis
	o Lower abdominal pain & fever	- Appendicitis
□ Hematochezia	o Massive rectal bleeding in elderly person	- Diverticulosis
	o Spotting blood & mucous in young person	- IBD
	o Blood in stool of older person	- Rectal CA
□ Abdominal mass	o Renal mass	- PKD/Renal cell carcinoma
	o Cecal mass	- CD, Crohn disease
	o Pulsatile midline mass	- Abdominal aortic aneurysm
	o LUQ mass	- Splenomegaly
□ Diarrhea	o Acute following travel	- Giardia
	o In elderly	- Drugs
	o With blood in stool	- Bacterial
	o Chronic diarrhea in Asian	- Lactose intolerance
	o Chronic diarrhea, microcytic anemia & rash in Caucasian	- Celiac
	o Chronic diarrhea, bronchospasm, murmur & flushing	- Carcinoid
	o Floating stools, pain, weight loss, alcohol abuse	- Pancreatic insufficiency
Primary Stem	Secondary Stem	Diagnosis

- Abnormal lab tests

- Jaundice	o Painless with pruritus, in older person	- Pancreatic cancer
	o Painless with pruritus , fatty diarrhea in middle aged female	- Primary biliary cirrhosis
	o Painless with pallor	- Hemolytic anemia
- Abdominal distension	o Signs of portal hypertension	- Pregnancy
	o Heartbeat	
	o Android obesity	- Cirrhosis 2° chronic hepatitis
	o Large kidneys	- Syndrome X
	o Massive splenomegaly	- PKD

- Other

Source: Kindly provided by Dr. P Hamilton.

"The difference between how a person treats the powerless versus the powerful is as good a measure of human character as I know."

Robert Sutton

HEMATOLOGY

HEMATOLOGY

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6. Perform a focused physical examination for pernicious anemia.
7. Perform a focused physical examination for anemia.
8. Give a systematic approach to the causes of immunoglobulin deficiency.
9. Give a systematic approach to the causes of sclerosis (increase in bone density).
10. Given systematic approach to other causes of mottling in the skull.

Bleeding disorders

- Take a directed history of thrombocytopenia

➢ Ideopathic

➢ Dilutional
  - Massive transfusion/ infusion
  - Pregnancy

➢ ↑ destruction
  - Autoimmune
  - Drugs 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 AK. *Mayo Clinic Scientific Press* 2008, Table 11-17, page 452.

Useful background: Inherited and acquired thrombophilias

➢ Inherited thrombophilia
  - Prothrombin G20210A mutation
  - Anticoagulant deficiencies (Antithrombin, 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
  - Postoperative state
- Senescence
- Idiopathic
  - Paroxysmal nocturnal hemoglobinuria (PNH)

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

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 11-19, page 454.

Useful background: Causes of DIC

- Infection
  - Infection or sepsis (bacterial)
- Infiltration
  - Malignancies (hematologic & solid organs)
  - Solid tumors
- Drugs/ toxins
  - Snake bite
- Liver
  - Advanced liver disease
- Hemolysis
  - Hemolytic transfusion reaction
- Blood vessels
  - Aortic aneurysm
  - Giant hemangiomas
- Trauma
  - Massive trauma
  - Burns
- Obstetrical disorders
  - Obstetric complications (abruption, amniotic fluid embolism)
  - Obstetric complications (retained dead fetus)

Abbreviations: DIC, disseminated intravascular coagulation.

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 11.16, page 450.

- 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 AK. *Mayo Clinic Scientific Press* 2008, page 450.

Useful background:

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

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

- Coagulation defects
  - Hemophilia
  - Anticoagulants
  - Christmas disease

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

Useful background: The classes of drugs that interact with warfarin ("8 A's")

Drug or drug class	Risk of hemorrhage	Mechanism
➢ Antibiotics		
○ Most agents, but especially co-trimoxazole, metronidazole, macrolides and fluoroquinolones	↑	- ↓ vitamin K synthesis - ↓ hepatic warfarin metabolism
○ Rifampin	↓	- ↑ cytochrome P450 (CYP)
➢ Antifungals		
○ Fluconazole, miconazole	↑	- ↓ CYP 2C9
➢ Antidepressants		
○ Serotonergic agents (selective serotonin reuptake inhibitors [SSRIs])	↑	- ↓ primary hemostasis (may also inhibit CYP2C9)
➢ Antiplatelet agents		
○ Acetylsalicylic acid, clopidogrel, ticlopidine	↑	- ↓ primary hemostasis
➢ Amiodarone	↑	- ↓ CYP 2C9
➢ Anti-inflammatory agents		
○ All, including selective NSAIDs, Coxibs	↑	- ↑ mucosal injury - ↓ primary hemostasis
➢ Acetaminophen	↑	- ↓ vitamin K cycle
➢ Alternative 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.

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.

Remember

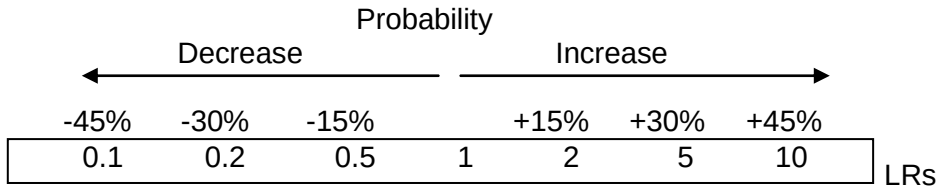
To describe lymphadenopathy: "this patient has a swelling involving anatomy, which may be general pathology, such as specific pathology.

Useful background: Performance Characteristics for Lymphadenopathy

Finding	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 SR. *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.*

Useful background: Generalized Lymph Node Enlargement

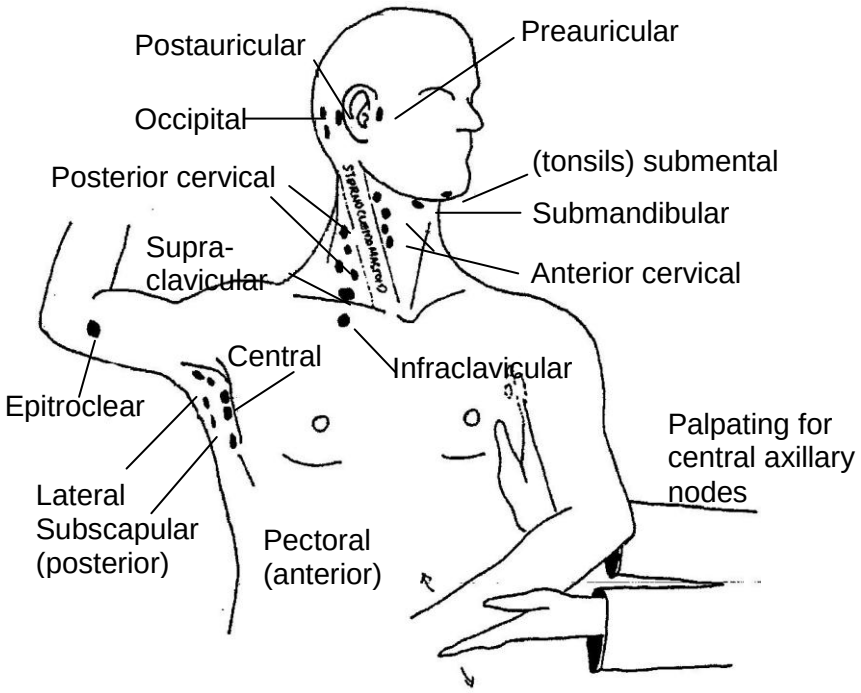
- Examine the mouth for the following signs:
  - Tonsillar lymph nodes
  - Palatal petechiae and pharyngitis (glandular fever)
  - Neoplastic tumors and ulcers
- Examine other lymph node areas in a systemic manner: submental, submadibular, deep cervical (upper and lower), occipital, posterior triangle, 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.

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

Robert Louis Stevenson

- Lymph nodes of head, neck and axilla



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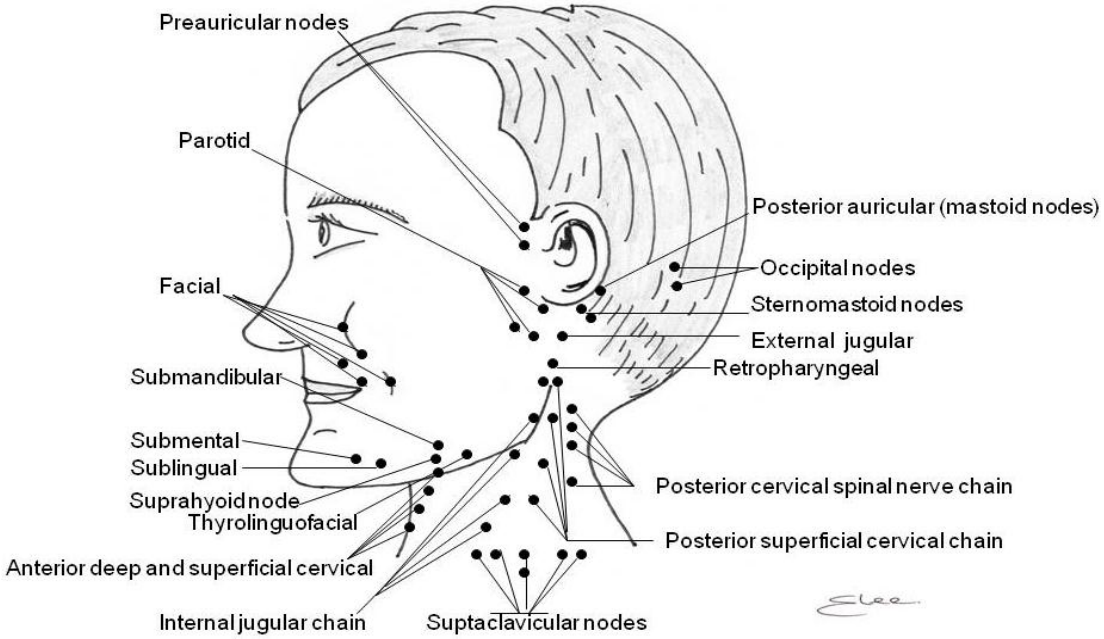
Useful background: Perform a focused examination for cervical lymphadenopathy



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

SO YOU WANT TO BE A HEMATOLOGIST!

