Mastering The Boards and Clinical Examinations In Internal Medicine

Gastroenterology

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A.B.R. Thomson

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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 nor an OSCE. These examinations are to be passed, a process with which we may not necessarily agree. Yet this is the game in which we have thus far invested over half of our youthful lives. So let us know the rules, follow the rules, work with the rules, and succeed. So that we may move on to do what we have been trained to do, do what we may long to do, 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,

Alan BR Thomson

Emeritus Distinguished University Professor, U of A
Adjunct Professor, Western University

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

DISCLAIMER

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

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Thank you

DEDICATION

À Jeannette

Je penserai à toi avec amour,

Aujourd'hui et pour toujours.

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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 (Vitamin B3 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 (specifically iron)
    - Smoking
    - Alcoholism
    - Infections
    - Drugs
      - Antibiotics
      - Ototoxic drugs
      - Phenytoin
      - Heavy metals
    - Trauma
      - Poorly fitting dentures
    - Tumor

  - Systemic diseases
    - GI
    - Crohn disease
    - Ulerative colitis
    - Celiac disease
    - MSK
      - Behcet
      - Reiter
      - Lupus
    - Hematology
      - Leukemia and its treatment
      - Neutropenia
      - Iron deficiency

  - Skin diseases (associated, including angular stomatitis)
    - Benign pemphigoid of mucous membranes
    - Dermatitis herpetiformis
    - Eczema
    - Epidermolysis bullosa
    - Erythema multiforme (Stevens– Johnson Syndrome)
    - Lichen planus
    - Pemphigoid
    - Pemphigus vulgaris

- HIV/AIDS associated infections
  - Viral
    - Exanthemata
    - Hand, foot and mouth disease
    - Herpes simplex
    - Herpangina
  - Bacterial
    - Pyorrhea and alveolar abscess
    - Vincent angina
    - TB
    - Syphilis
  - Fungal
    - Actinomyocosis
    - Candidiasis

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 amount of sputum)
  - Metabolic
    - Fetor hepaticus (a sweet smell)
    - Ketosis (diabetic ketoacidosis caused by excretion of ketones in exhaled air resulting to a sickly sweet smell)
    - Uremia (fish breath – an ammoniacal odour)
  - Drugs
    - Cigarettes, tobacco
    - Alcohol (distinctive)
    - Paraldehyde

Adapted from: Talley NJ, *et al*. *Maclennan & Petty Pty Limited* 2003, Table 5.8, page 161.

- Give the non-dental causes of halitosis.
  - Infection
    - Poor oral hygiene
    - Putrid (due to anaerobic chest infections with large amount of sputum)
  - Metabolic
    - Fetor hepaticus (a sweet smell)
    - Ketosis (diabetic ketoacidosis caused by excretion of ketones in exhaled air resulting to a sickly sweet smell)
  - Drugs
    - Alcohol (distinctive)
    - Paraldehyde
    - Cigarettes, tobacco

Adapted from: Talley NJ, *et al*. 4th ed. *Blackwell Science* 2001.

GUMS

- Give the causes of gum hypertrophy.
  - Gingivitis
    - From smoking
    - Calculus
    - Plaque
    - Vincent angina (fusobacterial membranous tonsillitis)
  - Drugs (eg. 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.

TONGUE

- Give the 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
            - Antimalarial
            - Oral contraceptive pill (brown or black areas of pigmentation in the mouth)
    - Endocrine
        - Addison disease (blotches of dark brown pigment in the mouth)
    - Tumor
        - Malignant melanoma (raised, painless black lesions 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.

- Give the findings on examination of 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 frenulum of tongue)
    - Scrotal tongue (normal for some, can also be seen 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 the causes of an enlarged tongue (macroglossia).
    - Acromegaly
    - Hypothyroidism
    - Amyloidosis
    - Down syndrome

SO YOU WANT TO BE A GASTROENTEROLOGIST! – Coloured Mouth

- Name the pigmented lesions (not white) seen in the mouth.
    - Amalgam tattoo
    - Peutz–Jegher 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, may be palpable; often ulcerates)
    - Addison disease - scattered melanotic spots
    - Melanoplakia - normal in African–Americans

Source: Mangione S. *Hanley & Belfus* 2000, page 127.

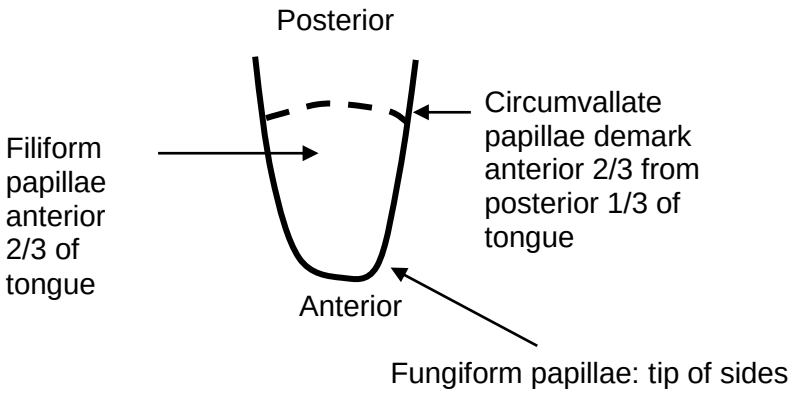
SO YOU WANT TO BE A GASTROENTEROLOGIST! – White Spots in Mouth

- Give the causes of white spots on the oral mucosa.
    - Thickened oral mucosa
        - Broken teeth
        - Poorly fitting dentures
    - Squamous cell carcinoma
    - Infection
        - Candidiasis
        - Rubeola, echovirus, adenovirus, (cluster of tinge white macules on buccal mucosa or on the first and second molars, known as Koplik's spots)
        - HIV - hairy leukoplakia on lateral aspects of tongue and buccal mucosa
    - Leucoplakia is a term used to imply a malignant lesion in the past. However, this is not recommended today since **not all white lesions are malignant**. The same is true with Koplik's spots, which are caused not only by Rubeola virus.

Adapted from: Mangione S. *Hanley & Belfus* 2000, page 125.

"Tongues"

Papillae of tongue



Geographical tongue

Patchy red with furry surrounding areas due to loss of papillae of tongue

Causes of atrophic glossitis

Deficiency of iron, riboflavin or nicotinic acid

Loss of papillae secondary to antibiotic therapy

SALIVARY GLANDS

- 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
    - Sjögren's syndrome (keratoconjunctivitis sicca: xerophthalmia and xerostomia)
    - Systemic Lupus Erythematosus (SLE)
  - Infection
    - Staphylococcus
    - Streptococcus viridans
    - 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 macroglobulinemia
  - Malnutrition: anorexia nervosa, bulimia, starvation, Kwashiorkor
  - Alcoholism
  - Keratoconjunctivitis sicca (dry eyes and mouth)
    - Autoimmune (Sjögren's syndrome)
    - Mikulicz syndrome (non–autoimmune keratoconjunctivitis sicca): TB, lupus, sarcoid, Waldenstrom 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 Sjögren's syndrome)
    - Drugs / toxins
      - 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

DYSPHAGIA

➢ Clinical

- Take a directed history of dysphagia.
- Key points 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

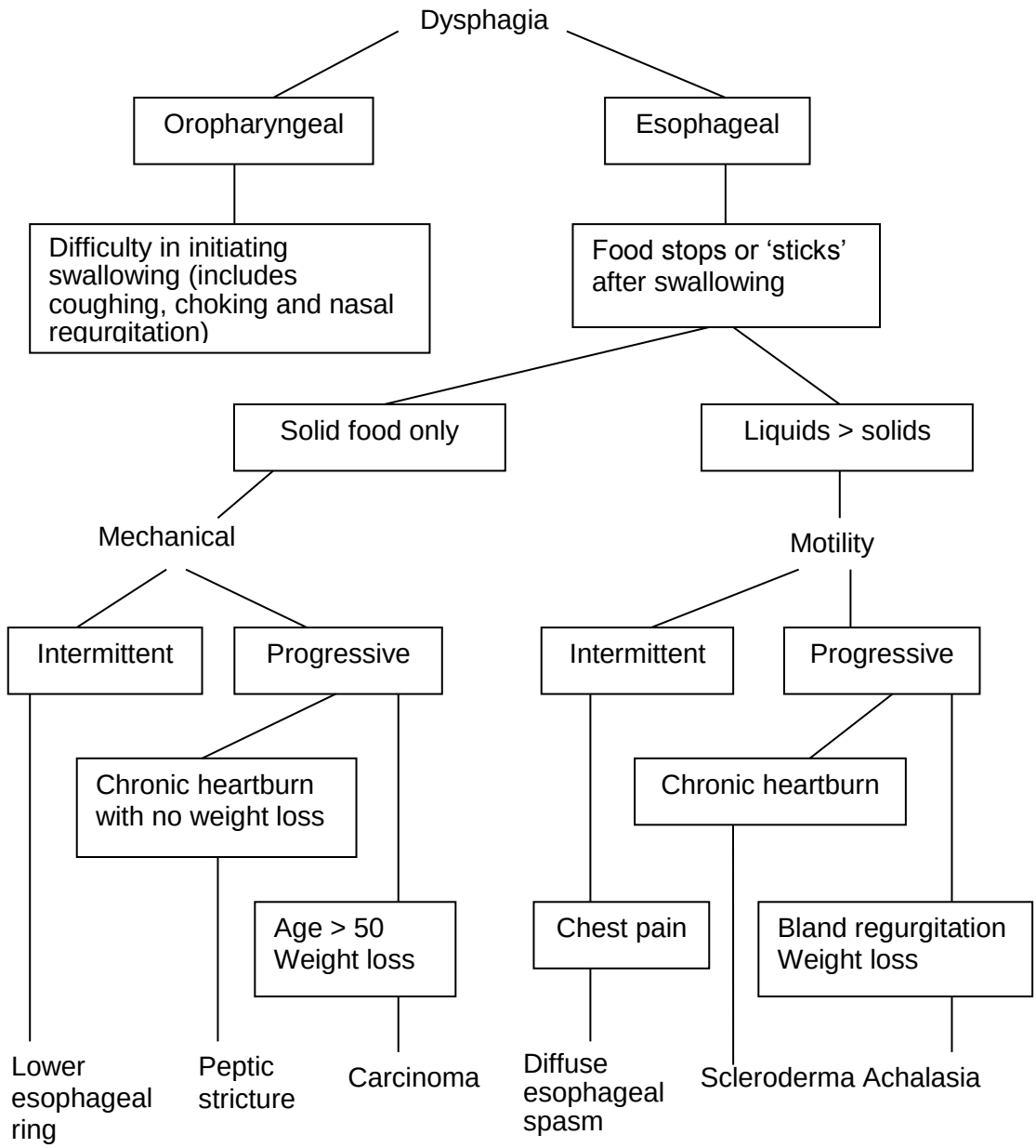
- CNS
    - E.g. CVA, Parkinsonism
- Lung
    - Compression
- Stomach
    - Tumor
    - Gastric retention
- Colon
    - Constipation (rare)
- Drugs
- Pregnancy
- Diet

- MSK
  - Scleroderma
  - Skeletal muscle disease

- Complications
  - Hemorrhage
  - Obstruction
  - Perforation
  - Malnutrition
  - ENT
    - Cough
    - Sinusitis
    - Dysphonia
  - Quality of life
  - Drug treatment
  - Lifestyle modifications

- Give the **Best Test** to evaluate the following:
  - Oropharyngeal dysphagia
    - Videofluoroscopy, **not** ECD
  - Patient with symptoms of GERD
    - EGD + biopsy, **not** upper GI barium study
  - Any kind of esophageal or gastric symptoms in the patient over age 55.
    - EGD, EGD, EGD, even if a motility disorder is mentioned in the stem as a "red herring".
  - Your are given a patient, <55 years old, with no alarming symptoms but has dyspepsia, and the MCQ asks you to choose between, first, doing a trial of PPIs, or, second, to test and treat for H. pylori.
    - The best test depends upon the pretest probability of the diagnosis. The symptoms of GERD are neither sensitive nor specific. If the MCQ stem suggests that the patient has a high pretest probability for an H. pylori infection (new Canadian from S. America or Middle East, or First Nation's person), then do the T&T first. Otherwise, for persons with a low risk of H. pylori (prevalence in Canada overall is ~20%), then do EGD to check for esophagitis.

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.

SO YOU WANT TO BE A GASTROENTEROLOGIST! – GERD / NERD

- A person complains of heartburn but with normal EGD (esophagogastro-duodenoscopy), give the performance characteristics of the Bernstein test.

    - 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 to symptoms following a spontaneous reflux in same individual suggests that heartburn are induced by different stimuli.

Abbreviations: NCCP, non-cardiac chest pain; NERD, normal endoscopy reflux disease

- Differentiate Virchow Node from Troisier Node.

    - Virchow 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 node (!!).

- Causes of an absent gastric air bubble on plain film of the abdomen.

    - Large hiatal 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).

- Give the Neuromuscular Disorders Commonly Associated with Oropharyngeal Dysphagia.

  - Post–polio muscular atrophy
    - Atrophy/weakness of muscles of palate, pharynx and larynx
    - New symptoms of weakness appear 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's disease
    - Video Fluoroscopy Swallowing Study (VFSS) showed abnormal in 95%, but oropharyngeal dysphagia in about 20%
    - Oropharyngeal dysphagia due to
      - decreased pharyngeal contraction
      - decreased relaxation of UES
  - Myotonic dystrophy
    - VFSS is abnormal in ~95%, but symptoms seen in only ~50%
    - Aspiration
      - During swallowing
        - increased weakness of muscles of pharynx and larynx
      - After swallowing
        - Laryngeal muscles open
        - Residue food/fluid in pharynx passes into airway → aspiration
    - Definition
      - Longer contraction time and poor relaxation of affected skeletal muscles

- Myasthenia gravis (MG)
  - Definition: "….a progressive autoimmune disease, characterized by:
    - High circulating levels of acetylcholine receptor antibody; and
    - 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 resulting to oropharyngeal dysphagia
  - Oropharyngeal dysphagia is seen in ~ 33% of patients

GLOBUS

- Give the neurologic conditions associated with the development of globus and a cricopharyngeal bar.
  - CVA (cerebrovascular accident)
  - MS (multiple sclerosis)
  - MG (myasthenia gravis)
  - ALS (amyotrophic lateral sclerosis)
  - Myopathies

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- What features in the history of the patient would help you establish "the feeling of a lump in the throat" diagnosis is globus rather than dysphagia?

  - Globus

  -- Present between meals, not with swallowing food unlike dysphagia
  -- Swallowing food/ liquids makes globus better, not worse
  -- Emotional stress makes globus worse
  -- Frequently associated with psychiatic and somatization disorders

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the endoscopic definition of a nonreducable esophageal hernia.
  - A non-reducable esuphageal hiatal hernia on endoscopy shows "….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).

BARRETT EPITHELIUM (BE)

- Give the molecular biological events in the progression of esophageal mucosa from normal to Barrett epithelium (BE) (metaplasia and dysplasia) to esophageal adenocarcinoma (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–alpha.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

BE (Barrett epithelium) occurs in about one in ten persons with GERD.

- Give the criteria for the definition of BE taking into account the current controversies.
  - Prague CM criteria
    - C, circumference
    - M, maximum extent (length)
  - Long segment BE seen in 3% to 5% of GERD patients, while in 10% to 20% are short segment BE

  - Country
  - Criteria
    - Endoscopic abnormality
    - "long" (> 3 cm) versus "short" (< 3 cm) segment

*Note: 5% of adults with non-GERD symptoms have BE
  - USA
    - 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

- Give the definition of "dysplasia", and the changes in tissue architecture and cell morphology which are seen in the following conditions.

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!

- Give the approximate risks of BE metaplasia progressing to LGD (low grade dysplasia), HGD (high grade dysplasia), or ECa (esophageal adenocarcinoma) each year.

BE metaplasia	LCD	HGD	ECa

o----------→ 0.5% / year, or lower

o----------→ 4.3% / year

o----------→ 0.9% / year

o---------→ 4% to 6% /year

- In symptomatic patients with GERD or BE, elimination of any symptoms does not mean that the gastric percentage risk with pH of < 4 is less than 4% to 5%, or that the esophagitis has resolves. Explain physiologically.
  - PPIs gastric acid suppression targeting 24 hr pH of < 4 to lower than 5% is for the gastric pH; not for esophageal pH to decrease (↑ H^+).
  - Hence, the use of gastric pH as a surrogate marker for esophageal pH needs more testing.

Some health professionals recommend endoscopic surveillance for BE, and discourage antireflux surgery for the prevention of the development of esophageal adenocarcinoma. While endoscopic mucosal resection (EMR), provides 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), the "suck and cut" or "band and snare" has a significant risk for recurrent or metachronous cancer. Ablation methods for BE do not provide tissue samples for pathological assessment, and there is a risk of metaplastic tissue left "buried" under the healing squamous mucosa which looks endoscopically normal.

- Give the percentage risk of recurrent or metachronous esophageal adenomas in BE patients treated with the following modalities.
  - The risks 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
  - ASA plus PPI should be considered for the prevention and to lower the incidence of recurrent cancers
  - If BE spreads out to a large portion of the circumference of the esophagus, then do EMR over several sessions in order to reduce the risk of formation of strictures.
  -

There is progressively increasing genetic instability of the normal esophageal mucosa from metaplasia to dysplasia, and from dysplasia to esophageal adenocarcinoma.

- Give the "….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.

  - 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])

  - Adenocarcinoma
    - Self-sufficiency in growth signals
      - ↑ oncogene (K-Ras)
    - self-sufficiency in growth signals
      - ↑ oncogenes

*Note: At least 10% of the tissues with HGD (high–grade dysplasia) already develop 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!

Some medications will injury the esophagus because of their inherent chemical properties (e.g. ASA, NSAIDs, bisphosphonates).

- Give the non-medication related predispositions for "pill esophagitis".

Esophageal conditions	- Decrease motility - Dysmotility - Strictures - Diverticula - Trough zone (of mid esophagus where the upper skeletal and lower esophageal muscle overlap)
Esophageal compression	- Left atrial enlargement - Aortic compression - Left bronchial impression

ACHALASIA

- Demography

Incidence - $1/10^5$ per year
Prevalence - ~ $10/10^5$
Familial clustering

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- What makes up the "genetic achalasia syndrome"? (Hint: 6As).
  - Genetic achalasia syndrome
    - Autosomal recessive
    - AAAS gene mutations
    - ALADIN protein encoded by AAAS
    - Achalasia
    - Adrenal insufficiency
    - Alacrima

- Pathophysiology
  - Latent HSV-1 infection (HSV-1 antibodies in 84%, and HSV-1 DNA in 63%)
  - Autoimmune process
    - Increase in number of 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
    - Found in myenteric (Auerbach) plexus
    - The longer the history of achalasia, the greater the loss of myenteric ganglion cells
    - Loss of inhibitory ganglion nerve function
      - LES relaxation (deglutitive inhibition)
      - Decrease sequenced propagation of esophageal peristalsis
  - The loss of myenteric ganglion cells → postganglionic excitation
    - ↓ NO synthase → ↓ NA, ↓ VIP effect

- Manometry changes
  - Smooth muscle esophagus
    - Aperistalsis
    - Non-peristaltic contractions (spastic [vigorous] achalasia)
  - LES
    - ↓ relaxation
    - ↑ pressure (in 60%)
- Associations
  - Post-fundoplication
  - Chagas disease
  - Neurological conditions, e.g. Parkinsonism

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- On HREP manometry, define the three esophageal segments; give the method of calculation and the use of the CFV (contractile front velocity) in defining an esophageal spastic contraction.
  - There is one proximal esophageal body segment (S_1) and 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, arising from skeletal muscle.
  - The lower two thirds of the esophageal body represent the distal esophageal segment formed from smooth muscle.
  - The distal esophageal segments have three pressure peaks, S_2, S_3, and S_4.
  - The proximal margin of S_2 connects the distal margin of S_3.
  - Calculate the slope of the line connecting the 30 cm Hg isobaric contour (IBC) line.

Using HREP manometry terms, distinguish between the three subtypes of achalasia (both aperistalsis and impaired deglutitive EGJ relaxation 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 dilatation, but present in type III

**
- In panesophageal compression achalasia, the increase in integrated relaxation pressure (IRP), 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).
- The result of the intrabolus pressure compartmentalization is that the slope of the 30 cm isobar contour line will no longer represent the CFV. Hence, "….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!

Accordingly, the major pathophysiological defect in achalasia is dysfunction or loss of inhibitory ganglion nerve (IGN).

- Based on the typical manometric changes in achalasia, give two evidences explaining IGN dysfunction theory is correct.
  - Important in "deglutitive inhibition", i.e., swallow-associated LES, relaxation
  - Impaired deglutitive inhibition results to failure of relaxation of LES with swallowing which occurs in achalasia
  - Important in "sequenced propagation" of esophageal peristalsis
    - The impaired sequence propagation leads to aperistalsis of the smooth muscles in the body of the esophagus.

Achalasia may be associated with degenerative neurological disorders, such as Parkinson disease. The typical pathophysiological defect seen in the biopsies of the esophagus of patients with achalasia is reduced (inhibitory) ganglion cells.

- In patients with achalasia associated with Parkinsonism, what are the characteristics of the degenerating esophageal ganglion cells?
  - The degenerating ganglion cells show intracytocytoplasmic hyaline or spherical eosinophilic inclusions called "Lewy bodies."

- What are the normal effects of CCK on esophageal muscles and in achalasia?
  - Normal - CCK → ↓ LES (i.e., ↑ LES contraction)
  - Achalasia - CCK paradoxically ↑ LES pressure (i.e. ↓ LES relaxation)
    - This explains why LES pressure is increased in 60% of patients with achalasia

Pulmonary aspiration of solids and fluids trapped in the esophagus from impaired relaxation of the LES is common in achalasia.

- Explain the development of stridor (large airway compromise) in achalasia.
  - Failure of relaxation of the LES and aperistalsis in achalasia, the esophagus dilates significantly resulting to the compression of the trachea.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Patients with achalasia may experience regurgitation of food and fluids resulting to an empty stomach.

- Explain the mechanism of the development of "heartburn" in achalasia patients.
    - Myotomy treatment or the use of smooth muscle relaxant drugs has a high risk of gastroesophageal reflux
    - Food retained in the esophagus became fermented producing acidic short chain fatty acids (e.g., acetic, butyric, proprionic acids)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A chest pain, distinctive from heartburn–like retrosternal burning discomfort, occurs in as many as two thirds of achalasia patients.

- Explain the mechanism of the pain.
    - Spasm of longitudinal smooth muscles of the esophagus
    - Dilatation of esophagus (megaesophagus)

- Give the manometric features differentiating spastic achalasia from distal diffuse esophageal spasm (DES).
    - 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.

- Why should patients with opharyngeal dysphagia be assessed for a possible development of any esophageal diseases or disorders?
    - The localization of the site for esophageal disease is poor.
    - Half of the patients with a disease in the lower esophagus may experience their symptoms in the upper esophageal area.
    - Symptoms perceived from the upper esophagus may in fact arise from the upper portion of the lower esophagus.

Secondary Achalasia Associated with Chagas Disease

- Trypanosoma (T.) cruzi enters the host, and over a long interval (up to approximately 20 years), there is destruction of the autonomic ganglion cells of the GI tract (spicifically the esophagus [with 90% destruction of ganglion cells]) and heart (cardiomyopathy resulting to arrhythmias), urinary tract (megaureter) and the respiratory tract.
- In the intestine, there is 50% destruction of ganglion cells, especially duodenum, leading to abnormal peristalsis and dilatation.
- 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 Polymerase Chain Reaction (PCR)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the causes of postsurgical pseudoachalasia (secondary achalasia).

o After fundoplication	– Motility changes may be similar – Amyl nitrates markedly reduce LES in primary than in postsurgical achalasia – Ensure that post–fundoplication dysphagia and possibly achalasia–like associated symptoms are not due to a paraesophageal hernia.
o After laproscopic adjustable gastric banding (GB, bariatric surgery)	– 14% of LAGB have postoperative dilatation of the esophagus measuring approximately >3.5 cm – Mechanism is unknown – Secondary achalasia usually resolves after removal of the gastric band

Tricks Up Your Sleeve – Connect the Dots

When the MCQ mentions a South American patient, who is having an esophageal motility disorder causing dysphagia that worsens with liquids → think of Chagas disease.

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: Trypanosoma cruzi → Chagas disease

DISTAL ESOPHAGEAL SPASM (DES)

- Definition
  - There is loss of normal latency interval in the lower thirds of esophagus causing lower deglutitive inhibition, and a low sequenced propagation peristalsis.
  - The modern meaning of DES is "distal esophageal spasm" and not diffuse esophageal spasm since the defect is in the lower third of the esophagus, which mainly consists of smooth muscles.

- Pathophysiology
  - Normally
    - There is a lag period between neural stimulation and smooth contraction in a latency interval.
    - This lag period leads to proximal smooth muscle contraction that moves along the length of the esophagus.
  - Defect in DES
    - "….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)
  - decreased deglutitive inhibition
  - decreased sequenced propogation of esophageal peristalsis
- When the 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
  - increased sensitivity to cholinergic agents (↑ excitation)
  - Contraction
    - ↑ amplitude
    - Longer

- It is possible that DES and achalasia are two conditions on a spectrum, wherein there is dysfunction (↓ inhibition, ↑ excitation) first which is followed by detectable changes in the number of inhibitory ganglion cells, and in the amount of NO synthase as well as release of NO and VIP.

➢ Clinical
- Dysphagia
- Non-cardiac chest pain (NCCP)

- Give the second–most common cause of esophageal–related chest pain.

  - Esophageal peristaltic contraction > 180 mm Hg ("nutcracker esophagus")

- Give the clinical and manometric differences between "nutcracker esophagus" (NES) and diffuse esophageal spasm (DES).

Findings	NE	DES
Chest pain	+	+
Dysphagia during bouts of pain	No	Yes
Wave propagation	Yes	No
Multi-peaked waves	-	+
Simultaneous, non-peristaltic waves	-	+

GASTROESOPHAGEAL REFLUX DISORDER (GERD)

- Pathophysiology
  - ↑ tLESR (transient lower esophageal sphincter relaxation)
    - 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 – Spinal ▪ Thoracic splanchnic ▪ mGluR5 (metabotropic glutamate receptor) antagonists inhibit tLESR	– Jugular – Nodose – Cervical of thoracic dorsal root

Abbreviations:

- IGLEs
  - Intraganglionic laminar [free nerve] endings in the myenteric ganglia
  - Found 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).
  - Predominantly 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
  - Form 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

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the means by which the presence of a sliding esophageal hiatus hernia (HH) contributes to GERD.
  - In the presence of HH, the EGJ has a lower compliance, so that the EGJ may open at a pressure lower than the intragastric pressure.
  - Esophagitis associated with HH may release mediators which decrease 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
    - 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)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- About 10% of reflux episodes in healthy individuals occur when there is swallow–associated LESR, and the rest occur can be seen in incomplete peristalsis. Give the reasons why reflux during swallowing–induced LESR is uncommon.
  - LESR lasts only 5 to 10 seconds; very minimal time for reflux to occur.
  - The crural diaphragm does not relax during swallowing, thereby acting as a barrier to reflux.
  - Peristaltic waves push any refluxate materials back to the stomach.

- Give the definition of esophageal peristaltic dysfunction (EPD).
  - Incidence of EPD increases with increasing degree of esophagitis, e.g. EPD in 25% of patients with mild GERD; and up to 50% with severe GERD.

- Over half of GERD patients have sleep disturbances. Give the changes in esophageal function during sleep.
  - During sleep in the supine position, there is:
    - ↓ effect of gravity
    - ↓ salivation
    - ↓ esophageal secondary peristalsis
- The contents of the esophageal lumen are buffered by the alkaline, bicarbonate (HCO_3^-)–rich submucosal glands of the esophagus. Give the chemicals that buffer the intracellular pH of the esophagus.
  - The intracellular contents of the squamous mucosa of the esophagus are buffered by
    - HCO_3^-
    - Phosphates
    - Protein
- In the context of GERD, give the meaning of “acid pocket”.
  - From the lower esophagus sphincter extending to the cardia, there is an acid pocket, which is not neutralized by the food that buffers the gastric acidity.
  - In the LES area, the pH <4 is about one quarter in a 24–hour day (a reflux episode is defined as a pH drop of <4).
  - Physiological reflux is limited to pH <4 for about 5.5% of the 24–hour day.
  - The repeated increased acid exposure of the area predisposes to damage from GE reflux.
  - Sensitivity to esophagitis is 77 to 100%, and specificity of 85 to 100%.

➢ Clinical

SO YOU WANT TO BE A GI JOE/JILL!

- Give the mechanism of cold–induced esophageal pain.
  - Esophageal spasm. Nope – you're back in the last century! Cold–induced esophageal pain results from distention or dilatation of the esophagus since cold causes decreased in esophageal peristalsis.

- A simple question; define "heartburn."
  - "A burning feeling rising from the stomach or lower chest up towards the neck." (www.expertconsult.com)

- Give the difference between "uninvestigated dyspepsia" and "functional dyspepsia."
  - "Uninvestigated dyspepsia" is a pain or discomfort in the upper abdomen which is first thought to be caused by a disorder in the upper GI tract specifically in patients wherein diagnostic investigations and dyspeptic symptomatic explanations are limited.
  - "Functional dyspepsia" is a dyspepsia seen in patients who underwent an esophagogastroduodenoscopy (EGD) but is normal.

Dyspepsia is a symptom complex condition with large heterogeneity of symptoms. There are several pathophysiological changes seen in patients with functional dyspepsia. The Rome criteria are recommended as definitions for and guidance in the management of translucence GI disorders. The Rome III committee recommended that functional dyspepsia is classified into two subgroups:

- PDS (meal–related dyspeptic symptoms)
- EPS (meal–unrelated dyspeptic symptoms)

- Validate the use of the terms, PDS and EPS, in patients with functional dyspepsia.
  - The classification and distinction is not evidence-based.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- TRPV1 (vanilloid receptor 1) is expressed on sensory neurons of the esophagus; give its function.
    - TRPV1 is activated by
        - Chemicals (H^+, bile acids)
        - Heat
        - Distention
    - TRPV1 mediates sensation which is reported by patients as "heartburn"
    - It is unknown why only ~20% of GE reflux episodes are associated with presenting symptoms.

➢ Associations

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Obesity is associated with an increased risk of GERD, BE and esophageal adenocarcinoma (ECa).

- Name 3 peptides which may be linked to this association above.
    - Obesity is associated with an ↑ risk of GERD, BE and Eca by:
        - ↑ IGF-1 (insulin–like growth factor 1) (proliferative peptide)
        - ↑ leptin
        - ↓ adiponectin (anti–proliferative effect of adiponectin)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the possible causes of the narrowing of the esophagus (stricture) seen on a barium esophagogram.
    - Mid – esophagus – Barrett epithelium–associated adenocarcinoma
    - Lower esophagus – Schatzki ring

- Pathology
  - Dilatation (>1.69 mm, intercellular spaces) is the earliest sign of damage to the esophageal epithelial cells.
    - The resulting increased in paracellular permeability to hydrochloric acid, pepsin, and bile acids stimulates receptors of the sensory neurons in the intercellular space which subsequestly leads to "heartburn".
  - The severity of gastropharyngeal reflux symptoms decreases after age 31 to 40 years, but the risk of esophagitis–associated necrosis symptoms increases.

- Give the earliest cellular marker of GERD, and its dimensions.
  - The normal intercellular spaces in the esophagus is <1.69 µm.
  - Dilation more than this value occurs by unknown mechanisms, and is the earliest sign of mucosal damage from H^+, pepsin, and bile acids.

- Esophageal biopsy
  - "things with holes in the middle"
    - Gland
    - Vessel
    - Duct
    - Esophagus has submucosal glands, hence, ducts are also present.
  - Hyphae can be in the esophageal tissues rather than just on the surface
    - PAS – positive diastase – sensitive (glycogen)
      - Suspect glycogenic acanthosis

- Manometry

Conventional manometry plus Intraluminal Impedence Measurement (IIM)

- 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 Video Fluoroscopy Swallowing Study (VFSS) to assess the transit of the bolus

➢ Endoscopy

- You suspect that your patient's hoarseness is due to GERD. An EHT consultation agrees the patient has "reflux laryngitis." Give the expected laryngoscopic findings of your patient.
  - Reflux laryngitis is characterized endoscopically by:
    - Redness of the medial arytenoid walls, in the interarytenoid areas
    - Red streaks on the posterior third of the vocal cord folds

- Over half of patients with typical GERD symptoms have a normal EGD. These patients are said to have normal endoscopy reflux disease, non-erosive reflux disease, or functional dyspepsia. Give the role of esophageal pH testing in the subclassification of the 3 types of NERD.

Findings	Types 1	2	3
○ Abnormal esophageal pH testing	+	-	-
○ Response to PPI: correlation between symptoms and episodes of reflux	+	+	-

➢ Treatment

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Compare the performance characteristics of an empirical PPI trial for GERD versus NCPP (non-cardiac chest pain).
  - For GERD, the PPI test represents standard dose of PPI given *bid* for 2 weeks, with 50% decrease in heartburn.
  - For NCCP, the PPI test represents twice the normal PPI dose in the AM and night time of 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)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In a patient complaining of symptoms of GERD, many treatment algorithms emphasize the importance of numerous "lifestyle changes." Mention the lifestyle changes for your patient that demonstrated efficacy in GERD.
    - While the results from lifestyle changes may vary from one patient to another with symptoms of GERD, appropriately designed studies provided evidences for benefit only:
        - Elevation of the head while in bed
        - Weight loss (if there is increased in BMI)
        - Lying down in the left lateral decubitus position
        - *Note that while the evidence for benefit from smoking cessation in GERD is not strong, physicians often take the opportunity to advise GERD patients of the overall benefits when patients stop smoking.
- In the context of increased transient lower esophageal sphincter relaxation (tLESRs) in patients with GERD, name the four classes of drugs that reduce tLESRs.
    - ↓ tLESRs may be achieved with
        - Agonists $GABA_B$ (γ-amino butyric acid)
        - CCK-1 receptor antagonists (CCKA)
        - Anticholinergics (atropine)
        - Nitric Oxide (NO) synthase (NOS) inhibitors
        - Morphine

We get old too soon,
And smart too late.