Q. What is regional lymphadenopathy and what are its causes?

A.
- 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 head & neck
- Virchow's node (anterior left supraclavicular lymph node). (Also known asTroiser's ganglion)
  - Carcinoma of 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 scatch fever
    - Tularaemia
    - Sporotrichosis
  - Malignant
    - Hodgkin's disease
    - Non-Hodgkin's lymphoma
    - Carcinoma of breast and melanoma
- Epitrochlear lymphadenopathy
  - Most common causes are lymphoma/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 RR. *Saunders/Elsevier* 2007, pages 570 and 571.

Useful background: Lymph node drainage

Location	Area drained
➢ Cervical	
o Anterior	- Pharynx, tonsils, face, scalp
o Posterior	- Posterior scalp, ear
➢ 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
➢ Lower extremities	
o Upper portion of leg	- Superficial tissue of upper portion of 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

- Lymph node area, source of drainage, and causes of lymphadenopathy

Lymph node area	Source of drainage
Head and neck	
○ Pre-/ postauricular	- Eye, scalp
○ Occipital	- Posterior scalp
○ Submental	- Lower face, floor of mouth
○ Submandibular	- Face, oral cavity
○ Cervical	
- Anterior	- Pharynx, tonsils, face, scalp
- Posterior	- Posterior scalp, ear
Clavicular/ axillary	
○ Clavicular	
- Supra-/ infraclavicular	- Cervical lymph node chains, abdomen, thorax, arm and breast
○ Axillary	
- Central	- Other axillary nodes
- Lateral	- Most of arm
- Posterior (subscapular)	- Posterior chest wall, upper arm
- Anterior (pectoral)	- Anterior chest wall, most of breast
Common causes	
○ Head and neck	- Infections - Malignancy - Hodgkins', non-Hodgkin's lymphoma
○ Axilla	- Infections - Malignancy - Hodgkins', non-Hodgkin's lymphoma - Carcinoma of breast, melanoma
○ Epitrochlear	- HIV - Infectious mononucleosis - Sarcoidosis - Connective tissue diseases - Lymphoma/ CLC

Lymph node area	Source of drainage

- Cause
  - Cancer
    - Myeloproliferative disorders
    - Myeloma
    - Carcinoma
  - Nutrients
    - B12, folic acid deficiency
    - Pyridoxine deficiency
  - Collagen vascular disorders
  - Poison - Lead poisoning

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

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

- History

- Onset of symptoms, duration, alleviating or aggravating factors, other associated symptoms, progression of symptoms
  - Unilateral/bilateral
  - Delimitation (borders)
  - Epistaxis/nasal obstruction
  - Oral pain
  - Otalgia (referred)
  - Dysphagia,hoarseness, stridor
  - Environmental/occupational exposures (e.g. radiation, asbestos)
  - Travel history
  - HIV, EBV, TB
  - Symptoms of thyroid dysfunction
  - Medications (e.g. phenytoin, allopurinol)
  - Exposure to animals
  - History of cancer
  - IV drug use
  - Cardiac problems, review of systems

Physical examination

- Myositis, torticolis

- Salivary gland
  - Calculi
  - Thyroid, thyroglossal duct cyst*, thyroid tumor, goitre, or pyramidal lobe

- General considerations
  - Lymph nodes found in normal persons 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 local./generalized
  - Size
  - Shape
  - Consistency (hardness of node is neither sensitive nor specific of malignancy)
  - Tenderness
  - Mobility
  - Confluence/matting with other nodes
  - Dimpling or drainage to overlying skin

- Take a directed history and perform a focused physical examination of the patient with lymphadenopathy:

- Use the pneumonic **ALL AGES** to approach a patient with lymphadenopathy

- History
  - **A**ge at presentation (e.g. infectious mononucleosis is commoner in younger age groups; Hodgkin's disease has a bimodal peak).
  - **L**ocation(s) of lymph nodes (lymph nodes present outside the inguinal regions, 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)

- Examination
  - **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.

- 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, they usually reflect a generalized lymphadenopathy, such as may be encountered in HIV infection

- Posterior cervical lymphadenopathy
  - Dandruff or nasopharyngeal tumor

- Preauricular nodes
  - Lymphoma or on the same side of conjunctivitis (often referred to as Parinarud's syndrome)

- Nodes scattered around the two branches of the mandible
  - Localized pathology, such as periodontitis or other teeth infection
  - Or submental and submandibular nodes reflect cancer of the nose, lip, anterior tongue, or anterior floor of the mouth

- Midjugular nodes
  - Cancer of the base of the tongue or larynx

- Lower jugular nodes
  - Primary cancer of the thyroid or cervical esophagus

Adapted from: Mangione S. *Hanley & Belfus* 2000, pages 400, 401; Talley NJ, et al. *Maclennan & Petty Pty Limited*, 2003, page 233, 235; McGee SR. *Saunders/Elsevier*, 2007, pages 284 to 290; Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 119-121; and Davey P. *Wiley-Blackwell* 2006, pages 82 and 83 and Baliga RR. *Saunders/Elsevier* 2007, pages 570 and 571.

Red Blood Cells

Useful background: 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 JL. *Churchill Livingstone* 1971, page 25 and 58.

What is “the best test for anemia”? The ‘best test’ for anemia is pallor in conjunctive, palms, face.

- Take a directed history and perform a focused physical examination for anemia.
- History
- Fatigue
  - Duration
  - Onset
  - Course
  - Frequency
  - Limitations in activities

- Associated symptoms
  - Malaise
  - Weakness
  - Dyspnea
  - Chest pain
  - Palpitations
  - Headache
  - Tinnitus
  - Presyncope/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/ renal bleeding (hematuria)
  - Previous multiple blood donations (frequency, last donation, amount donated)

- Dietary history
  - Iron deficiency
  - Folic acid/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 pernicious anemia.

- General
  - Middle age
  - Blue eyes
  - Hair
    - Blondish
    - Prematurely grey

- Signs of anemia

- CNS/PNS
  - Mental changes
  - ↓ position and vibration sensation (dorso-lateral column changes)
  - Peripheral neuropathy

- Eyes
  - Optic atrophy
  - Nystagmus

- Hepatosplenomegaly

- Causes of vitamin B12 deficiency
  - Acquired
    - Lack of intrinsic factor
      - Pernicious anemia
      - Partial or total gastrectomy
    - Changed intestinal flora
      - Stricture
      - Blind-loop syndrome
      - Diverticulosis of small bowel
      - Fistulae
    - Ileal damage
      - Crohn disease
      - Resection
    - Parasites: Diphyllobothrium latum
    - Dietary (rare)
    - Pancreatitis (rare)

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

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

- Causes of polycythemia

- Absolute

- Primary

- Secondary
  - Hypoxic
    - Intake
      - High altitude (Monge's disease)
      - Cerebral (decreased respiratory drive)
      - Obesity
    - Circulation
      - Cardiac or pulmonary disease
    - Blinding
      - Methemoglobinemia and sulphemoglobinemia
  - ↑ Erythropoietin
    - CNS
      - Cerebellar hemangioblastoma
    - Kidney disease
    - Liver
      - Carcinoma of liver
    - Uterus
      - Uterine myomata
    - Adrenal
      - Virilizing tumor
      - Pheochromocytoma

- Relative
  - Dehydration
  - 'Stress' polycythemia

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

Useful background: Cases of polycythemia

- CNS
  - Hemangiomas
- Lung
  - Bronchial Ca
- Kidney
  - Renal Ca
  - Benign tumors

- GU
  - fibroids
  - ovarian tumors
- GI
  - Hepatomas
- Endocrine
  - Adrenal cancer/hyperplasia
  - Pheochromocytoma

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

Useful background:

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

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

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

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

- Howell-Jolly bodies: Nuclear remnants seen as small dense 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 reticulocyte
  - Causes
    - Hemolytic anemia due to drugs and chemicals
    - Familial RBC defects (e.g. G6PD deficiency)
    - Rare hemoglobinopathies (e.g. Hb Koln) after splenectomy

- Causes of target cells
  - Iron
    - Iron deficiency anemia
  - Hemolysis
    - Thalassemia
    - Sickle-cell anemia
  - Hemoglobin
    - Hemoglobin –C disease
  - Liver/spleen
    - Liver disease and obstructive jaundice
    - Splenectomy
  - Dehydration

Source: Burton JL. *Churchill Livingstone* 1971, page 52.