~Grandad

ESOPHAGEAL FOREIGN BODIES

SO YOU WANT TO BE A GASTROENTEROLOGIST! – Esophageal bolus obstruction

Incidence of esophageal food bolus impaction: $16/10^5$ per year

- A patient with an esophageal food–associated obstruction is given glucagon. Give the success rate of glucagon, what is the mechanism of action, and why is EGD still necessary if the food bolus passes.
    - Success rate of glucagon ~ 50%
    - Relaxation of LES pressure using glucagon ~50%
    - Associated esophageal pathology, 75%
        - Peptic stricture
        - Schatzki's ring
        - Eosinophilic esophagitis

EOSINOPHILLIC ESOPHAGITIS

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the laboratory features of allergic gastroenteropathy.
    - ↓ serum
        - Albumin and total protein
        - Immunoglobubins
        - Transferrin
        - ↑ eosinophils in lamina propria of affected GI tissues
        - Stool samples contain Charcot–Leyden Crystals

CLINICAL VIGNETTE

- Case: Dyspepsia and dysphagia in a young patient, responds to dietary changes, asthma and eczema, peripheral eosinophilia
    - Answer: Eosinophilic esophagitis

HIGHER–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 is "….coupled with sophisticated algorithms to display the manometric data as pressure topography plots, [so that] esophageal contractility is visualized with isobaric conditions a month sesers indicated by colored 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).

- Give the limitations of conventional (i.e., non–high resolution esophageal) manometry.
  - 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 inhibition
      - Contraction of the crural diaphragm
      - Shortening of the esophagus
      - Movement of the recording sensors
  - Diagnosis of subtypes of achalasia and DES not possible

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Using high-resolution esophageal pressure topography (HREPT), give the three components, which are measured and used 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).
  - Integrated Relaxation Pressure (IRP), EGJ deglutitive relaxation
  - Contraction Front Velocity (CFV)
  - Distal Contractile Interval (DCI)

- Give the main advantages of high–resolution esophageal pressure topography (HREPT).

    - Measure Integrated Relaxation Pressure (IRP):
        - Normally, the IRP of ≤15 mmHg is used as the optimum assessment for "deglutitive relaxation" of the EGJ (esophageal–gastric junction).
    - 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).
    - Make the diagnosis of achalasia: HREPT for diagnosis of achalasia, using IRP:
        - Sensitivity, 98%
        - Specificity, 96%
    - Distinguish the 3 types of achalasia
    - Characterize other forms of esophageal motility abnormalities, such as Distal [diffuse] Esophageal Spasm (DES)

Oropharyngeal dysfunction (OPD) may be due to impaired neuromuscular function or to structural changes.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A Cricopharyngeal bar is the most common structural cause of OPD. It is clinically important to distinguish between oropharyngeal versus esophageal causes of dysphagia.

- Give the use of the finding of a loss of the gag reflex to diagnose oropharyngeal dysfunction (OPD).

    - Since ~one third of normal persons lack a gag reflex, this finding is neither sensitive nor specific for OPD.

- Is a cortical stroke more likely to cause dysphagia and to be permanent than a brain stem stroke?

    - Cortical stroke
        - Less likely than brainstem stroke to cause oropharyngeal dysphagia
        - Dysphagia is more likely to improve

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of high–resolution esophageal pressure topography (HREPT) manometry, define Distal Contractile Integrity (DCI), and give two examples of its use.
    - 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 has >180 mm Hg)
        - DCI > 5000 mm Hg.s.cm
    - "Spastic nutcracker" pattern
        - DCI > 8000 mm Hg.s.cm
    - Hypertensive LES

ESOPHAGEAL DIVERTICULA

Zenker diverticulum (ZD)

- The incidence of the 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 patients 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.

- Give the role of surgery in Zenker diverticulum.
    - Over 80% of patients with a hypopharyngeal (Zenker) diverticulum and cricopharyngeal bar respond to diverticulectomy plus myotomy; neither of these is recommended by itself, except possibly of 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.

CLINICAL VIGNETTE

- Case: Pharyngeal dysphagia and untreated osteoarthritis (OA); difficulty in intubation at EGD
  - Answer: Cervical osteophyte (not pill esophagitis, since OA is not treated)

Epiphrenic Diverticulum (ED)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the rationale of performing myotomy plus fundoplication in patients with an ED.
  - 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 myotomy, there is risk of post-resection GERD, so a nondestructing fundoplication is performed.

Esophageal Intramural Pseudodiverticular (EIP)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Define EIP, and list 4 complications.

EIP are abnormally dilated ducts of the esophageal submucosal glands, leading to:

- Periductal inflammation and fibrosis
- Strictures
- Communication between adjacent pseudodiverticula
- Ulceration, hemorrhage
- Perforation → mediastinitis
- Misdiagnosis of esophageal cancer

Mallory–Weiss Tear

SO YOU WANT TO BE A GASTROENTEROLOGIST!

The Mallory–Weiss (MW) syndrome arises from a tear in the esophagus, usually within 2 cm of the esophagogastric junction (EGJ), along the lesser curve of the cordia. The bleeding resulted from the tear is followed by vomiting in about two thirds of patients.

- Give the mechanism of MW syndrome or tear.

○ 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 the 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).

- Give the distinction between a Mallory–Weiss tear (MW) and Boerhaave syndrome.
  - ○ Boerhaave syndrome
    - An MW tear with perforation
    - Retrosternal pain
    - Subcutaneous crepitus
    - Mediastinal air
    - L–sided pleural effusion
    - Surgical emergency

INFECTIONS

CLINICAL TIPS

- ○ Infectious esophagitis often causes odynophagia.
- ○ When an immunosuppressed patient has odynophagia, but the stem of MCQ states that the examination of the mouth is normal → think candidiasis, CMV or HSV infection in the esophagus, even though there are no signs of infection in the mouth.

- Give the causes of **infectious esophagitis** and corresponding recommended antimicrobial therapy.
    - Candida Albicans
        - Fluconazole or itraconazole
    - CMV
        - IV ganciclovir foscarnet
    - HSV
        - Oral acyclovir or famciclovir

Candidiasis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of the immunosuppressed patient in the ICU who develop dysphagia and retrosternal pain, define the “black esophagus”.
    - “Black Esophagus” is an endoscopic finding of acute esophageal necrosis.
    - This may arise from esophageal ischemia, or infections such as candidiasis or HSV.

Human papillomavirus (HPV) is a DNA virus, which infects squamous epithelium of normal, immune competent individuals. HPV infection is often asymptomatic.

- Give the endoscopic findings of HPV esophagitis.

    - Because HPV is often asymptomatic, the diagnosis may be missed. When EGD is performed, the following endoscopic characteristic changes are seen:
        - Red macules
        - White patches
        - Nodules
        - Frond–like lesions
        - Associated esophageal squamous cell cancer in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Esophageal candidiasis is common in patients who are profoundly immunosuppressed (e.g. HIV/AIDS, or post-transplantation).

- Give additional conditions predisposing the patient to candida esophagitis.
  - Esophageal stasis
    - Scleroderma
    - Achalasia
    - Stricture
    - Intramural pseudodiverticulosis
    - Eosinophilic esophagitis (possibly from treatment with topical steroids)
  - Medications
    - PPIs
    - Topical steroids
  - Immunosuppression
    - Old age
    - Diabetes
    - Alcoholism

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A 60 year old patient with dyspepsia has EGD showing multiple white patches.

- Distinguish candidiasis from glycogenic acanthosis.

Features	Candidiasis	Glycogenic acanthosis
○ History, immunosuppression	+/-	-
○ White patches wash away with EGD water infusion	+	-
○ Brushing for cytology showing hyphae	+	-
○ Biopsy	Hyphae	Large squamous cells because of ↑ glycogen in cytoplasm

Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV)

An immunosuppressed patient with dyspepsia and odynophagia is found to have EGD.

- Give the endoscopic and biopsy changes which differentiate CMV from HSV esophagitis.

	CMV	HSV
○ Ulcers	– Few long, large, deep, serpiginous ulcers with undermined edges	▪ Numerous small, round, superficial "ulcer–like" ulcers
○ Location	– Mid and distal third	▪ Any part of esophagus
○ Biopsy	– Center of lesion – "Owl's eyes" inclusion bodies	▪ Edge of lesion ▪ Nuclei, "ground glass" ▪ Multinucleated giant cells ▪ 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, page 180

Herpes Simplex Virus Infections (HSV)

➢ Clinical

- Give the sites and types of involvement of HSV infection in the immunocompetent and immunocompromised (immunosuppressed) person.

Site	Immunocompetent	Additional sites in immunocompromised
○ CNS	– Encephalitis – Hemorrhagic necrosis	▪ Aseptic meningitis
○ Eye	– Keratitis – Dendritic ulcers	
○ Skin	– Anywhere	▪ Disseminated ▪ Severe oral and genital lesions ▪ Esophagitis ▪ Colitis ▪ Hepatitis

- Give the treatment of HSV.
    - Immunocompetent
        - Acyclovir
    - Immunosuppressed
        - Valacyclovir
        - Famciclovir
    - HSV encephalitis
        - IV acyclovir
    - Topical (eye)
        - Trifluorothymidine, vidarabine, and cidofovir
        - Do not give local steroids

ESOPHAGEAL VARICES

➢ Demography

- The risk of any patient with compensated cirrhosis having Esophageal Varices (EV) is ~50%.
- The risk of EV bleeding is ~30% in the next 2 years.
- The risk of dying from first EV bleeding is high, about 20%.
- It is important to identify all cirrhotic patients who might have EV and therefore would benefit from primary prophylaxis using Esophageal Variceal Band Ligation (EVBL).

➢ Clinical

- Give the factors used to predict the presence of EV in a patient with cirrhosis (↑ HVPG > 12 mmHg), and which thereby be used to increase the pretest probability of finding EV on EGD.
    - Physical examination
        - Splenomegaly
    - Laboratory
        - Platelets < 88,000/mL
        - ↑ INR
    - Diagnostic imaging (abdominal ultrasound)
        - Portal vein diameter > 13mm

Abbreviations: EGD, esophagastroduodenoscopy; HVPG, hepatic vein pressure gradient

- Treatment
  - Endoscopic variceal band ligation (EVBL) is the endoscopic method of choice to treat esophageal varices.
  - No beneficial effects have been observed combining endoscopic sclerotherapy (EST) and EVBL.

- Give the pathophysiological basis for EVBL being superior to β-blockers for primary (before the first EV bleed) or secondary (after the first EV bleed) prophylaxis of EV (esophageal variceal) bleeding (EVB).

- B-blockers
  - The risk of EVB is related to the HVPG.
  - The threshold for EVB is HVPG > 12 mmHg.
  - B–blocker (BB) dosage is targeted to decrease the HVPG < 12 mmHg, but it is not routinely possible to have HVPG measurements.
  - Surrogate markers for BB ↓ HVPG < 12 mmHg include:
    - ↓ HR to 55-60 bpm
    - ↓ SBP by 25%
  - Even with ↓ HR/↓ SBP to these targets, the HVPG may still be > 12 mmHg
  - The BB dosage may cause adverse effects and dose–escalation may need to be stopped before these HR/SBP endpoints are reached.
  - Compliance in taking BB may be an issue if the HR/SBP endpoints are reached.
  - Risk reduction for EVB with BB is only 50%.

- Endoscopic Variceal Band Ligation (EVBL)
  - Risk reduction, 66%
  - Less compliance issue
  - May still provide some benefit, even when HVPG > 12 mmHg

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- A cirrhotic patient wishes to be informed about the efficacy of EVBL for his bleeding esophageal varices and why he is not being offered with sclerotherapy.
  - Initial homeostasis from EVBL 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 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

Junctional Varices and Fundic Varices

Useful background

- Varices may appear in the esophagus, specifically at the junction of the esophagus and stomach (called, 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 hepatic venous pressure gradient (HVPG) is normal (< 12 mmHg).

- Give the anatomical basis for isolated fundic varices.
  - 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 from the spleen to the gastric fundus will cause isolated gastric fundal varices.

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.

    - 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.

Pregnancy and EV

- Give the risks of a splenic artery aneurysm (SAA) in a pregnant woman with cirrhosis.
    - Risk of rupture, 5%
    - Mortality rate in – Mother, 75%
      – Fetus, 90%
    - Risk of rupture increases when SAA > 2cm

- In pregnancy, the portal pressure increases because of the physiological increase in plasma volume. Give the risks of variceal bleeding in a pregnant woman with cirrhosis.
    - The risk of bleeding from esophageal varices during pregnancy depends on the size:
        - Small varices, 25%
        - Large varices, 75%

- In a pregnant cirrhotic woman, there is a high risk of bleeding from EV. There are no trials of the efficacy or safety of esophageal variceal band ligation (EVBL) in pregnant cirrhotic patients. Beta–blockers are useful for primary and secondary prophylaxis of esophageal variceal bleeding in non–pregnant cirrhotics, and beta–blockers are FDA pregnancy class C.

- Why should beta-blockers **not** be used in the pregnant woman with cirrhosis?
    - 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.
    - This class D rating in the second and third trimester is due to the adverse effects on the fetus, such as:
        - 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

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Define "hamartoma."
  - 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).

Malignant Esophageal Cancers (ECa)

- Incidence (per 10^5)
  - USA
    - Men 7.5
    - Women 1.8
  - "Asian esophageal cancer belt" (from Northern to North–Central China)
  - Southeast Africa and South America, Northern France, Switzerland ~25
  - Type
    - In North America, esophageal adenocarcinoma > squamous
    - About 20% increase per year; especially among:
      - Middle–aged Caucasian men
      - Long history of frequent, moderately severe GERD symptoms

- Pathophysiology

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 esophageal adenocarcinoma:
  - Epidermal growth factor (EGF)
  - Transforming growth factor (TGF-α)
  - Connective tissue growth factor (CTGF)
  - Endoglin
  - HER2/NEU gene expression, coding for Cerb B2
  - CCND1 gene expression, coding for cyclin D1
  - Cyclin B

- Proliferation
  - Loss of heterozygosity (LOH) of the antiproliferative protein of retinoblastoma (Rb)
  - Hypermethylation (functional repression) of:
    - Tumor suppressor gene, p16
    - Allelic deletion of 5q where APC resides (↑ plasma level of hypermethylated APC DNA)

- Apoptosis

Disordered apoptosis reduces the effectiveness of the important 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*

➢ Definition: "….telomeres are composed of several thousands 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).

- ↑ telomerase → slowing of the usual shortening of the telomeres with each cell cycle → unlimited replication of cells
- With each replication of the cell cycle, the length of the telomeres become shorter
- Shorter telomeres lead to less replication
- At one point, the telomeres are become 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").

- Invasion
  - Metastasis results from:
    - ↑ disruption of CAMs (cell–cell adhesion molecule):
      - ↓ E–cadherins, ↓ B–catenin
      - Integrins
      - CD44 transmembrane glycoproteins
      - uPA (cysteine protease)
      - CTSB (cathepsin 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

➢ Clinical

- Give the factors that increase the risk of development of esophageal cancers (ECa).

- 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, Paterson–Brown–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)
    - Esophageal Squamous Cell Cancer (ESCC) susceptibility gene
  - Barrett epithelium (BE)
    - 7% familial aggregation
  - Polymorphism (specific variant alleles) in genes affecting metabolism
    - Alcohol
    - Folate carcinogens
    - DNA repair
    - Control of cell cycle
    - Oncogenes

- Give the factors which decrease the risk of the development of esophageal cancer.

- 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

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of esophageal dysphagia, give the components of the Howe–Evans syndrome.
  - Tylosis, or Howel–Evans syndrome
    - Autosomal dominant
    - GI associations
      - Oral leukoplakia
      - Squamous cell cancer of esophagus (SCCE)
    - Surveillance EGD (for SCCE) age 30, then q2 years

➢ Diagnostic imaging

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- 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.
  - FDG PET CT is equivalent to EUS and superior to CT alone in evaluating post–chemoradiotherapy status of nodal ECa by 85% and 86%, respectively.

CLINICAL VIGNETTES

- Case: A 70–year–old patient with weight loss, cough, and dysphagia has chest–X–ray before a barium esophagogram is performed. Give the change on chest–X–ray (CHX) which suggests esophageal cancer (ECa).

o Trachea	– Deviation – Thick retrotracheal stripe
o Esophagus	– Dilated – Esophagorespiratory fistula – Air–fluid level
o Mediastinum	– Wide – Air (pneumomediastinum) – Abscess
o Lung	– Aspiration pneumonia – Metastases – Pleural effusion

CLINICAL VIGNETTE

- Case: A patient with cough, fever, and weight loss is diagnosed with pulmonary TB. Give the complications which you suspect when the patient develops dysphagia, choking on swallowing, chronic cough, and recurrent pneumonia.
  - The development of dysphagia may be from mural compression of mediastinal nodes, or tuberculosis involvement of the esophagus, with ulcers and leaped up mucosa.
  - The choking on swallowing suggests a fistula that has developed between esophagus and the respiratory tract.
  - A fistula between the esophagus and the respiratory tree may also cause chronic and recurrent pneumonia.

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.
  - 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 65 year old patient is diagnosed with esophageal cancer (ECa). Give the recommended diagnostic imaging test in staging ECa.
  - First, 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 improves the survival of the patient because ECa is staged accurately, hence, appropriate treatments could be given. The same is true in diagnosing difficult-to-detect and more advanced diseases. Thereby, improving mortality rate in patients when detected earlier (stage migration).

- In restaging ECa after neoadjuvant chemoradiotherapy, EUS distinguishes ECa from fibrosis and scarring.
- Ability to obtain fine needle aspiration (FNA) for cytological diagnosis)

CLINICAL VIGNETTE

- Case: Keratoderma of palms and hands and soles of feet, family history of esophageal cancer, personal history dysphagia.
  - Tylosis (aka tylosis palmaris)

CLINICAL VIGNETTE

- Case: Sudden onset of dysphagia, gastroparesis, and constipation.
  - Paraneoplastic syndrome

- Give the therapeutic modalities available for 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 Endoscopic Ablative Therapy (EAT)
    - PDT (photodynamic therapy)
    - Laser/ablation (also used for tumor in–growth or overgrowth)
    - Radiofrequency ablation
      - APC (argon plasma coagulation)
      - Nd:YAG (neodymium–doped:yttrium–aluminium–garnet)
      - KTP (potassium titanyl phosphate)
  - Palliation
    - Ablation (as above)
    - SEMS (self–expanding metal stents used to cover esophagorespiratory fistula)

- Radiotherapy
  - External beam
    - 3–dimensional conformal radiotherapy (3D–CRT)
    - Intensity Modulated Radiotherapy (IMRT)
  - Brachytherapy (with or without concurrent chemotherapy)

- Chemoradiotherapy
  - Primary (by itself, no surgery)
  - Given before surgery (neoadjuvant)
    - Concomitant
    - Sequential
  - Neoadjuvant chemoradiotherapy 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 (anti 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

- Give the tumors for which adjuvant chemotherapy has been shown to be beneficial.
  - Brain
  - Breast
  - Lung
  - GI
    - Esophagus
    - Stomach
    - Pancreas
    - Colon

    ▪ Chemoradiotherapy for local or locoregional tumors of stages I, II, and III
    ▪ Screening/surveillance for BE (Barrett esophagus)

GE Junction Adenocarcinoma

- Give the recommended treatment for stage III (locally advanced) adenocarcinoma of the gastroesophageal (GE) junction.
  - Resection plus epirubicin, cisplatin, and 5-FU [5-fluorouracil] (ECF)

STOMACH

HYPERSECRETION, GASTRIN AND ZES

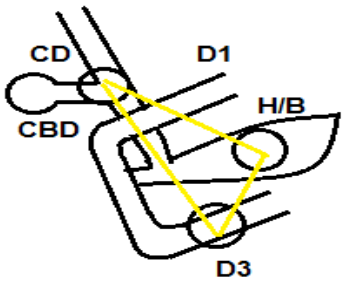
Hypergastrinemia and Hypersecretion

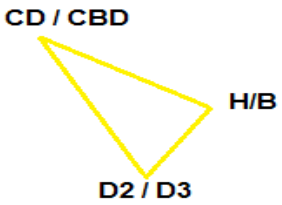
➢ Pathology

Positive secretion stimulation test: serum gastrin increases by at least 200 U in response to IV infusion of a weight determined dose of secretin.

- In the context of hypergastrinemia, hyperchlorhydria, parietal cell hypertrophy and a positive secretin stimulation test, define "gastrinoma triangle".

○ 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

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 as well as of HCl (hence, there is loss of normal autoregulation)

➢ Pathophysiology

SO YOU WANT TO BE A GASTRENTEROLOGIST!

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) and the gastric antrum (antral predominant).

- 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

➢ Clinical

SO YOU WANT TO BE A GASTROENTEROLOGIST OR HEMATOLOGIST!

A 45 year old man presents with severe recurrent ulceration in the stomach and duodenum with occasional ulcers in the esophagus and jejunum. While not on magnesium–containing antacids, he develops diarrhea which occursduring the night and when fasting especially when PPI is stopped or switched. The diarrhea became worse with 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 lesions in the pancreas. EUS shows no lesions in the wall of the duodenum.

The patient is referred for a second opinion, and the consultant made the diagnosis when she asked the patient to remove his shirt, and by performing a colonoscopy.

- The diagnosis:
  - The reddish–brown freckle–like lesions on the patient's back are characteristics of 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.

➢ Laboratory

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the effects of parathyroidectomy on gastric physiology in MEN–1–ZES–associated hyperparathyroidism.

Parathyroidectomy for hyperthyroidism in MEN–1–ZES has the following benefits:

- ↓ serum calcium
- ↓ fasting gastrin
- ↓ gastrin increases with secretin infusion
- ↓ basal acid output
- ↓ resistance to PPIs

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.

- Give the sensitivity of the measurement of basal acid output (BAO) in mEq/hr and the secretin provocative test to make the diagnosis of ZES.

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 results in ↓ serum gastrin
  - Secretin infusion increases serum gastrin by ≥ 120 pg/ml, the test is positive and a ZES sensitivity of 94% and specificity of 100%

- ZES may be sporatic (S–ZES; 75%), or associated with MEN–1 (MEN–1–ZES; 25%). Give the clinical features which suggest MEN–1–ZES rather than S-ZES.
  - Renal stones 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

➢ Treatment

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- We are taught that treatment with proton PPIs do not cause gastric carcinoid tumors, but what does the literature on the longterm follow-up of MEN–1–ZES patients treated with PPIs says so?
  - In MEN–1–ZES patients treated with longterm PPIs, half had ECL changes and 23% develop gastric carcinoids.
- Gastrin stimulates the growth of the colonic mucosa. What is the prevalence of colorectal carcinoma (CRC) in persons with ZES?
  - Epidemiologic studies have not shown any increase in the risks of CRC in ZES.

- Give the theoretical basis reflex hyperchlorhydria following withdrawal of longterm PPI therapy.
  - 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

Systemic Mastocytosis

- In the context of the patient with dyspepsia, diarrhea and flushing, give the meaning of Darier sign.
  - Darier sign is the scratching of the skin causing visible urticaria resulting from the histamine release from mast cells in systemic mastocytosis.

- Dyspepsia associated with hyperchlorhydria is usually treated most efficaciously with PPIs. Give the hypersecretory condition which responds well to H2 receptor antagonists as well as to PPIs and its mechanism.
  - The hyperchlorhydria–associated dyspepsia from systemic mastocytosis is due to the release of ↑ amount of histamine from mast cells.
  - Histamine acts directly on the H2–receptors on parietal cells.
- Hence, blocking the H2–receptors with H2–receptor antagonists is as effective as blocking the proton pumps.

UPPER GASTROINTESTINAL BLEEDING (UGIB)

- Demography
  - Incidence of hospitalizations for upper GI bleeding (UGIB) is $70/10^5$

SO YOU WANT TO BE A GASTROENTEROLOGIST!

IV somatostatin and octreotide reduces the risk of rebleeding from peptic ulcers compared to placebo and H_2 receptor blockers.

- Give the postulated mechanisms of these beneficial effects.
  - ↓ splanchnic and 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 to PPIs), hence, these should only be used with UGIB continuously as EHT plus PPI.

- 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%)
  - Dry mucous membranes and axilla
  - Sunken eyes
  - Longitudinal tongue furrows

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

- Give the performance characteristics of hypotension and its prognosis.

Findings	PLR
○ Systolic blood pressure <90 mmHg	
– Predicting mortality in intensive care unit	4.0
– Predicting mortality in patients with bacteremia	4.9
– Predicting mortality in patients with pneumonia	10.0
○ Systolic blood pressure ≤ 80 mmHg	
– Predicting mortality in patients with acute myocardial infarction	15.5

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

Vital Signs and Acute Blood Loss

Physical Findings	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 mmHg decrease in SBP)	9	...	90–98
○ Supine tachycardia (pulse >100/min)	1	10	99
○ Supine hypotension (SBP <95 mmHg)	13	31	98

Source: McGee SR. *Saunders/Elsevier*, 2007, Table 15.2 page. 167.

➢ Pathology

- ○ Checking for H. pylori infection during UGIB – blood reduces the sensitivity of rapid urease test (RUT) giving a false negative result, but not in biopsy detection of H. pylori.
- ○ In patients with an H. pylori ulcers complicated by bleeding, confirmation of eradications must be confirmed (no H. pylori, no ulcer, no rebleeding).

- Special considerations
  - 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 1–3 mm submucosal artery
    - EHT is 90% effective, but banding is associated with high rate of rebleeding and perforation
  - In patients with **esophageal varices plus bleeding from Mallory–Weiss tear**, focus on esophageal variceal band ligation (EVBL) of the varices
  - Argon Plasma Coagulation (APC) is 80% effective to achieve homeostasis from bleeding from gastric antral vascular ectasia (**GAVE**), even in patients with chronic renal failure.

SO YOU WANT TO BE A GASTROENTEROLOGIST! – UGIB

- Give the patterns of portal hypertensive gastropathy (PHG) seen on EGD.
  - On EGD:
    - Diffuse, subepithelial bleeding, giving a red, mosaic pattern of the mucosa (snake–skin appearance)
    - Fine red speckles on the mucosa
    - Red tips of the gastric rugae
  - On biopsy:
    - Irregular, tortuous, dilated veins in the mucosa and submucosa
    - Thickened intima
    - No inflammation (no gastritis)

In patient with UGIB (upper GI bleeding) and with signs of chronic liver disease, give the best treatment and diagnostic modalities.

- Octreotide scan
- Antibiotics (fluoroquinolone) before and 7 days after UGIB if EV is found
- Recurrent EV bleeding is common. EGD must be performed with each presentation since EV causes not all bleeding.
- Characteristic signs on the varices are seen on EGD will establish whether the acute UGIB in the patient with liver disease or known EV came from bleeding EV, from PUD, from a Mallory–Weiss tear of the gastroesophageal junction, from portal hypertensive gastropathy, gastric antral vascular ectasia (GAVE), or a Dieulafoy vascular disease.

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 with variable phenotypic expressions
- Mutations in 4 genes
  - ENG (gene which codes for endoglin)
  - ALK–1 (activin receptor–like kinase 1)
  - MADH, HHT–3 (code proteins which maintain the integrity of the vascular endothelium)

➢ 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 ACVR1, 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 tissue
  - Arterioles
    - Thrombi (vascular stasis)
    - Proliferation of the intima
  - Venules
    - Thickened walls (recall that the walls of venules in AE is thin)

- 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 lungs, liver, brain

- Diagnostic criteria
  - Spontaneous and recurrent epistaxis
  - Multiple mucocutaneous telangiectasias
  - Visceral AVMs
  - A first–degree relative with HHT

Of interest, ≥ 5 telangiectasias on upper endoscopy (EGD), has a sensitivity of 75% and a PPV of 86% for the diagnosis of HHT.

Source: Feldman M, *et al*. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 317.

SO YOU WANT TO BE A GASTROENTEROLOGIST! – EHT

- Give examples of lesions that cause UGIB when 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!

- Give examples of effective EHT.
  - Multipolar electrocoagulation (MPEC) probe
  - Injection
  - Hemoclips
  - Band ligation
  - Hemostatic spray
  - Doppler probe ultrasound (cost–minimizing strategy)
- Give evidences of the use of pre–endoscopy and pre–EHT PPIs (proton pump inhibitors).
  - 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)

➢ Treatment

- If severe rebleeding occurs after endoscopic hemostatic therapy (EHT)/PPI for peptic ulcer disease, repeated EGD and EHT stops the bleeding in ~75%, and thereby obviates the need for surgery.
- Systemic hypertension at the time of the initial presentation, and an ulcer > 2 cm predicts failure of EHT to stop the bleeding.
- What's new: Non–Variceal Upper GI Bleeding
  - A methodology has been recommended for all the future RCTs in patients with non–variceal gastrointestinal bleeding (NVUGIB)
  - No scoring system has been validated to use in predicting rebleeding occurences after endoscopic hemostatic therapy (EHT) (El munzer *et al*, 2008). Thus, it is not generally recommended to routinely undergo a second–look EGD.
- Proton pump inhibitors may enhance the safety of EVL.
- Variceal bleeding is markedly reduced when the HVPG decreases to <12 mmHg, or decreases by >20% from baseline
- EVL may reduce variceal size until obliteration
- EVL has no effect on portal pressure
- Variceal obliteration with tissue adhesives (e.g. 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!

Suggest clinical endpoints when second–look of EGD is indicated for rebleeding after EHT.

- 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

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In a patient who presents with melena, a nasogastric (NG) tube is inserted and no blood is aspirated; give the false-negative rate of a non–bleeding NG aspirate in a patient with upper GI bleeding (UGIB) proximal to the ligament of Treitz.

NG aspirate	No blood, but bile	No blood and no bile
False negative for UGIB	< 5%	< 15%

- Asked differently, if an NG aspirate is negative for blood, what is the likelihood of an upper GI cause of bleeding being the etiology?
  - Clear but bilious NG aspirate in patient with melena is 95% specific for bleeding from below the ligament of Treitz.
  - A clear but non–bilious NG aspirate in this setting is only 85% specific. Hence, there is a 15% chance that the melena was caused by bleeding in the duodenum, stomach or esophagus.

OBSCURE BLEEDING

A case: A patient has iron deficiency anemia, FOB–positive melenotic stools, a normal EGD with normal duodenal biopsies (exclude celiac disease), and normal colonoscopy with intubation of the terminal ileum. You are asked to give the "best test" from a long list of diagnostic options for obscure GI bleeding, such as:

- Diagnostic imaging
  - Small bowel
  - Enteroclysis
  - CT or MR enteroscopy
  - RBC scan
  - Meckel's scan
  - Angiopathy
- Endoscopy
  - Capsule endoscopy
  - Push enteroscopy
  - Double balloon enteroscopy

And the right answer is……..**None of these**. Repeat the EGD or colonoscopy, perhaps by a more experienced operator.

PPI infusion before EGD is recommended in the care of patients with non-variceal UGIB. Give the benefits of this empiric therapy.

- Down grade the severity of the lesion and the risk of rebleeding or the need of surgery
- Activation of platelets
- Reduced peptic digestion of clot will increase cost effectiveness

- Endoscopy
  - The rate of complete enteroscopy is three times higher with double enteroscopy than with single–balloon enteroscopy, 66% and 22%, respectively (May *et al*., 2010; 105: 575-81).

➢ Treatment

- Why should a patient with isolated IgA deficiency not be given a blood transfusion?
    - The patient has IgG and IgE antibodies (anti–IgA antibodies) that will react against the IgA in the transfused blood; the same thing with IV immunoglobulins.

If a blood transfusion is contraindicated in a patient with isolated IgA deficiency, give what is best to be done if an urgent situation is faced and a blood transfusion would be the only life–saving.

- The RBCs should be washed to remove most of the serum containing the IgA in the blood to be transfused. The washed and packed RBCs can now be used safely.

GASTRIC VARICES

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Name the methods in diagnosing splenic vein thrombosis (SVT), which may lead to UGIB from gastric varices.
    - Doppler ultrasound
    - MRI
    - Angiography

- Compare the efficacy of banding, gluing, or injecting gastric varices from SVT.
    - None of these choices is effective!
        - The definitive treatment for bleeding gastric varices from SVT is splenectomy.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Bad examsmanship – never offer information which you cannot explain an obvious follow–up questions. You said it, so give the differences between the main types of balloon tamponade tubes used for bleeding esophageal varices!

			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

GASTRIC VOLVULUS

- Define gastric volvulus, and give the pathogenesis based on the bisecting axis and the associated rotation.

➢ Definition

- ○ Thrusting 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
○ Mesenteroaxial (40%)	– Lesser and greater curves	– Anterior rotation of the antrum along the axis bisecting the lesser and greater curves

Name of volvulus	Bisection	Pathogenesis
○ 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
○ Organoaxial, passing through the GE junction and pylorus	– Body of stomach	– Anterior–superior rotation of the antrum, and posterior–inferior rotation of the fundus

Feldman M., *et al*. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 708.

BARIATRIC SURGERY

- Prepare a patient for informed consent prior to possible bariatric surgery and explain the perioperative surgical complications.
    - ○ Surgery/ anesthesia
        - Anastomotic 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 disturbances
        - Protein deficiency
    - ○ Risks if obesity is not corrected

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, page 516.

- Give the mechanisms or benefits 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.

Relative Efficacy

BPD – DS >	Gastroplasty	=	Bypass	>	Banding
(38%)	(18%)		(17%)		(7%)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Why does an EGD is recommended to all patients prior to bariatric surgery?
  - 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, Roux-en-Y gastric bypass

- Draw the most commonly performed gastric bypass procedures.
  - 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 Gastro-intestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 116.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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 co–morbidities.

- Give the approximated rates of improvements in these categories overall, or by specific types of weight loss operations, in the mortality rates, resolution of co–morbidities.

  - % ↓ 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 co–morbidities (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 post–operatively)
- 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.

- Give the adverse effects of bariatric surgery on the esophagus, stomach and gallbladder.

  - Esophagus
    - While these procedures generally improve pre–existing GERD symptoms, some patients will develop GERD after surgery (eg. about 50% with LAGB).
    - LAGB 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 use of NSAIDs or steroids.

  - Gallbladder
    - The increased incidence of post bariatric surgical cholelithiasis may be reduced with the use of UDCA for 6 months after surgery.

Abbreviation: UDCA, ursodeoxycholic acid; NHL, non-Hodgkin lymphoma; MM, multiple myeloma

GASTRIC TUMORS AND POLYPS

- Name the GI cancers that are of infectious origin.

o H. pylori	– Gastric ▪ Adenocarcinoma ▪ MALT lymphoma
o HBV (hepatitis B virus)	– HCC (hepatocellular cancer)
o EBV (Epstein–Barr virus)	– Hodgkin lymphoma – Burkitt lymphoma – Nasopharynx cancer
o HPV (human papilloma virus)	– Oropharyngeal cancer – Cervical and anal cancer
o Herpes virus 8	– Kaposi sarcoma
o HIV (human immunodeficiency virus)	– Non–Hodgkin lymphoma (NHL)

Trick Question

- You are asked to give the head and neck cancers of infectious origin.
- Remember
  - Nasopharyngeal - EBV
  - Oropharyngeal - HPV

Gastrointestinal Lymphomas

- Hodgkin lymphoma is very rare in GI tract, but non–Hodgkin lymphoma (NHL) has an incidence of $1/10^5$ per year

- 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.