- Causes of hypochromic anemia

- Sideropenic, non sideropenic, sideroblastic
  - Non- sideropenic anemia
    - Anemia of chronic disease (may be normochromic) e. g., RA, Ca, CRF
    - Thalassemia
    - Sideroblastic anemias
  - Sideroblastic anemia
    - Myeloproliferative disorders

- Causes of aplasia anemia
  - Idiopathic
  - Drugs, chemicals (e.g., iodine)

- Take a directed history for 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 septicaemia
    - Clostridium welchii
    - Oroya fever
    - TB.
    - Typhoid
    - 'H.influenzae' meningitis
  - Protozoal
    - Malaria (Blackwater fever)
    - Kala-azar
- Renal
  - Chronic renal failure
  - 'Hemolytic-uraemia' syndrome (infants and children)
  - Thrombotic thrombocytopaenic purpura (TTP)
  - Malignant hypertension
  - Eclampsia, or post-partum
- Pregnancy
- Endocrine disease
  - Myxedema
  - Hypopituitarism
  - Hypoadrenalism
- Hypersplenism

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

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

- Perform a focused physical examination for anemia.
  - Eyes
    - Palor
  - Mouth
    - Glossitis
  - Thyroid
    - Goiter
  - Hands
    - Palor,
    - Lose of palmar crease
  - Heart
    - CHF
    - Atrial myxoma
  - Lung
    - Bronchiectasis
    - Abscess
    - Cancer
  - Liver
    - Cirrhosis
  - Spleen
    - Splenomegaly
  - Nodes
    - Lymphadenopathy
  - MSK
    - Rheumatoid arthritis
    - Lupus
  - Malnutrition

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

Useful background: Performance characteristics of findings of anemia

Finding	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 SR. *Saunders/Elsevier* 2007, Box 8-1, page 91.

Useful background: Comparisons of most common hypochromic microcytic anemia.

➢ Disease state	MCV	RBC	TIBC	Transferrin saturation	Serum Ferritin	Bone Marrow Iron
○ Iron deficiency anemia	↓	↓	↑	Low	Low	0
○ Anemia of chronic disease	N/ ↓	↓	N	N /↑	N/↑	N/↑
○ Thalassemia minor	↓	Usually ↓	N l	N	N /↑	N

Source: Ghosh A.K. *Mayo Clinic Scientific Press* 2008, Table 11.2, page 410.

White blood cells

Useful background:

- Causes of eosinophilia (>440/cu.mm.)
  - Allergy
  - Infection: Hookworms, tapeworm, hydatid, ascaris, bilharzias, strongyloides, filarial, trichina, 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 JL. *Churchill Livingstone* 1971, page 61.

- Causes of pancytopenia, neutropenia
    - Marrow infiltration
    - Hypersplenism
    - Deficiency
        - Megaloblastic anemia
        - Iron deficient anemia
    - PNH (paroxysmal nocturnal hemoglobinuria)
    - Endocrine
        - Hypo-/hyperthyroidism
        - Cirrhosis
    - Immune
        - Lupus

- Causes of neutropenia
    - Infection
        - Viral
        - Chronic bacterial,
    - Malignancy infiltration
        - Carcinomatous metastasis to bone
        - Myelosclerosis
        - Myeloma
        - Malignant lymphoma

- Non-malignant infiltration
  - Gauchers
  - Niemann-Picks
  - Histiocytosis X

- Causes of monocytosis (>800/cu.mm)
  - Infectious
    - Viral –infectious mononucleosis
    - Rickettsial- Rocky Mountain spotted fever
    - Bacterial- Listeria monocytogenes
    - TB
    - Brucellosis
    - Typhoid
    - SBE
    - Protozoal- Malaria, kala-azar, trypanosomiasis
  - Malignancy
    - Hodgkin's disease
    - Monocytic leukemia

- Causes of leukocytosis (>10,000/cu.mm in adults)
  - Physiological
    - Infancy
    - Pregnancy and post-partum
  - 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

- Causes of myeloid leukamoid reaction (WCC>50,000/ cu.mm or myelocytes or myeloblasts present in peripheral blood)
  - Infections
  - Malignancy
  - Acute hemolysis
  - Leuco-erythroblastic anemia

- Marble bone disease (Albers-Schonberg)

- Lymphocytosis (>3500/cu.mm)
  - 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
    - Lymphatic leukemia
    - Carcinoma
    - Myeloma
  - Endocrine
    - Myasthenia gravis
    - Thyrotoxicosis
    - Hypopituitarism
  - Physiological (in early childhood)

- Causes of agranulocytosis
  - Drugs
  - Aplastic anemia
  - Leukemia in subleukemic phase
  - Hypersplenism
  - Idiopathic

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

SO YOU WANT TO BE A HEMATOLOGIST!

Q1. What is the difference between “myeloid metaplasia” and “extramedullary hematopoiesis”?

A1. None: they both represent ectopic hematopoietic activity, usually in liver and spleen, and may not be associated with myelofibrosis (bone marrow fibrosis).

Q2. OK. What is “myelofibrosis with myeloid metaplasia”?

A2. By convention, is idiopathic myelofibrosis

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

SO YOU WANT TO BE A HEMATOLOGIST!

Q. Got any more for me: What are the "chronic myeloid disorders"?

A.
- Chronic myeloid leukemia
- Myelodysplastic syndrome
- Atypical chronic myeloid disorder
- Chronic myeloproliferative disease
  - Polycythamia vera
  - Myelofibrosis with myeloid metaplasia
  - Essential thrombocythemia
  - Agnogenic myeloid metaplasia
  - Post-polycythemic myeloid metaplasia
  - Post-thrombocythemic myeloid metaplasia

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

Splenomegaly

- Causes of Hypersplenism (reduction of 1 or more of the formed elements of the blood due to functional hyperactivity of the spleen)

Useful background: Factors which increase the pretest probability of 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 DL, et al. *JAMA* 2009, page 613.

Useful background: Causes of splenomegaly

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

- Infiltration
  - Lymphoma
  - Leukemia (especially CML*)
  - Amyloid
  - Sarcoidosis
  - Gaucher, Nieman Pick disease
  - Benign tumors/ cysts
  - Myelofibrosis*
- Immune
  - Rheumatoid arthritis (Felty syndrome)
  - SLE
- Hematological
  - Hemolytic anemia
  - Myelofibrosis
  - Polycythaemia rubra vera
  - Occasionally in
    - ITP
    - Myelomatosis
    - megaloblastic anemia
    - chronic Fe-deficiency anemia
- Liver portal hypertension
- Endocrine
  - hyperthyroidism

*hugh spleen

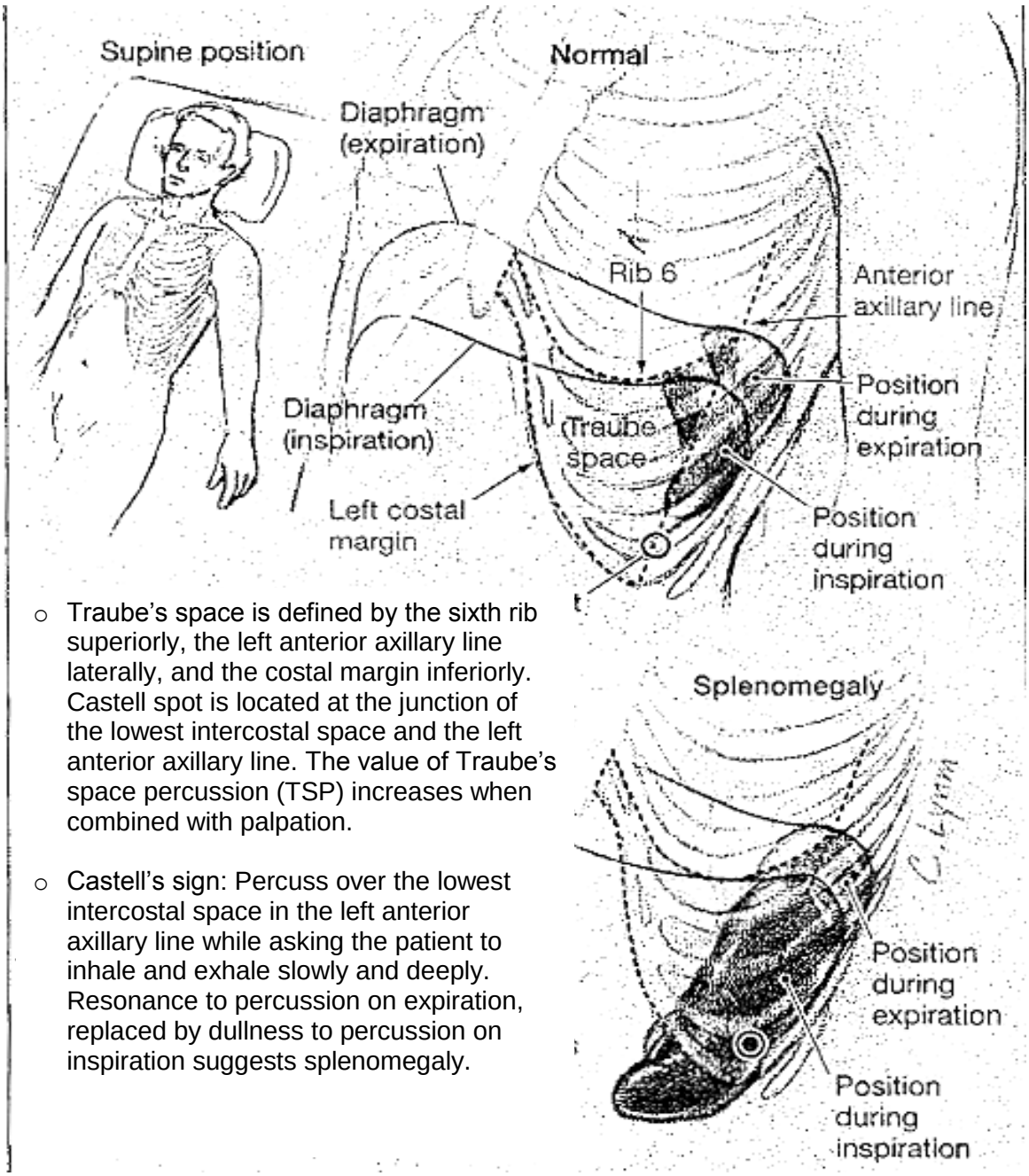
Adapted from: Burton JL. *Churchill Livingstone* 1971, page 63; and Baliga RR. *Saunders/Elsevier* 2007, page 31.