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 center of the MALT.
- These germinal centers are 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

- Pathophysiology
  - Some GI tract lymphomas arise from germinal center (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)

- Pathology
  - CD20–positive
  - B cells,
  - ~1/2 of all gastric lymphomas
  - May be extranodal
    - Eye
    - Salivary glands
    - Thyroid
    - Lung
    - Colon
    - Bladder
  - May be limited to spleen, with or without lymphadenopathy

- Association
  - Most gastric MALT lymphomas are associated with an H. pylori infection (98% serological and 90% histological association).
  - Autoimmune
    - Sjögren syndrome
    - Hashimoto thyroiditis

- Treatment
  - 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%).
  - Triple therapy to eradicate H. pylori
  - Localized MALT
    - Radiation therapy
  - Advanced disease
    - Radiation plus rituximab, or
    - R–CVP (rituximab)
  - Splenectomy for MALT that is localized in the spleen

SO YOU WANT TO BE A GASTROENTEROLOGIST!

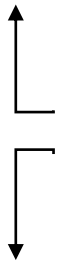
- Explain why the 25% of gastric MALT show no response to H. pylori eradication.
  - May be due to:
    - One of the chromosomal translocations [t (11, 18)], as suggested by IHC staining for nuclear BCL-10.
    - Possibly due to expression of Cag A protein.
    - High grade and/or extensive disease state.
  - Gastric H. pylori infection causes chronic gastritis wherein an immune response 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 lymphoma cells invade the lamina propria, grow around reactive follicles, and invade the germinal centres (follicular colonization); MALT lymphoma results.

Half of gastric lymphoma are MALT and the remainder are diffuse large B cell lymphomas (DLBCL) with areas of marginal zone MALT–type lymphoma.

- Give the use of PET scans to distinguish the diffuse superficial gastric infiltration of MALT lymphoma from the masses seen in diffuse large B cell (DLBCL) lymphoma.
  - Very little of fluorodeoxyglucose (^{18}F-FDG) used for PET scanning is taken up by gastric lymphomas, so better do EGD with biopsy, EUS or CT scan.
  - In contrast to the > 90% association of MALT lymphoma with H. pylori, the association with DLBCL is only absent in one third, even if MALT and DLBCL co-exist.

Endoscopic Ultrasound (EUS)

Errosion



Layer	Colour / echoic nature	Layer	
1	Light, hyperechoic	Superficial epithelial layer	Mucosa
2	Dark, hyperechoic	Deep epithelial layer	Muscularis mucosa
3	Light	Submucosa	Lamina propria
4	Light	Muscularis propria	
5	Light	Serosa	

Ulcer

→ GCa arises

Abbreviation: GCa, gastric cancer

- EUS and Submucosal Gastric Tumors

Layer	Tumor
1	
2	○ Carcinoids ○ (GIST)
3	○ Lipomas ○ Carcinoids
4	○ GIST ○ Leiomyoma ○ Glomus tumor ○ Schwannoma
5	

- Give the differences on EUS of the different gastric submucosal tumors.

	GIST	Leioyoma	ECL cell carcinoid tumors	Glomus tumor	Lipoma	Schwannoma
○ IHC						
– CD 117	+	-	-	-	-	-
– Actin	-	+	-	-	-	-
– Vimenten	-	-	-	+	-	-
– S–100	-	-	-	-	-	+
○ EUS						
– Layer	4, 2	4	2, 3	4	3	4
– Hypoechoic	+	+	+	+	-	+

Abbreviations: EUS, endoscopic ultrasound; IHC, immunohistochemistry

Gastrointestinal Stromal Tumor (GIST)

- Arise from interstitial cells of Cajal
- Usually in EUS layers 4 and 2
- Positive immunohistochemical staining for CD 117 (c–kit positive; C–kit is a tyrosine kinase receptor)
- ~ 20% may be malignant

- Give the differences on EUS of benign and 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	-	+

Neuroendocrine Tumors (NETs)

- Non–secretory (75%)
- Secretory (25%)
  - "Carcinoid"
    - Serotonin
  - "NET"
    - Gastrin
    - Somatostatin
    - Insulin
    - Glucagon

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the 4 types of inherited neuroendocrine tumors (NETs), for which family screening may be appropriate.
  - MEN–1 (Werner syndrome)
  - Von Hippel–Lindau disease
  - Tuberous sclerosis
  - Neurofibromatosis–1 (Von Recklinghausen Disease)

➢ Pathology
- Sheets of homogeneous, small round cells
- Uniform nuclei and cytoplasm
- High vascularity
- Few mitotoc figures

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Name the types cells in endocrine tumors of the stomach.
  - 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)

- Treatment
  - Follow with
    - 3 phrase–contrast CT
    - MRI with galodinium
  - Indium^{111}
  - Octreotide scan
    - To detect somatostatin receptors
  - Growing or symptomatic tumors with somatostatin receptors
    - Octreotide scan
  - Chemotherapy
    - Anti–VEGF
      Sunitab
    - Bevacizumab
      Anti–mToR

Lipoma

- Definition: pressure on a lesion causes an indentation which lasts for a short interval after the forceps is removed.
- Positive “pillow sign”

Duplication Cyst

- A duplication cyst (DC) may cause a spherical, anechoic, subepithelial gastric mass. Give the pathological associations of DC.
  - Carcinoid tumors
  - Gastric cancer

CLINICAL VIGNETTE

EGD shows a gastric nodule; EUS shows lesion is spherical, extramural, with no echo.

- Give the most likely diagnosis.
  - Duplication cyst

Treatable Premalignant Gastric Conditions

- Give the 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 (if not detected earlier and no treatment with vit B_{12}, this will lead to the development of gastric carcinoid tumors or adenocarcinoma)

Fundic Gland Polyps

- 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 distinguish sporatic from familial FGPs.
    - 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%

Gastric Cancer

- Causes
  - H. pylori infection
  - Smoking
  - Family history
  - Dietary influences
- Clinical

- In the context of gastric cancer, give the meaning of Virchow node, Sister Mary Joseph node, Krukenberg tumor and Blumer shelf.
  - Virchow node
    - Supraclavicular lymphadenopathy, left side
  - Sister Mary Joseph node
    - Periumbilical node
  - Krukenberg tumor
    - Enlarge ovary from metastatic gastric cancer
  - Blumer shelf
    - Palpation of rectal mass in the cul–de–sac from metastatic gastric cancer

- Treatment
  - Surgical resection plus pre– or post–operative ECF (5-FU, cisplatin, epirubicine)
  - Surgical resection plus post-operative
    - 5-FU plus leucovorin and radiation
  - Metastatic disease – bevacizumab
  - HER2 expression by tumor
    - 5-FU plus cisplatin and trastuzumab

MÉNÉTRIER DISEASE

- Pathophysiology
  - Associated with ↑EGF receptors

- Pathology
  - “corkscrew” foveolar hyperplasia of gastric body
  - Protein–losing enteropathy
  - Premalignant may lead to:
    - Gastric lymphoma
    - Gastric 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
  - Antral gastritis (usually H. pylori infection)
- Case: Dyspepsia, age 70, weight loss with anemia; acanthosis nigricans in axilla
  - Gastric cancer
- Case: Dyspepsia, numerous “sheets” of T cells in gastric mucosal biopsy, blunted mucosa and hyperplastic crypts on small bowel biopsy
  - Lymphocytic 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.
  - Billroth II surgery, Retained Antrum Syndrome
- Case: Upper GI bleeding, recurrent abdominal pain, reddish lesions on lips and tongue
  - Cavernous hemangioma associated with blue rubber blue nevus (BRBN) syndrome
- Case: Abdominal pain, diarrhea, bleeding in a “vasculopath” (extensive atherosclerosis), ↑ ESR and eosinophilia, rectal or gastric yellow nodule on endoscopy; give the most likely mucosal pathology?
  - “Needle–shaped clefts” on mucosal biopsy from cholesterol embolization

ABDOMINAL PAIN AND MASSES

- Take a directed history to determine the causes of RUQ pain.
    - Heart
        - Heart failure (HF)
        - Pericarditis
    - Lung
        - Pleurisy
        - Pneumonia
        - Pulmonary embolus (PE)
    - Aorta
        - Dissection/rupture
    - Stomach/duodenum
        - Peptic gastric ulcer (GU)
        - Peptic duodenal ulcer DU
    - Liver
        - Hepatitis
    - Gall bladder
        - Cholecystitis
        - Choledocholithiasis
    - Pancreas
        - Pancreatitis
    - Kidney
        - Calculi

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 diseases 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!

A sexually active woman of reproductive potential presents with acute abdominal pain three weeks after a missed menses.

- Give the most likely diagnoses.
    - 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.

- Attempt to differentiate between involuntary and malingering pain.
    - Try to distract patient by pretending to auscultate but pushing in the stethoscope, and watch the patient's face for signs of discomfort.

Hyperalgesia and allodynia are both types of pains, but differ in the type of signal referred by the pain.

- Give the signal that causes the pain in each of these.

Pain	↑ pain response to signal
○ Hyperalgesia	– Noxious
○ Allodynia	– Non–noxious

- Give the portions of the visceral pain transmission to the CNS that are abnormal or dysfunctional in IBS?
    - ACC (anterior cingulate cortex)
    - PACC (perigenual anterior cingulate cortex)
    - Dorsal ACC
    - MCC (mid cingulate cortex)

- Give the main mediators of the stress–immune response.
    - CRF (corticotropin releasing factor)
    - HPA (hypothalamic–pituitary–adrenal axis)
    - Pro–inflammatory cytokines
    - LC–NE (locus–coeruleus–norepinephrine) systems in CNS

NSAIDS

Prepare a patient for informed consent for the use of non-steroidal anti-inflammatory drugs and explain the potential adverse effects.

- Neurologic
  - Delirium or confusion
  - Headache
  - Dizziness
  - Blurred vision
  - Mood swings
  - Aseptic meningitis
- Cardiac
  - Peripheral edema
  - Pulmonary hypertension
- Pulmonary
  - Nasal polyps
  - Pulmonary infiltrates
  - Non–cardiac pulmonary edema (aspirin toxicity)
  - Anaphylaxis
  - Bronchospasm
- 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
    - Agranulocytosis
    - Aplastic anemia
  - Iron deficiency anemia
  - Platelet–aggregating defect
- Dermatologic
  - Urticaria
  - Erythema multiforme
  - Exfoliative syndromes (toxic epidermal necrolysis)
  - Stevens–Johnson syndrome
  - Oral ulcers
  - Dermatitis
- Drug interactions
  - ↓ effect of warfarin
  - ↓ antihypertensive effect of diuretics, beta–blockers, angiotensin–converting enzyme inhibitors
  - Influenced by drug metabolism:
    - Methotrexate (high doses only)
    - Lithium
    - Oral hypoglycemic agents

Adapted from: Ghosh AK. *Mayo Clinic Scientific Press* 2008, Table 24-21, page 999.

- Give the risk factors for the development of upper GI adverse effects with NSAIDs–and the need for co–therapy with PPI or PEG_2.
  - Age ≥ 65
  - Co–morbid medical conditions:
    - 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.

APPENDICITIS AND PERITONITIS

- Demography
  - Incidence $110/10^5$
  - Lifetime risks F 6.4%
    M 8.6%

- Diagnostic imaging
  - CT scans
    - 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%

- Clinical

Epiploic appendages are fat tags along the anti–mesenteric border of the colon, especially the transverse and sigmoid colons. Give the clinical, laboratory and diagnostic imaging differences between epiploic appendagitis and appendicitis.

Clinical	Epiploic appendagitis	Appendicitis
○ Acute abdominal pain	+, L side	+, right side
○ Peritoneal signs	-	+
○ Fever, sweats	-	+
○ CT scan of abdomen	– Focal, oval area of fat – Inflammatory stranding – Central, linear, attenuating line (from thrombosis of central vein)	– Obstructed lumen – Thickened wall

- Terminology
  - McBurney's point tenderness
    - Tenderness along 1/3 of the 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; pain elicited 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 McBurney'ss 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 a suspected acute appendicitis case.

- 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).

- Give the physical findings that suggest the presence of peritonitis.

    - Guarding
    - Rigidity
    - Rebound tenderness
    - Percussion tenderness

    - Abnormal bowel sounds
    - Positive abdominal wall tenderness test
    - Positive cough test
    - Rectal tenderness

Abbreviation: likelihood ratio (LR); if finding is present = positive LR (PLR)
Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 48.1, page 576.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of the patient with intra–abdominal pathology, give the meaning of Kehr sign, and its mechanism.

    - 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).

- In the context of abdominal pain and tenderness, give the meaning of Hover, Carnett and Jump signs.

    - Hover – the patient "hovers" their hand(s) over the abdomen during physical examination of the abdomen
    - Carnet – ↑ tenderness of the abdominal wall 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

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.

- Give the 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.

- Give the 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 into inguinal canal during straining – Touched with examining 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.

- Give the 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.

NAUSEA (N) AND VOMITING (V)

- From the clinical history, mention what you can suspect to be the cause of nausea and vomitng of a patient.

o Early morning or fasting N/V of miscellanea 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
o Vomiting of semi–digested food in late postprandial period	- Gastric outlet obstruction
o “vomiting” of indigested food, without prior nausea	- Addison, Zenker diverticulum

o Feculent vomitus	- Lengstanding cystic outlet obstruction, ileus, intestinal obstruction, colonic fistula
o Projectile vomiting without preceding retching/nausea	- Tumor, abscess or increased intravisceral pressure
o 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).

GASTROPARESIS

- 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, and ileus.

    - The small cell cancer of the lungs 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.

- Is there a best test to diagnose gastroparesis?

    - A gastric emptying study performed with a solid and a liquid test meal will correctly establish whether the gastric emptying was slow at the time of testing.
        - However, there may be a poor correlation between the patient's symptoms, the T1/2 of emptying provided by the emptying study, or their response to prokinetic medications.

- Give the mechanisms for the development of hypernatremia, hypokalemia, hypochloremic, metabolic alkalosis (↑ Na^+, ↓ K^+, ↑ Cl^-, ↑ HCO_3^-) which occur with gastric outlet obstruction.
    - Gastric outlet obstruction → vomiting HCl
    - HCO_3^- secreted by the pancreas and parietal cell's basolateral membrane ("alkaline tide")
    - HCO_3^- is not nebulized by HCl, since HCl was lost during vomiting
    - The resulting metabolic state 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.

FUNCTIONAL ABDOMINAL PAIN SYNDROME (FAPS)

- Pathophysiology
    - Explanation of FAPS arises from the biopsychosocial model of illness, the experience 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 and enteral nervous systems)
        - ↑ pain perception
        - ↓ coping strategies
        - ↓ social networks

Clinical Alert: Avoid Common Mistakes!

- Do not withhold analgesia in person with an "acute abdomen", since several studies have shown that giving such patients sufficient pain-relieving analgesia does not delay in making the correct diagnosis of the cause of the pain.
- There is no reason to delay the giving of broad–spectrum antibiotics to an immunocompetent patient with peritonitis.
- Surgical lysis of adhesions – avoid laparoscopic adhesiolysis – not evidence – based

INTRA-ABDOMINAL ABSCESS (IAA)

- Give the bacterial adjuvant or host defense factors, which influence the transition from bacterial contamination to infection.

Bacterial Factors	Adjuvant Factors	Host Defense Factors
○ Adherence capacity	– Barium	▪ Fibrin sequestration
○ Invasiveness	– Blood	▪ Lymphatic clearance
○ Metabolic systems	– Fecal matter	▪ Neutrophil influx
○ Resistance to antibiotics	– Fibrin – Foreign material – Necrotic tissue	

Printed with permission: Feldman M, *et al*. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 412.

- Give the causes of intra–abdominal abscesses (IAA), and 7 clinical risk factors.

  - Stomach or abdomen
    - Penetration and 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)

- Give the clinical risk factors for intra-abdominal abscess (IAA).
    - Systemic Factors
        - Chronic glucocorticoid use
        - Increasing age
        - Malnutrition
        - Preexisting organ dysfunction
        - Transfusion
        - Malignancy
    - Local Factors
        - Delay in performing surgery for underlying disease
        - Formation of an ostomy
        - Non–appendiceal source of infection
        - Severe of illness, infection
        - Severe trauma

Source: Feldman M, *et al*. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 26-1 and 26-2, page 412.

- Give the abdominal diagnostic imaging findings suggestive of IAA.
    - Plain films
        - Mass effect
        - Extraluminal gas
        - Localized ileus
    - Abdominal ultrasound
        - Round/oval mass with:
            - ↓central echogenicity (fluid, gas)
            - thickened walls
            - internal debris

*Note: The false negative findings may be due to overlying bowel gas blocking the ultrasound waves.

    - Computed tomography (CT) scan
        - Extraluminal mass homogeneous fluid density, or heterogeneous solid density if IAA contains phlegmon
        - Extraluminal gas
        - Thick wall enhancement
        - Adjacent inflammatory changes
    - Gallium 67 (^{67}Ga) or nuclear imaging scanning
        - Useful to follow–up CT scan
    - Magnetic resonance imaging (MRI)
        - 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% in normal individuals
  - 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 AAA is rare in patients with essential hypertension.
    - In patients with renovascular hypertension, an AAA is found in 77% with fibromascular disease, and 35% of those with atherosclerotic diseases.

Adapted from: Filate W, *et al*. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 33.

"Success is liking yourself, liking what you do, and liking how you do it."

Maya Angelou

- Give the characteristic findings in 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!

About 3 individuals in 4 have the classic triad for ruptures of a “triple A” (AAA, abdominal aortic aneurysm).

- Give the components of the triad:
    - Abdominal pain
    - Tender, pulsatile abdominal mass
    - Hypotension

- Give the two signs of abdominal wall discolouration which suggest the presence of an ectopic pregnancy, ruptured AAA and pancreatic necrosis.

    - Cullen Sign: Purple–blue discoloration around umbilicus, peritoneal hemorrhage; caused by acute pancreatitis, ectopic pregnancy

    - Grey–Turner Sign: Flank discolouration, retroperitoneal hemorrhage; caused by acute pancreatitis, ruptured abdominal aortic aneurysm (AAA), strangulated bowel

Adapted from: Filate W, *et al*. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 37.

SMALL BOWEL

BOWEL OBSTRUCTION

- Take a directed history for bowel obstruction.
- Abdominal pain (where, when, what, why, how), plus:
  - Associated symptoms
    - Appetite
    - Weight change
    - Nausea, vomiting (bilious, feculent, blood)
    - Jaundice, dark urine
    - Recent weight
    - Pale stools
    - Bloating
    - Borborygmi
  - 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
  - Large bowel
    - Cancer
    - Volvulus
    - Diverticulitis
    - Ileus
    - Narcotic ileus
    - Mesenteric ischemia
    - IBD with stricture
    - Ogilvie's syndrome
    - Adhesions
    - Intussusception
    - Endometriosis

Adapted from: Jugovic PJ, *et al*. *Saunders/ Elsevier* 2004, pages 58 and 59.

- Give the performance characteristics for a focused physical examination for bowel obstruction.
  - There are numerous abnormal physical findings which have been traditionally thought to be useful in diagnosing bowel obstruction:
  - The four best tests in terms of the value their positive likelihood ratio (PLR) are:
    - visible peristalsis (PLR, 18.8)
    - distended abdomen (9.6)
    - hyperactive (5.0)
    - 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

MCQ Alert

The diagnosis of mesenteric ischemia and ischemic colitis may be missed until late, when the bowel becomes necrotic or perforated. To encourage us all to have this diagnostic possibility at the front of our mind, this topic is often tested.

- In the MCQ stem, look for:
  - Several abdominal pain with minimal findings on examination of the abdomen
  - Risk factors for low flow, thrombosis or embolism causing mesenteric ischemia
    - Atrial fibrillation
    - Athrosclerosis
    - Vasculitis
    - Drugs, such as:
      - Digitalis
      - Cocaine
      - 5–HT3 antagonists
      - 5–HT4 agonists
      - Vasopressors
      - Octreotide

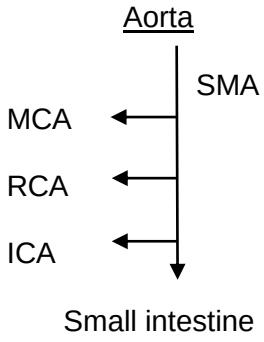
SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the histopathologic features suggesting a microangiopathic antiphospholipid–associated disorder causing ischemic colitis.
  - Vasculitis
  - Deposits of immune complexes
  - C3 complement
  - Fibrinogen

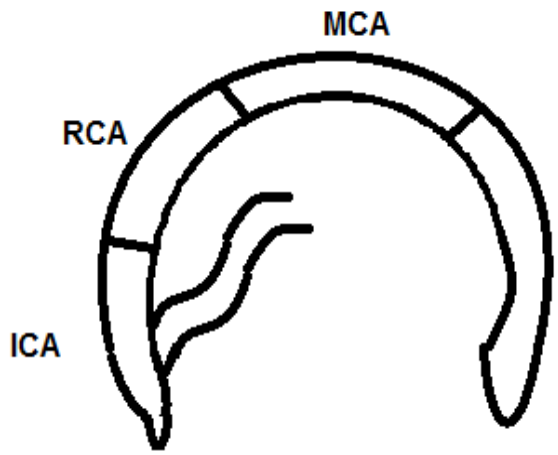
SUPERIOR MESENTERIC ARTERY EMBOLISM

- Superior mesenteric artery embolism (SMAE) causes about half of all cases of acute mesenteric ischemia (AMI).
- 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 the reasons for performing an emergent angiographic study rather than a CT scan of the abdomen in the patient with suspected superior mesenteric artery embolism (SMAE).
  - Angiography
    - Sensitive in 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); ICA, ileocolic artery (to proximal ascending colon)



CROHN DISEASE

➢ Clinical

- Give the differences between hereditary angioedema (HA), Familial Mediterranean Fever (FMF), and MR (Melkersson–Rosenthal) syndrome* (MRS).

Findings	HA	FMF	MRS
o Severe, recurrent abdominal pain	+	+	+
o Edema of lips and periphery	+	-	-*
o Familial	+	+	+
o Tongue swelling	+	-	+
o Facial paralysis	-	-	+

o Melkersson–Rosenthal syndrome (MRS) is a facial Crohn diseases with:
  - Recurrent tongue swelling
  - Fissured tongue
  - Granulomas on tongue biopsy
  - Facial paralysis

The timing of the use of anti–TNF for drugs chronic inflammatory CD is moving towards early introduction for patients suspected of being at risk for future severe disease.

- Give the risk factors for severe Crohn disease (CD).

o Patient
  - Age of onset <35 years
  - NOD positive
  - Smoking
  - Early need of steroid treatment

o Disease
  - Ileum
  - Fistula
  - Deep ulcers

MCQ ALERT

It is increasingly recognized that “attacks “ or flares of IBD may be associated with enteric infection, should you anticipate the MCQ asking whether you appreciate the association and are prepared to act upon, rather than on the reflex action of placing every IBD patient with recurrent symptoms on corticosteroids, immunosuppressants, or biological.

– Name the microorganisms that cause **recurrence** of IBD.

○ Toxin	– Clostridium difficile – Salmonella – Shigella – Campylobacter – Yersinia
○ Special request	– Escherichia Coli O157: H7
○ Ova and parasites	– Entamoeba histolytica, specifically in: ▪ First nations ▪ Patients visiting from endemic areas including Southern USA
○ Viruses	– CMV (cytomegalovirus)

A patient may have an increased risk of infection if they are being treated with immunosuppressants or anti–TNF therapy.

- Give the conditions associated with an **increased risk of infection** in the patient who is not receiving immunosuppressants.
  - Granulocytes (chronic granulomatous disease)
    - ↑ risk of invading skin infections
  - Cell–mediated defects (e.g. HIV infection, ↓ CD4 T cells)
    - Viral or fungal infections
  - Immunoglobulins
    - Encapsulated bacteria
  - Cystic fibrosis transmembrane conductance regulator (CFTR)
    - Infection of sinuses and lung
  - Complement deficiency
    - Neisseria meningitides gonorrhea

Adapted from: Board Basics 3, 2012, page 9.

A patient with inflammatory bowel disease (IBD) presents with pain in the groin, which is considered to arise from the hip.

- Give the causes of hip pain in the person with IBD.
    - Osteonecrosis (aka avascular necrosis)
    - Osteoporosis
    - IBD–associated arthritis
    - Trochanteric bursitis
        - Lateral joint tenderness
        - ↓ abduction

CLINICAL VIGNETTE

- Chronic diarrhea with abdominal pain and dyspepsia; ↑ WBC, platelets, CRP and ↓ hemoglobin; colonoscopy normal; EGD shows red particles which on biopsy reveals H. pylori negative focal gastritis. Give the most likely diagnosis.
    - Crohn disease of small bowel (proximal to "reach" by the colonoscope) and distal to the reach of the EGD

CLINICAL VIGNETTE

- Diarrhea with oral ulcers, anterior uveritis, genital ulcers, terminal ileal ulcers; it's not Crohn disease – what is it?
    - Behcet disease

➢ Treatment

- Prediction of azathioprine (AZA) toxicity
    - Immunosuppression. Consult *http://www.immunize.org/reports041.asp*
    - Genotype - TPMT only predicts early development (< 1 month) of leucopenia
    - Phenotype - IBD 6–TGN therapeutic benefit
    - 6–MMP risk of hepatotoxicity
    - If AZA od is causing elevated hepatic transaminases, try to half 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)
  - Inactivated vaccine does not exasperate disease activity in multiple sclerosis or in SLE (lupus); but more long–term studies on IBD is needed
  - Vaccinate for HPV available in young males, not just for females
  - Vaccinate all family members of IBD patient to protect everybody in the family, including the patient
  - MDs should be vacinated because the risk of active viremia to immunosuppressed 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 her 3rd trimester of pregnancy.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the IBD patient who fails to respond to adequate doses of AZA/6–MP, give the possible reasons why need to measure the metabolites of these drugs.
  - 70% – ↓ 6–TG: too low a dose
  - 25% – ↓ 6–TG + ↑ 6–MMP: predominant metabolism by TPMT
  - 5% – ↓ 6–TG + ↓6–MMP; poor adherence

- Give the pros and cons of the use of concomitant immunomodulators with anti–TNF therapy.
  - 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
    - Increase long–term toxicity
      - Serious infections
      - Risk of infections (across all trials)

Adapted from: Hanauer SB. *ACG Annual Scientific Meeting Symposia Sessions 2009*, page16-18.

CLINICAL ALERT

- In a woman with IBD who wishes to breastfeed her baby needs to **avoid** the use of:
  - Cipro'
  - Cyclosporine
  - Methotrexate

GASTROINTESTINAL FISTULAS

- Give the classification of fistulas.

  - Anatomic
    - Internal (e.g., ileocolic, colovesical)
    - External (e.g., enterocutaneous)

  - 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.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the prognostic indicators of successful spontaneous fistula closure.

Parameter	Spontaneous Closure Likely
○ Output (mL/day)	– < 500
○ Age (yr)	– < 40
○ Site	– Proximal small bowel
○ Nutritional status	– Well–nourished
○ Cause	– Anastomotic breakdown
	– No malignancy, inflammatory or infectious disease, no complete anastomotic dehiscence
○ Anatomic characteristics	– Long fistulous tract
	– No eversion of mucosa
○ Duration	– Acute

- Give the 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 stricturoplasty in CD, besides the relief of a partial small bowel obstruction.
  - ↑ regression
  - ↓ recurrence
  - ↑ mucosal healing

*Note
  - The successful use of octreotide to close intestinal fistulas has not been confirmed by randomized, placebo–controlled, double–blind studies, in terms of:
    - Closure of fistula
    - Rate of complications
    - Mortality rate

CORTICOSTEROIDS

- Prepare a patient with IBD for an informed consent for the use of steroids (GCS, glucocorticosteroids) 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
    - Facial erythema
    - Hirsutism
    - Acne
  - Dermatological
    - Buffalo hump striae
    - Necrotizing angiitis
    - Impaired wound healing
    - Petechiae, ecchymoses
    - Allergic dermatitis, urticaria, angioneurotic edema
    - Perianal burning
    - Hypo– or hyperpigmentation
    - Scarring, induration
    - Sterile abscesses
    - Cutaneous and subcutaneous atrophy

- MSK
  - Muscle wasting (steroid myopathy)
- Cardiovascular
  - Hypertension
  - Thromboembolism, fat embolism
  - Hypercholesterolemia
  - Accelerated atherosclerosis
  - K^+ deficiency → cardiac arrhythmias
  - Cardiac rupture after MI (myocardial infarction)
- GI
  - Interaction with peptic ulcer disease
  - Cautions in concurrent use of steroids with ASA/NSAIDs to increase INR
  - Anorexia, nausea, vomiting
  - Increased or decreased appetite → change in body weight
  - Increased or decreased BMs (bowel movements)
  - Ulcerative esophagitis
  - Perforation of small bowel or colon (especially in IBD)
- Adrenal glands
  - Risk of adrenal insufficiency (if GCS is quickly withdrawn)
- Kidneys
  - 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 HF (heart failure)
  - Hypokalemic alkalosis
  - Hypocalcemia
- Bone
  - Osteoporosis
  - Fractures
  - Avascular (aseptic) necrosis (more likely in rheumatoid arthritis or lupus)

- Endocrine
  - Pancreas
  - Type II diabetes, adipose cells
  - Obesity
  - Increased requirement for injectable or oral insulin
  - Hypoglycemia in diabetis
  - Secondary adrenocortical and pituitary responsiveness in stress situations
  - Menstrual irregularities
  - Increased sweating
  - Protein catabolism
- Infections
  - Activation of amebiasis, TB
  - Suppression of skin 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, ↓lymphocytes, ↓platelets
  - Thrombophlebitis
- Pregnancy
  - Possible increased risk of oral cleft in fetus
  - Possible hypercortisolism effects in fetus of pregnant mothers on high dose steroids

IMMUNOSUPPRESSION

- Give hepatic conditions associated with the use of azathioprine or 6–MP.
  - Fatty liver
  - 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.

CLINICAL CHALLENGE

A patient with acute Crohn disease (CD) requires steroid therapy (glucocorticosteroids), immunosuppressants and/or anti–TNF therapy. She is an HBV positive carrier. Give the therapeutic management of the CD and HBV.

- These therapies can cause flare of the disease activity and hepatic decompensation in 50% of patients, regardless of HBV DNA level.
- Hopefully, the HBV status was diagnosed before treatment for the active CD began.
- Ideally then, the therapy for HBV is started before prednisolone, immunosuppressants or anti–TNF therapy (or before chemotherapy) if that is a relevant consideration in a different patient.
- Nucleoside or nucleotide therapy is given in the duration of the CD therapy, plus 6 months longer.
- *Note that it is the interval when the dose of prednisolone is being tapered when the HBV carrier is at risk for a flare.

Azathioprine dosing and metabolism

	6–TG	6–MMP
Intake		
– ↓ (poor compliance)	↓	↓
– ↑ (overdose)	↑	↑
TPMT activity ↓/o inheritance low		
– low (9%)	↑	↓
– ↑ high / high (1%)	↓	↑

- Give the implication of ↑ 6–MMP (> 5700) due to overdosing, or to highlight TPMT.
  - ↑ 6–MMP - ↑ hepatotoxicity

CELIAC DISEASE

Is there a “best” test to diagnose celiac disease?

- Possibly not tissue transglutaminase (tTG)
  - False positives and false negatives of ~5%
- Not serum anti–glutaminase
  - False negatives of ~10-15%
    - Patient is not recently on a gluten free diet, NPO, on immunosuppressants or had a bone marrow transplantation
- Insufficient number of biopsies (6)
  - False positives may be seen in IBD, chronic liver or autoimmune disease, or severe CHF
  - 4 to 6 duodenal or jejunal mucosa biopsies is the correct answer, although beware
    - The mucosal biopsy may be compatible with celiac disease, but there are no pathognomonic features.

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 patients with symptomatic celiac disease increases and varies from 1.26 in Finland to 3.6 in Sicily (Biagi & Corazza, 2010).

Dermatitis Herpetiformis

- Definition
  - Bilateral, symmetrical, dry and itchy vesicles or urticarial plagues on extensor surfaces, neck, back, buttocks, elbows, knees

- Associations
  - Celiac disease
  - GI lymphoma
  - Hypothyroidism; More details in *www.giandhepatology.com*, ISBN 978-1500855321

ACUTE DIARRHEA

Acute diarrhea is usually caused by drugs and toxins or enteric infections, and may be initially presented with a condition, wherein over time, will become chronic and associated with diarrhea.

MCQ ALERT: The treatment Noose

The stem of the MCQ describes the patient with sudden onset of diarrhea and you are informed of the duration after the onset of diarrhea until the patient sees you. He asked what treatment to use. Watch out! – This is where they may put a noose around your neck.

Ingestion	Time (hr) of onset of symptoms after ingestion	Likely organism
----------→	6	Staphylococcus aureus
		Bacillus cereus
----------→	8 to 12	Clostridium perfringes (canned food)
----------→	14	Virus, e.g. rotavirus, Norwalk, ETEC, EHEC (O157:H7)

Caution – The Treatment Noose

- EHEC
  - No antibiotics
  - No antidiarrheals (loperamide, diphenoxylate)
- C. difficile
  - No antidiarrheals → toxic megacolon

→ EHEC → HUS/TTP

- HUS, TTP ←----- EHEC ←------- antidiarrheals, antibiotics

Abbreviations: TTP, thrombocytopenic thrombotic purpura; HUS, hemolytic uremic syndrome; EHEC (O157: H7), enterohemorrhagic E. coli); ETEC, enterotoxigenic E. coli

ENTERIC INFECTIONS

- Give the indications for stool cultures in patients with acute diarrhea.
  - Acute diarrhea
    - Outpatients
      - > 3 days (for symptoms < 3 days, stool cultures do not change management)
    - Inpatients
      - In hospital > 3 days, do not obtain stool cultures
  - C. difficile stool cultures
    - Liquid
      - Active toxin producing infection
    - Solid
      - Colonization

➢ Causes of acute diarrhea

  - Preformed toxin ingested
    - Upper GI symptoms within 6 hours
      - Staphylococcus aureus
      - Bacillus cereus
  - Viable bacteria ingested
    - Diarrhea with or without blood
      - Within 1 to 3 days
        - Suspected organism depends on risk factors

- Give the risks for acute infectious diarrhea, and 10–linked infectious organisms.
  - Bloody stools
    - Salmonella
    - Shigella
    - E. coli
    - Shigella toxin–producing E. coli (STEC):
      - O157:H7
      - O104:H4
    - Campylobacter
    - Entamoeba
  - Suspected acute appendicitis
    - Yersinia

- Setting
  - Day care, residential facilities
    - Shigella
    - G. lamblia
    - Norovirus
    - Rotavirus
  - Cruise ship
    - Norovirus
  - Travel to developing countries
    - All causes of Traveller's diarrhea
  - Hospital
    - Clostridium difficile
- Foods
  - Eggs
    - Salmonella
  - Undercooked food, poultry
    - Campylobacter
  - Pig guts
    - Yersinia
  - Shellfish
    - Aeromonas
    - Plesiomonas
  - Seafood
  - Seawater
    - Vibrio
  - Antibiotics
    - C. difficile
- Pets
  - Reptiles
    - Salmonella
  - Puppy and kitten with diarrhea
    - Campylobacter

Cryptosporidium

- Associations
  - Immunocompetent and immunocompromised
  - Recreational water exposure
  - Viable oocytes ingested
  - Site
    - Day care
    - Nursing home
    - Fecal–oral (poor hand sanitation)

- Complication
  - Acalculous 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

- Give the location of Isospora and Cryptococcus on small bowel biopsy.