Useful background: Examination of the spleen

Clinical detection of splenomegaly

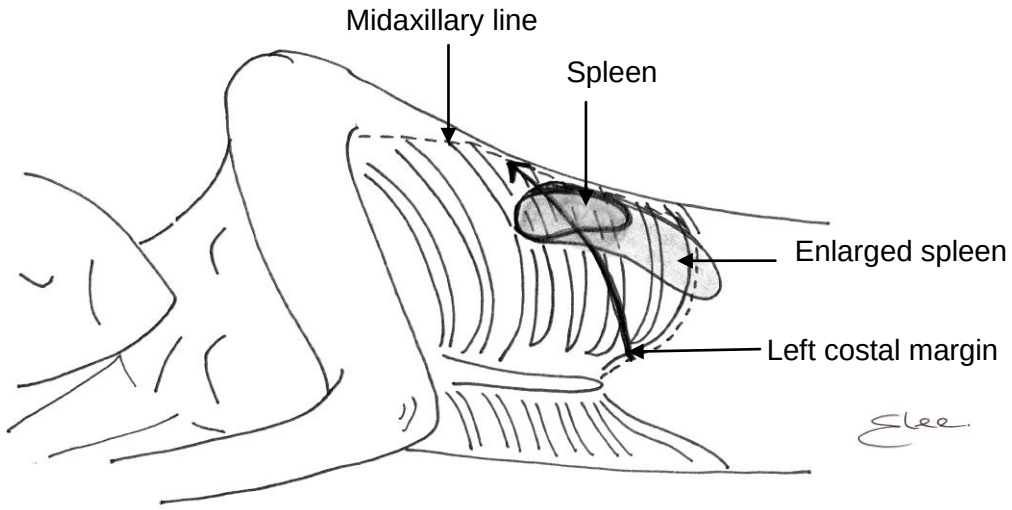
- Several percent of the normal presumably healthy population may have palpable spleens. The “normal” spleen lies posterior to the left mid-axillary line, and between the 9^{th} and 11^{th} ribs. Normal dimensions are 3 x 7 x 12cm or less.
- Because the spleen enlarges anteriorly and posteriorly, spleen 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 breath in deeply several times as well as looking at the “static” abdomen.

- Percussion in Traube's Space and at Castell Spot



- Traube's space is defined by the sixth rib superiorly, the left anterior axillary line laterally, and the costal margin inferiorly. Castell 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.

Nixon method detect splenomegaly



Positive indication: dullness is present more than 8 cm above the costal margin

- 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, with 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 is not 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.
  - 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

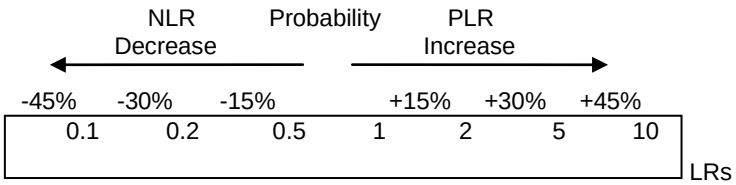
- Below the costal margin the relatively superficial spleen is dull to percussion; because of overlying bowel the enlarged kidney may sound resonant to percussion
- You cannot interpose your fingers between an enlarged spleen and the costal margin, it is however possible to palpate “above” a kidney.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

Adapted from: Simel DL, 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.

Useful background: Perform characteristics for detection of enlarged spleen

Finding	PLR	NLR
➢ Palpation		
One handed	8.5	0.5
Two handed		
➢ 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 that the Castell sign has a 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 SR. *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

- The likelihood of a high PLR for splenomegaly depends on the clinical setting for example, in a returning traveler and fever where there is splenomegaly from malaria (PLR,6.6), with much lower values to detect hepatocellular disease in a person with non-obstructive jaundice (2.9), or detecting cirrhosis in the person with chronic liver disease (2.3).

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

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 47.2, pages 556 and 557.

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

- Primary
  - Physiological (in infancy)
  - Congenital sex-linked (Bruton)
  - A 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

Useful background: Examples of drug interactions with warfarin

- Direct gastrointestinal injury (e.g. non-steroidal anti-inflammatory drugs)
- Altered gut vitamin K synthesis (e.g. antibiotics)
- Altered warfarin metabolism (e.g. cotrimoxazole, metronidazole, fluconazole, amiodarone)
- Interference with vitamin K cycle (e.g. acetaminophen)
- Altered platelet function (e.g. acetylsalicylic acid, clopidogrel)

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

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

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

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

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

- Given systematic approach to other causes of mottling in the skull.

- Cancer
  - Metastases
  - Leukemia
  - Myeloma

- Hematological disorders
  - Sickle cell anemia
  - Histiocytosis X
- Endocrine disorders
  - Cushing disease

SO YOU WANT TO BE A HEMATOLOGIST!

Q1. Percussion in Traub's space is not specific for splenomegaly. What other conditions cause dullness here?

A1.
- Left pleural effusion
- Large pericardial effusion
- Massive cardiomegaly
- Stomach full of food
- Splenic flexure of colon full of feces
- Enlarged left kidney

Q2. Splenomegaly accompanies hepatomegaly in persons with portal hypertension. What are the exceptions to this clinical "rule"?

A2.
- Congenital asplenia
- Post-surgical asplenia
- Splenic vein thrombosis
- Multiple splenic vein infarctions

SO YOU WANT TO BE A HEMATOLOGIST!

Q. In the setting of a patient with purpura, what is Moschcowitz's syndrome?

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

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

Immunoglobulins

SO YOU WANT TO BE HEMATOLOGIST!

Q1. In the adult, a deficiency of serum immunoglobulins may be the result of protein deficiency, hypercatabolic states, or from decreased synthesis resulting from bone marrow disorders, reticuloendothelial neoplasia, or toxic factors. Give 10 causes of secondary immunoglobulin deficiency.

A1.
- ↓ intake of protein
- ↓ absorption
  - Malabsorption e.g. 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 disease
- "toxic" factors
  - Irradiation
  - Diabetes
  - Thyrotoxicosis
  - Sepsis
  - Steroids, cytotoxic drugs

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

Q2. Macroglobulinemia occurs in Waldenstrom macroglobulinemia (WM) as well as in multiple myeloma (MM). What complications of MM are rare in WM?

A2.
- Kidney
  - Chronic renal failure
- Bone
  - Hypercalcemia
  - Osteolytic bone lesions
  - Amyloidosis

SO YOU WANT TO BE HEMATOLOGIST!

Q. In the context of serum immunoglobulins, what are the features of Waldenstrom macroglobulinemia, and what are the causes of an M band?

A.
- 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 one clonal production of increased amounts of immunoglobulin is called "monoclonal gammopathy"
  - Waldenstrom
    - Hepatosplenomegaly
    - Lymphadenopathy
    - Anemia
    - Coagulopathy
    - ↑ macroglobulins
    - ↑ blood viscosity
      - Organ ischemia (e.g. CHF, SOB, retinal bleeding, paresis, neuropathies, myelopathies)
- Causes
  - Idiopathic
  - Myeloma
  - Bence Jones proteinuria without myeloma
  - Heavy chain disease
  - Leukemia, lymphoma, carcinoma

Suggested practice case scenarios for OSCE examinations

Primary Stem	Secondary Stem	Diagnosis
➢ Lymphadenopathy	○ Diffuse	- Lymphoma
➢ Petechiae	○ No splenomegaly	- ITP
	○ With splenomegaly	- Wide differential diagnosis

Source: Kindly provided by Dr. P Hamilton

NEPHROLOGY

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19. Take a focused history and perform a focused physical examination for obstructive sleep apnea (aka Pickwickian Syndrome).
20. Take a directed history and perform a focused physical examination for autosomal dominant polycystic kidney disease (ADPKD)
21. Take a directed history for the causes of discolored urine

Useful reminders

- Depression / bulging of renal outline
  - Scarring or floresis
  - From infection of infarction

- Decreased renal substance
  - Stenosis
  - Fibrosis
  - Back preserve
  - Old age

- Causes of bilateral renal swellings
  - Polycystic renal disease
  - Bilateral hydronephrosis
  - Subacute glomerulosclerosis
  - Amyloidosis
  - Leukemia

- Measurements
  - Normal long axis length of kidney, 12-14 cm.
  - Normal difference on length of kidneys, < 1.5 cm.

- Functions
  - Diluting the urine – loop of Henle
  - Concentrating the urine – collecting ducts

- Symptoms of hypokalemia
  - Tired
  - Ileus
  - Weak
  - Arrhythmia
  - Renal interstitial fibrosis

- Tubular excretory function – H^+, K^+, NH_3^+

- Tubular reabsorptive function – glucose, PO_4^{2-}, amino acids, water, Na^+

- Main types of diabetic nephropathy
  - 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 bacteria/ urinary tract infection – in pregnancy
  - Prematurity of fetus
  - Toxemia
  - Acute pyelonephritis in mother

- Nephrotic syndrome – not associated with uremia or hypertension

Systemic hypertension

Useful background: Definitions

- 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 plus end organ damage)

Definition: 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.

➢ Classification of blood pressure for adults 18 years of 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 AK. *Mayo Clinic Scientific Press* 2008, Table 14-1, page 425.

- Perform a directed physical examination systemic hypertension.

➢ Eyes
  - ○ Vessels
    - Arteriolar narrowing
    - A-V nicking
    - Hemorrhages
    - Exudates
    - Papilledema

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

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

➢ Neck
  - ○ Thyromegaly
  - ○ Carotid bruits
  - ○ ↑ JVP

- Heart
  - Ischemia
  - L-CHF
  - Dissecting aortic aneurysm

- 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 to suggest 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

- 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 PJ, et al. *Saunders/ Elsevier* 2004, pages 172 and 173.

- 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
    - Conn's syndrome
- 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
- Drug
    - 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 JL. *Churchill Livingstone* 1971, page 14 and Jugovic PJ, et al. *Saunders/ Elsevier* 2004, pages 48-50, and 172.

- Take a focused history for complications of malignant hypertensive emergency.

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

Abbreviations: CNS, central nervous system.

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

Useful background: Definitions

- ➢ 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 plus end organ damage)

Definition: SBP $\geq$ 180 mm Hg, DBP > 100 mm Hg

- ➢ End-organ damage
  - o Eye
    - Retinal hemorrhages
    - Optic nerve edema
    - Blurred vision
  - o Brain
    - CVA (thrombosis; intracerebral / or subarachnoid hemorrhage)
    - Confusion
    - Headaches
    - Seizures

- Heart
  - Ischemia
  - L-CHF
  - Dissecting aortic aneurysm
- Lung
  - Acute pulmonary edema
- Kidney
  - Rapid ↑Cr, ↓CCR
  - Acute renal failure

➢ May be a disconnect between BP and end-organ damage

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.

- Perform a focused physical examination of the heart in the patient with systemic hypertension.

➢ Left ventricular hypertrophy

➢ ↑ S2

➢ Functional mitral regurgitation

➢ Systolic bruit at base of heart, radiating to right side of neck

➢ Bruit due to kinked carotid artery

➢ Classification of blood pressure for adults 18 years of 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 AK. *Mayo Clinic Scientific Press* 2008, Table 14-1, page 425.

- Perform a directed physical examination of the patient with systemic hypertension.

- Eye
  - Vessels
    - Arteriolar narrowing
    - A-V nicking
    - Hemorrhages
    - Exudates
    - Papilledema

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

- CNS
  - Evidence of CVA (effect on cranial nerves, cerebellum, motor/ sensory systems)

- Neck
  - Thyromegaly
  - Carotid bruits
  - ↑ JVP

- Cardiovascular examination: evidence of
  - Left ventricular hypertrophy
  - Congestive heart failure)

- 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 to suggest renovascular hypertension
    - Renal masses to suggest PCK disease

- Arteries
  - Abnormal aortic pulsations
  - Femoral bruits to suggest peripheral vascular disease
  - Radio-femoral delay to suggest coarctation of the aorta

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 PJ, et al. *Saunders/ Elsevier* 2004, pages 172 and 173.

- Take a focused history for complications of malignant hypertensive emergency.

- CNS
  - Confusion
  - Seizures
  - Headaches
  - Visual changes
  - Cerebral thrombosis
  - 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 PJ, et al. *Saunders/ Elsevier* 2004, page 50.

SO YOU WANT TO BE A CARDIOLOGIST!

Q1. Differentiate between Pseudohypertension and Pseudohypotension

A1.
- 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's maneuver). Positive Osler's sign, indicating the presence of arterosclerosis, and both SBP and DBP be overestimated.
- Pseudohypotension – in conditions of high peripheral vascular resistance such as shock, Korotkoff sounds are difficult to use to measure accurately systolic or diastolic pressure.

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

Q2. In primary hyperaldosteronism, what are the effects of variations in the intake of salt (NaCl) on aldosterone and rennin?

A2.
- High salt intake – no effect on aldosterone
- Low salt intake – no effect on renin

- Give 4 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 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 per day)
- Smoking
- Stress manage

Abbreviation: BMI, body mass index

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

Renal calculi

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

➢ History
  - Pain
    - Location of pain (unilateral vs. bilateral, radiation to 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/nocturia
    - Urgency
    - Dysuria
  - Obstructive urinary symptoms
    - Hesitancy
    - Diminished stream
    - Postvoid dribbling
    - Postvoid suprapubic fullness
  - Conditions predisposing to renal stones
    - 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 (e.g. cystinuria)
    - Repeated infections
  - Concentrated urine
    - Chronically low fluid intake (<2 L/day)/ high insensible
    - Structural abnormality
    - Renal tract obstruction (e.g. sloughed papilla, prostate enlargement, neurogenic bladder)
    - Nephrocalcinosis
    - Renal tubular acidosis (distal-type I)
  - Associated symptoms
    - Hematuria
    - Diaphoresis
    - Constitutional (fever/chills/night sweats/weight loss)
    - Abdominal (nausea/vomiting)

- 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 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 PJ, et al. *Saunders/ Elsevier* 2004, page 82; Burton JL. *Churchill Livingstone* 1971, page 105.

GI Drugs in Renal Impairment

<u>Nephrotoxic-Avoid</u>
- ASA, NSAIDs
- Etidronate (bisphosphonate, used for osteoporosis e.g. Crohn disease, celiac disease)
- Methrotrexate (IBD)
- Penicillamine (Wilson disease)
- Ribavirin (NCV)
- Sucralfate (in high doses)

<u>Dose reduction</u>

Drug Active metabolite
Assume ≥ 75% renal elimination for dosage adjustment

- AZAthioprine and Mercaptopurine
- Diphennoxylate
- Lamivudine
- Meperidine
- Metoclopramine

- Morphine
- Octreotide

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

Urinary Tract Infection (UTI)

- Definitions
  - Relapse of a UTI is a recurrence with the same organism
    - Usually occurs within 4 weeks

Reinfection of a UTI is recurrence with a different organism
    - Usually occurs > 2 weeks after treatment of the first UTI

Nephrotic syndrome

Useful background: Causes of nephrotic syndrome

- Obstruction
- Toxins/Drugs Glomerulonephritis
- Metabolic
- 'Collagen vascular' disease
- Infection
-
- Congenital and familial
- Diseases causing nephrocalcinosis and renal stones

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

Useful background: Causes of radiologically visible nephrocalcinosis

- 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
- Non-opaque
  - Uric acid
  - Xanthine
  - Matrix

Abbreviation: TB, tuberculosis

Source: Burton JL. *Churchill Livingstone* 1971, page 106.

Useful background: Differential diagnosis of non-opaque nephrocalcinosis

- Stone (uric acid, xanthine)
- Tumor, cyst
- Clot
- Papillae
- Varix

Useful background: Differential diagnosis of renal calculi

- Blood clot
- Sloughed papillae
- Tumor
- Varices

Source: Burton JL. *Churchill Livingstone* 1971, page 106.

Acute interstitial nephritis

- Give 20 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*

- Drug
  - 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
    - Furosimide
    - Bumetanide (sulfa derivatives)
  - Cimetidine
  - Allopurinol, phenytoin, phenindione

- Immune
  - Systemic lupus erythematosus (SLE)
  - Sjogren syndrome
  - Sarcoidosis
  - Renal transplant rejection

- Infiltration
  - Lymphoma
  - Leukemia

Abbreviations: ASAs, acetylsalicylic acids; CMV, cytomegalovirus; HIV, human immunodeficiency virus

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 18-6, page 703.