	Isospora	Cryptococcus
○ Brush border membrane	+	+
○ Intracytoplasmic vacuoles	+	-

Giardia

- Diagnosis
  - 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.

Neisseria gonorrhoeae

- Demography
  - High rate in
    - Sexually active young women
    - Men who have sex with men (MSM)
- Clinical (in addition to cerviates, urethritis, proctitis)
  - Pharyngitis
  - Disseminated gonococcal infection (DGI)

- Give the clinical presentation of disseminated gonococcal infection (DGI).
  - Fever
  - Joints
    - Migratory polyarthralgia
    - Tenosynovitis
    - Monoarticular septic arthritis
  - Skin
    - Several necrotic vesicopustulus on a red base

➢ Diagnosis
- Smear of discharge with intracellular gram–negative diplococci, NAA test
- Swab cervix, urethra, rectum, pharynx culture
- Look for co–infection with C. trachomatis
- Screen sexual partners

➢ Treatment
- Ceftriaxone, 250 mg IM one dose, plus
- Azithromycin, 1 g po one dose, or
- Doxycycline, 100 mg po bid fo 7 days
- For disseminated infection, ceftriaxone, 1 g IM / IV q 24 h, or
- Cefotaxime, 1 g IV q 8 h, or
- Ceftrizoxime, 1 g IV q 8 h

Condylomata acuminata

➢ Cause
- Human papillomavirus (HPV), serotype 6 and 11

➢ Clinical
- Exophytic pedunculate hyperkeratotic lesions (Genital Warts)

➢ Treatment
- Males
  - Age 12 years
  - 3 doses of quadrivalent HPV
  - Catch–up males with age 19 to 21 years
  - MSM
  - HIV infection
  - Immunosuppression
- Females 19-26 years

TRAVELLER'S DIARRHEA

- Causes
  - Bacterial
    - Campylobacter
    - Escherichia coli
    - Salmonella
    - Shigella
  - Viral
    - Rotavirus
  - Protozoal
    - Cryptosporidium
    - Giardia lamblia
    - Isospora
    - Microspora

- Treatment

Drug	Prevention	Treatment 3 day
Ciprofloxacin	500 mg OD	500 mg bid
Norfloxacin	400 mg OD	400 mg bid
Rifaximin	200 mg od or bid	200 mg tid
Bismuth subsalicylate	2 tablets chewed qid	1 oz q 30 min for 8 doses

Please see standard textbook or recent reviews such as MKSAP 16, Infectious disease 2012, Table 35, page 63.

- Antidiarrheal agents given only when antibiotics are necessary, but generally not especially when diarrhea is bloody.

Campylobacter

- Undercooked food, especially poultry
- Bloody diarrhea in 10%
- Associated with
  - Reactive arthritis
  - Gullain–Barre syndrome

- Treatment
  - Indications
    - Very young or old
    - Co–morbidities
    - Immunosuppression
    - Symptoms
      - Severe
      - > 7 days
  - Antibiotics
    - Azithromycin or erythromycin
    - In low fluoroquinolone resistant areas

Shigella Infection

- Cause
  - Shigella
    - Dysentery
    - Boydii
    - Flexneri
    - Sonnei
- Clinical
  - Outbreaks
    - Day care centers
    - Residential facilities
  - Bloody diarrhea
  - Reactive arthritis
- Treatment
  - Fluoroquinolones for positive stool cultures, even if symptoms resolved

Once a microbial diagnosis of Shigellosis is made, even in asymptomatic patients, treatment with ciprofloxacin is recommended.

- Give the reason why Shigellosis is always treated.
  - Ciprofloxacin reduces the risk of infection being transmitted to others.

Salmonella

- Cause
  - Salmonella enteritidis (aka S. enterica serotype Enteritidis)
- Clinical
  - Typhoidal Traveller's diarrhea
  - Non–typhoidal
    - Undercooked or raw egg consumption
    - Contaminated meat, poultry
    - Exposure to reptiles
    - Bacteremia (5%) → aortitis
    - Osteomyelitis
  - Risk factors
    - Age > 65 years
    - ↓ gastric acidity
    - Immune suppression
    - Sickle cell disease
- Treatment
  - Antibiotics
    - < 6 mon or > 50 yr
    - Severe disease
    - Immune suppression
    - Heart
      - Prosthetic heart valves
      - Atherosclerosis (risk of infectious arteritis)
    - MSK
      - Prosthetic joints
    - Kidney
      - Chronic kidney disease (CKD)
    - Blood
      - Sickle cell disease
  - Duration
    - Fluoroquinolones
    - 1 wk, longer for ↓ cellular immunity
  - Hand hygiene to ↓ person–to–person transmission → secondary salmonella infection

Esherichia coli

- Name the 5 strains of E. coli that cause diarrhea, and its associated type of bloody diarrhea (AIPTT E. coli).

A	EAEC	Enteroaggregative
I	EIEC	Enteroinvasive
P	EPEC	Enteropathogenic
T	ETEC	Enterotoxigenic
T	STEC	Shiga–toxin producing

  - STEC (O157:H7; O104:H7) and EIEC cause bleeding
  - O157:H7 10% develop hemolytic uremic syndrome (HUS)
    → Renal failure
    → Hemolysis
    → Thrombocytopenia

➢ Diagnosis
  - Stool cultures are helpful only for STEC (O157:H7)
  - Culture medium for STEC is Sorbitol–MacConkey agar
  - Immunoassay useful for O157:H7 and O104:H4

➢ Treatment
  - Clinical Alert
    - Do not use antibiotics for E. coli–associated diarrhea if caused by STEC O157:H7
    - Antibiotics shorten the duration of diarrhea for STEC-O157:H7 E. coli, as well as increase the risk of HUS

Yersinia

➢ Cause
  - Yersinia enterocolitica
  - Y. pseudotuberculosis
  - Yersinia pests → plaque
  - May mimic appendicitis (from infection of Peyer's patches and mesenteric lymph nodes)
  - Associated with post–infections
    - Reactive arthritis
    - Erythema nodosum

➢ Diagnosis
  - Special medium

- Treatment
  - Symptoms
    - Severe
    - Prolonged
  - Antibiotics
    - Fluoroquinolones

CLINICAL ALERT

- Appendicitis–like symptoms, suspect Yersinia enterocolitica

Vibrio Infection

- Cause
  - Vibrio cholera
  - V. parahaemoliticus
    - Common in N. America
    - Severe with cirrhosis
  - V. vulnificus
  - Contaminated raw shellfish
- Treatment
  - Severe infection or individuals with cirrhosis:
    - Doxycycline, or fluoroquinolones

Clostridium difficile

- Clinical
  - Diarrhea is usually non–bloody
  - Fever and leukocytosis (> 30 x 10^9/L) occurs

Pearl and Gem

Clostridium difficile antibiotic–associated diarrhea (CDAAD) presents with the following symptoms other than diarrhea:

- Fever
- Rectal bleeding
- Ileus

- Asscociations
  - Use of
    - Antibiotics in the past 8 weeks
    - Chemotherapy
    - PPIs / H2RA (small risk)
  - IBD (inflammatory bowel disease)
  - Poor hand–washing, especially in hospital
  - Severe disease caused by NAP1 or BI or O27

Abbreviations: H2RA, H2 receptor antagonists; PPIs, proton pump inhibitors

- Diagnosis
  - Endoscopy
  - Stool–cultures, with special testing, detect toxins A and B
    - ELISA for toxin A and B
    - Two step method
      - Immunoassay for glutamate dehydrogenase (GDH), and if positive, then either
      - Cytotoxicity assay, or
      - Culture for toxins
    - PCR for toxin–producing genes

- Risk factors

C. difficile is a “big deal” organism these days, because of its wide range of disease scopes, as well as its morbidity and mortality. Usual **risk factors** are:

- Dirty hospitals
- Dirty hands
- Recent use of antibiotics

But there are new risk factors on the block:

- Anybody, even healthy individuals in the community
- Recent use of PPIs
- Postpartum women
- Hand washing with alcohol–containing dispensers which are now found throughout most hospitals (only soap and water destroys C.difficile)
- Patients with UC and CD

Abbreviations: UC, ulcerative colitis; CD, Chronic disease; PPIs, proton pump inhibitors

CLINICAL ALERT

- A normal colonic mucosa on sigmoidoscopy does **not** exclude C. difficile infection beyond the reach of the scope, in the colon or small intestine.

GEMS and PEARLS

- Why it is not appropriate to test the formed stools for C. difficile?
  - Asymptomatic colonization occurs and does not require treatment.
- Why it is wise to consider C. difficile infection in the appropriate setting, even then there is no diarrhea.
  - If the colon is dilated or there is an ileus associated with a CDI, then there may be no diarrhea due toa enteropooling.

➢ Treatment

○ Prevention	-	Frequent hand wshing with non–alcoholic soaps
○ Mild / moderate	-	Metronidazole 500 mg po q 8 h, for 10–14 d
○ Severe	-	Vancomycin 125 mg po q 6 h, for 10–14 d
○ Severe plus hypotension or with multi-origin system failure	-	Vancomycin 500 mg po q 6 h, for 10–14 d, plus - Metronidazole 500 mg IV q 8 h, for 10–14 d
○ Sever plus ileus / toxic megacolon	-	As above (vancomycin plus metronidazole) plus vancomycin PR (rectal tube)

GEMS and PEARLS

- Give the manner of administration of vancomycin if the patient has nausea and vomiting.
  - By nasogastric or rectal tube
- Give the role of enthusiastic and frequent hand washing with alcohol–based hand sanitizers to ↓ risk of C. difficile infections (CDI) in hospitals.
  - None; CDI prevention requires washing with soap and water

➢ Recurrence

- About 20% of patients with CDI have a recurrence
- For the first recurrence, retreat as per initial episode, but carefully access severity (e.g., consider using vancomycin instead of or with metronidazole)

	Drug	Dose	Duration
○	Vancomycin	125 mg PO qid	10–14 d
		125 mg PO bid	7 d
		125 mg PO od	7 d
		125 mg PO q 2-3 d	2–8 wk

Adapted from: Infect Control Hosp Epidemiol 2010; 31: 431-455.

MCQ Alert: Fidaxomicin is a newly approved for CDI and is as effective as vancomycin. Although much more expensive than already costly vancomycin, it has not been as well studied, but may still appear on a multiple–choice question.

- Fecal transplantation
  - Evidence for treatment of resistant / recurrent C. difficile–associated colitis

TPN CATHETER–RELATED INFECTIONS

- Prevention
  - Chlorhexidine skin cleaning
  - Antibiotic–coated catheters, dressings
  - Catheter–care team, e.g. TPN team

- Indications for Treatment

	Cultures		Antibiotic	Catheter
	Catheter	Blood	treatment	removal
○ Colonization	+	-	No	-*
○ Catheter–related bacteremia	+	+	1–3 wk	+/-
○ Complications	+	+	4–6 wk	+
	Skin site culture			
○ Exit–site	+	-	1 wk	+/-
○ Tunnel	+	-	1–3 wk	+/-

* Catheter positive, blood culture negative, or transiently positive for coagulase–negative staph' bacteremia

- Anti–microbials
  - Vancomycin is for MRSA or no coagulase–positive Staphylococcus
  - Neutropenia or sepsis
  - Candidemia
    - Fluconazole
  - Candidemia with sepsis
    - Amphotericin B or echinocandin especially if caused by Candida tropicalis, C. keusei

- Give the indications in performing transesophageal echocardiography (TEE) in patients with catheter–related infection.
  - Blood culture positive for S. aureus
  - Signs of endocarditis, such as new murmur

FEBRILE NEUTROPENIA

PEARLS and GEMS

- A patient with febrile neutropenia and right lower quadrant (RLQ) tenderness → think typhlitis, and do CT of abdomen (not OC [optical colonoscopy]).

VIRAL GASTROENTERITIS

- Causes
  - Child < 5 yr
    - Rotavirus
  - Others
    - Norovirus
  - Outbreaks in day cares, schools, ships, care facilities
- Clinical
  - Fever in 50%
  - Diarrhea may last > 3 d in:
    - Older persons
    - Immunocompromised
- Treatment
  - Supportive care

Patients 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.
  - Epstein–Barr lymphoproliferative disease (EBV–LPD)
  - De novo cancer of non–lymphomatous origin

CLINICAL VIGNETTE

- Case: Diarrhea on a cruise ship
  - Norwalk virus
- Case: Bloody diarrhea, HIV+, saddle distribution paresthesia. Give the most likely diagnosis.
  - HSV proctitis
- Case: Diarrhea with anemia, ↑ MCV, found in Puerto Rica. What is the diagnosis?
  - Tropical sprue

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- EBV does not usually form mucosal ulcers and cause GI tract bleeding. Give the exception of this "rule".
  - When Epstein–Barr lymphoproliferative disease (EBV–LPD) develops, ulceration and bleeding may occur.
  - This is the cause of post–transplant lymphoprolifertive disorder (PTLD), a B or T cell lymphoma, which require reduction of immunosuppressive drug, rituximab.

PARASITIC INFECTIONS

- Fecal excretion of parasites may be intermittent so 3 stool cultures are needed for O/P (ova and parasites)

Blastocystis

- Unclear whether this protozoa is a pathogen
- Treat for diarrhea > 7 days

Giardia Lamblia Infection

- Diagnosis
  - Campers at risk
  - Stool
    - Culture
    - Antigen testing
- Clinical
  - May be asymptomatic and cleared spontaneously in 50%
  - Patient with hypogammaglobulinemia may have longer or more severe clinical course
  - Symptoms of lactose intolerance may persist for months, even after clearing the infection
- Treatment
  - Symptomatic persons
  - Antibiotics
    - Metronidazole 7–10 days
      - Tinidazole
      - Nitazoxanide
      - Mebendazole
      - Albendazole
  - Second line therapy

CLINICAL VIGNETTE

- Case: Diarrhea, exposure to Beavers, sprue-like biopsy, “eyelike” nuclei in flagellated trophozoites. Give the likely diagnosis.
  - Giardiasis

Cryptosporidium

- Cause
  - Protozoa *Cryptosporidium parvum*
- Course
  - Often asymptomatic
  - In immunosuppressed persons
    - More
      - Severe
      - Prolonged
    - May be associated with acalculous cholecystitis

- Diagnosis
  - Serological testing
  - Stool culture; requires acid–fast stain
- Treatment
  - Nitazoxanide for severe symptoms
  - For disease states associated with HIV infection

Amebiasis

- Cause
  - Protozoa *Entamoeba histolytica*
  - Shedding of cysts may be prolonged
- Course
  - Invasive disease
    - very young / old
    - Immunosuppression
    - Hemorrhagic colitis
    - Amebic liver abscess

Diagnostic Pearl

The *E. histolytica* infection is localized in the liver (abscess) and not in the lumen of the intestine (surprise!), the stool cultures may be negative and serology is required to make the diagnosis.

- Treatment
  - Indication
    - Both symptomatic and asymptomatic persons
  - Antibiotics
    - Metronidazole followed by paromomycin or iodoquinol

WHIPPLE DISEASE

- Name 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

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

➢ Diagnosis

In the diagnosis of small bowel bacterial overgrowth (SIBO), the jejunal aspirate (JA) is the "gold standard".

- Explain why this needs to have a second thought.
  - ○ False negative JA
    - – SIBA in the distal end of aspirating tube
    - – Recent use of antibiotics
    - – Species of bacterial aspirate which is not described or cultivated (use DNA fingerprinting)
  - ○ False positive JA – Contamination by oral or gastric organisms

- Give the pathogenesis of a "double peak" in a positive lactulose hydrogen breath test for SIBO.
  - ○ 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.

- 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.
  - ○ 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 are not associated with enteropathy

- Immunodeficiency-Related Lymphoma
  - Post–transplantation
  - HIV–associated

Abbreviations: HIV, human immunodeficiency virus; IPSID, immune-proliferative 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!

A middle–aged male smoker presents with symptoms suggestive of motility disorders of the esophagus, stomach, small bowel and colon.

- Give the serum biochemical measurements that would help the diagnosis and its affected organ.
  - This man most likely has a paraneoplastic lung tumor, with cross–reacting autoantibodies from the tumor causing an inflammatory infiltrate and neuronal degeneration of the myenteric plexus.
  - 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)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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.

○ Esophagus	– Stomach – Lung
○ Stomach	– Breast
○ Pancreas	– Lung – Kidney – Luminal GI
○ Small bowel	– Stomach – Pancreas – Biliary tree – Kidney – Retroperitoneum – Melanoma

➢ Classification

- 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
    - Immuno–Proliferative Small Intestinal Disease (IPSID)
    - Lymphoproliferative disorders
    - HIV–associated non–Hodgkin lymphoma
    - Primary effusion lymphoma

- **Immunoproliferative Small Intestinal Disease** (IPSID)
  - 2 heavy–chain disease or Mediterranean Lymphoma
  - Plasma cells secrete 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*, stimulates lymphocytes in the small intestine, resulting initially in a monoclonal response.
- Management for IPSID:
  - Stage the disease properly
  - For early stage
    - Nutritional care
    - Antibiotics
      - Tetracycline, or
      - Metrodinazole and ampicillin
  - For lack of response to 6 months of the above treatment,
    - Chemotherapy

- Give the features which distinguish IPSID from MALT–lymphoma.

Features	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.

- **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 leukocyte infusions (PTLD following allogeneic bone marrow transplantation)

- **Enteropathy**–T**ype Intestinal Cell Lymphoma** (**EITL**)
  - The normal polyclonal $CD3^+$/ $CD8^+$ intraepithelial (IE) T–cells undergo 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.
  - The results:
    - Refractory celiac disease, type I and II
    - Ulcerative jejunitis (may progress to EITL
    - enteropathy–type intestinal T–cell lymphoma (EITL)
  - Monoclonal T–cells may be seen adjacent non–involved mucosa
  - Large, highly pleomorphic cells with numerous, bizzare, multinucleated forms
  - Single or multiple sites, ulcerating or circumferential
  - Demonstrated in ^{18}F-FDG

GASTROINTESTINAL STROMA TUMORS (GIST)

- Demography
  - Prevalence $1/10^5$
  - Precursors of cells of Cajal are similar to the cells which form GISTs
  - GISTs are the most common form of sarcoma in the GI tract

- Genetic
  - Great diversity in the molecular pattern of GISTs (family of molecular subtype disease)
  - KIT mutation in 85%
    - Small bowel, exon 9
    - Stomach, colon, exon 9

➢ Pathology

- Site
  - GISTs have some histological features and common precursor cell to ICCs (interstitial cells of Cajal)
  - Often in muscularis mucosa
  - Stomach (60%), small bowel (30%), duodenum (5%), colon (<5%)
  - Colonic GISTs are most aggressive: colon > small bowel > stomach
  - Malignancy diagnosed by:
    - Size > 2 cm
    - # of mitoses, > 5/hpf

- Histologically
  - Spindle cell, 20%
  - Epithelioid or round cell, 30%

- Special studies
  - 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 immunohistochemical (IHC) assay in > 95% of GISTs (*Note: normal ICCs and mast cells express CD117)
  - CD34 positive stem cells in the wall of the intestines seen in 2/3 of patients

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the immunohistochemical (IHC) strains which help to distinguish GISTs, leiomyosarcomas and schwannomas?
  - Leiomyosarcomas positive for both smooth muscle actin (SMA) and desmin, negative for CD117
  - Schwannomas, positive for S100 (a neural antigen), CD117 negative
  - GISTs are usually (>95%) CD117 positive

- Give the non–KIT signals for those GISTs, which are KIT–negative.
  - Mutational activation and aberrant signaling from platelet–derived growth factor receptor–alpha (PDGFRA)

- Diagnostic imaging
  - The prognosis of a GIST is not determined by its histology, but rather on the size and number of mitosis.
  - On EUS, the features of GIST 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

- Treatment
  - GISTs are resistant to chemotherapy because of the expression of MDR–1 gene, increased levels of P–glycoprotein and multidrug resistance protein (pumping some drugs out of cells).
  - Inhibitors of KIT, RTK and PDGFR: Imatinib mesylate; Gleevec ®, Glivec ®), or other kinase inhibitors (Sunitinib).
  - Treatment for pain or focal bleeding (bleeding bulky vascular tumor) is intensity modulated radiotherapy (IMRT) or proton beam radiation.
  - Surgery for early–stage localized GISTs, followed by adjuvant (postsurgical resection) is Imatinib.
  - 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 and not on CT.
  - Bleeding from GIST occurs only when tumor is bulky (5%).
  - AEs of TKI: dyspepsia, rash, diarrhea, pain
  - Causes of non–responsive to imatinib
    - Primary KIT$^-$, PDGFRA$^-$
    - Secondary emergence of new secondary mutations
  - Non–responsive to imatinib, use sunitinib, nilotinib, or regorafenib

GASTROINTESTINAL CARCINOID TUMORS (GASTROINTESTINAL NEUROENDOCRINE TUMORS, GI NETS)

Causative curiosity MCT Disorders

- The mixed connective tissue disorders may be associated with microangiopathic antiphospholipid–associated syndromes, such as systemic lupus erythematosus (SLE).

- Demography
  - Incidence, 5/10^5 per year; prevalence 35/10^5

- Definition
  - A worsening of carcinoid syndrome|:
    - Hypo- or hypertension
    - Tachyarythmias
    - Bronchospasm
    - Flushing
    - Hyperglycemia

- Give the management of the patient with known carcinoid syndrome to avoid carcinoid crisis.

- Management
  - IV fluids
  - Octreotide (IV treatment during surgery, SC as pre– and post–op care)
  - Glucocorticosteroids
  - BEWARE – avoid pressors which may worsen the crisis by further releasing serotonin and other peptides

- Pathophysiology

SO YOU WANT TO BE A GASTROENTEROLOGIST!

GI NETs are associated with gene point mutations, deletions, methylation, as well as chromosomal gains and losses.

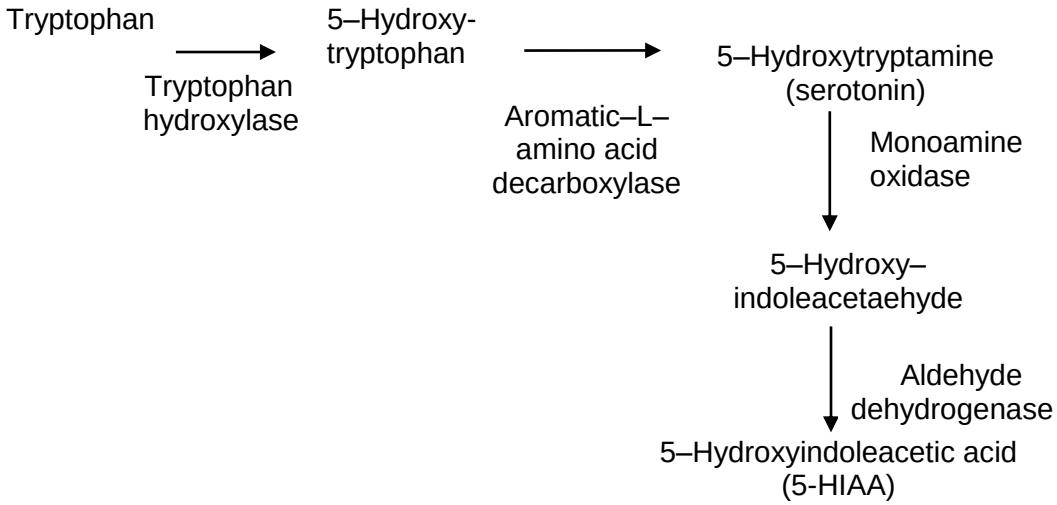
- Give examples.
  - Foregut (stomach)
    - MENIN gene (tumor suppressor gene), common in MEN–1 syndrome
    - MENIN intracts with numerous factors such as the AP1 transcription factor, JUN D and NF–κβ
    - Loss of heterozygosity on chromosome II in MEN–1 gene
  - Mid–gut (small intestine)
    - Deletions on chromosome 18
  - Hind–gut (colon)
    - TGF-α
    - EGF
  - Others
    - MAGE D2
    - MTA1

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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.

Synthesis of serotonin (5–hydroxytryptamine [5–HT]) 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.

➢ Pathology

- Site
  - GI tract, 67%
  - Lungs, 25%
  - Other sites: hepatobiliary, pancreas, testes, ovaries

- Histopathology
  - GI–NETs are related to medullary carcinoma of the thyroid, pheochromocytoma or the adrenal gland, and pancreatic neuroendocrine tumors (P–NETs).
  - Obstruction from mesenteric fibrosis, 50%
  - Ischemia from thickening of the 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 or insular (common in small intestinal)
  - Trabecular
  - Acinar or tubular
  - Atypical solid
  - Mixed
- Definition of enterochromafin (EC) cell carcinoid
  - Staining: silver (argentaffin)
  - Production: serotonin
- Markers which are positive for EC cell carcinoids
  - Chromogranin A
  - Synaptophysin
  - Leu 7
  - NSE (neurospecific endolase)
  - VMAT–1 and –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)

- Special studies

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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 the pathological features which help to distinguish the type III sporatic tumors from the type I and II gastric NETs.

Pathological Features	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!

- Give the most common NET (carcinoid tumors) in the duodenum.
  - Gastrin, 70%
  - Somatostatin, 25%
  - Gangliocytic paraganglioma, 5% (a benign humartoma)

- Give the cytosolic markers of poorly differentiated GI–NET.
  - NSE (non–specific endolase)
  - PEP 9.5
  - Synaptophysin (marker for synaptic–like vesicles)

➢ Clinical

- Perform a focused physical examination for carcinoid syndrome.

○ Face	– Telangiectasia – Flushing – Tearing – Periorbital edema
○ Lung	– Wheezing (bronchial carcinoid)
○ Heart	– Tricuspid or pulmonary regurgitation and stenosis – Aortic or mitral stenosis and regurgitation – HF – Endocardial fibrosis
○ Liver	– Hepatomegaly ▪ HF ▪ Metastases – Pulsation, bruit ▪ TR

Abbreviation: CHF, congestive heart failure; TR, tricuspid regurgitation

CLINICAL VIGNETTE

- Case: Recurrent crampy abdominal pain and small bowel obstruction; hypercalcemia; dyspepsia with hypergastrinemia; flushing. Give the likely diagnosis.
  - Carcinoid tumor associated with MEN–1 (gastrinoma → ↑ gastrin; parathyroid adenoma → ↑ Ca^{2+})

CLINICAL VIGNETTE

- Case: Small gastric tumor, right–sided congestive heart failure; flushing; ↑ serum chromogranin A. Give the most likely diagnosis.
  - Carcinoid syndrome

- Treatment
  - Surgery
    - Resection
    - Hepatic resection
    - Liver transplantation
  - Chemotherapy
    - Systemic
    - Transcatheter arterial chemoembolization (TACE)
  - Somatostatin analogs (to improve symptoms)
  - Interferon–α (may be combined with somatostatin analogs)
  - New agents
    - Biologic
      - VEGF inhibitor (Bevacizumab)
      - mToR inhibitor (RAD 001)
    - PRR T (peptide receptor radionucleotide therapy)
      - 90 Y – DOTA octreotate,
      - 177 Lu – DOTA octreotate

- Give the 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 (metaiodo-benzylguanidine), 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.

DIARRHEA AND MALABSORPTION

Diarrhea

- Take a directed history for diarrhea.
    - Stools
        - Timing (duration, onset, and course)
        - Frequency
        - Aggravating and 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 and 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 of 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!

- 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.
  - 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)
  - Serum
    - Hypokalemia (senna)
  - Stool
    - ↑ fecal osmotic gap
    - ↑/ ↓ osmolality (addition of hypertonic urine, or of water)
  - Sigmoid mucosa
    - Pseudomelanosis coli (anthracene)

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Medullary carcinoma of the thyroid (MCT) is often associated with diarhea.

- Give the causes of diarrhea in medullary carcinoma of the thyroid (MCT).
  - ↑ calcitonin
  - ↑ VIP
  - ↑ prostaglandins
  - ↑ rate of colonic transit (etiology is unknown)
  - Men II
    - Hyperparathyroidism (usually causes constipation, rather than diarrhea)
    - Pheochromocytomas

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).

- Give substances which can cause chronic diarrhea when SOG > 50.

  - 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 SOG > 50
    - Carbohydrates
      - Lactose – milk
      - Sucrose, Fructose] soda, pop, sweeteners
      - Sorbitol – chewing gum, diabetic candy
      - Lactulose – laxative
      - Trehalose – mushrooms
    - Magnesium–laxatives

*Note: It is not understood why Mg causes an ↑ SOG

- In the context of chronic diarrhea and SOG > 50 mOsm/kg, indicate how to distinguish patients' use of sorbitol versus magnesium.

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)

Intestinal Lymphangiectasias

- ➢ Causes and associations
  - ○ Child
    - – Autosomal dominant
      - ▪ Primary lymphangiectasias
  - ○ Adult
    - – Secondary to
      - ▪ Heart Failure
      - ▪ Abdominal – lymphoma
        - – Other malignancies
      - ▪ Tuberculosis
      - ▪ Sarcoidosis
      - ▪ Whipple disease
      - ▪ Miscellaneous fibrotic conditions e.g. retroperitoneal fibrosis
- ➢ Pathology
  - ○ Gross / Endoscopy
    - – white spots (fat–filled dilated lacteals)
  - ○ Small bowel biopsy
    - – Fat globules present in enterocytes and villi
    - – Lymphocytic infiltration

SO YOU WANT TO BE AN ENDOCRINOLOGIST!

Apolipoprotein B is contained in chylomicrons, low density lipoprotein (LDL) and very low density lipoproteins (VLDL). Lack of apoprotein B results in recessive disorder, and abetalipoproteinemia. Abetalipoproteinemia is characterized by steatorrhea, ataxia, atypical acanthosis pigmentosa, acanthotic red blood cells, and absence of chylomicrons in the serum, LDL and VLDL. Give the histological features of abetalipoproteinemia seen on small bowel biopsy.

- Mucosal cells – Abundant lipid droplets
- Submucosa and lamina propria – Little lipid

MCQ Heads Up: “Guess what I’m thinking?"

The patient has chronic diarrhea.

Added information	You need to think of:
Perianal disease, smoking	Crohn disease
Irish, DH, iron deficiency	Celiac disease
Immune suppressed	Enteric infection
Dyspepsia treated with PPI	Drug–induced, microscopic colitis, C. difficile
Holiday in Mexico	Traveller’s diarrhea
Eating	*E. coli* O157:H7
– Hamburger	
– Rice	
– Whipped cream	*Staphylococcus* Toxin
Gastric surgery	Dumping syndrome
Alcohol consumption	Direct lactose, pancreatic insufficiency
Nasal polyps, dyspnea	Cystic fibrosis
Middle aged male with MSK symptoms, pleurisy or pericarditis	Whipple disease
Travel to India or Puerto Rico, low serum folate and B12	Tropical sprue

Added information	You need to think of
○ Small bowel resection – Short – Long	 – Bile acid–induced – Short bowel syndrome
○ Low serum iron and B12, high serum folate	– SIBO
○ Camping in Banff	– Giardiasis

Abbreviation: SIBO, small intestinal bacterial overgrowth; PPI, proton pump inhibitor

- ○ Immunosuppressed patient, or outbreaks of diarrhea in immunocompetent individuals, suspect *Cryptosporidia*

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 that causes bleeding

CLINICAL VIGNETTEs

- Case: 3 Ds: diarrhea, dermatitis, dementia. Give the likely diagnosis.
  - ○ Niacin deficiency
- Case: More 3 Ds: diarrhea, dysmotility, autonomic dysfunction; heart failure (HF). Give the most likely diagnosis.
  - ○ Amyloidosis of GI tract and heart
- Case: Diarrhea, ↓ K^+; pancreatic mass; gastric achlorhydria
  - ○ VIPoma
- Case: Diarrhea and recurrent abdominal pain; asthma
  - ○ Churg–Strauss syndrome

CLINICAL VIGNETTE

- Case: Diarrhea and steatorrhea with weight loss and diabetes; pancreatic mass; gallstones. Give the most likely diagnosis.
  - Somatostatinoma

- Case: GI symptoms, fundoscopy shows “angioid streaks”. Give the two most likely diagnosis.
  - Pseudoxanthoma elasticum (PXE)
  - Paget disease

- Case: Small gastric tumor, right–sided heart failure; flushing; ↑ serum chromogranin A. Give the likely diagnosis.
  - Carcinoid syndrome

- Case: Female with butterfly rash, abdominal pain, red plaque skin lesions with follicular plugging. Give the likely diagnosis.
  - SLE affecting pancreas

- Case: Diarrhea, weight loss, beer drinker; red, scaly, vesticopustular plaques on face and legs. Give the likely nutritional deficiency.
  - Dermatitis enterohepatica from zinc deficiency

- Case: Give the circumstances by which a macrocytic, megaloblastic anemia may develop in gluten sensitive enteropathy.
  - Folate deficiency
  - B12 deficiency
    - Severe maldigestion or absorption,
      - Associated atrophic gastritis (pernicious anemia)
      - Associated small intestinal bacterial overgrowth (SIBO)

Case: A patient presents with diarrhea, endoscopic and biopsy changes suggestive of celiac disease, but does not respond to a gluten free diet.

- Give features which would suggest tropical sprue.
  - Acute symptoms (fatigue, abdominal discomfort, but not always with diarrhea) occur 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 electron microscopy (EM) of small bowel biopsies
  - Response to tetracycline and folic acid, not to gluten free diet

COLON

DIVERTICULITIS

- Definition
  - Diverticulosis is simply the harmless and common uncomplicated diverticulae in the colon.
  - Diverticulitis is occurs when there is local perforation occurs and development of systemic complications.

- Pathology
  - Look for additional information in the MCQ stem that suggests presence of microperforation (e.g. rebound, guarding, fever, leucocytosis, "shift-to-the-left") which would prompt for 2 choices.
    - Treat with bowel–directed antibiotics
    - Don't – that is! Do **not** – do colonoscopy for fear of causing a perforation ,which may be deadly in this setting.

- Treatment

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the treatment for acute diverticulitis, based on the Hinchey grading system of abdominal CT.