- 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 insufficiency ('failure')

Useful background: Causes of renal failure

- Pre-renal
  - Hypovolemia
  - Sepsis
  - Post surgery
  - Cardiogenic shock
  - Hepatic failure
  - Drugs (e.g. NSAIDs)
  - Renal artery/ vein obstruction

- Renal
  - Glomurulonephritis
  - Nephrotoxic drugs (e.g. gentamycin, NSAIDs)
  - Rhabdomyolysis
  - Interstitial nephritis
  - Myeloma
  - Hemolytic-uremic syndrome

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

- CNS
  - Headache
  - Lethargy
  - Dizziness and ataxia
  - Mild confusion
  - Psychosis
  - Seizures
  - Coma

- Dehydration
  - Decreased fluid intake
  - Vomiting
  - Diarrhea
  - Excessive sweating
  - Use of diuretics

- Expanded fluid volume
  - CHF
  - Cirrhosis
  - Nephrotic syndrome
- Drugs causing hyponatremia

- SIADH

Abbreviations: CCF, congestive cardiac failure; CNS, central nervous system; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; NSAIDs, non-steroidal anti-inflammatory drugs

Adapted from Davey P. *Wiley-Blackwell* 2006, pages 250 and 268.

- Take a directed history to determine the causes of acute renal failure (ARF).

- Pre-renal
  - CHF
    - ↓ intake
    - ↑ losses, vomiting, diarrhea, bleeding
    - Fluid redistribution – internal bleeding, sepsis, CHF
  - Hypertension

- Post-renal (including reflex anuria due to stones, etc.)

- Renal
  - Glomerulus –acute glomerulonephritis
  - Tubule – ATN
  - Cortex – cortical necrosis (dehydration in children, ante-partum hemorrhage)
  - Vascular
    - Hypertension
    - Hypotension (ischemia)
    - Renal artery thrombosis
    - Stenosis
    - IVC thrombosis
    - Fat emboli
  - Infection – sepsis
    - Systemic infections (OM, lupus)
  - Metabolic
    - Diabetes
    - Hypothyroidism
    - Hypoadrenalism
    - Hypercalcemia
    - Hyperuricemia
    - Diabetes mellitus
    - Hepatorenal syndrome
    - Hypercalcemia
    - Toxemia of pregnancy
  - Acute collagen-vascular disease
  - Acute or chronic (often precipitated by infection or electrolyte disturbance)
  - Medications
    - Drugs (aminoglycosides, contrast, NSAIDs, sulfanilamide, thiazides, rifampin, allopurinol, cimetidine, phenytoin, analgesics, chemotherapy)
    - Infections - renal (post streptococcal glomerulonephritis; pyelonephritis)

Abbreviations: ARF, acute renal failure; ATN, acute tubular necrosis; CCF, congestive cardiac failure; IVC, inferior vena cava

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 18-9, page 712.

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

- Acute- on-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 (e.g. 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, e.g. hypercalcemia
- Pregnancy (Toxemia)
- Hepatorenal syndrome
- Reflex anuria due to obstruction (e.g. renal stone)

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

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

- Renal
  - Glomerulus
    - Glomerulonephritis
  - Tubule
    - Renal tubular acidosis
    - Chronic hypokalemia
    - Fanconi syndrome (generalized proximal tubular damage)

- Obstruction
  - Stones
  - Tumours
  - Fibrosis
  - BPH
- Vascular
  - Hypertension
  - Hypotension (ischemia)
  - Hypovolemia
- Infection
  - Chronic pyelonephritis
  - Renal TB
  - Sarcoidosis

- Cardiac
  - CHF
- Metabolic
  - Diabetes
  - Hypercalcemia
  - Amyloid
  - Hypothyroidism
  - Hypoadrenalism
  - Hyperuricemia
- Medications
  - Phenacetin
  - Radiation
- Collagen-vascular
  - Polyarteritis nodosa
  - SLE
  - Scleroderma
  - Wegeners
  - Goodpasteur's disease
  - Henoch-Schonlein
  - Hemolytic uremia syndrome
  - Thrombotic thrombocytopenia
- Congenital
  - Polycystic renal disease
  - Hypoplasia

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

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

- Perform a focused physical examination for chronic renal failure and its causes.

- General inspection
  - Mental state
  - Hyperventilation (acidosis), hiccups
  - Sallow complexion
  - Hydration
  - Subcutaneous nodules (calcium phosphate deposits)
- 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 etc
  - Mouth- dryness, ulcers, fetor
  - Rash (vasculitis etc)
- Chest
  - Heart- pericarditis, failure
  - Blood pressure- lying and standing
  - Lungs- infection, pulmonary edema
- Abdomen
  - Scars- dialysis, operations
  - Kidneys- transplant kidney
  - Bladder
  - Liver
  - Lymph nodes
  - Ascties
  - Bruits
  - Rectal examination (BPH, bleeding)
- Back
  - Tenderness
  - Edema
- Legs
  - Edema- nephrotic syndrome, CHF
  - Bruising
  - Pigmentation

- Scratch marks
- Neuropathy
- Vascular access

- Causes
  - Glomerulonephritis
  - Primary tubular disease
    - Fanconi syndrome
    - Tubular acidosis
    - Chronic potassium depletion
  - Congenital anomalies
    - Polycystic kidney
    - Renal hypoplasia
  - Infections
    - Chronic pyelonephritis
    - Renal TB
  - Vascular
    - Ischemia
    - Hypertension
  - 'Collagen vascular' disease
    - Polyarteritis nodosa
    - Wegener's granuloma
    - Hypersensitivity angiitis
    - SLE
    - Systemic sclerosis
    - Goodpasture's disease
    - Henoch-Schonlein
    - 'Hemolytic uremia' syndrome
    - Thrombotic thrombocytopenia of Moschcowitz
  - 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 syndrome
  - Tubular acidosis
  - Chronic potassium depletion
- Congenital anomalies
  - Polycystic kidney
  - Renal hypoplasia
- Radiation nephritis

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

Source: Burton JL. *Churchill Livingstone* 1971, page 103.

Useful background: Stages of chronic kidney disease

Stage	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.

Useful background: Medications to avoid in late stage chronic kidney disease

Medication	Complication
○ Baclofen	➢ Increased neurotoxicity even at very low doses
○ Magnesium-containing medications, e.g., antacids, laxatives	➢ Magnesium accumulation
○ Meperidine	➢ Accumulation of an active metabolite that can lead to seizures
Medication	Complication

o Metformin	➢ Risk of lactic acidosis with ClCr < 30 mL/mil
o NSAIDs, COX-2 inhibitors and nephrotoxins	➢ Increased risk of acute kidney injury
o Phosphorus-containing products (e.g., Fleet Phospho-soda)	➢ Death due to hyperphosphophatemia and resulting hypocalcemia have been reported and these products can also cause acute phosphate nephropathy.
o Potassium-sparing diuretics and herbals such as alfalfa, dandelion, noni juice	➢ Risk of hyperkalemia
o Sotalol	➢ Increased accumulation as renally excreted and risk of torsades de pointes
o Vitamin A	➢ Risk of accumulation secondary to decreased renal catabolism and increased serum levels of retinal-binding protein.
o 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.

Useful background: Risk factors for chronic kidney disease

- Atherosclerotic vascular disease
- Autoimmune disease such as lupus, rheumatoid arthritis, connective tissue disease and vasculitis
- Chronic urinary tract obstruction from prostatic enlargement, neurogenic bladder, kidney stones
- Chronic viral infections such as 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 (e.g., congenital single kidney, post-nephrectomy, scarring from reflux nephropathy)
- Use of known nephrotoxic drugs (e.g., 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.

- Perform a focused physical examination for uremia.

- CNS
  - Hypertensive encephalopathy
    - Headache
    - Visual disturbance
    - Confusion
    - Coma
  - Epilepsy
  - Mania
  - Focal neurological signs
  - Peripheral neuropathy

- Heart
  - Increased risk of ischemic heart disease
  - CHF
  - Pericarditis

- Lungs
  - R – CHF from L – CHF
  - Pulmonary edema
  - Pleural effusions
  - Infection
  - Abnormal breathing
    - Cheyne Stokes
    - Kussmaul

- GI tract
  - Anorexia, nausea, vomiting
  - Hiccups
  - Diarrhea
  - Furred tongue
  - Stomatitis
  - Gastritis
  - Bleeding

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

- Systemic
  - Fever, even in absence of infection

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 60 mL/min / 1.73 m^2 with abnormalities
      - of urine sediment
      - imaging studies
      - kidney biopsy

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

Fluid and Electrolyte Disorders

- Definitions
  - Hypovolemia
    - General term meaning volume depletion and dehydration
  - Volume depletion
    - Low of salt and water from IVS (intravascular space)
    - Associated with ↓ BP and ↑ HR
  - Dehydration
    - Loss of water from extracellular (intravascular and interstitial) and intracellular spaces (associated with ↑ serum Na^+ and osmolality)
  - Edema
    - ↑ ECFV (extracellular fluid volume)
  - Peripheral edema
    - Edema in a palpable area
  - Anasarca
    - Severe, generalized edema

Abbreviations: BP, blood pressure; HR, heart rate

- Perform a focused physical examination for hypovolemia.