Hinchey CT grade		Treatment
0	Perforation with no co–morbidity	- Outpatient oral antibiotics
I	Abscess pericolic or pericolic inflammation	- IV antibiotics
II	Abscess (pelvis, abdomen, retroperitoneal)	- IV antibiotics
II	Generalized purulent peritonitis	- CT–guided drainage of abscess
IV	Generalized fecal peritonitis	- Surgery

LOWER GI BLEEDING (LGIB)

- Definition
  - Diverticular bleeding is the "stigmata of recent hemorrhage (e.g. active bleeding, visible vessel, adherent clot) as seen on colonoscopy. Acute bleeding is demonstrated on angiography or on nuclear red blood cell scanning, with later confirmation of a diverticulum in a certain location, as the source of bleeding by colonoscopy or surgery.
  - "Presumptive" diverticular hemorrhage is diagnosed when colonoscopy reveals diverticulosis "....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).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give why colonic diverticulae are misnamed.
  - Colonic diverticulae are "…..herniations of colonic mucosa and submucosa through the muscular layer of the colo at a point 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). These "diverticulae" do not contain all layers of the colonic wall, they are actually pseudodiverticulae.

- Demography

- Diverticulae
  - Diverticulae occur in about half pf persons over 50 years, and bleeding occurs in about 5% of individuals with diverticulae.
  - Diverticular bleeding occurs from the base or the neck of the diverticulum in about similar ratios.
  - Most diverticulae are on the left side of the colon, but 2/3 of bleeding came from diverticulae at or proximal to the splenic flexure.
  - The ratio of these three types of diverticular bleeding are definitive (52%), presumptive (31%) and definite (17%)
  - In patients with definitive or presumptive diverticular bleeding, over a four year–period, 9% had recurrent diverticular bleeding and 9% bleed from other GI sources at a clinical point; do not presume the LGIB after a previous diverticular bleed is from the same source.

- Ischemic colitis
    - Incidence approximately $25/10^5$ per year
- Postpolypectomy bleeding (PPB)
    - ~1% occurs after 1 to 14 days of polypectomies (usually days 5 to 7); and, half require blood transfusions

➢ Risk factors predicting severe LGIB

- Age
    - > 70 years
- Clinical
    - Syncope
    - Rectal bleeding within 4–hour of evaluation
    - In–hospital bleeding for a different condition
- Physical
    - HR ≥ 100 bpm
    - SBP ≤ 115 mmHg
    - Non–tendern abdomen
    - Hypovolemia
- Drug
    - Use of ASA (aspirin)
- Co–morbidities
    - > 20 co–morbidities
    - Coagulopathy
- Causes
    - Intestinal ischemia
- Treatment
    - P–RBC transfusion

*Note: The MR from LGIB is lower if the source is hemorrhoids or colonic polyps.

Abbreviations: HR, heart rate; SBP, systolic blood pressure

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Define severe LGIB, give the predictors of severe LGIB, and the predictors of in–hospital mortality.

  - 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.

- Calculate the 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 (P–RBC) used.

	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
P–RBC	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.

- Testing
  - Multi–detector CT is more accurate than technetium–tagged RBC in LGIB.
  - Colonoscopy has s of limited use in LGIB, visualizing presumetive or definitive causes in about 2/3 only.

Performance characteristics of radiologic imaging for GI bleeding

	Sensitivity	Specificity
○ Angiography, (> 0.5 mL blood/min)	30% to 50%	100%
○ Radionuclide scan (> 0.04 mL blood/ min; technetium sulfur colloid, or technetium–pertechnetate–labeled autologous RBCs – latter has higher Sens. & Spec.)	45%	78%
○ Meckel scan	>25 year	< 50%
	< 25 year	90%

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the risk factors for post polypectomy bleeding (PPB).
  - ○ Polyp
    - − > 2 cm
    - − Thick stalk
    - − Sessile
    - − Right colon
  - ○ Patient
    - − Use of ASA, NSAIDs, anticoagulants

Source: Feldman M, *et al*. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 313.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the disadvantages of angiography for LGIB.
  - ○ Positive results in only ~ half of patients (bleeding may be 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
    - − Transient [cerebral] Ischemic Attacks (TIA)

ANGIOECTASIAS (AE) LESION

- Pathophysiology
  - It is speculated that repeated obstruction of submucosal veins leads to
    - Dilated, tortuous and thin–walled submucosal veins
    - Capillary ring becomes dilated
    - Precapillary sphincters become leaky or incompetent
    - Small arteriovenous (AV) lesion develops
- Pathology
  - The AV itself is comprised of venules, capillaries, and arterioles, and is thus an arteriolar–capillary–venular unit, an AV fistula. Vascular endothelial growth factor (VEGF) and VEGF receptor 1 may also play a role in the pathogenesis of angioectasia.
  - These angioectasia (AE) involves the colon and small intestine, but not other organs of the body nor the skin.
- Clinical
  - The proximal and distal colons are affected equally by AEs.
  - Bleeding AEs are not as common as severe lower GI bleeding (LGIB) as diverticulosis (10% vs 30%, respectively).
  - Up to half of people over 60 years have AEs; in a patient with LGIB, seeing AEs does not prove that AEs are the cause of bleeding.
  - In any way, you see a diverticula, it does not prove that it causes LGIB.
  - The AEs are no more common in persons with chronic renal failure, but they bleed more frequently.

SO YOU WANT TO BE A GASROENTEROLOGIST!

- In the context of lower gastrointestinal intestinal bleeding (LGIB), what is Heyde syndrome?
  - Heyde syndrome is LGIB from colonic angiodysplasia in the patient with aortic sclerosis. It is 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).

- Treatment
  - Colonoscopy is useful in demonstrating 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.
  - Low fiber diets are no longer recommended for persons with diverticular disease.
  - The recurrence of symptoms of diverticulitis is lower in persons treated prophylactically with 5–ASA with probiotic *Lactobacillus* CAE, than when either is given alone.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the angiographic signs of angioectasias (AE).

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

FECAL INCONTINENCE

- 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 muscle contraction
  - ↓ internal anal sphincter (IAS) pressure causing relaxation

- Failure of relaxation of IAS
  - Pelvic dyssynergia (functional anorectal outlet obstruction)
  - Hirschsprung disease

- Give the use of rectal pressure measurements to distinguish between pelvic dyssynergy and Hirschprung disease.

	Pelvic dyssynergy	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

Constipation

- ➢ Definition
  - Medical ≤ 3 BMs/wk
  - Public terms used to describe constipation
    - Straining (52%)
    - Hard stools (44%)
    - Inability to have a BM (34%)

- ➢ Types

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give a clinical classification of the mechanisms of functional constipation.
  - 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

- Give the abnormalities of colonic functions in patients with slow–transit constipation.
  - ↓ 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

- Pathophysiology: Disorders in -
  - 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 slow transit constipation (STC)

The colon transit time (CTT) is ~12 hours.

- Give what the measurement of CTT indicates about the pathophysiology of constipation.

  - CTT is delayed in transit disorders, whereas in defecatory disorders of the rectoanal inhibitory reflex or pelvic floor dysfunction (anismus) will have a held–up of fecal marks in the rectal area.

  - Enteric nerves
    - Hirschsprung 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* (Chagas disease)
      - Paraneoplastic visceral neuropathy

- Give examples of disorders of the CNS, spinal cord, smooth muscles and enteric neurons, which are associated with constipation, and give its mechanisms responsible for the development of 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 the 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
    - ↓ 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
  - LMN spinal cord disorders
    - ↓ left colonic contractions
    - ↑ colonic compliance
    - ↑ caliber of distal colon and rectum (distention)
    - ↑ pressure in anal canal
    - ↓ sensation of rectum, anus, perianal skin
  - Smooth muscles
    - Congenital or acquired myopathy, hereditary IAS myopathy
    - Progressive systemic sclerosis (PSS) – smooth muscle atrophy
    - Muscular dystrophies – visceral smooth muscles may accompany dystrophy of skeletal (striated) muscles

Laxatives

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Classify laxatives, give its mechanisms, and examples of each.
  - 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, laparoscopy with open subtotal colectomy with ileorectal anastomosis may be necessary for severe constipation.

- There are many laxatives available for the treatment of chronic constipation. Which of these is used based on two or more randomized controlled trials (RCTs) with adequate sample sizes and appropriate methodologies?
  - Lactulose, PEG, Tegaserod®.

  - In patients with non–responsive defecatory disorders, the stapled transanal rectal resection (STARR), a surgical procedure needs to be considered.

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).

- Diagnostic imaging

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- From the lateral view of the rectum on barium enema examination, give the features that suggest descending perineum syndrome.
  - Rectum is more vertical than normal
  - Anorectal angle is wide
  - Perineal discent is > 3 cm
- What is the pathophysiology of the solitary rectal ulcer syndrome (SRUS)?
  - SRUS is caused by paroxysmal contraction of the puborectalis muscles from excessive straining during defecation.
- Give the pathophysiology of constipation in hypothyroidism.
  - Myxedematous infiltration in the wall of the colon
  - Reduced peristalsis

IRRITABLE BOWEL SYNDROME (IBS)

- Definition
  - Irritable bowel syndrome (IBS) is a collection of symptoms attributed to the intestine, related to defecation and unpredictable habit which can be recognized by its characteristic pattern of abdominal pain and discomfort and is relieved by defecation and associated with a change in bowel habit but 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.

- Terms
  - Allodynia – pain caused by non–noxious stimulus
  - Hypersensitivity – excessive pain caused by noxious stimulus
  - Distention – mobile fullness
  - Bloating – subjective sensation of abdominal fullness caused by gas

- Pathophysiology
  - Biopsychosocial disorder ("brain – gut dysregulation")
  - ↑ cytokines & chemokines (in blood, but not in colonic tissue maladaptive cognition)

- 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 change in frequency of stool
    - Onset associated with change in form or appearance of stool
    - Criteria fulfilled for the last 3 months with onset of symptom 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; (e) defecation straining; (f) urgency or feeling of incomplete bowel movement, passing mucus and bloating
    - "Discomfort" means an uncomfortable sensation but not pain.

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: Canadian Pharmacist Association 2012, Table 1, page 857.

- Give alarming symptoms that cannot be explained by irritable bowel syndrome.
    - Fever
    - Anemia
    - Bleeding from the gut
    - Significant and unexpected weight loss
    - Family history
        - Cancer
        - Inflammatory bowel disease
        - Celiac disease
    - Recent consistent change in bowel habit
    - Persistent, daily diarrhea or constipation
    - Abnormal physical findings, e.g. abdominal mass or malnutrition

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: Canadian Pharmacist Association 2012, Table 2, page 857.

MCQ ALERT

The MCQ stem may suggest IBS, but IBS symptoms may masquerade in several treatable conditions.

- Give treatable conditions which mimic IBS.
    - Celiac disease
    - Lactose intolerance
    - Gluten intolerance (different from celiac disease)
    - Small Intestinal Bacterial Overgrowth (SIBO)
    - Cholerrheic diarrhea (bile salt wastage)
    - Microscopic colitis (collagenous colitis and lymphocystic colitis)

The therapeutic placebo response rate (PRR) in IBS varies over time, rising to a PRR to 40% 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 with $1.1/10^3$ cases per year.

- Even patients with proven IBS need a screening colonoscopy for colorectal cancer at age 50, or earlier depending on the family history.

- Give evidences in the use of Mesalazine for IBS.
  - Observational data suggests benefits of mesalazine for IBS
  - Randomized, placebo controlled pilot study in IBS patients from Italy
  - Compared to placebo, mesalazine:
    - Reduce
      - Mast cell infiltration
      - Mast cell histamine release ($p<0.001$)
      - Abdominal pain intensity scores ($p=0.0026$)
    - Improve
      - General well–being ($p=0.0007$)

TYPHLITIS

When CT scan shows thickening of the bowel wall of the appendix, terminal ileum or cecum, typhlitis is suspected.

- Give the clinical and laboratory abnormalities that would alert you to the right diagnosis, and why the diagnosis must not be missed.
  - Typhlitis is also known as neutropenic enterocolitis where most of the conditions in the differentials (WBC is increased or at least normal, neutrophil count is low) are pointing to the diagnosis.
  - Typhlitis is highly prone to perforate (mortality rate, 50%) because of the necrotizing nature of the process, hence, colonoscopy or barium enema studies should not be done.

PROBIOTICS

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- How are your 10^{14} cells today?
  - They are fine, but I am experiencing destructive interference from gut microbiotic cells!

- Funny! We all know what probiotics, prebiotics and symbiotics are. But what about bacteriocins, what are these?
  - Bacteriocins are substances that are produced by some bacteria which modify the growth of other bacteria.

TOTAL TRIVIA

- The commensal bacterium *Faecalibacterium prausnitzii* has an anti-inflammatory action, and helps to reduce Crohn disease (CD) recurrence after surgery.

COLONIC INFECTIONS

Amebiasis

- Clinical
  - 90% of *E. histolytica* infections are asymptomatic, but should be treated because the patient,
    - May become symptomatic soon after
    - May be passed on to others (food–handlers, infectious!)

- Pathology
  - Colon
    - Flask–shaped ulcer
    - Ameboma
  - Liver
    - Abscess
    - Usually R. lobe of the liver
  - Metastatic amebiasis
    - Usually direct or via hematogenous spread
    - CNS, lung, pericardium, skin

CLINICAL VIGNETTE

○ Male traveler, with single, low–attenuating lesion on CT with enhancement of rim, elevated right hemidiaphragm on chest X-ray, “anchovy paste” substance on aspiration of abscess	– Amebic abscess
○ Mild diarrheal illness, bright red blood per rectum of traveler or patient who lives in Southern USA (e.g., Texas), ulcerative colitis–like appearance of mucosa sigmoidoscopy, “flask-shaped ulcers” on biopsy	– Amebic colitis

E. coli

- Give the antibiotic recommended for the treatment of hemorrhagic colitis due to *E. coli* O157:H7 infection.
    - There is none; in fact, antibiotic treatment for *E. coli* O157:H7 infection may precipitate hemorrhagic uremic syndrome and thrombotic thrombocytopenic purpura (HUS–TTS).

Sorry to trick (i.e. mislead you, but…….)

OBSTRUCTION / PSEUDO-OBSTRUCTION

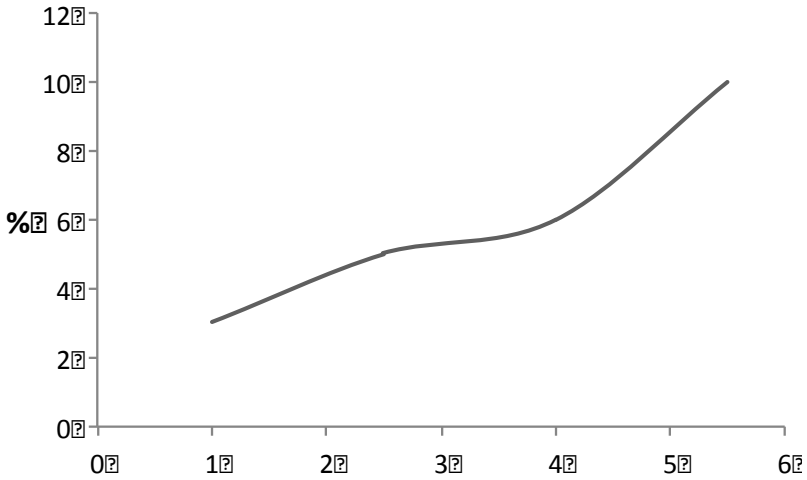
- Define "Ogilvie Syndrome" and give the commonly associated causative conditions.
    - Ogilvie Syndrome is an acute colonic pseudo–obstruction, "....characterized by marked dilatation of the cecum [> 10 cm] and ascending colon in the absence of mechanical obstruction" (Spiegel, BMR, *et al*. Acing the Hepatology Questions on the GI Board Exam: The Ultimate Crunch-Time Resource. *Slack Incorporated* 2011, page 110).

- Give the most common clinical conditions associated with Ogilvie syndrome.
    - ICU patients
    - Sepsis
    - Recent surgery
    - Electrolyte abnormalities
    - Trauma
    - Drugs
    - Immobilization

COLONIC ISCHEMIA (CI)

- Definition
  - "….condition that results when blood flow to the colon is reduced to a level that is insufficient enough to maintain a [colonic] cellular metabolic function."

- Demography
  - Incidence 16 / 10^5
  - Women > Men (women < 40 represent > 95% of cases of CI)
  - Mortality rate ~ 10%
  - Recurrence rates



- Anatomy
  - Blood supply of colon
    - SMA (superior mesenteric artery)
    - IMA (inferior mesenteric artery)
    - SHA (superior hemorrhoidal artery)

CLINICAL DI TIP

About 10% of persons > 60 years have an asymptomatic occlusion of the IMA.

Site	Postulated usual cause	Linking of vessels	Name of water shed area
– Splenic flexure	Non–occlusive disease	L–branch of middle colic artery of SMA with ascending branch of left colic artery of IMA	Graffith point
– Sigmoid colon	Sigmoid colon	Final branch of sigmoid artery branch of IMA	IMA occlusion

➢ Risk factors (severe ~ 5% of CI patients)

- Give the risk factors for CI.

Risk factors		Odds ratio
CNS	- Cerebrovascular disease	3.20
CV	- PVD	7.9
	- Shock	4.32
	- ↑ BP	3.21
	- IHD / HF	2.6 – 4.75
	- AF	2.21
	- ↓ BP	1.85
Lung	- COPD	2.70-3.13
Blood	- Thrombophilia	
	- Sickle cell crisis	
Kidney	- CKD	8.50
GI	- Any cancer	3.20
	- ↑ BM	2.36
	- IBS	2.01
	- Colon cancer	1.68
	- ↓ BM	1.62

Risk factors		Odds ratio
○ Metabolic	- Dyslipidemia	2.13
	- Diabetes	1.82
○ MSK	- Systemic disorders	4.67
	- RA	3.27
○ Surgery	- Abdominal	18.4
	- Ileostomy	3.80
	- Aortic	3.58
	- Laparoscopy	2.90
○ Drugs		

Abbreviations: AF, atrial fibrillation; BM, bowel movement; CKD, chronic kidney disease; CNS, central nervous system; COPD, chronic obstructive disease; CRC, colorectal cancer; CV, cardiovascular; BP, blood pressure; HF, heart failure; IBS, irritable bowel syndrome; IHD, ischemic heart disease; MSK, musculoskeletal; OR, odds ratio; PVD, peripheral vascular disease; RA, rheumatoid arthritis

Adapted from: ACG Clinical Guideline, Brandt LJ, *et al*. Am J Gastroenterol 2015, Tables 110-18-44, page 22; Table 7, page 2.

- ○ Drugs
  - The evidence is not strong for most of the drugs suggested to be associated with colonic ischemia.

		↑ risk	Odds ratio
– CNS	▪ Psychotropic		3.7
– GI	▪ Constipation–associated drugs		
	– All drugs	0.68	
	– Opioids	1.96	
	– Non–opioids	1.75	
	– Warfarin	4.33	
	▪ Laxatives		4.73
	▪ Colitis, antibiotic–associated		3.3
– Metabolic	Hormones (“female hormones”)		1.88

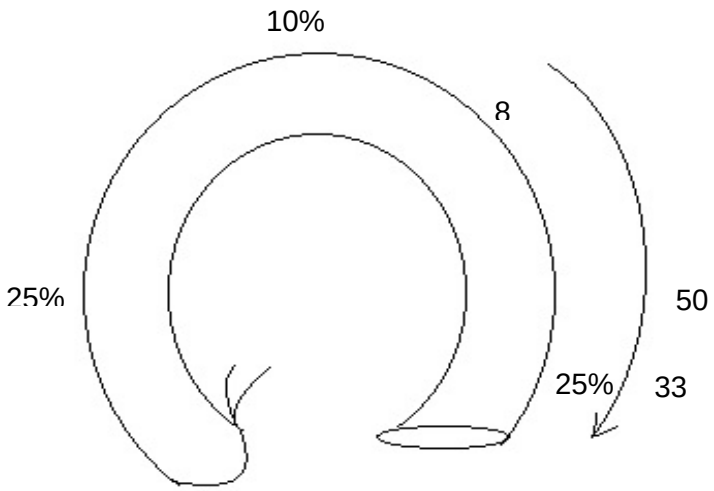
➢ Clinical

- Non–isolated R–colon ischemia
  - Sudden, central abdominal pain (milder than with AMI [acute mesenteric ischemia])
    - 78–87%
    - Sequence: pain – urgency – bloody diarrhea 50%
  - Diarrhea
    - Watery 19–56%
    - Bloody 35%
  - Urge to defecate
  - Bright Red / Maroon–Colored Blood Per Rectum (BRBPR)
    - 58–84%
  - Pertained signs
  - Vomiting nausea 30%

- Isolated R–colon ischemia (IRCI)
  - More pain but less bleeding
  - When bleeding occurs
    - ↑ severity

➢ Pathology

- Gross
  - Site



Pancolonic 7%

- Reversible changes
  - Subepithelial bleeding
  - Edema
  - Colitis
  - Ulceration
- Irreversible changes
  - Hemorrhagic nodules
  - Early
    Fulminant colitis (5%)
    Stricture (14%)
    Gangrene
    Late
    - Chronic ischemic colitis
- Pathognomic changes
  - Infarction (60%) plus
  - Ghost cells (in 20%)
- Non–specific changes
  - Bleeding
    - Mucosal
    - Submucosal
  - Edema
  - Inflammation
    - ↑ PMNs (↑ neutrophils)
- Fibrin thrombi

CLINICAL CAUTION

The mortality rate is higher for isolated, right–sided CI (IRCI).

- Laboratory
  - Diagnosis of CI is clinical
  - Laboratory tests are largely non–specific and non–sensitive
  - Blood
    - In the appropriate clinical setting, suspect severe CI with
      - ↓ Hg < 12 g/dL
      - ↓ Albumin < 2.8 g/L
      - ↓ pH (metabolic acidosis)
      - ↓ Na^{+}_{s} < 136 mEq/L
      - ↑ WBC > 15 cells / cm
      - ↑ LDH > 350 U/L
      - ↑ BUN > 20 mg/dL

- Stool cultures
  - Because CI may be associated with
    - *C. difficile* infection
    - *E. coli* O57:H7

Abbreviations: BUN, blood urea nitrogen; Hg, hemoglobin; LDH, lactate dehydrogenase; Na^+_s, serum sodium concentration; WBC, white blood cells

- Diagnostic imaging
  - Abdominal film
    - Dilation of colon
    - Thick wall
    - Edema
    - "thumb printing" (pseudotumors)
    - Pneumatosis coli (circumferential intramural air)
    - Venous gas in portomesenteric system (36%)
  - CT with contrast
    - Superior performance characteristics for
      - Gangrene
      - Pneumatosis
    - Also
      - Ascites ~ 1/3
      - Target sign or halo sign ~ ¼
      - Fat stranding (100% in one study)
  - CTA (multiphase CT angiography)
    - For suspected
      - Acute Mesenteric Ischemia (AMI)
      - Isolated Right–Colonic Ischemia (IRCI)
  - Angiography
    - CTA negative, but suspected
      - Acute Mesenteric Ischemia (AMI)
      - Isolated Right–Colonic Ischemia (IRCI)
  - Colonoscopy
    - Within 48 hours, using minimal air insufflation
    - Severe disease
      - Confirm localization of CI seen on CT
    - Biopsy
      - Except for severe disease or possible gangrene (peritoneal signs)

➢ Risk stratification (indicators of severe disease) of Ischemic Colitis Mortality Risk (ICMR):

	Odds ratio
• ≥ 3 of the following	
○ Clinical	3.90
– Male - Abdominal pain but no rectal bleeding	
– Hypotension	4.45
▪ SBP < 90 mm Hg	
– Tachycardia	4.40
▪ HR > 100 bpm	
○ Laboratory	
– ↑	
▪ WBC > 15 cells / mm (white blood cells)	
▪ LDH > 350–450 U/L (lactate dehydrogenase)	14.25
▪ BUN > 20 mg/dL (blood urea nitrogen)	4.35
– ↓	
▪ Hg < 12 g/dL (hemoglobin concentration)	4.5
▪ Albumin	
▪ pH (metabolic acidosis)	4.98
▪ Na+s < 136 mEq/L (serum sodium concentration)	
○ Colonoscopy	
– Ulceration of colonic mucosa	2.30
– Pancolitis	14.64
– R–colon only (IRCI)	5.75
OR	
○ Clinical	
– Peritoneal signs	7.3
○ Diagnostic imaging pneumatosis	
– Venous gas in portomesenteric system	7.3
○ Colonoscopy	
– Gangrene	
– Distribution	
▪ Pancolitis	
▪ IRCI	5.75

Source: ACG Clinical Guideline, Brandt LJ, *et al*. Am J Gastroenterol 2015, Table 6, page 31.

- Treatment
  - Mild disease
    - Supportive care
      - IV fluids
      - Correction of electrolytes
    - Observation
      - Type I CI, no causes found
    - Correct any risk factor
      - Targeted therapy
  - Moderate or severe disease
    - As above for mild disease
    - Antibiotics (≥ 72 h)
      - Anaerobic
      - Fluoroquinolone, or aminoglycoside cephalosporin, 3rd generation
    - Surgical resection

- Prognosis

Outcome	Non IRCI	IRCI
30–day mortality	23%	12%
Surgery	55%	11%
Colectomy or death	59%	17%

- Management

  Medical (mild CI in 80%) ~ 6%
  Surgical (severe CI in 20%) ~ 40%

  - Mortality rate with associated:
    COPD
    CKD

Abbreviation: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IRCI, isolated right colonic ischemia;

- Indications for surgery
  - Acute
    - Gangrenous bowel (peritoneal signs)
    - Bleeding, massive
    - Toxic megacolon (pancolitis)
    - Pneumatosis intestinalis
    - Venous gas, portomesenteric system

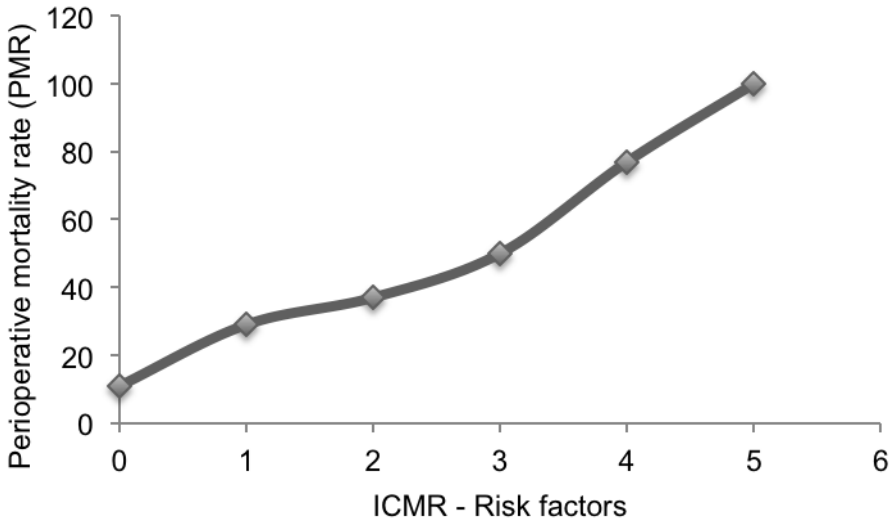
- Subacute
  - Failure to respond within 2–3 weeks to standard medical care for recurrent sepsis
- Chronic
  - Strictures
  - Symptoms from segmental CI

Adapted from: ACG Clinical Guideline, Brandt LJ, *et al*. Am J Gastroenterol 2015, Table 9, page 39.

- Types of colectomy required
  - Total or subtotal ~ 40%
  - Right hemicolectomy ~ 35%
  - Segmental resection ~ 20%
  - Left hemicolectomy ~ 50%
- Risk of perioperative mortality
  - Ischemic colitis mortality risk score (ICMR)
- Perioperative mortality ~ 40% (depends on risk factors, e.g. ICMR [please see below])

- Comorbidities
  - Heart
    - Cardiac ejection fraction < 20%
  - Kidney
    - *Acute Kidney Injury (AKI) requires hemodialysis
  - Drugs
    - *Catecholamine (vasopressive) use pre– and intra–operatively
  - Laboratory
    - *Lactate > 2.5 mmol/L (preoperative value)
  - Surgery
    - Total or subtotal colectomy
  - Score 1 for each risk factor

- Predictive value of perioperative mortality with number of risk factors from ICMR.



*predictive value of individual components of ICMR

Abbreviations: ICMR, ischemic colitis mortality risk score

- American Society of Anesthesiologists Status (ASA)

Predictors of peri–operative mortality	Odds ratio
ASA class > 4	6.91
Post–operative hemodialysis for AKI	5.11
Bleeding > 500 mL	2.63
Intra–operative catecholamine (vasopressor) use	2.07
Lactate (peak pre–operative value)	1.26

Abbreviation: AKI, acute kidney injury

ULCERATIVE COLITIS

➢ Complications

- 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.

PATHOLOGY TIP

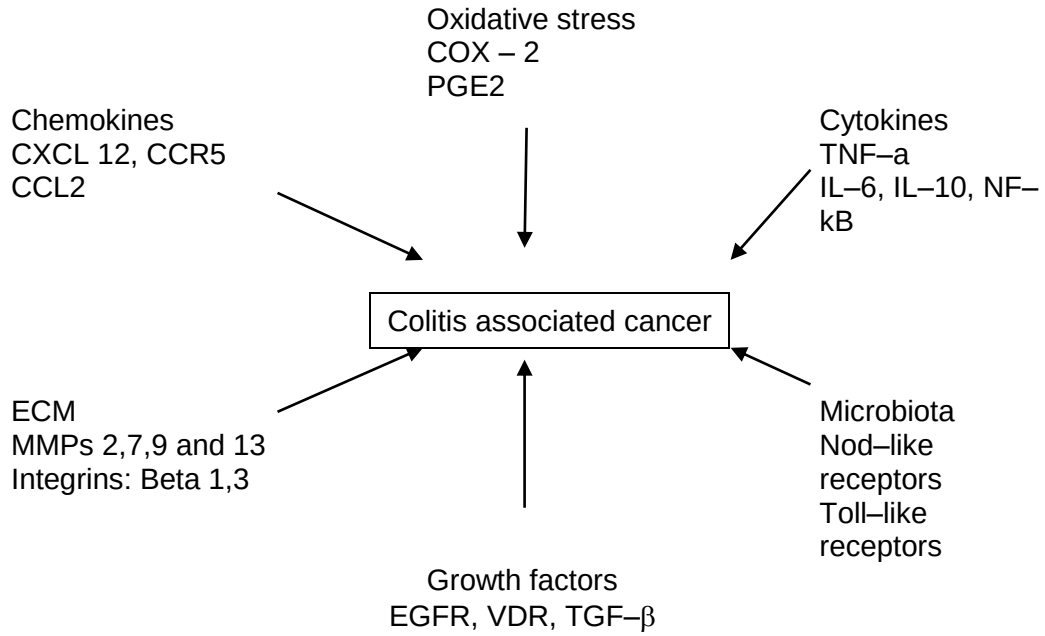
Branching colonic crypts – the "trouser" or pyjamas" sign, is a sign for an event that has occurred previously (i.e. chronic disease).

CLINICAL VIGNETTE

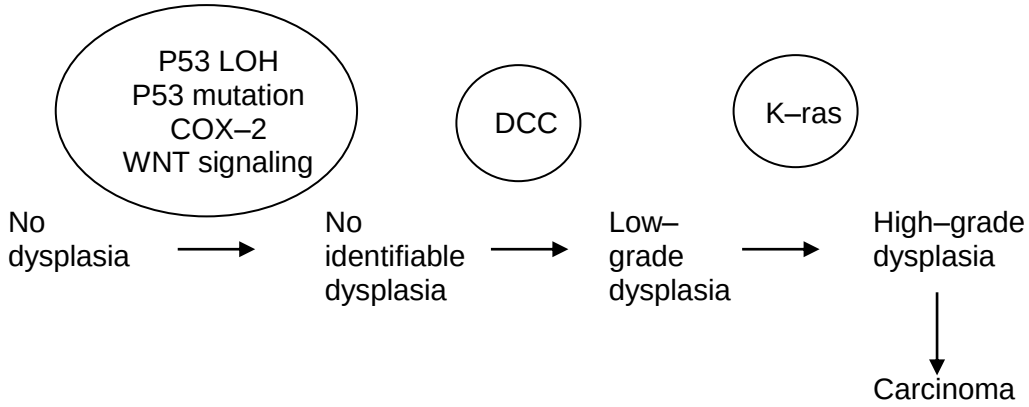
- Case: Dysphagia or globus, sensation of foreign body in the mouth
    - Examine upper esophagus, throat and uvula for fibrovascular polyp on long stalk
    - If polyp < 2 cm and EUS does not show penetrating blood vessels, remove endoscopically

CRC in IBD

- Postulated mechanisms of IBD–associated colorectal cancer
  - Mediators



- Genetics



Abbreviations: COX–2, cyclooxygenase-2; DCC, deleted in colorectal cancer; K–ras, V–Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LOH, loss of heterozygosity; 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.

MCQ ALERT

- If the MCQ describes a patient with long standing UC, and on biopsy shows dysplasia, then the action which "they" wish you to undertake is for you to refer the patient for a possible colectomy.
  - In real life, there are subtle aspects that need to be assessed and considered, but this is not what your answer on an MCQ.

- Serological tests are seldom performed to distinguish ulcerative colitis (UC) from Crohn disease (CD), however:
  - They frequently make an appearance on MCQs
  - Smoking has a different effect in UC and CD

	UC	CD
ASCA	Positive in 10%	Positive 60%
p–ANCA	Positive in 75%	Positive in 10%
Smoking	Helps UC	Worsen CD

➢ Diagnosis

"Buzzwords" which suggest the type of IBD

UC	CD
○ Crypt abscess	○ Granuloma ○ Perianal and disease ○ Rectal sparing ○ Skip lesions ○ Fistula

➢ Clinical

There are endoscopic scoring systems to determine the severity of UC.

- Give the clinical features suggestive of severe UC.
  - > 6 BM per day
  - Bleeding
  - Fever
  - HR / PR > 90 bpm
  - ESR > 30 mm/h
  - Anemia

SO YOU WANT TO BE A GASTROENTEROLOGIST OR ENDOCRINOLOGIST!

- Give the endocrine disease which may co–exist with ulcerative colitis (UC), worsen the symptoms, and reduce the response of the UC to therapy.
  - Hyperthyroidism may occur in UC

- You should know this!

  - If the patient has severe UC, their treatment moves beyond outpatient care with 5–ASA and sulfasalazine + immunosuppressants (azathioprine or 6–MP).
  - Such patients with severe UC require:
    - Hospitalization
    - IV steroids with IV fluids and electrolytes
    - If no response in 3 to 5 days, then give
      - IV cyclosporine
      - IV infliximab
      - Colectomy

CROHN COLITIS

- Look at the subtle differences of Crohn colitis.
  - 5–ASA or sulfasalazine
    - Limited use for treating a relapse
      - For maintaining remission
  - Immunosuppressants, including IM or SC methrotrexate, are used after 2 acute attacks requiring steroids (ealier introduction than in UC)
  - Cyclosporine is not effective for severe active disease
  - Biologics (anti–TNF therapy) are used
    - For steroid with immunosuppressant–resistant disease
    - For fistulising CD, or ascites
  - Because of the transmural thickness of CD and often associated–fibrosis, megacolon is much less common in the patient with CD unless there is fibrotic stricture or cancer.