Hypovolemia is suggested by the finding of

- 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

- ↓ JVP (jugular venous pressure)

- Dry
  - Mucous membranes
  - Axillar

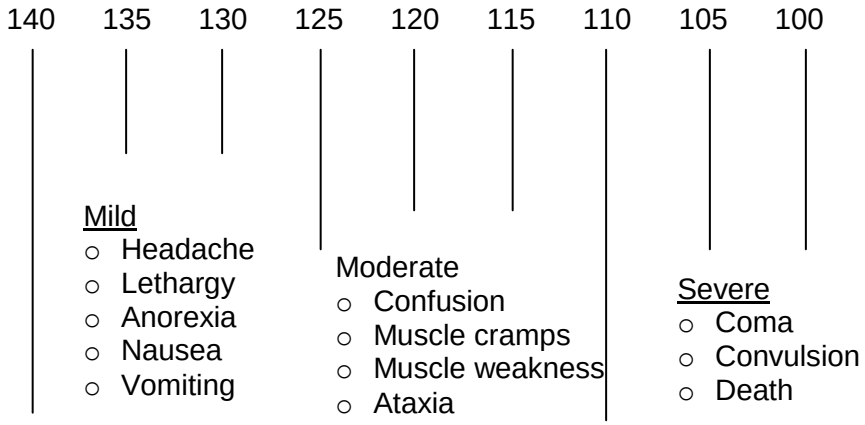
Note: In children, hypovolemia is suggested by the above signs plus:

  - Skin turgor
  - ↓ eyeball tension
  - ↓ capillary refill time

Hyponatremia

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

Clinical features of hyponatremia



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

Useful background: Characteristics of hyponatremia

➢ Variable	➢ Contracted ECF	➢ Normal or near - normal ECF	➢ Expanded ECF
○ Causes	○ Diarrhea ○ Vomiting ○ Excessive sweating ○ ↓ water intake ○ Diuretic use	○ SIADH ○ Hypothyroidism ○ Adrenal insufficiency	○ CHF ○ Cirrhosis ○ Nephrotic syndrome
○ Serum osmolality	○ Low	○ Low	○ Low
○ Urine osmolality, mOsm/L	○ >500	○ >100	○ >100
○ Urine volume	○ Usually decreased	○ Varies with intake	○ Usually decreased
○ 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 antidiuretic hormone; ECF, extracellular fluid; CHF, congestive heart failure

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

Useful background: Causes of the syndrome of inappropriate antidiuretic hormone (SIADH)

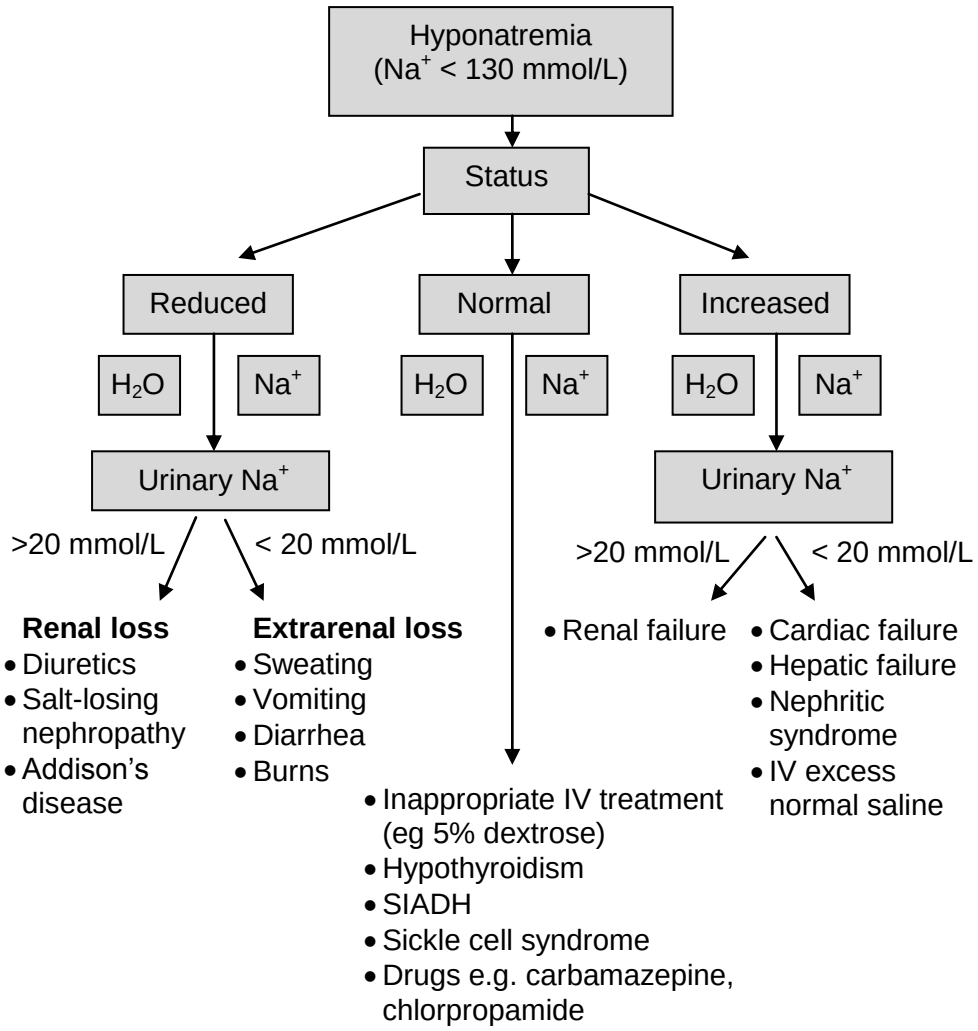
- CNS
  - Infection
  - Stroke
  - Neoplasia
  - Trauma
  - Alcohol withdrawal
  - Acute psychosis
  - Meningitis
  - Encephalitis
- Lung
  - Infection
    - Viral/bacterial pneumonias
    - Bronchogenic tumor
    - TB
  - COPD + lung infection
- GI
  - Cancer
- Renal
  - Prostate cancer
- Blood
  - Malignancies
- Endocrine
  - Acute intermittent porphyria
- Infection
  - HIV/ AIDS, aka ADH
  - ↑H2O permeability of nephron (e.g. vasopressin)
  - ↑ADH release (e.g. carbamazepine)
  - ↑ADH action (e.g. cyclophosphamide)
  - ↓Prostaglandin synthesis (e.g. aspirin)
- Ideopathic

Abbreviations: ADH, antidiuretic 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.

Useful background: Approach to hyponatremia

Hyponatremia - [Na^+] <130 mmol/L



Abbreviation: SIADH, syndrome of inappropriate secretion of antidiuretic hormone

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

Hypovolemia and Dehydration

Useful background: Detecting the likelihood of hypovolemia caused by blood loss (e.g. risk of serious amounts of blood loss)

	Sensitivity (%)	Specificity(%)
➢ Cause by blood loss		
o Pulse increment 30/min or postural dizziness	22	98
o Moderate blood loss (450-630 mL)	97	
o Larger blood loss (630-1150 mL)		

➢ Findings	PLR	NLR
o Urine specific gravity > 1.020 - Young, healthy college wrestlers - Dehydration secondary to sweating	11	0.09
o Dry axilla	2.8	0.6

Note that 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; Abbreviation: NLR, negative likelihood ratio; PLR, positive likelihood ratio.

Adapted from: Simel DL, et al. *McGraw-Hill Medical* 2009, Table 24-8 and 24-9, page 327.

- Perform a focused physical examination for dehydration (extracellular volume depletion)

➢ CNS	o Confused o Weakness o Speech not clear or expressive
➢ Mouth	o Dry mucous membranes
➢ Eye and face	o Decreased eyeball pressure o Sunken eyes o ‘gaunt’ face
➢ JVP	o Collapsed veins
➢ CVS	o Tachycardia o Postural hypotension

- Skin
  - Reduced skin turgor (elasticity) especially arms, forehead, chest, abdomen
  - Dry axilla
  - Dry mucous membranes of mouth and nose
  - Longitudinal furrows on tongue
- Oliguria
  - <400 mL urine/24 hours

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

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

- 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 utility.

Source: Filate W, et al. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 326.

SO YOU WANT TO BE A NEPHROLOGIST!

Q. What's the difference between hypovolemia (volume depletion) and dehydration

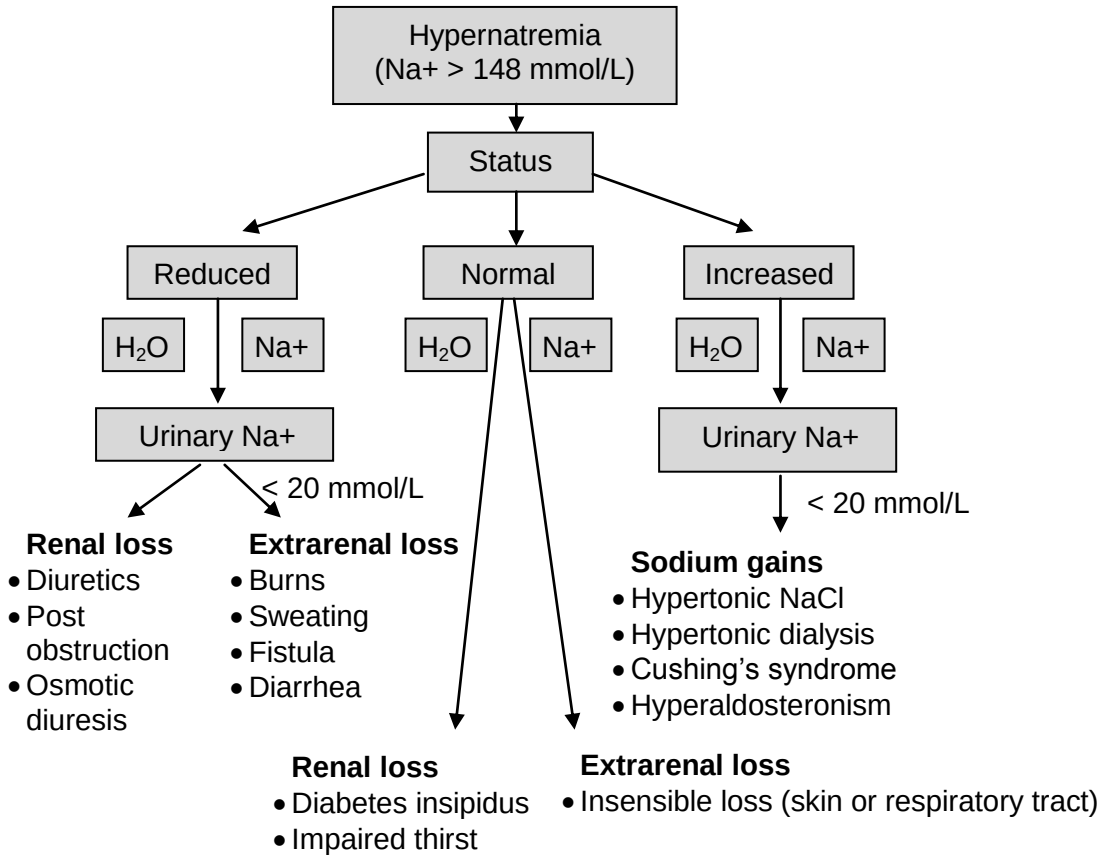
A.
- Hypovolemia: volume depletion is the loss of extracellular Na^+ from the GI tract or kidneys, leading to an increase in the serum urea nitrogen-to creatinine, corrected by the rapid IV infusion of 0.9% "normal" saline to correct and associate hemodynamic instability
- Dehydration is the loss of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

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

"Hard work and good intentions are admirable, but for the successes of life, you have to put the puck in the net."

Grandad

Hypernatremia



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

Useful background: Take a directed history for the causes of lactic acidosis*

Mechanism	Associations
➢ ↑ Production	○ Hypoxia ○ ↑ Skeletal muscle activity (e.g. status epilepticus or marathon runners) ○ ↑ Destruction of large tumour masses (e.g. lymphoma or leukaemia) ○ Poisoning (e.g. CO or cyanide)
➢ ↓ Transport	○ ↓ Cardiac output

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

* Types A ↓ tissue perfusion/oxygenation
  Types 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 hyper natremia.

➢ **Renal loss**
- ○ Diuretic
- ○ Glycosuria
- ○ Diabetes insipidus
- ○ Central nephrogenic

➢ **GI loss**
- ○ Vomiting
- ○ Diarrhea

➢ **Skin loss**
- ○ Excessive sweating

➢ **Lung loss**
- ○ Respiratory loss

➢ **Extrarenal loss**
- ○ GI vomiting
- ○ GI diarrhea
- ○ Excessive sweating
- ○ Respiratory loss

➢ **Iatrogenic**
- ○ Hypertonic NaHCO3
- ○ NaCl tablets
- ○ Hypertonic solutions

Mineralocorticoid
- ○ 1^0 hyperaldosteronism
- ○ Cushing disease
- ○ Adrenal

Hypertonic dialysis
- ○ Hemodialysis
- ○ Peritoneal dialysis

Treatment
- ○ Saline then hypotonic solutions

Treatment
- Diuretics dialysis

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

Useful background: 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 diuretic
  - Excess mineralocorticoid- steroids, Cushing's syndrome, Conn's tumor
  - Renal disease
    - ARF followed by diuretic
    - RTA
    - Fanconi 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 JL. *Churchill Livingstone* 1971, page 109.

Useful background: Causes of proteinuria

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 JG. *Ann Intern Med* 1983;98:186-91.

Disorders of acid-base balance

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

Useful background

- 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 mmHg increases in pCO_2
    - Chronic: the kidney forms new bicarbonate, resulting in a rise of 3 mmol/L for every 10 mmHg increases in pCO_2
- Respiratory alkalosis
  - General idea: 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 mmHg decrease in pCO_2
  - Chronic: the kidney excretes bicarbonate, resulting in a drop of 3 mmol/L for every mmHg decrease in pCO_2

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

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

➢ Metabolic acidosis

- General idea: reduction in ECF bicarbonate concentration results in a lower pH. This can be caused directly by the addition of H+ (which binds to bicarbonate), or 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

- Common causes of increased PAG (plasma anionic gap) metabolic acidosis: KARMEL
  - **K**etoacidosis
  - **A**cetylsalicylic acid
  - **R**enal failure
  - **M**ethanol
  - **E**thylene glycol
  - **L**actic acidosis
- Common causes of non-PAG (non-plasma anion gap) metabolic acidosis:
  - GI
    - Diarrhea
  - Kidney
    - Renal failure
    - Renal tubular acidosis
  - Endocrine
    - Mineralocorticoid deficiency
  - Hyperventilation *Kussmaul's breathing* should compensate for metabolic acidosis by decreasing the pCO_2 by the same amount as the decrease in bicarbonate

➢ Metabolic alkalosis

- General idea: increase in ECF bicarbonate raises the pH+; caused initially by Na^+-H^+ exchange in the distal nephron; 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.

- Take a focused history and perform a focused physical examination for obstructive sleep apnea (aka Pickwickian Syndrome).

- Sleep
  - Night
    - Unrefreshing sleep
    - Snoring
    - Poor quality of life
  - Day
    - Daytime somnolence
    - Daytime fatigue
- CNS
  - Headache, particularly in the morning
  - Poor concentration
- CVS
  - Shortness of breath
  - Systemic hypertension
  - Swelling of feet
- GI
  - Gastroesophageal reflux disease
- Physical examination
  - ↑ BMI
  - Short, stocky neck
  - Lung
    - ↓ ventilation
  - CVS
    - R-CHF
    - Pulmonary hypertension

Adapted from: Burton JL. *Churchill Livingstone* 1971, pages 290 and 291.

Useful background:

- 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 - e.g. respiratory and metabolic acidosis in hypo-ventilated hypoxic patients; respiratory alkalosis and metabolic acidosis in salicylate poisoning

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

➢ History
  - Back pain
  - Hematuria (also proteinuria)
  - Urinary tract infection
  - Hypertension-associated complications
  - Renal calculi
  - Cyst infection
  - Family history
  - Renal failure – associated complications

➢ 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 RR. *Saunders/Elsevier* 2007, pages 322 and 323.

Useful background: Unilateral palpable kidney disease

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

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

Useful background: 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, page 102.

Useful background:

- Respiratory acidosis
  - General idea: ↓ ventilation leads to accumulation of CO_2 from metabolism, which ↓ pH of body fluids
  - Common causes
    - COPD
    - Drugs (narcotics, anesthetics)
    - Decreased LOC (level of consciousness)

- Compensation
  - The addition of HCO_3^- (bicarbonate) raises the pH and buffers against respiratory acidosis
  - Acute: HCO_3^- increases 1 mmol/L for every 10 mmHg increases in pCO_2
  - Chronic: the kidney forms new HCO_3^-, resulting in a rise of 3 mmol/L for every 10 mmHg increases in pCO_2

- Respiratory alkalosis
  - General idea: ↑ ventilation blows off pCO_2 and thereby raises pH of body fluids
  - Common causes
    - Pneumonia
    - Pulmonary embolism
    - Sepsis
    - Pregnancy
    - Aspirin
  - Compensation
    - Reduction in HCO_3^- lowers the pH and buffers against respiratory alkalosis
    - Acute: HCO_3^- decreases 1 mmol/L for every 10 mmHg decrease in pCO_2
    - Chronic: the kidney excretes bicarbonate, resulting in a drop of 3 mmol/L for every mmHg decrease in pCO_2

- Metabolic acidosis
  - General idea: reduction in ECF bicarbonate concentration results in a lower pH. This can be caused directly by the addition of H^+ (which binds to bicarbonate), or 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^-)
    - Normal PAG: 12 mmol/L when albumin is 40 g/L (proportional to albumin concentration)
    - 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 HCO_3^- exactly matches the XXX in PAG
    - If the drop in HCO_3^- is greater than the increase in PAG, it is either a XXXXX non-anion gap acidosis
  - Common causes of increased PAG metabolic acidosis: (KARMEL):
    - Ketoacidosis
    - Acetylsalicylic acid

- Renal failure
- Methanol
- Ethylene glycol
- Lactic acidosis

- Common causes of non-anion gap metabolic acidosis:
  - Diarrhea
  - Renal failure
  - Renal tubular acidosis
  - Mineralocorticoid deficiency

- Compensation
  - Hyperventilation (*Kussmaul's breathing)* should decrease the pCO_2 by the same amount as the decrease in bicarbonate

➢ Metabolic alkalosis
- General idea: ↑ ECF bicarbonate raises the pH+;
- Initially caused by Na^+- H^+ exchange in the distal renal nephron
- Perpetuated by proximal tubule HCO_3^- reabsorption

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

- Normal compensation
  - ↓ ventilation with a variable increase in pCO_2 to a maximum of 50 mm Hg

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

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*Note: Page references to Parts One and Two of the text are preceded by **I:** and **II:** respectively.*