CLINICAL CAUTION

- In a patient with severe colitis, avoid doing barium enema (with or without contrast) or colonoscopy, to avoid megacolon, including toxic severe UC.

MICROSCOPIC COLITIS

A patient with IBS–like symptoms underwent colonoscopy, which is normal. You are asked if this excludes IBD.

- No
  - Very mild and early UC or CD may be seen only on mucosal biopsy of the colon
  - CD may be in the small bowel, unreachable by a colonoscope
  - The patient may have microscopic colitis (MC), either collagenous colitis or lymphocytic colitis, where biopsies and other diagnostics are positive but colonic mucosa appears normal on colonoscopy

POLYPS

Test Yourself

- Give the name of the Colonic Adenomatous Polyp Syndrome from its associations.

Case 1
- Congenital hypertrophy of the retinal pigmentation epithelium (CHRPE)
- Desmoid tumors
- Lipomas
- Fibromas
- Epithelioid cysts
- Sebaceous cysts
- Osteoma jaw
- Mesenteric fibromatosis
- Supernumerary teeth

- Answer: Gardner syndrome (FAP, plus extraintestinal associations)

Case 2
- Endometrium
- Ovary
- Kidney
- Ureter

- Answer: HNPCC

Case 3
- Medulloblastoma
  - CNS
  - Bone
  - Heart
  - Kidney

- Answer: Turcot Syndrome (FAP plus brain tumor)

Case 4
- Non–colonic associations
  - Biliary tract disease
  - Gastric cancer
  - Small intestinal cancer
- Answer: HNPCC (Muir–Torre Variant)

Case 5
- Testicular tumor (Sertoli)
- Ovarian tumor (Sex–cord)

- Answer: Tuberous sclerosis (autosomal dominant; hamartomas)

Case 6
- Differential of GI hamartomatous
  - Peutz–Jegher
  - Juvenile polyposis
  - Tuberous sclerosis
  - Cronkhite–Canada
- Skin changes
  - Alopecia
  - Dystrophy of nails

- Answer: Cronkhite-Canada syndrome

CLINICAL VIGNETTE

- Case: Hamartomatous polyps of stomach, small intestine or colon; weight loss and edema, balding; negative family history. Give the likely diagnosis.
  - Cronkhite–Canada Syndrome

ENDOMETRIOSIS

➢ Definition: “Endometriosis 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 endometriotic tissue and the severity of symptoms”.

CLINICAL VIGNETTE

- Case: Colonic “polyp” in a female patient who appears when abdominal pain is present, then disappears. Give the likely diagnosis.
  - Endometriosis

CLINICAL VIGNETTE

- Case: Screen colonoscopy, larger polypoid lesion which disappears with a “pop” on mucosal biopsy, patient has COPD. Give the likely diagnosis.
  - Pneumatosis Cystoides intestinalis (PCI)

COLORECTAL CANCER (CRC)

➢ Clinical

- Take a directed history for colon cancer screening, and surveillance.

Screening	Surveillance
o Age	o When polyps found
o Gender	o Size > site and number
o Race	o Histology
o GI symptoms	o Removal
o Family history – Colon polyps – Cancer - Bowel - Abdomen - Brain	o Who did the colonoscopy
o Previous screening - Stool - Imaging - Colonoscopy	
o Diet - Alcohol - Obesity - Fresh fruit - Vegetables - Fiber	
o Smoking	
o Drugs (ASA, NSAIDs, Coxibs)	

- Give the link between endocarditis and colorectal cancer (CRC).
    - Persons with endocarditis from
        - *Streptococcus bovis*
        - *Clostridium septicum*

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: Colorectal Cancer (CRC)

- Pathology

- Give the goals of staging cancer.
    - To identify who can receive treatment to cure as quickly and efficiently as possible
    - To minimize exposure and invasion testing
    - To identify patients with incurable diseases and to diminish the risk associated with surgery or combined–medication approaches (MKSAP 16, Oncology and Hematology 2012, page 200)

The Dukes Classification of CRC is no longer used, and replaced with TNM staging system, which is predictable of prognosis (mortality).

- Give the TNM staging (I to IV) of CRC cancer.

Stage	Tumor (T)	Nodes (N)	Metastases (M)
I	T1, T2	N0	M0
II	T3, T4 full thickness of bowel wall, pericolonic rectal fat)	N0	M0
III	T1 to T4	N1, N2	M0
IV	T1 to T4	Any N	M1

- Treatment
  - Colon
    - Hemicolectomy
      - Stage II - 5–FU (fluorouracil) plus leucovorin
    - Adjuvant chemotherapy
      - Stage III 5–FU plus leucovorin plus oxaliplatin (FLOLFOX)
  - Rectum
    - Stage with endoscopic ultrasound (EUS) of rectum or MRI
    - T1–2, N0 (stage I)
      - Primary total mesorectal excision
    - T3–4 (stage II, III)
      - Neoadjuvant radiochemotherapy (5–FU, or capecitabine)
    - Oxaliplatin or irenotecan
    - Bevacizumab plus chemotherapy
    - Cetuximab or panitumumab (only for K–ras negative tumors)

- Surveillance
  - Colonoscopy year 1 and 3, and then every 5 yr
  - Serum carcinoembryonic antigen (CEA) q 3 month for 3 years, then q 6 mon for 2 years
  - Advise family members to have colonoscopy at age 50 or 10 years before the age of diagnosis of index patient

- Give the current accepted standard post–operative adjuvant chemotherapy for stage III colon cancer.
  - FLOLFOX
    5–fluorouracil, leucovorin and oxaliplatin

- Give the type or name of targeted therapies against 3 of the following malignant tumors.

Site	Mechanism	Therapeutic agent
Colon	VEGF–MA, EGfr–MR	Bevacizumab; cetuximab or panitumumab
Liver	VEGF–TK1	Sorafenib or sunitinib
Pancreas	EGFR–TK1	Imatinib or gefitinib
GIST	VEGF–TKI, EGFR–TKI	Sorafenib or sunitinib; imatinib or gefitinib

- Give the major adverse effects (AE) of the following:

  - VEGF–TKI (sorafenib, sunitinib)
    - Hand–foot syndrome

Bevacizumab is an anti–VEGF (vascular endothelial growth factor) biological which may be used for late stage colon cancer.

- Give serious complications of this agent.

  - Disrupts normal blood vessels
    - Bleeding
    - Thrombosis
  - Bowel perforation
  - Hypertension
  - ↓ wound healing
  - Nephrotic syndrome

CLINICAL PEARLS AND GEMS

Monoclonal antibody against vascular endothelial growth factor (VEGF), bevacizumab, and monoclonal antibody against epidermal growth factor receptor (EGFR), cetuximab and panitumumab are used for metastatic colorectal cancer. Here are some useful pointers.

- Measure K–ras status in CRC tissue
- If K–ras positive, use anti–EGFR agent
- Do not use anti–VEGF plus anti–EGFR, since this combination actually ↓ survival in persons with metastatic CRC
- Do **not** use either anti–VEGF on anti–EGFR in non–metastatic disease, since they are only effective for metastatic disease

CLINICAL CHALLENGE

A patient with metastatic colorectal cancer (CRC) is treated with the monoclonal antibody, EGFR, cetuximab. As the quality of her life is not already bad enough, she develops a severe active form of rash on her face.

- Give the duration that the cetuximab must be stopped before resuming it.
  - Trick question? The more severe the acne–like rashes, the greater the anti–tumor effect of the anti–EGFR drugs.
  - Treat the skin condition, and encourage the patient to continue the cetuximab for the anti–tumor effect against metastatic CRC.

- Hepatic metastases

Lobectomy of small lesions in one hepatic lobe may be beneficial for patients with metastatic colorectal cancer.

- Give the post–operative follow–up schedules for Stage III colon cancer.

Procedure	Frequency
History and physical examination	– q 3 to 6 mon
carcinoembryonic antigen (CEA)	– q 3 to 6 mon
CT scanning of chest, abdomen, pelvis	– Annually for 3 to 5 yr
Colonoscopy	– Year 1, then q 3 to 5 yr

➢ Clinical

- Give the clinical features of leukemic invasion to the bowel and other related structures.
  - Local invasion
    - Intussusception
    - Adynamic ileus
    - Mucosal ulceration
      - Perforation, hemorrhage

- Hepatosplenomegaly
  - Splenic infarction, rupture
- Portal hypertension
  - Ascites, variceal hemorrhage, encephalopathy
- Biliary and pancreatic duct obstruction
- Protein–losing enteropathy
- Pneumatosis intestinalis
- Watermelon rectum

- Immunodeficiency
  - Necrotizing enterocolitis (typhlitis)
  - Increased susceptibility to common infections
    - Appendicitis, wound infections, perirectal abscess, sepsis
  - Opportunistic infections
    - Esophageal or hepatic candidiasis, mucositis
    - *Herpes* infections (HSV < CMV); protozoa
    - Pseudomembranous colitis

- Coagulation Defects
  - Intramural hemorrhage
    - Hemorrhagic necrosis, obstruction
    - Gastrointestinal hemorrhage

- Drug Toxicity
  - Mucositis
  - Nausea and vomiting
  - Ileus, megacolon
  - Bowel necrosis
  - Pancreatitis

ANAL CANCER

- Strongly associated with human papilloma virus (HPV) infection
- Treat with radiation, plus chemotherapy with 5–FU plus mitomycin
- Don't forget that developing anal cancer does **not** protect against adenocarcinoma of the colon or rectum, hence, screening for colonoscopy is indicated.

LIVER

HEPATOSPLENOMEGALY

- Give the 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 Disease
    - Niemann–Pick disease
    - Histiocytosis X
    - Glycogen storage disease
    - Haemochromatosis
    - Hurler disease (Gargoylism)
  - Infections
    - Viral
      - Infective and serum hepatitis
      - Infectious mononucleosis
    - Bacterial
      - Hepatic abscess
      - TB
      - Syphilis
      - Weil's disease (leptospirosis)
    - Protozoal
      - Amoebic abscess
      - Malaria
      - Toxoplasmosis
      - Kala-azar
    - Fungal
      - Histoplasmosis
    - Parasitic
      - Hydatid cyst

Source: Burton JL. *Churchill Livingstone* 1971, pages 43 and 44.

- Give the causes of **hepatosplenomegaly**.

    - Infective e.g. infectious mononucleosis
    - Myeloproliferative e.g. myelofibrosis, chronic myeloid leukemia
    - Some causes of portal hypertension e.g. Budd-Chiari syndrome
    - Reticulosis
    - 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.

- Give causes of a hard knobbly liver.

    - Carcinoma metastases
    - Post–necrotic cirrhosis
    - Congenital cystic liver
    - Hydatid cysts
    - Hepar lobatum (syphilis)

➢ Clinical

- Perform a focused physical examination for hepatosplenomegaly.

    - Liver
        - Palpable liver in patients with chronic liver disease
        - Palpable liver along epigastrium in patients with chronic liver disease
        - Firm liver edge 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

- Performance characteristics
  - 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 in a patient 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; e.g. in a returning traveler with fever where there is splenomegaly from malaria (PLR, 6.6).
    - Hepatocellular disease in a person with non–obstructive jaundice (2.9)
    - Detecting cirrhosis in the person with chronic liver disease (2.3).

Adapted from: McGee SR. *Saunders/Elsevier* 2007, Box 47.2, pages 556-9.

- There are numerous findings on physical examination of a patient with chronic liver disease that give a positive likelihood ratio in the 2's or 3's
  - Spider angiomata (telangiectasias), 3.7
  - Peripheral edema, 3.0
  - Palmar erythema, 2.6
  - Splenomegaly (2.3 or hepatomegaly, 2.0)
- 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.

A LITTLE PEARL

- Case: Jaundice, pruritis, bradycardia. Give the likely diagnosis.
  - Hemolytic anemia causing jaundice and is not associated with pruritus or bradycardia.
  - Cholestasis caused by jaundice, pruritis and bradycardia.

- Give the positive likelihood ratio (PLR) for the physical finding in the patient with suspected chronic liver disease.

Sign	PLR
○ Encephalopathy	8.8
○ Ascites	6.6
○ Dilated abdominal wall veins	5.4
○ Spider angiomata	3.7
○ Palpable edema	3.0
○ Palmar erythema	2.6

CLINICAL CLUE

- Give the more likely viral cause of hepatomegaly or splenomegaly when tenderness is present.

	HBV/ HCV	EBV
○ Liver	+	(-)
○ Spleen	(-)	+

Tricks for Examination of the abdomen

- ○ Pancreatic cysts may be palpable, but cancer is usually not
- ○ Ovarian tumors may be palpated in the 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 a patient with hematemesis, the common cause is a bleeding peptic ulcer; in the patient with hematemesis and splenomegaly or hepatomegaly and ascites, or skin changes due to portal hypertension, the most common cause is bleeding from a duodenal or gastric ulcer, followed closely in frequency by bleeding esophageal varices.

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

- Skin diseases
  - Infection
  - Eczema
  - Urticaria
  - Lichen simplex
  - Dermatitis herpetiformis

- Systemic
  - Hepatic
    - Obstructive jaundice
    - Recurrent pruritus of pregnancy
  - Blood disorders
    - Reticulosis
    - Leukemia
    - Polycythemia
    - Fe–deficiency
    - Mastocytosis
  - Endocrine
    - Diabetes mellitus
    - Diabetes insipidus
    - Myxedema
    - Hyperthyroidism
    - Gout
    - Carcinoid
  - Neurological
    - Tabes
    - GPI
    - Thalamic tumor
  - Carcinoma (especially lungs, stomach, colon, breast, prostate)
  - Chronic renal failure (probably due to secondary hyperparathyroidism)
  - Drugs
    - Cocaine
    - Morphine
    - Allergic drug reactions

Adapted from: Burton JL. *Churchill Livingstone* 1971, page 122.

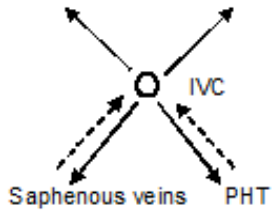
SO YOU WANT TO BE A GASTROENTEROLOGIST!

Give the way how to properly perform the examination of the abdominal veins to distinguish between obstruction of the inferior vena cava (IVC), and portal hypertension (PHT).

- The normal flow of blood in the veins of the abdominal wall below the umbilicus is going down into the saphenous veins, and the veins above the umbilicus is upwards into the veins of the thoracic wall. In portal hypertension, dilated veins show normal direction of flow.
- In IVC obstruction, flow in veins below umbilicus is reversed; instead, it flows upwards.

➢ Blood flow in umbilical veins

Normal thoracic wall veins



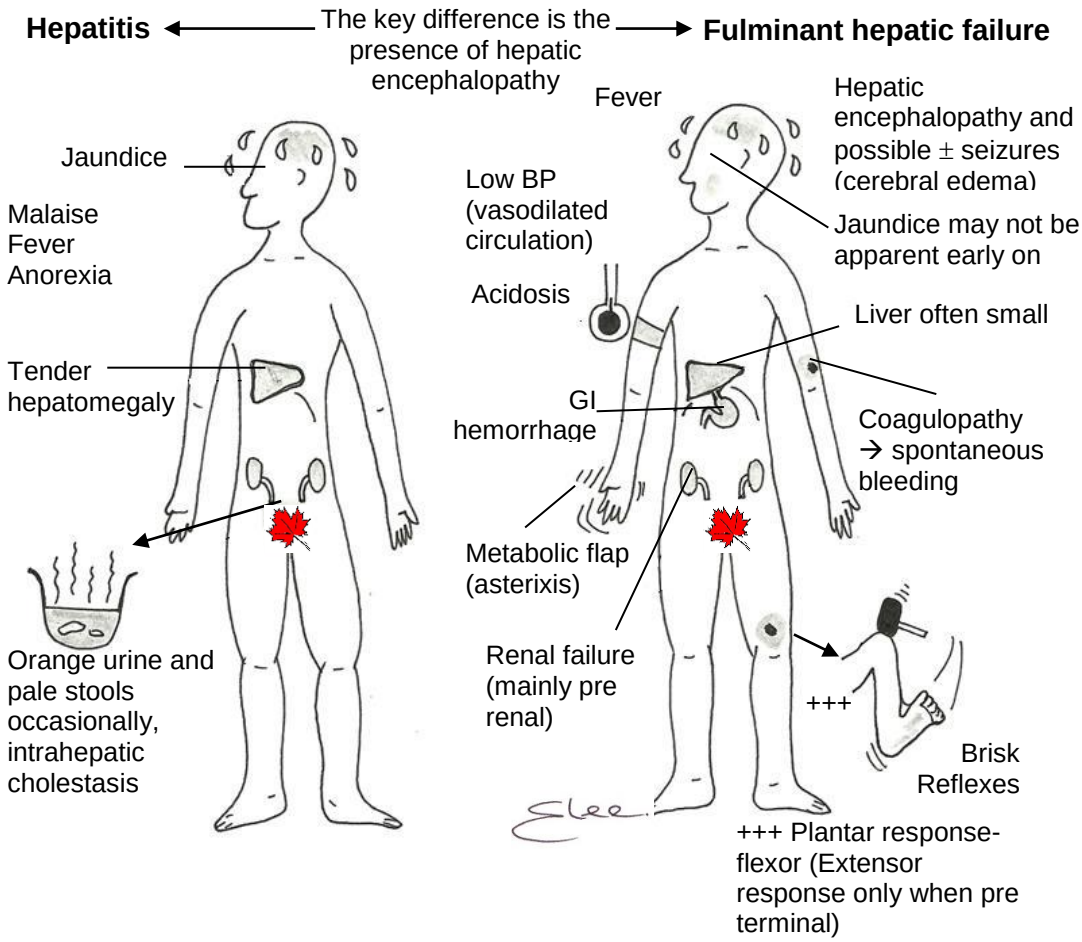
- In obstruction of inferior vena cava (IVC), blood does not flow away from the umbilicus towards the saphenous veins
- In PHT, the enhanced blood flow is still through the normal route, upwards to veins of the thoracic wall, and downwards to the saphenous veins

- The umbilicus is a common site of infiltration by cancer metastases (Sister Mary Joseph nodule).
- Protuberance from ascites (an “outie”)

- Give the functions of the liver.
  - Synthesis
    - Albumin
    - Glycogen
    - Urea
    - Coagulation factor
  - Storage
    - Fat
    - Vitamins A, D, B12
  - Detoxification
    - Hormones
    - Drugs

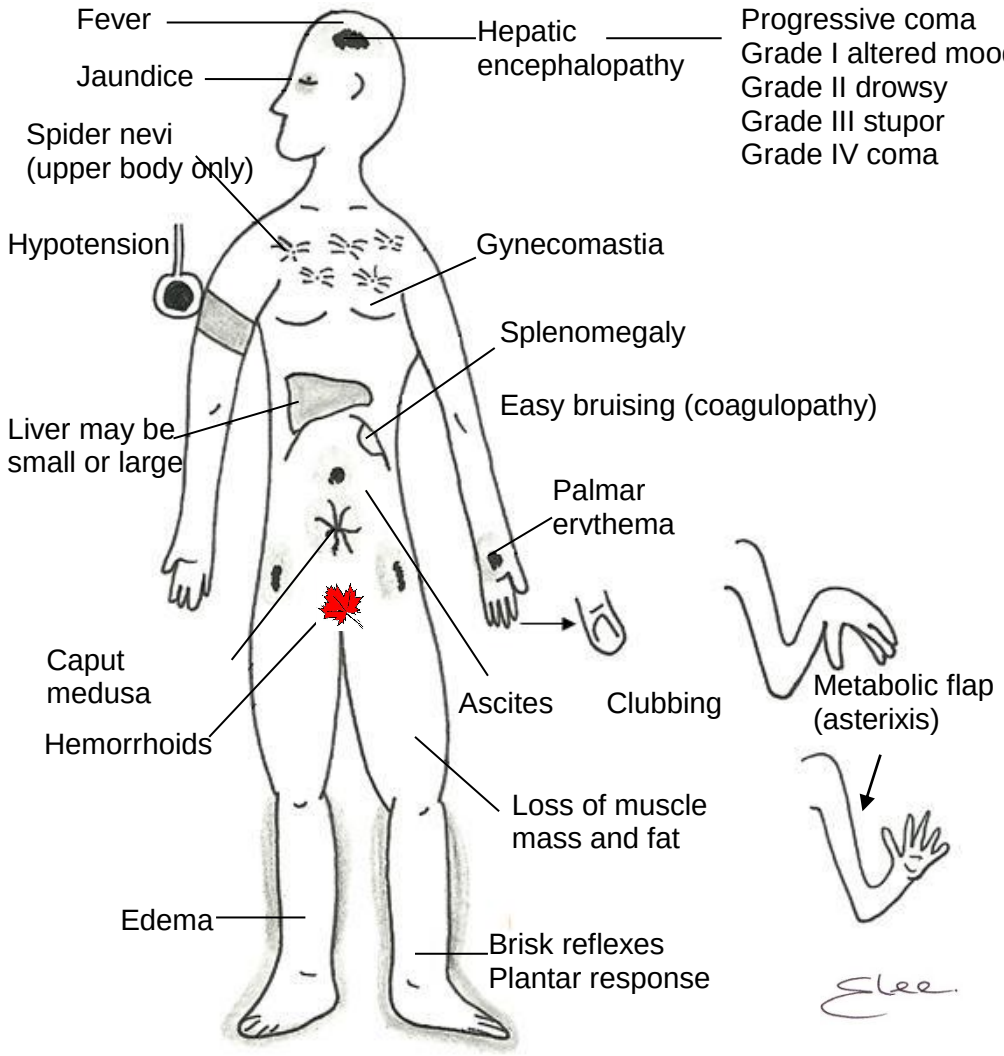
- Secretion
  - Bilirubin
  - Bile salts
  - Cholesterol

- Perform a physical examination for acute liver disease (acute hepatitis and fulminant liver failure).



Adapted from: Davey P. *Wiley-Blackwell* 2006, page 234.

- Perform a focused physical examination focusing on the signs of chronic liver disease (portal hypertension).



*Note that the signs of hepatic encephalopathy (HE), hypotension, fever, acidosis and coagulopathy may occur in acute liver failure. The liver may be normal in size or small early on. Jaundice may be present. The patient may also experience seizures, which is not a feature of HE.

Adapted from: Davey P. *Wiley-Blackwell* 2006, page 234.

- Give the **causes of acute deterioration in known chronic liver disease**.

  - Drugs (including alcohol)
  - Electrolyte disturbances, including renal failure
  - Sepsis (especially spontaneous bacterial peritonitis)
  - GI bleed
  - Hepatoma (HCC)

Examiners "Read my Mind"!

Can you guess what liver disease am I thinking about?

- Mild transaminitis with diarrhea – celiac disease
- ↑ ALP / GGT
  - In a middle aged woman – PBC
  - In a young man with UC – PSC
- ↑ IgA, ↓ folate, ↑ MCV, mildly ↑ ALT/ AST with AST > ALT – alcoholic hepatitis
- AST / ALT
  - > 5000 U/L – ischemic hepatitis, acetaminophen toxicity
  - > 1000 U/L – acute viral hepatitis, drug–induced hepatitis
- Metabolic syndrome + mildly ↑ ALT, AST – NAFLD
- AST, ALT – NASH (NAFLD, ALT > AST, suspect fibrosis if AST > ALT)
- ↓ AP, ↑ uric acid – WD

ALCOHOL AND THE LIVER

Alcohol Abuse

- Terminology
  - 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 period
  - Presence of withdrawal symptoms
  - Excessive amount of time spent in obtaining alcohol
  - Important activities are 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.

- Give the **differences** between alcohol abuse and alcohol dependence.

  - Abuse ≥ 1 of the following in 1 year "HOLS"
    - Using alcohol in **H**azardous situation
    - ↓ fulfillment of **O**bligations
    - **L**egal problems
    - **S**ocial or interpersonal problems
  - Dependence: a physiological state, with ≥ 3 of the following in 1 year "DAAD"
    Desire to ↓ intake
    Activities ↓ because of alcohol
    Acquisition behaviour*
    Drinking ↑

*Acquisition behaviour: "….tolerance, withdrawal, and overwhelming in acquisition and use despite adverse social, psychosocial, or physical consequences" (BB 2013, page 265).

Clinical Reminder
- Alcohol tolerance
  - Just what the word "tolerance" means - ↑ need for ↑ amounts of alcohol to achieve the same analgesic effects
- Alcohol addiction
  - Abnormal behaviour to obtain and to use alcohol

- 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?)
- Social consequences
  - Occupation
  - Family
  - Leisure
  - Financial problems
  - Legal problems
  - Accidents and fights
  - Driving intoxication

- Alcohol withdrawal
  - Shakes, seizures, hallucinations, DTs

- Alcohol–related problems
  - Neurologic
    - Wernicke's Encephalopathy
    - Korsakoff's Psychosis
    - Cerebellar degeneration
    - Peripheral neuropathy
    - Myopathy
    - Seizures
    - Blackouts
    - Sleep disturbances
  - Mental
    - Depression
    - Attempted suicide
    - Family Hx of alcoholism
    - Other substance abuse
    - Stressors
      - Family
      - Spouse
      - Friends
      - Work and employment
      - Money

- Cardiac
  - Hypertension
  - Cardiomyopathy
  - Arrhythmias
- Liver
  - Cirrhosis
  - Hepatitis
  - Acute liver failure
  - Esophageal varices
  - Ascites
  - Fatty liver
- GI
  - Esophagitis
  - Gastritis
  - Hepatitis
  - Pancreatitis
  - Peptic ulcers
  - Esophageal
  - Rectal varices
  - Oral and esophageal cancers
  - Malabsorption
  - UGIB
  - Variceal or non–variceal upper GI bleeding
- Hematologic
  - Iron or folate anemia
  - Thrombocytopenia
  - Coagulopathies
- Endocrine
  - Impotence
  - Hyperlipidemia
- Immunologic
  - Immune system impairment
- Kidney
  - Low serum calcium
  - Magnesium
  - Phosphate
  - Ketosis

Adapted from: Jugovic PJ, *et al*. *Saunders/ Elsevier* 2004, pages 103 and 105.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of alcohol abuse, give what is Zieve's syndrome.
  - Zieve's syndrome is jaundice, hemolytic anemia and hyperlipidemia with hypercholesterolemia.

- Give the **time-course** for the changes found on physical examination of the patient with alcohol withdrawal.

Day	Time after last drink (hours)
1	6-36
1-2	12-48

➢ Treatment

- Alcohol abuse.
  - Behaviour counseling (5 A' and R's)
    - "Five A's"
      - Assess
      - Advise
      - Agree
      - Assist
      - Arrange
    - Five R's"
      - Relevance
      - Risks
      - Rewards
      - Road blocks
      - Repetition
  - ↑ abstinence
    - Acamprosate
    - Disulfiram
    - Anxiety
    - Depression (with alcohol but not benzodiazepine cessation)

- Treat complications
  - Alcohol withdrawal
    - Symptom–triggered regime of regular fixed schedule protocol–driven injections of long–acting benzodiazepine
    - β–blockers, clonidine for ↑ HR, ↑ BP
    - Hydration of thiamine, then IV D5W
  - Alcoholic liver disease
  - Patients psychosocial challenges

Clinical Alert

In the patient with alcoholic liver disease with alcohol withdrawal, give the cautions about the use of benzodiazepines and anti–psychotics.

- Benzodiazepines
  - Too much may cause hepatic encephalopathy
- Anti–psychotic agents
  - A "no-no": do **not** use because anti–psychotics may ↓ threshold for seizures, and patients in alcohol withdrawal are at risks of seizures.

- Recognize at–risk drinking

	Per occasion	Per week
M	> 4	> 14
F	> 3	> 7

- In the context of substance withdrawal, take a directed history and perform a focused physical examination for alcohol and benzodiazepine withdrawal syndromes.

- History
  - Alcohol and benzodiazepine use, and discontinuation
  - Specific assessment tools
    - Clinical Institute Withdrawal Assessment for Alcohol (CIWA-AR)
    - Clinical Institute Withdrawal Assessment for Benzodiazepines (CIWA-Bezo)
  - Withdrawal syndrome

Time after stopping alcohol	Name of withdrawal syndrome	Clinical picture
○ 6–8 hours	Shake	- Tremor - Nausea and 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 and anxiety, death

- 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's encephalopathy
  - CVS
    - Arrhythmias
    - Cardiac death

Adapted from: Grey J, Therapeutic Choices. 6th Edition, *Canadian Pharmacists Association* 2012, Table 1, page 141.

Alcoholic Hepatitis

- In addition to supportive therapy, corticosteroids and pentoxifylline are standard of care for alcoholic hepatitis (AH)
- There are two important caveats:
  - First, the patient must be stratified by severity of the hepatitis.
  - There must be no contraindications to these treatments.

- Give the factors that would be used as **indicators for the use of corticosteroids** with pentoxifylline in alcoholic hepatitis*.

  - There are several scoring systems used to determine the severity of AH.
  - Unless you are doing a GI subspecialty exam, you will not be expected to know how to calculate these scores, or the individual components of the scores.
  - But, if you are given one of the three major scores, you must recognize these and know the levels at which therapy with corticosteroids and pentoxifylline are started:
    - Maddrey Discriminant function (MDF) score ≥ 32
    - MELD score ≥ 9
    - Glasgow Alcoholic Hepatitis score (GAHS) ≥ 9
  - Remember: Glasgow Melds–Discrimination (GASH–MELD–MDF) ≥ 9 and18 ≥ 32
  - Also, independent of these scores, if the patient with AH has either
  - Hepatic encephalopathy, or
  - Ascites

* Note: A recent well–conducted RCT has challenged the previous study supporting the use of pentoxifylline

- Give the contraindications for corticosteroids and pentoxifylline use in AH
  - Criteria for severity of AH not satisfied
  - Kidney diseases (such as HRS, hepatorenal syndrome, which commonly may accompany ascites)
  - Infection (which may be worsened by corticosteroids)
  - GI bleeding
  - Pancreatitis

MCQ ALERT- Watch out for the red herring:

- If the patient has ascites in the context of AH, then the MCQ stem may provide the analysis of the ascitic fluid (WBC > 250/μL), with the view in seeing if they can mislead you to treat spontaneous bacterial peritonitis (SBP), rather than recognizing that ascites in AH represents an indication for the use of corticosteroids and pentoxifylline.

ACUTE LIVER FAILURE

- Definition
  - Acute hepatic injury leading to hepatic encephalopathy (HE) and coagulopathy (↑ INR) in the patient without cirrhosis is acute liver failure (ALF).
  - We all know how to examine the case stem for acute onset of HAV, HBV, HBV plus HDV, or acetaminophen toxicity.

MCQ ALERT. Watch out for "What am I thinking?"

- HE, ↑ INR, no cirrhosis, acute onset. Suspect ALF!

Added information	Think of
○ Holiday in Mexico	– HAV
○ Holiday in India	– HBV + HDV
○ Hypotension in hospitalized patient, ALT, AST > 1000 U/L	– Hepatic ischemia
○ Pregnancy	– HELLP or AFLD
○ Pregnancy, hypotension and proteinuria	– Preeclampsia, usually associated with HELLP, but may also be seen in AFLD
○ Pregnancy, HE, hypoglycemia	– AFLD
○ RBC hemolysis, renal tubular acidosis, psychiatric or CNS symptoms, KF rings	– Wilson disease
○ Eating mushrooms	– Poisoning from *Amanita phalloides*

Abbreviations: AFLD, acute encephalopathy; HELLP, hemolysis elevated liver enzymes low platelets; KF, Kayser–Fleischer rings

- Why is it “reasonable” for a GI and GIM candidate to know about such rare causes of LF as WD, HELLP, AFLD, or mushroom poisoning?
    - While these may be very rare causes of ALF, which itself is rare, these causes of ALF are:
        - Treatable
        - The patient might survive if the diagnosis were made early
        - The patient might survive if treatment started early
        - Possibly avoids liver transplantation

➢ Treatment

- Give the treatment for the following causes of acute live failure.
    - HELLP, AFLD → emergency delivery of the baby
    - *Amanita phalloides* poisoning → penicillin, milk thistle
    - Wilson disease → copper chelation therapy

LIVER TRANSPLANTATION

➢ Complications

- Infections cause ~ ½ of the deaths from solid organ transplants, such as liver transplants (LT)

➢ Treatment

- Combinations of immunosuppressant agents used:
    - Prednisolone
    - Calcineurin inhibitor
        - Cyclosporin
        - Tacrolimus
    - Antimetabolite (cytotoxic)
        - Azathioprine
        - Methotrexate
        - Mycophenolate mofetil
        - Cyclophosphamide
- Other agents include
    - mTOR
    - Monoclonal or polyclonal lymphocyte–depleting antibodies
        - Anti–Cd3, 20, 52
        - Anti–IL2 receptor

- Adverse events
  - In transplant–related "cocktails", cytotoxic drugs are associated with ↑ risk of infection, as compared with calcineurin–pathway inhibitors (e.g. cyclosporine)
  - Corticosteroids are associated with ↑ risk of Pneumocystis (*P. jirovecii*)
    - ↑ longlist of other major corticosteroid–associated adverse effects
  - Lymphocyte–depleting antibodies
  - Agents used in cocktails for transplantation have ↑ risk of AEs:
    - Cytomegalovirus (CMV)
    - EBV–associated Ebstein–Barr virus post–transplant lymphoproliferative disorder (PTLD)
    - Polyoma BK virus (PBKV) → nephropathy, strictures of ureter, hemorrhagic cystitis (in HSCT)
    - *P. jirovecii*

➢ Prophylaxis for infections

- Name the antimicrobial agents given pre–transplantation for prophylaxis of post–transplantation infections.

Organism	Antimicrobials
○ *Candida*	– Fluoroquinolone
○ CMV	– Ganciclovir IV, Valganciclovir po – Continue 3-4 mon post–transplantation
○ Pneumocystitis	– Trimethoprim–sulfamethoxazole – Continue 12 months post–transplantation – Also effective prophylaxis for ▪ *Listeria* ▪ *Nocardia* ▪ *Toxoplasma*
○ TB (latent)	– Isoniazid
○ HBV, HCV	– Appropriate anti–viral therapy

➢ Vaccinations

- Name the vaccines given to liver transplantation patients (or other recipients of solid organs).
  - Pre–transplantation
    - TDAP
      - Tetanus, diphtheria, acellular pertussis
    - MMR
      - Measles
      - Mumps
      - Rubella
    - Polio
      - Inactivated
    - HAV
      - Hepatitis A virus
    - HBV
      - Hepatitis B virus
    - Varicella
  - As a general recommendation for all non–transplantation individuals
    - Pre–transplant only
      - Zoster
      - Human papilloma virus (HPV)
    - Pre– and post–transplantation
      - Pneumococcal vaccine
      - Influenza (inactivated)
      - Meningococcal vaccine

- What organisms need to be screened from the donor prior to liver transplantation?
  - CMV
  - EBV
  - HBV
  - HCV
  - HIV
  - TB

- Indications for liver transplantation, a rule of thumb:
  - Hepatic encephalopathy (HE)
  - Jaundice
  - Esophageal varices (EV)
  - Ascites
  - MELD score
    - 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^+
      - **A**scites
      - **A**lbumin
      - **B**ilirubin
      - **C**reatinine
      - **C**oagulation (INR)
      - **H**epatic Encephalopathy
      - **Na^+** (risk for central pontine myelinolysis)
        - The MELD – Na^+ score is better than the original MELD score in predicting mortality of patient on liver transplantation.

- Contraindications
  - Sepsis
  - Cancer
  - Hemodynamic instability

- Prognosis
  - 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 transplantation of livers from brain–dead donors is superior to heart–dead donors.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

About half of all patients having a transplantation of the heart (HT), lung (LT), or heart plus lung (HLT) will develop GI symptoms.

- Give the complications usually develop after HT, LT and HLT.
  - Esophagus
    - GERD
    - Severe necrotizing fungal esophagitis complicated with esophageal perforation
    - Increased risk of obliterative bronchiolitis
  - Stomach
    - Gastroparesis (possibly due to CMV V2V)
    - Giant (>3 cm) gastric ulcers (↑ risk of *H. pylori* infection)
  - Bowel
    - Diverticulitis
    - Ischemic colitis
    - Infectious colitis
      - CMV
      - *C. difficile*
  - Pancreas
    - Pancreatitis
  - Galbladder
    - Cholelithiasis
  - Graft-versus-host disease (GVHD)
    - Fever, skin rash, GI symptoms
    - Increased incidence of non–infectious diarrhea with fatal outcome

- Give the GI conditions in the post–operative course of kidney transplant, or kidney and pancreatic transplant.
  - GERD develops in ~ 50%
    - Associated with ↑ kidney graft loss and eventually, death
  - ↑ risk of HBV or HCV (~50%)
  - Interferon α and ribavirin cannot 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)

COMPLICATIONS OF POST–LIVER TRANSPLANTATION

➢ About 1/3 of patients with a solid organ transplant (SOT) (e.g., liver) will develop post–operative complications.

- Give the post-operative complications of liver transplantation.
  - Graft dysfunction
  - Medications (Rx) causing adverse effects (AEs)
  - Infections (please see later extensive list)
    - Bacterial sepsis (cholangitis lenta syndrome)
    - CMV, V2V, HSV, EBV
      - Hepatitis
      - Acute liver failure (V2V, HSV)
    - HBV, HCV
      - Primary disease or recurrence
    - Fungal abscess
  - Malignancy
    - Acquired
      - Present prior to surgery
      - Complications from surgery
      - Transmitted from the allograft
      - HCC
      - PLTD
  - Immune
    - GVHD
  - Vascular
    - Post–KT
      - NRH (nodular regenerative hyperplasia)
      - Peliosis hepatis
    - Ischemic liver injury
    - Veno–occlusive disease (aka sinusoidal obstructive syndrome [SOS])
  - Hepatobiliary
    - Recurrence of original (pre–transplantation) liver disease
  - Complications unique to underlying disease (eg. Cystic fibrosis)

- Liver
  - Drug-induced liver injury (DILI)
    - Azathioprine
      - ↑ transaminases
      - Cholestatis
      - Centrilobular hepatocyte damage
      - Veno–occlusive disease (sinusoidal obstruction syndrome) → PHT
    - Cyclosporin, tacrolimus
      - Cholestasis
    - Sirolimus
      - Dose–dependent ↑ ALT/AST

- Biliary tree
  - Acalculous cholelithiasis
  - Cholelithiasis → cholecystitis
    - Mortality rate for acute cholecystitis is 29%
    - Use UDCA prophylaxis

Abbreviations: EBV, Epstein–Barr virus; GVHD, graft-versus-host disease; HCC, hepatocellular cancer; HCT, hematopoietic cell transplantation; HHV-6, human herpesvirus-6; NRH, nodular regenerative hyperplasia; PHT, portal hypertension; PTLD, post transplant lymphoproliferative disease; UDCA, ursodeoxycholic acid; VZV, varicella-zoster virus

Bacterial Infections

- Give the common bacterial infections in post–liver transplantation which are related to surgical site and organ transplant.
  - CNS
    - *Listeria monocytogenes* (meningoencephalitis, cranial nerves, brainstem)
    - *Nocadia* (brain ascess)
    - *Toxoplasma gondii* (infected transplanted heart)
  - Lung
    - Pneumonia
    - *Burkholderia crucia* in CF (cystic fibrosis; patient receiving lung transplant)
    - *Legionella*
    - *Nocardia*
    - TB (tuberculosis)
    - *Strongyloides stercoralis*

- Heart
  - *Toxoplasma gondii*
- Liver
  - Peritonitis
  - Cholangitis
  - *E. coli*
  - *Klebsiella*
  - *Staphylococci*
  - MDRO (multidrug–resistant organisms)
    - *Pseudomonas aeruginosa*
    - MRSA (methicillin–resistant *Staphylococcus aureus*)
- GI tract
  - *Clostridium difficile*
  - *Strongyloides*

Fungal Infections

- Aspergillus and non-Aspergillus mold species
  - *Mucor*
  - *Rhizopus*
- Procedures commonly associated
  - Lung transplantation
  - ASCT
- Sites
  - Lung
  - Brain

"Consent is a dialogue, not a signature"

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the clinical course of *C. difficile* in Solid organ transplantation (SOT).
  - Common
  - May be clinically mild
  - Severe
    - Megacolon
    - Death
  - Poor response to antibiotics (only ~70%)

- Give the benefits of probiotics for *C. difficile* infection in immunosuppressed SOT patient?
  - None. In fact beware! There may be an ↑ risk of yeast infection and dissemination!

Pancreatitis is common in SOT setting (liver –Tx, 5%, KT, ~2%).

- Give the common causes of the post–SOT for pancreatitis.
  - Infiltration
    - Malignancy
  - Drug and toxins
    - Alcohol
    - Azathioprine
    - Steroids
    - Cyclosporin
    - Tacrolimus
  - Cholelithiasis (perhaps due to precipitation of cyclosporin in bile, forming the nidus for crystalization and stone formation)
  - Surgical manipulation of pancreas

➢ ***Candida***

- *Candida albicans* and *C. glabrata*
- ↓ overall risk with fluconazole as prophylaxis
- Fluconazole prophylaxis has led to ↑ drug resistance

- Give the anti–fungal treatment for life–threatening *Candida* fungemia.
  - Echinocandin agents
    - Caspofungin
    - Anidulafungin
    - Micafungin

- Other Common Fungal Infections
  - Histoplasmosis
  - Coccidioidomycosis
  - *Cryptococcus neoformans*

Hematopoietic Stem Cell Transplantation and the Liver

SO YOU WANT TO BE A GASTROENTEROLOGIST!

In the context of hematopoietic stem cell transplantation (HSCT), give the early causes of anorexia and vomiting, other than from medications (e.g. calcineurin inhibitors, Septra®).

- GI
  - Mucositis
  - Drug adverse effects of opioids in myeloablation therapy
  - Gastroduodenal GVHD
    - Patchy condition, which may be missed on biopsy
    - EGD
      - Gastric retention
      - Patchy erythema
    - Biopsy
      - Edema
      - Apoptosis of epithelial cells
      - Lymphoid infiltrate
  - Infection
    - CMV (may be in mucosa and not in the blood stream)
    - HSV
  - Gastric retention
  - TPN
- Non–GI
  - CNS disease
  - Adrenal insufficiency

GI complications of HSCT

- Give the GI and liver complications associated with hematopoetic stem cell transplantation (HSCT), and examples.
  - Liver: space occupying lesions
    - 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!

- What is Typhlitis Syndrome?
  - Cecal inflammation, friability, ulceration and edema in patients who are neutropenic
  - Usually caused by *C. septicum*
  - Often results in polymicrobial sepsis

- Give methods to diagnose hepatic fungal infection in HSCT.
  - Diagnostic imaging
    - CT, MRI
  - Serum fungal biomarker assays
    - Galactomannan assay
    - Glucan
  - Liver biopsy
    - PCR
    - Culture

VENO OCCLUSIVE DISEASE (VOD) OR SINUSOIDAL OBSTRUCTIVE SYNDROME (SOS)

- Definition
  - Veno–occlusive disease (aka sinusoidal obstruction syndrome [SOS]) occurs in up to 20% of HST patients, depending on the myeloid–ablative conditioning used, and the presence of pre–existing liver disease.

- Clinical
  - A clinical diagnosis may be made in the first three weeks after HCT. In difficult cases, wedge hepatic venous pressure gradient (WHVPG) and liver biopsy may be necessary.
  - Painful hepatomegaly
  - Abnormal LE's (liver enzymes)
  - Associated with:
    - Bone marrow transplantation (BMT; up to 21 days post BMT)
    - Chemotherapy
    - Therapy with azathioprine

- Histopathology
  - Sinusoids
    - Dilated, disrupted
    - Non–thrombotic occlusion
    - RBC accumulation (congestion)
    - 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!

Unfortunately, liver diseases which led to the need for a liver transplantation (LT) may recur in the transplanted liver.

- Give the types of liver diseases which recurs after LT (liver transplantation).
  - Infection – HBV
    – HCV
  - Immune – PBC
    – PSC
    – AIH
  - Metabolic – NASH
  - Toxins – ALD

Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus (99^{+} % recurrence); NASH, non–alcoholic steatohepatitis; PBC, primary biliary cirrhosis

CYSTIC FIBROSIS

➢ Clinical

- Give the GI and Hepatobiliary clinical manifestations of cystic fibrosis.
  - Esophagus
    - Gastroesophageal reflux disease (GERD)
  - 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.

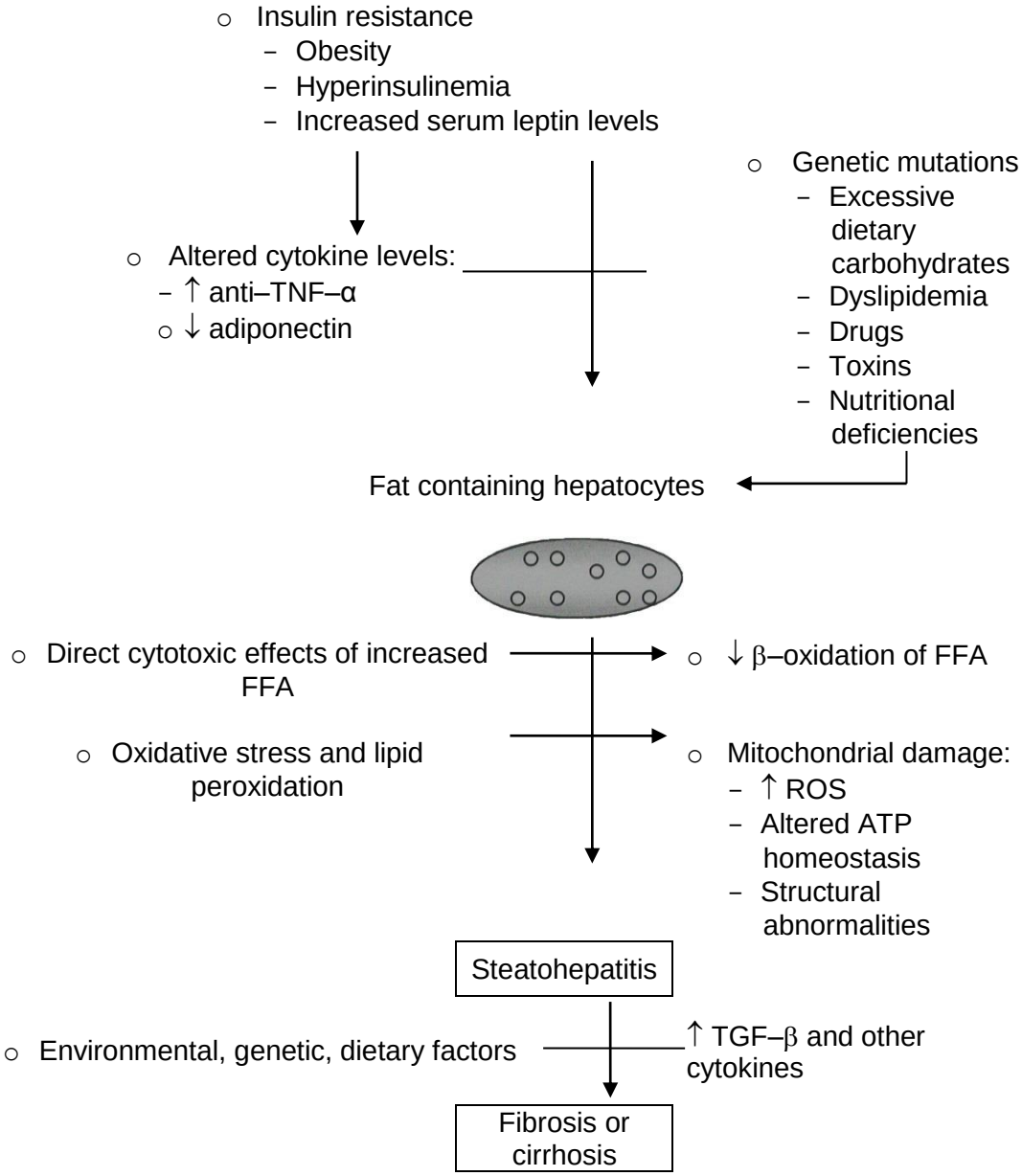
SO YOU WANT TO BE A GASTROENTEROLOGIST!

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 liver transplantations in cystic fibrosis patients.

- Give the unique GI complications of LT in CF.
  - Secondary biliary cirrhosis → ↓ absorption of fat–soluble drugs; such as cyclosporin
  - Distal intestinal obstructive syndrome (20%)

NON–ALCOHOLIC LIVER DISEASE (NAFLD) AND NON-ALCOHOLIC STEATOHEPATITIS (NASH)

- Give the pathogenesis of non–alcoholic 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.

- **Dyslipidemia**
  - Patients with NAFLD often have metabolic syndrome wherein they may have hyperlipidemia (triglycerides ≥ 150 mg/dL; HDL–cholesterol < 40 mg/dL in men; < 50 mg/dL in women). Under circumstances where the LDL cholesterol is increased, use statins followed if necessary by statins with bile acid sequestrants such as cholestyramine.
  - If the serum triglyceride (TG) concentration is increased as well as the LDL–cholesterol, use statins.
  - Non–HDL cholesterol concentration is a secondary target for patients with serum TG ≥ 200 mg/dL.
  - If TG is increased and LDL–cholesterol is "at goal", use fribrates or nicotinic acid.
  - Note: do not say that cholesterol level is high or normal, since the acceptable level depends on the number of risk factors for coronary heart disease (CHD) and for patient's risks of having myocardial infarction (MI).
  - A patient with NAFLD may have ↑ LDL–cholesterol + ↑ TG, and the use of statins is indicated. Even if there is ↑ ALT, AST in NAFLD, statins are safe, and should be chosen as a treatment option.

- Treatment

- Give the benefits and adverse effects (AEs) of pioglitazone (TZD) in the treatment of NAFLD.

Benefit	AEs
↓ adipokinins	– ↑ BMI
↑ adiponection (a protector of the liver)	– ↑ CV event
↑ β–oxidation	– ↑ osteoporosis
↓ TG, ↓ VLDL	– ↑ bladder cancer
Converts "bad" into "good" fat	
↓ insulin resistance	

SO YOU WANT TO BE A HEPATOLOGIST!

- Patients with NAFLD may have elevated serum levels of ALT and AST.
- Give the level of these liver enzymes indicating the need for a liver transplantation (LT).
  - No level!
  - The decision for LT is based on the risk factors in progressing to NASH, and not on the level of their ALT or AST.
  - In fact, ~60% of patients with NASH–cirrhosis have normal transaminases.

SO YOU WANT TO BE A HEPATOLOGIST!

- Bariatric surgery improves NASH; give the use of dieting for patients with NASH.
  - There is an inverse linear relationship between increasing weight loss and a decline in NASH and NAFLD activity score.
  - Even just a 5% loss of body weight has a clinically meaningful decline in the severity of NASH.
- Does weight loss in NAFLD ↓mortality from liver disease?
  - Patients with NAFLD treated with weight loss showed decreased in mortality rate from both cardiovascular as well as hepatic causes of death.

The pathogenesis of the progression of NAFLD to NASH involves insulin resistance, as well as oxidative stress. There is evidence that Vitamin E may benefit NASH. Treatment for insulin resistance with pioglitazone (TZD) for instance, is not sufficient by itself.

- Give the best laboratory test to establish the presence of insulin resistance.
  - ↑ blood insulin suggests the presence of insulin resistance, and is a good measure for more complicated end points such as HOMA, to predict the presence or degree of insulin resistance.

CIRRHOSIS

- Give the mechanisms causing a hyperdynamic circulation in patients with cirrhosis.
    - ↓ blood volume
    - ↑ cardiac output
        - Vasodilation
        - Shunts
        - Anemia
        - Fever

- Give the best **treatment** for the three **complications of cirrhosis**, esogeal variced bleeding (EVB), spontaneous bacterial peritonitis (SBP), and hepatic encephalopathy (HE).
    - Know the complications, the menu of options for both prophylaxis and treatment of active complications, and what is no longer "fashionable" (i.e., wrong answer on MCQ).

- EV bleeding
    - Prevention (1º, before first [index] bleeding; 2º after index bleed)
        - Menu
            - Non–selective beta–blocker
                - Nadolol
                - Propranolol
            - Endoscopic variceal ligation (EVL)
    - Active EV bleeding
        - Menu
            - Octreotide SC
            - Fluoroquinolones for 7 days to prevent SBP
            - EVL
                - If unsuccessful → TIPS
                - Surgical shunt
            - Consider liver transplantation

- SBP
    - Prevention (fluoroquinolones)
        - Ascites, if fluid protein < 1.0 g/dL, Rx during time in hospital
        - EV bleeding, 7 days Rx
        - Previous SBP, maintenance Rx

- Hepatic encephalopathy (HE)
  - Prevention
    - Lactulose
    - Note: low protein diet is no longer used, and is considered an incorrect answer
  - Treatment
    - Lactulose
    - Rifaximin, if lactulose fails
    - Treat possible precipitants of HE
    - Consider possible liver transplantation
    - Note: Neomycin is no longer used, and is considered an incorrect answer

- A patient who is on warfarin for VTE prophylaxis develops life–threatening bleeding. In addition to giving vitamin K 10 mg over 60 min, give the additional therapeutic options.
  - The vitamin K reversal on the effects of warfarin on the vitamin K–dependent coagulation factors II, VII, IX, and X effects slowly even when given intravenously.
  - Prothrombin complex concentrate (PCC) contains all the vitamin K–dependent factors
  - Recombinant human factor VIIa (rhF VIIa) is the second choice for rapid reversal since it does not contain factors II, IX or X
  - Fresh frozen plasma (FFP) is slow to prepare and to administer
  - If FFP is given, it must also be co–administered with vitamin K
  - Jaundice
  - Hepatocellular cancer

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- A patient with portal hypertension is examined, and does not have splenomegaly. Give the possible explanations.
  - Asplenism
    - Congenital
    - Surgical removal
  - Dextrocardia
  - Multiple splenic infarcts (e.g. Sickle cell disease)
  - Splenic vein thrombosis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the locations or parts of the nervous systemw which are affected by hepatic encephalopathy (HE)?
  - Cortex
  - Cerebellums
  - Basal ganglia
  - Spinal cord
  - Peripheral nerves
  - Muscles

ASCITES

- Ascites is associated with the development of:
  - Spontaneous bacterial peritonitis (SBP)
  - Hepatorenal syndrome (HRS)

➢ Clinical

- Take a directed history and perform a focused physical examination for ascites, and give the performance characteristics of the major clinical points.

Item	PLR	NLR
History		
– Increased girth	4.2	0.2
– Recent weight gain	3.2	0.4
– Hepatitis	3.2	0.8
– Ankle swelling	2.8	0.1
– Heart failure	2.0	0.7
Physical		
– Fluid wave	5.0	0.4
– Shifting dullness	2.7	0.3
– Bulging flanks	2.0	0.2
– Flank dullness	2.0	0.3

*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 findings of a fluid wave and shifting dullness have an LR >2 to detect 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.

Give the co–existing diseases, which increase the pretest probability of finding ascites.

- Heart
  - Heart failure (HF)
  - Pericarditis
- Liver – cirrhosis
- Kidney – nephrotic syndrome
- GI
  - Protein losing enteropathy
  - Malabsorption
  - Malnutrition
- Cause
  - Systemic infection
  - Blunt abdominal trauma

Refractory Ascites

- Definition
  - Ascites that is not eliminated even with maximum diuretic therapy
    - Furosemide 400 mg po od
    - Aldactone 160 mg po od
  - Ascites that is not eliminated because of the maximum dosages of diuretics cannot be attained, given the development of diuretic induced complications
- Treatment
  - Salt restriction and diuretic therapy as tolerated
  - Total paracentesis + I.V. albumin (6-8 g/L of ascites removed)
    - If <5 L of ascites is removed, a synthetic plasma volume expander may be used instead of albumin

- Alternative therapy
  - TIPS for patients who require paracenteses (every 1-2 weeks) and whose CTP score is <11
  - Peritoneovenous shunt for patients who are not on TIPS or liver transplant candidates
  - Liver transplantation
  - Vasopressin blocker
  - 5 RCTs show that TIPS is superior than Large volume paracentesis (LVP) for:
    - Control of ascites
    - Need for repeat paracentesis
    - Mortality rate

Abbreviation: CTP, Child Turcotte Pugh; HRS, hepatorenal syndrome; I.V., intravenous; PHT, portal hypertension; RBF, renal blood flow; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt

Give the mechanisms for the development of the paracentesis–induced circulatory disorder (PICD).

- PHT or ascites may develop as a result of an inappropriate signal to the kidney to reabsorb Na^+/ H_2O
- The intravascular volume is normal or ↑ in cirrhotic patients with ascites
- Loop diuretics, but not paracentesis, cause mild (14%) depletion of intravascular volume

Vasopressin Blockers

- Mechanism

- 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

PICD – parecentesis → circulatory dysfunction → ↓ RBF to cortex → HRS

Printed with permission: Garcia T, *et al*. *Am J Gastroenterol* 2009; 104:1802-29.

➢ Treatment

- 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

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (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.)

➢ Clinical indication
  - Bridge to liver transplantation (LT)
  - Reduces portal pressure
    - May be useful for short–term control of bleeding esophageal varices

– Give the name of the genetic study which should be performed in all patients with Budd-Chiari syndrome (BCS) to establish appropriate hematological follow-up.

  - JAK2 VG17F mutational analysis will be positive in BCS associated with polycythemia vera (PV; 97%) as well as essential thrombocythemia (ET, 50%).
  - Polycytemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative disorders which may benefit from myeloproliferative therapy.

MCQ TIP

The MCQ stem has a patient with ascites. You are provided with a multitude of results of the analysis of the tapped ascitic fluid. These are the three most important findings you have to focus on:

- WBC count
  - WBC ≥ 250/μL (equals spontaneous bacterial peritonitis [SBP])
- Ascitic fluid
- Total protein concentration
  - < 25 g/dL
  - > 25 g/dL
- Serum and ascitic fluid concentrations of albumin (so that the SAAG may be calculated)
  - SAAG > 1.1
  - SAAG < 1.1

- SAAG > 1.1, or < 1.1; ascitic fluid protein < 2.5 g/dL or > 25 g/dL

Ascitic fluid protein	SAAG > 1.1	SAAG < 1.1
< 25 g/dL	○ Cirrhosis	– Nephrotic syndrome
> 25 g/dL	○ R–HF	– Malignancy
	○ B–CS	– TB

Abbreviations: BCS, Budd-Chiari syndrome (hepatic vein thrombosis); R-HF, right-sided congestive heart failure

JAUNDICE

Findings predicting hepatocellular cause in patients with jaundice

➢ The peripheral findings on physical examinations for dilated abdominal wall veins (17.5), palmar erythema (9.8) and spider angiomata (4.7) have the highest values for a positive likelihood ratios (PLR) in predicting a hepatocellular cause of jaundice. The PLRs for the presence of ascites and palpable spleen are 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!

- Give the best test to assess the size of the liver in a patient with suggested cirrhosis on abdominal ultrasound with doppler, or transient elastography.

    - 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), but is not used to assess liver size.

In most patients with viral hepatitis, the liver is usually enlarged and tender whereas the spleen is enlarged and non–tender.

- Which virus causes a large, tender spleen but non–tender hepatomegaly?

    - Epstein–Barr Virus (EBV)

Dupuytren;s contracture (DC) is caused by thickening and flexure contraction of the palmar tendons, usually of the 4th and 5th digit (never on the 1st digit, i.e. thrumb). This is associated with alcoholism (~40%) or alcoholic liver disease (~40%).

- Give the other GI or non–GI conditions commonly associated with DC.

    - Other GI conditions
        - Peptic ulcer disease
        - Cholecystitis
    - Non–GI conditions
        - Lungs – tuberculosis
            - smokering
            - lung cancer
            - bronchiectasis
        - CNS – epilepsy
        - Endocrine – diabetic retinopathy

HEPATOCELLULAR CANCER (HCC)

- Demography
  - M:F 2:1–4:1
  - 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
    - NAFLD and NASH
    - Hemochromatosis
    - HCV
    - Increased BMI
    - Androgenic hormones
- Risk factors

- Give the risk factors for HCC in HBV.
  - Patient
    - Presence of cirrhosis
    - Young age of acquisition
    - Asian or African race
    - Male gender
    - Older 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 the risk factors for HCC in HCV.
  - Patient
    - Alcohol drinking (heavy > 50 gm/d)
    - Male gender
    - Larger BMI
  - Liver
    - Degree of hepatic fibrosis
  - Infection
    - HBV co–infection
    - 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.

➢ Clinical

SO YOU WANT TO BE A GASTROENTEROLOGIST!

– Give the clinical use in auscultating hepatic bruit and friction rub?

o Hepatic arterial bruit	- Alcoholic hepatitis - Hepatocellular cancer (HCC) - Metastases
o Venous hum	- Portal hypertension (PHT, usually from cirrhosis, or Cruveilhier–Baumgarten syndrome)
o Venous hum plus hepatic arterial bruit	
- PHT + alcoholic hepatitis	
- PHT + HCC	
o Rub + bruit	- HCC
o Rub and bruit + venous hum	- Cirrhosis - HCC
o Friction rub	- Infection in and around the liver (e.g. gonococcal perihepatitis [Fitz–Hugh–Curtis syndrome])

- Give the patient groups who require screening for HCC.

➢ Hepatitis B Carriers
  - o Asian males >40
  - o Asian females >50
  - o Family history of HCC
  - o African >20 years
  - o All causes of cirrhosis

 Non–Hepatitis B Carriers
  - o Hepatitis C
  - o Alcoholic cirrhosis
  - o Hereditary hemochromatosis
  - o Primary biliary cirrhosis
  - o Possibly: alpha 1 antitrypsin, NASH, autoimmune

➢ Screening of HCC

- Give the methods used to screen hepatocellular cancer (HCC).
  - o Risk stratification, including HBV and HCV
  - o q 6 months for alpha–fetoprotein (AFP) and abdominal ultrasound over 5 years improve the survival of HCC in HBV–positive patients in China.

- Most of the detected HCC in the screened groups are 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 on the availability of effective therapy for the early detected lesions
- HCC screening in patients awaiting liver transplantation is cost–effective

Abbreviation: AFP, alpha–fetoprotein; HCC, hepatocellular cancer

➢ Associations

- Give the **paraneoplastic syndromes** associated with HCC.

o CNS	– Neuropathy
o Endocrine	– Sexual changes: isosexual precocity, gynecomastia, feminization
o MSK	– Carcinoid syndrome – Hypercalcemia – Hypertrophic osteoarthropathy – Hypoglycemia – Osteoporosis – Polymyositis – Thyrotoxicosis – Thrombophlebitis migrans
o CVS	– Systemic arterial hypertension
o Skin	– Porphyria
o GI	– Watery diarrhea syndrome
o Hematology	– 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.

➢ Diagnostic imaging

– Give the imaging criteria for confirming HCC in patients with cirrhosis and a nodule detected by ultrasound.

- Abdominal ultrasound
  - Sensitivity, > 60%
  - Specificity, > 90% (Bolondi L, *et al*. *Gut* 2001251-259.; Singal A, *et al*. *Aliment Pharmacol Ther* 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 only 30% for lesions measuring < 20 mm
  - For hyper–enhanced nodule > 1 cm, suspect HCC
  - Lesion has nodular configuration
  - Lesion is at least 1 cm in its longest diameter*
  - Lesion shows arterial hypervascularization:
    - Hyper–enhanced nodule in the arterial phase by two imaging techniques**
      - Contrast–enhanced US, contrast–enhanced spiral CT, and gadolinium–enhanced MRI
    - Hyper–enhanced nodule in the arterial phase and as hypo–enhanced nodule in the portal venous or delayed phase by one imaging technique**
      - 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

Source: El-serag HB. *2009 ACG Annual Postgraduate Course*: 39-43.

- Liver biopsy under guidance

Biopsy guidance	Sensitivity	Specificity
US	90%	91%
CT	92%	98%

- Laboratory

  - Alpha–fetoprotein (AFP)
    - Performance characteristics depends on cut–off value: 20 mg/mL, sensitivity of 25-65%
    - 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 occurs with a high rate of hepatocyte regeneration (e.g. HCV) of HCC (El-Serag HB, 2009)

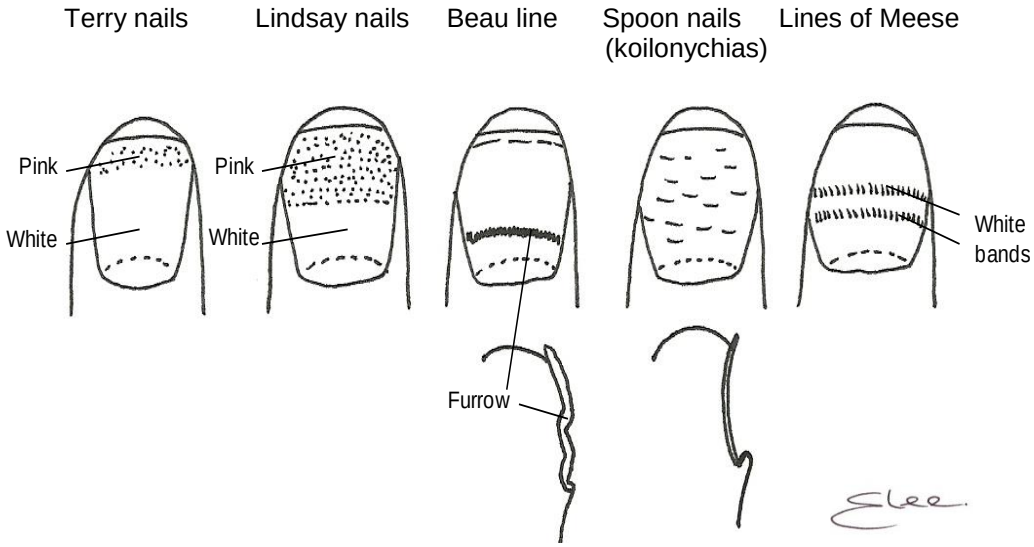
FINGERNAILS

- Give the liver and heart conditions which alter the normal appearance of the fingernails.

    - Liver
        - Terry's nails:
            - Whitening of the proximal 80% of the nail, leaving a small rim of peripheral reddening seen in
                - Older people
                - Heart failure
                - Cirrhosis
                - Non–insulin dependent diabetes
        - Azure half–moons nail beds
            - Wilson disease (hepatolenticular degeneration)
            - Lunulae are not white but light blue
        - Muehrcke lines
            - Two arcuate white lines parallel to the lunula separated by normal nail
            - Located in the nail bed (not in the nail plate); do not progress with the growth of the nail
            - Seen in hypoalbuminemia (<2 gm/100 mL) and disappear with its resolution
        - Leukonychia–white nails, beginning at the lunula; may be normal in:
            - Cirrhosis
            - Leprosy
            - Arsenic poisoning
            - Vasomotor disturbance of fingers
    - Heart
        - Red half–moons in nail beds (variety of Terry's nails; also described by Terry):
            - Lunula that are not white but red (aka "nails of cardiac failure")
        - Beau lines
            - Transverse grooves on the fingernails of patients recovering from a serious illness such as myocardial infarction
        - Meese lines (also called Reynold or Aldrich lines) are transverse white lines distal to the cuticle seen in:
            - Arsenic or thallium poisoning
            - Cancer chemotherapy
            - Hodgkin lymphoma
            - Other systemic disorders, e.g. severe cardiac or renal diseases
        - Splinter hemorrhages
            - Linear red hemorrhages, extending from the free margin of the nail bed towards the proximal margin; typical findings of subacute bacterial endocarditis, trichinosis, or trauma.

Interesting Clinical Trivia

- Koilonychia
  - Spoon shaped nails
  - Associated with chronic iron deficiency
- Nail pitting
  - An early (but non–specific) sign of psoriasis
- Yellow nail syndrome is a yellow discoloration of the plates due to abnormal lymphatic circulation.
- Brittle nails seen in
  - dysmetabolic states
    - Hyperthyroidism
    - Malnutrition
    - Iron or calcium deficiency
    - Irregular, frayed, and torn nail borders



Adapted from; Mangione S. *Hanley & Belfus* 2000, page 412.

JAUNDICE, HYPERBILIRUBINEMIA AND CHOLESTASIS

Post–operative Jaundice

➢ Diagnostic imaging

– Give the performance characteristics sensitivity [sens] and specificity [spec] for the diagnostic imaging studies in cholestasis.

	Sens	Spec
○ Ultrasound (gallbladder)	80%	90%
○ CT	80%	95%
○ MRCP	90%	95%
○ ERCP	90%	95%
○ PTC	99%	95%
○ EUS	95%	95%

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the typical histological changes seen on liver biopsy of a patient who has post–operative jaundice.

  - Intrahepatic cholestasis
  - Kupffer cell erythrophagocytosis
  - Centrilobular congestion

The most common cause of death in Adult–Onset Still Disease (A-OSD), adult form of juvenile RA, is liver failure. In milder cases with hepatitis, the clinical presentation include fever, sore throat, weight loss, abdominal pain, jaundice, hepatosplenomegaly, ↑ ALT / AST. Give the hepatic histological changes in A–OSD.

  - Hepatitis
    - Interface
    - Lobular
  - Lymphoplastic infiltration

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.

- Clinical

- Give the "best test" for Gilbert disease.
  - History
    - Exclude risk for liver diseases
  - Physical
    - Exclude signs of chronic liver diseases, and its causes

- Laboratory
  - Mild unconjugated hyperbilirubinemia (> 80% indirect), which increases with fasting or fever
  - Absence of hemolysis (normal hemoglobin concentration and normal reticulocyte count)
  - Normal ALT / AST

MCQ Help

If the MCQ case has a cholestatic serum biochemical screen, and any of these buzzwords are used, give "what are they thinking."

- "onion skin" biopsy findings
- "string of beads dominant stricture" on MRCP or ERCP
- "associated IBD"
- Primary Sclerosis Cholangitis (PSC). Now watch out for two tricks:
  - If the patient has a CD4 count < 00 /mL (too obvious to give you HIV serology), or
  - If they ask you to choose Ursodeoxycholic acid (UDCA) as treatment to initiate in a newly diagnosed patient, then BEWARE
  - AIDS cholangiopathy may mimic PSV, but of course is treated differently
  - PSC is no longer treated with high dose UDCA; but rather by:
    - Supportive therapy
    - Endoscopy dilation of an extrahepatic dominant stricture
    - Annual surveillance for cholangiocarcinoma, gallbladder carcinoma, and colorectal cancer if the PSC is associated with colonic IBD, and
    - Careful follow–up and assessment for possible liver transplantation

Where is the trick?

- Look at the answer to the MCQ. If there is a possibility of doing no further tests (no CT or MRI, no ERCP or liver biopsy), then that is often the correct answer.

CLINICAL VIGNETTE

- Case: Cholestatic liver disease, "florid duct lesion", plus
  - Granulomas
  - Onion skinning
  - PBC (primary biliary cirrhosis)
  - PSC (primary sclerosing cholangitis)

SO YOU WANT TO BE A GASTROENTEROLOGY!

- Give the proportion of patients having a human stem cells (bone marrow) transplant (HSCT) to develop jaundice due to GVHD (graft–versus–host disease).
  - 20%; implication – don't assume that jaundice in BMT patients is related to GVHD
  - Most MCQs don't revolve around your memorizing specific percentages.
- In the context of cholestasis, what is Stauffer syndrome?
  - Stauffer syndrome is an intrahepatic cholestasis and hepatosplenomegaly occurring as a paraneoplastic syndrome from lymphoma or renal cell carcinoma.

SO YOU WANT TO BE A GASTROENTEROLOGY!

- Give the molecular defect(s) causing benign recurrent cholestasis (BRC), sepsis–associated cholestasis (SAC), cholestatic jaundice in pregnancy (CJP), and estrogen–associated cholestasis (EAC).
    - 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!

- Give conditions in which ursodeoxycholic acid (UDCA) is therapeutically beneficial.
    - PBC
    - Intrahepatic cholestasis
    - TPN–associated cholestasis
    - CF–associated cholestasis
    - Bone marrow–associated cholestasis
    - Prevention or reduction of formation of gallstones in patients undergoing bariatric surgery

*__Note__: Deduct marks the use of UDCA in PSC (UDCA in PSC activity → ↑ mortality)

VIRAL INFECTIONS CAUSING HEPATITIS

"The Alphabet Soup" – A, B, C, CNV, D, E, EBV, etc

- Which of the following hepatic viral infections do not cause chronic disease HAV, EBV, CMV, HSV, HDV, HEV.
  - None of them causes chronic liver disease.

- Compare the clinical characteristics of inection with viruses "A" to "E".

	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	Percuta-neous, sexual, perinatal	Percuta-neous, perinatal (uncommon)	Percuta-neous, sexual, perinatal	Fecal-oral
Acute hepatitis progressing to chronic disease	No	Adults 2-7%, pre-schoolers 25%, neonates 90%	70-80%	In super-infection; 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.

Hepatitis A Virus (HAV)

- Vaccination
  - Active
    - HAV vaccine 1 month before travel and 6–12 months booster vaccination
  - Passive serum immunoglobulin only for special conditions
    - < 12 months
    - Immunocompromised persons
  - Is often combined with vaccination to HBV

Hepatitis B virus (HBV)

- Demography
  - Development of chronicity: adults, 5%
    children, 85%
- Pathophysiology
  - Mechanism of liver damage
    - HBV: host cellular immune response causing lysis of hepatocytes
    - HCV: cytotoxic liver damage
  - Prognosis of HBV cirrhosis, in 5 years
    - decompensation 15%
    - development of HCC 15%
  - Genotypes – HBV letters
    - HCV numbers

THINK OUTSIDE THE BOX – LIVER

- The MCQ presents a patient with disease of the kidney, musculoskeletal system (MSK) and blood (membranous glomerulonephritis, polyarteritis, cryoglobulinemia). Give the most likely diagnosis.
- This is an unusual combination or clustering That's why you will be asked to see if you would choose to perform a serological test for HBV infection.
- If there is glomerulonephritis, cryoglobulinemia, porphyria cutanea tarda, or vasculitis (especially leukocytoclastic vasculitis), think of HCV infection.

- Histology
  - Ground glass inclusions (HBs Ag) in hepatocytes
  - Mononuclear cells in portal tracts
  - Interface hepatitis
  - Steatosis (rare)

– Give the treatment for chronic HBV infection.

  - The best treatment for chronic HBV infection has two considerations. First is that they have the correct HBV serology for chronic hepatitis B infection. Second, they met the criteria for HBV DNA levels, and thirdly, that there is no contraindication to the medications chosen.

- Laboratory
  - From the following serological studies, give the **type** of the patient's **HBV infection**.

Type of HBV Infection	HBs Ag	Anti-HBs	Anti-HBe	HBV DNA	HBe Ag	Anti-HBe
Acute	+	-	IgM+	+	+	+/-
Inactive carrier	+	-	+	-	-	+
Chronic	+	-	IgG+	+	+/-	+/-
Previous exposure	-	+	IgG+	-	-	+/-
Previous vaccination	-	+	-	-	-	-

    - Mutations in HBV core may lead to immune clearance of HBe Ag

  - Give the interpretation of IgM anti–HBc.
    - Acute HBV infection
    - Flare of chronic HBV

- Give the **indications** for treatment of HBV infection, based on laboratory findings

  - Treat chronic HBV infection, <u>not</u>
    - Acute HBV
    - Inactive HBV carrier
    - Previous HBV exposure
    - Previous vaccination
  - HBeAg, HBV DNA

Cirrhosis	HBe Ag	HBV DNA	ALT
o No	+	>20,000 U/mL	>2 x ULN
o Compensated	+	>2,000 U/mL	-
o Decompensated	+	Detectable	-
	-	>2,000 U/mL	>2 x ULN

  - If liver transplantation is done for HBV, 20% develop recurrent HBV liver disease
  - Progression of HBV acute → chronic
    - Horizontal 5%
    - Vertical 95%

➢ No contraindications

- Interferon alfa (IFN–α)
  - Liver
    - Decompensated cirrhosis
  - CNS
    - Severe depression
  - Autoimmune disorders
  - Blood
    - Severe cytopenia
- Associated HIV
  - Pregnancy
  - Previous organ transplantation
  - Use emtricitabine
  - Tenofovir (not IFN–α) plus HAART

CLINICAL CAUTION: Vaccination in HBV

- Give the reason why it is not recommended to perform testing of the response to vaccination (anti–HBs positive) if the patient has a reduced serum concentration of immunoglobulins.
    - If immunoglobulin concentration is low, the antibody response to the vaccine will be low or absent.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

About 90% of HIV/AIDs patients are infected with HBV.

- Give the effects of HIV on HBV infection.
    - 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 the use of lamivudine
        - Clinical acute hepatitis
        - Seroconversion to anti–HBe and HBsAg
    - HBV does not cause progression of HIV disease

CLINICAL VIGNETTE

- Case: Acute hepatitis, hyperbilirubinemia, fever, temperature–pulse dissociation, conjunctival redness and jaundice, lymphadenopathy, cough, rhabdomyolysis, renal insufficiency. What is the diagnosis?
  - Leptospirosis

Hepatitis C Virus (HCV)

MCQ TIP

- The MCQ stem tells you a patient is negative for HBV, ALT and AST is normal. You are shown a picture of skin showing purpura, or was told that the patient experienced a recurrent palpable purpura of the skin. This is the "what am I thinking" game.
- Because HCV is so common, look out for such question.
- Too easy to tell you that the patient has high risk behaviour such as IV drug injection, or are middle aged hemophiliacs treated with blood products since early childhood; too easy to confuse with possible HBV if they have glomerulonephritis or cryoglobulinemia; too much of a give–away because porphyria cutanea tarda (PCT) in a liver patient triggers the connection of this buzzword with HCV infection.
- The challenge is to show you a photograph of palpable purpura or to tell you the diagnosis is made on skin biopsy.
- That's correct! Leukocytoclastic vasculitis associated with HCV, causing palpable purpura.

The best treatment for HCV infection requires satisfaction of criteria related to the patient and to the hepatic C virus.

CLINICAL GEM

A normal ALT/AST does **not** exclude HCV infection.

- Pathophysiology
  - In blood free or bound to
    - Lipoproteins
    - Immunoglobulins
  - Mechanism of HCV liver damage
    - Direct cytotoxicity
    - Possible humoral–mediated T cell response

- Clinical
  - 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% per year

- Laboratory
  - Anti–HCV is not a neutralizing antibody and does not clear
  - Remember there is also a fibrosing cholestatic form of HCV

- Treatment

- Interferon
  - The use of interferon (INF) in HCV is associated with an early anti–viral effect (type I, measured in days), and later, an 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%.

- Give the criteria for selection of treatment of HCV infection.
  - Host
    - Hepatic inflammation
      - ↑ ALT, AST
      - Biopsy positive for inflammation
    - No contraindications to use of interferon–α, ribavirin (Rib), or a protease inhibitor (boceprevir or telaprevir)
  - Virus genotype
    - I – IFN–α, rib plus PI
    - II, III, IV – IFN–α, Rib

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the effect of HIV on HCV infection.
  - 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 accelerated progression of HIV disease, but the converse is not true.

- Give the risk factors for the clinical worsening of HCV in HIV.
  - ↑ age at infection
  - ↑ ALT
  - ↑ inflammatory activity
  - ↑ alcohol (>50 g/day)
  - ↓ CD (< 500 cell/mm)
  - Steatohepatitis

Cytomegalovirus (CMV) in Post–Liver Transplant

- Reactivation of CMV
- Most common CMV(+ive) donor → CMV (–ive) recipient
- 2 to 17 weeks post–transplantation

➢ Pathology

Common sites

- Post-transplant
  - GI tract
    - Esophagus
    - Colon
    - Liver
  - Lung
    - Pneumonitis
  - Blood
    - Cytopenia

- CMV infection is common with
  - HIV infection
  - Post–transplantation

- CMV infection commonly affects
  - GI tract
  - Lung
  - Blood

- With HIV / AIDs

- Give the organs which are commonly affected by CMV infection in patients with AIDs and not post–transplantation.

  - CNS
  - Eye (retina)

"Medicine is not a popularity contest"

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

Pneumocystis

➢ Clinical

Pneumocystis pneumonia is common with HIV infection as well as post–transplantation.

- Give the differences in the clinical course of the pneumocystis pneumonia.
    - In patients with HIV / AIDs
        - Begins more suddenly
        - Progresses more rapidly

HEPATATIC MASS / TUMORS

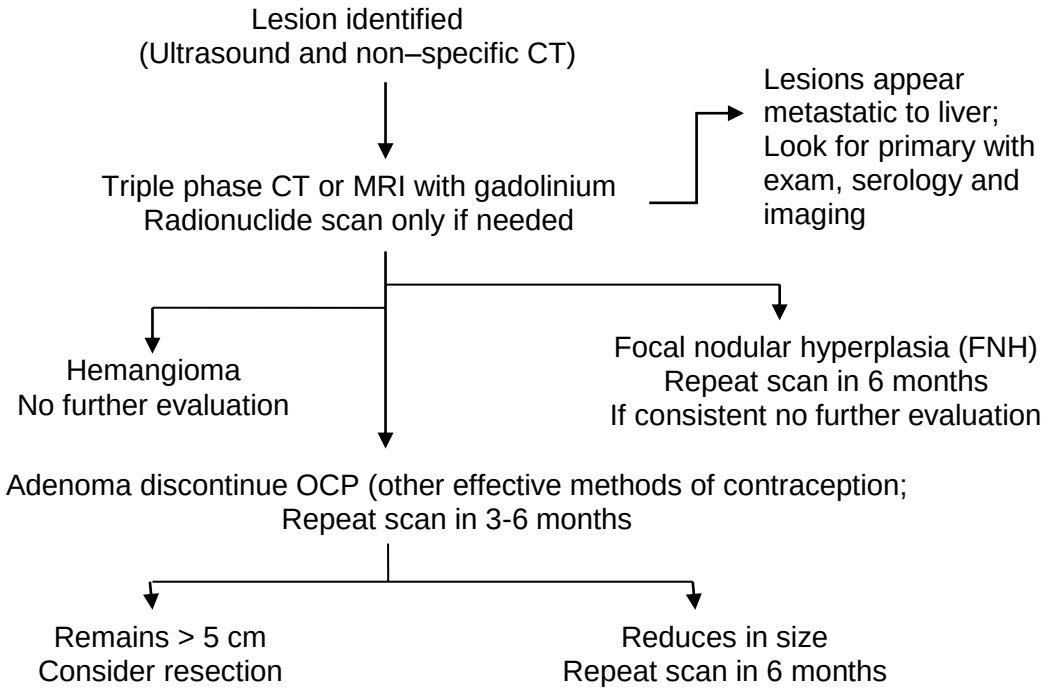
- Give the imaging features of the 3 common benign liver mass or lesions; hemangioma, focal nodular hyperplasia and adenoma.

	Hemangioma	Focal nodular hyperplasia	Adenoma
○ Ultrasound	– Hyperechoic – Well-defined borders	▪ Variable appearance well defined borders	– Non diagnostic
○ Triple phase CT	– Pre contrast: hypodense – Centripital globular enhancement – Retained contrast in delayed images	▪ Pre contrast: Hypo or isodense ▪ Homogenous arterial enhancement with hypodense central scar ▪ Isodense in delayed imaging	– Pre contrast: Hypo or isodense – Irregular enhancement = Delayed peripheral arterial enhancement during venous phase
○ MRI	– T1: well circumscribed low signal – T2: Hyperintense signal	▪ T1: low signal ▪ T2: Hyperintense signal with central scar	– T1: Low signal intensity with well-defined capsule on – T2: Heterogenous enhancement

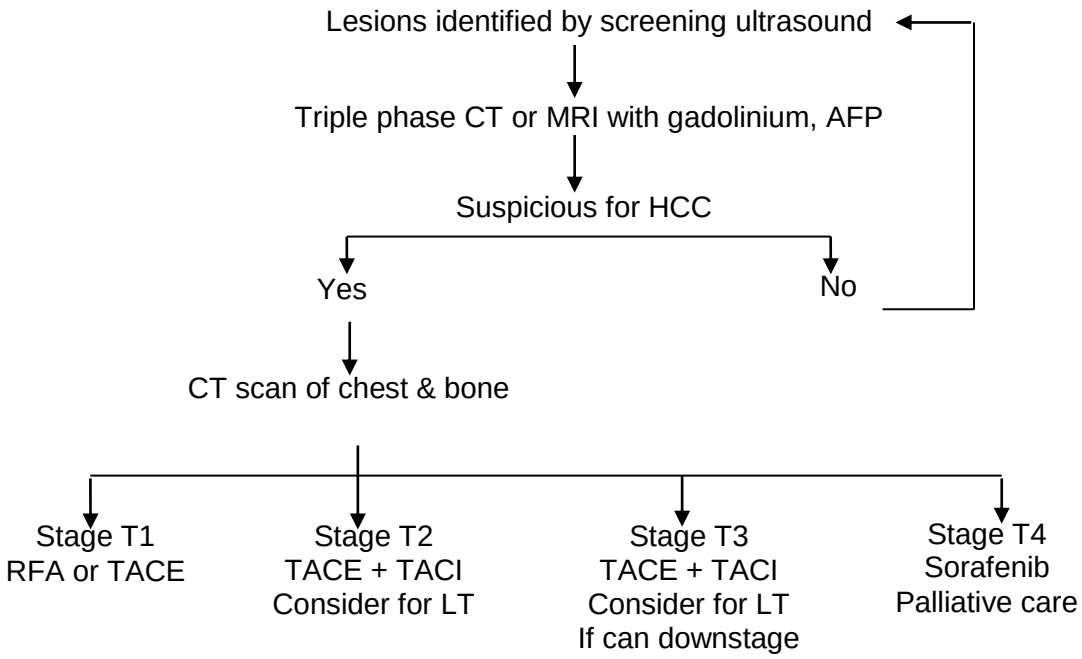
	Hemangioma	Focal nodular hyperplasia	Adenoma
○ Gadolinium enhanced MRI	– Progressive enhancement with delayed washout on venous phase	▪ Homogenous arterial enhancement ▪ Hypodense central scar ▪ Contrast accumulates in scar on delayed T1	– Irregular enhancement with delayed washout
○ Radionuclide scan	– Tagged red cell study: Increased uptake during venous phase and delayed emptying	▪ Equal or increased uptake compared to surrounding liver	– Reduced uptake compared to surrounding

Source: Shiffman ML. *2009 ACG Annual Postgraduate Course*, page167-171.

Evaluation of hepatic mass in patient <u>without</u> cirrhosis



Evaluation of mass – <u>with</u> cirrhosis



Source: Shiffman ML. *2009 ACG Annual Postgraduate Course*, page167-71.

- 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.

- Hepatic hemangioma
  - Common congenital malformations of the liver vasculature, with ectatic blood vessels with no malignant potential and not affected by oral contraceptive hormones. Thrombosis and pain may occur because of the tortuous vessels and stasis.
  - Radionucleotide scanning with RBC identifies a hepatic mass as a hemangioma.
- Focal nodular hyperplasia (FNH)
  - Common congenital malformations of the liver vasculature
  - 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 OCP (3x increased risk)
  - Premalignant, with risk of malignancy with increasing size
  - Features on triphasic CT or gadolinium–enhanced MRI which are difficult to distinguish from HCC

  - Technetium sulfur colloid nuclear scan may be needed to show the typical cold lesions (no sulfur colloid uptake)
  - AFP may become positive when hepatic adenomas become malignant

- Nuclear scintigraphy with technetium sulfur colloid is taken up by the Kupffer cells.
  - ↑ uptake in
    - Metastatic lesions
      - Thyroid
      - Breast
      - Lungs
      - Pancreas
      - Colon
    - Hemangioma or cysts
  - ↓ uptake in
    - Hepatic adenomas
    - HCC

Abbreviation: FNH, focal nodular hyperplasia; OCP, oral contraceptive pill

NODULAR REGENERATIVE HYPERPLASIA (NRH)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the pathophysiology of nodular regenerative hyperplasia (NRH).
  - Pathophysiology
    - Lesions form and obliterate small portal veins and hepatic veins leading to ischemia, atrophy and then to nodular regenerative hyperplasia (NRH)
    - Multiple, monoacinar nodules resulting in nodular proliferation of hepatocytes (nodular transformation)
    - Nodular proliferation of hepatocytes may compress the liver plates at the periphery of the nodules
    - No fibrous septa

- Give the conditions associated with NRH.
  - Drugs
    - Azathioprine
  - After orthotopic liver transplantation
  - Early stages of primary biliary cirrhosis (PBC)
  - Connective tissue disorders
    - SLE (systemic lupus erythematosus)
    - RSS (progressive systemic sclerosis)
    - PMR (polymyalgia rheumatica)
    - Sarcoidosis
    - Felty syndrome
    - Primary hypogammaglobulinemia
  - Hematological disorders
    - PCV (polycythemia vera)
    - AMH (agnogenic myeloid hyperplasia)

CLINICAL VIGNETTE

- Case: ↑ ALP and GGT with thrombocytosis; no use of oral contraceptive agents (OCA); CT abdomen does not show subcapsular mass; CT shows multiple hypodense hepatic nodules. Give the likely diagnosis.
  - Nodular Regenerative Hyperplasia (NRH)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Nodular regenerative hyperplasia (NRH) is associated with all the usual complications of portal hypertension.

- Give the abdominal liver function tests which occur in NRH.
  - 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.
  - These hepatic functions persist despite the associated portal hypertension because of the regenerative hyperplasia of the hepatocytes.

LYMPHOMA

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of Hodgkin's lymphoma (HL), what does ideopathic intrahepatic cholestasis (IIC) syndrome means?
  - The HL–IIC syndrome is cholestasis in HL with exclusion of all other causes with 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 is there a loss of small intrahepatic bile ducts.

In an autopsy of about half of patients with Hodgkin lymphoma (HL) have hepatic involvement including extrahepatic involvements (nodes in the porta hepatis, or compressing the bile ducts), but only about 10% of HL patients have histological hepatic abnormalities.

- Give the intrahepatic lesions seen in HL.
  - 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.

"Resources may influence the community standard of care"

Jacque Guilbert, MD,

CMPA, UWO, June 19, 2012

LIVER GRANULOMAS

➢ Causes and associations

- Infection
  - Bacterial Diseases
    - Tuberculosis
    - Disseminated *Mycobacterium avium* complex
    - Brucellosis
    - Tularemia
    - Listeriosis
    - Lepromatous leprosy
    - Disseminated BCG
    - Syphilis (secondary)
  - Rickettsiosis
    - Q fever
  - Viral
    - *Cytomegalovirus* (CMV)
    - Epstein–Barr virus (EBV)
  - Fungal
    - Histoplasmosis
    - Coccidioidomycosis
    - Cryptococcosis
  - Parasitic Diseases
    - Toxoplasmosis
    - Schistosomiasis
    - Visceral larva migrans
    - Fascioliasis
    - Hepatic capillariasis
    - Ascariasis
- Neoplastic diseases
  - Hodgkin's lymphoma
  - Non–Hodgkin's lymphoma
  - Renal cell carcinoma
- Medications
  - Allopurinol
  - Carbamazepine
  - Chlorpropamide
  - Diltiazem
  - Gold
  - Halothane
  - Hydralazine
  - Methyldopa
  - Nitrofurantoin
  - Penicillin
  - Phenylbutazone
  - Phenytoin
  - Procainamide
  - Quinidine
  - Quinine
  - Sulfonamides
- Miscellaneous
  - Immune
  - Sarcoidosis
  - Primary biliary cirrhosis
  - Drugs or Toxins
    - Berylliosis
    - Talc
  - Whipple disease
  - Inflammatory bowel disease
  - Wegener granulomatosis
  - Lymphomatoid granulomatosis
  - Idiopathic

Abbreviation: BCG, Bacillus 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.

HEPATIC SARCOIDOSIS

➢ Complications

- Give the complications of hepatic granulomas in sarcoidosis.
  - Incidental (active pulmonary, cutaneous or ocular disease)
  - Symptomatic (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.

  - Curiosity
    - Sarcoidosis does not usually affect the luminal GI tract. Sarcoidosis of the liver is usually affects the portal triads or the lobule.
  - Intrahepatic and extrahepatic sarcoidosis may recur after liver transplantation.

➢ Pathology

- Give the features of sarcoidosis seen on liver biopsy.
  - Granulomas
    - Site
      - Diffuse
      - In portal tracts and periportal areas
    - Composition
      - Epithelioid cells
      - Multinucleated giant cells
      - Lymphocytes, macrophage
    - Necrosis
      - Central, granular (non–caseating)
  - Kupffer cell hyperplasia
  - Portal tracts, hepatic lobules
    - Infiltration of mononuclear cells
  - Portal tracts of hepatic veins
    - Granulomatous phlebitis
  - NRH
  - Periductal
    - Onion skin fibrosis (like PSC)
    - Ductopenia
  - Cholestasis
    - Bile duct lesions (like PBC)
  - Cirrhosis

Abbreviations: NRH, nodular regenerative hyperplasia; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis

HEREDITARY HEMOCHROMATOSIS (HH)

MCQ ALERT

- It may be quaint or old fashioned to think outside of the box, but in medicine and especially on MCQs, watch out for both the "red herrings" and for the "canaries."
- The case is that of a young woman with thyroid disease, with non–specific and slightly raised liver enzymes, a high serum total protein concentration and low albumin, but no hyperalbuminemia and a normal INR. You are asked to mark which tests you would choose next to determine the cause of her liver disease.
- The trick is – don't fret about the slightly raised enzymes – that's so non–specific.
- Don't stand on your head trying to link a low serum albumin with a specific type of liver disease.
- Take a step back. If the albumin is low and the total protein is high, then what makes up the total protein? Of course, **globulins**.
- So if the globulins are increased, think of the following:
  - ↑ IgA – alcoholic liver disease
  - ↑ IgM – Primary Biliary Cirrhosis (PBC)
  - ↑ IgG – Autoimmune Hepatitis (AIH)
- If you have a choice of quantitative immunoglobulins, then make a good choice. If IgM is increased, your next choice should be anti–mitochondrial antibody (AMA) for PBC.
- If IgG is increased, think of AIH and choose AMA, anti–smooth muscle antibody titres, p–ANCA, and anti–LKM antibody (≥ 1:40).
- PBC links with pruritus, jaundice and possibly (80%) with associated chronic IBD. Another trick, if the history says presence of fatigue, hyperpigmentation and xanthomas, think of PBC.

- Diagnostic imaging
  - On a clinical examination, you are shown a photomicrography of the bones of the hand.
  - The image is blurry, and you're not sure what you are supposed to see (hook–like osteophytes).
  - Or perhaps, you are shown an x–ray of the shoulder, elbow or ankle, which looks like osteoarthritis (OA)

- But of course, you know that these are unusual joints to be damaged by OA.

- Then the question continues, giving you the information of the patient:
  - Erectile dysfunction
  - Tanning of the skin
  - Diabetes
  - Cardiac arrhythmias
- While there is no mention of transferrin saturation, serum ferritin concentration and HFE genotypes
- Because of the importance of serum blood tests in the diagnosis of hereditary hemochromatosis (HH), watch out for the causes of ↑TS and ↑ferritin besides HH

○ ↑ transferrin saturation (TS)	– Alcoholic Liver Disease (ALD) – Non–alcoholic liver disease (NALD) – HCV – Neoplasms
○ ↑ ferritin	– Acute phase reactant

CLINICAL VIGNETTES: The most likely diagnosis.

- Give the most likely diagnosis.
  - Case: Hepatitis, ↑ IgG interface hepatitis plus plasma cells
    - Autoimmune hepatitis (AIH)
  - Case: HIV /AIDS, jaundice; culture positive for *Batonella henselae*
    - Peliosis hepatis
  - Case: Third trimester jaundice; hypoglycemia and drowsiness; ↑ bilirubin and INR
    - Acute fatty liver of pregnancy (AFLP)
  - Case: Chronic hepatitis with itchy purple lesions on lower legs
    - Lichen planus associated with HCV

CLINICAL VIGNETTES

- Give the most likely diagnosis.
  - Case: Constipation with normal digital rectal examination (DRE); dilated sigmoid colon; abnormal rectal manometry; failure of relaxation of internal anal sphincter (IAS) on Valsava maneuver
    - Hirschsprung's Disease
  - Case: ↑↑ ALP with normal aminotransferases and "LFT's" (liver function tests); bone pain
    - Paget's disease
  - Case: Acute Liver Failure (ALF), ↑ ALT and AST but ↓ ALP; hemolytic anemia; neuropsychiatric changes; Fanconi syndrome
    - Wilson disease
  - Case: Stellate cells on liver biopsy filled with fat; normal serum cholesterol and triglycerides; first nations person
    - Overconsumption of Vitamin A
  - Case: Nodular Regenerative Hyperplasia (NRH), splenomegaly and portal hypertension; neutropenia; morning stiffness and subcutaneous nodules; positive rheumatoid factor
    - Rheumatoid Arthritis and Felty syndrome
  - Case: ↑ aminotransferases with arthritis in MCP joints; glucose intolerance; family history of liver cancer; benefit form "leaches" (phlebotomy)
    - Hereditary hemochromatosis
  - Case: 3 A's: Alcohol use, Ataxia, Acidosis; tachycardia
    - Thiamine deficiency

HEMATOLOGIC MALIGNANCIES AND HEPATIC INVOLVEMENT

Lesion	Approximate Hepatic Involvement from Clinical Evaluation (%)	Histologic Abnormalities (approximate frequency)
○ Hodgkin's lymphoma	10	- Portal lymphocytic infiltrates (32%) - Granulomas (9%-25%) - Steatosis (11%) - Hemosiderosis (9%) - Idiopathic cholestasis (<5%)
○ Non–Hodgkin's lymphoma	40	- Portal lymphocytic infiltrates (20%-25%), steatosis (7%)
○ Multiple myeloma	40	- Amyloidosis (10%) - Light–chain deposition - Extramedullary hematopoiesis
○ Hepatosplenic T–cell lymphoma	80	- Sinusoidal infiltrates
○ 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!

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. Blood testing showed mild unconjugated hyperbilirubinemia, elevated LDA, mild anemia yet increased serum ferritin concentration. Serology was negative for HBV and HCV, and testing for ANA and SMA were negative. Abdominal ultrasound was normal. Liver biopsy was performed.

- Give the most likely findings on this man's liver biopsy.

  - 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

Ah, still don't have the diagnosis. Give why was the erythrophagocytosis in a Kupffer cell in a hepatic sinusoid an important clue? And what is so special about St. Thomas?

- Sickle red blood cells are best seen in Kupffer cells
- St. Thomas was one of the communities which in 1861-1865 were terminals for the Underground Railroad from the Southern (confederate) states into Canada. Many of these African-Americans stayed.

- 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.

GALLBLADDER AND BILIARY TREE

- Give the meaning of the following terminology.
  - Murphy sign – Breathing in suddenly stops with RUQ palpation, suggesting cholecystitis
  - Courvoisier sign – Painless, palpable distended gallbladder, suggesting pancreatic cancer
  - Cullen sign – Bruising of periumbilical area from retroperitoneal due to acute hemorrhagic pancreatitis or ectopic pregnancy
  - Gray–Turner 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

- Give the performance characteristics for the palpation of gallbladder.

Findings	PLR	NLR
Palpable gallbladder		
– Detecting obstructed bile ducts in patients with jaundice	26.0	0.7
– Detecting malignant obstruction in patients with obstructive jaundice	2.6	0.7

*Note that Murphy 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.

  - Gallbladder (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)

- Give the causes of pneumobilia.
    - Sphincterotomy
    - Gallstone ileus
    - *Clostridium perfringens* infection (gas–forming organism)

- Give the likely sites of obstruction in gallstone ileus, depending on the size of gallstone.
    - Ileocecal valve, > 2 cm
    - Sigmoid colon, > 2.5 cm
    - "Rolling Obstruction" – site of mechanical obstruction moves ("rolls") distally as the gallstone passes along the small and large intestines

CHOLELITHIASIS AND PREGNANCY

About 10% of pregnant woman develop gallstones, and 1% have symptomatic cholelithiasis.

- When should cholecystectomy be performed in a pregnant woman for symptomatic biliary colic or gallstone pancreatitis?
    - 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 or pancreatitis.
    - Ideally, cholecystectomy is performed in T_2, because surgery in T_1 may lead to fetal mortality, and during T_3 surgery may lead to premature delivery.
    - Note:
        - Cholecystectomy (laparoscopic or open) during pregnancy → preterm delivery rate of 11%

ACUTE CHOLECYSTITIS

CLINICAL CAUTION

- The demonstration of gallstones on abdominal ultrasound in a patient with RUQ pain is only suggestive of the presence of acute cholecystitis.

- Diagnostic
  - Clinical
    - RUQ tenderness
    - Guarding
    - Murphy sign (stopping of inspiration during palpation of RUQ)
  - Ultrasound
    - Cholelithiasis
    - Thickening of gallbladder (GB) wall
    - Fluid around GB
    - Sonographic Murphy sign
  - HIDA scan
    - Non–filling of gallbladder

CLINICAL ‘Sweet Nothings’

- Knobbly liver with umbilication is pathognomonic of hepatic metastases (2°); jaundice with hepatic 2° is usually due to lesions at hepatic fissure.
- 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!

- In the context of a possible cholangiocarcinoma seen on diagnostic imaging, give the meaning of the Mirizzi syndrome.
    - Mirizzi syndrome is a stone in the cystic duct, which externally compresses the common bile duct (CBD).
    - On diagnostic imaging, it looks like a CBD filling defect
    - This could be easily confused to be a CBD tumor, such as cholangiocarcinoma.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the presence of obstructive jaundice, a palpable gallbladder is not due to cholelithiasis. Give the exceptions to this clinical "rule."
    - Stones in the cystic duct, or Hartmann's pouch.

GALLBLADDER POLYPS

➢ Treatment

o Premalignant	–	Abdominal ultrasound surveillance
o Symptoms	–	Cholecystectomy
o May be asymptomatic	–	≥ 1 cm – cholecystectomy
	–	< 1 cm + stones – cholescystectomy
	–	No stones → ultrasound (or EUS) surveillance until polyp ≥ 1 cm or stones develop → cholescystectomy

CLINICAL TIPS

A gallbladder polyp is at risk for being an adenocarcinoma when the size is ≥10 mm. Note: in the patient with Primary sclerosing cholangitis (PSC) and gallbladder polyp is considered to be malignant, and cholecystectomy is necessary.

PANCREAS

CONGENITAL ABNORMALITES

Pancreas divisum and annular pancreas are two common congenital abnormalities of the pancreas. Compare and contrast the two.

	Annular pancreas	Pancreas divisum
○ Frequency	– Second most common	▪ Most common
○ Embryology	– Failure of the left pancreatic bud to rotate completely	▪ Incomplete fusion of the dorsal and ventral pancreatic buds
○ Clinical symptoms	– Recurrent obstruction of stomach or duodenum from the pancreas wrapping around D2 (second part of duodenum)	▪ Recurrent pancreatitis (often asymptomatic)
○ Diagnostic imaging	– "double bubble" sign – "ring like" aberrant pancreatic duct surrounding the duodenum – Normal pancreatic duct	▪ No pancreas encircling the duodenum ▪ Two separate drainage systems of the pancreatic ducts
○ Treatment	– Surgical bypass of the encircling pancreas	▪ Sphincterotomy of minor duct

ACUTE PANCREATITIS

➢ Stratification of severity

- Give the Ranson's prognostic criteria for acute pancreatitis.

○ On admission		
– Age (years)	> 55	> 70
– White blood cell count (cells/mm^3)	> 16,000	> 18,000
– Blood glucose (mg/dL)	> 200	> 220
– Lactate dehydrogenase (IU/L)	> 350	> 400
– Aspartate aminotransferase (IU/L)	> 250	> 250

- During Initial 48 hours

– Decrease in hematocrit (%)	> 10	> 10
– Increase in blood urea nitrogen (mg/dL)	> 5	> 2
– Calcium (mg/dL)	< 8	< 8
– pO_2 (mm Hg)	< 60	NA
– Base deficit (mEq/L)	> 4	> 5
– 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.

➢ Causes

- Drugs

- There are literally hundreds of drugs which may cause acute pancreatitis. Give drugs that commonly seen being used in GI patients which are considered to have a moderately strong association with the development of pancreatitis.

o PUD	– Cimetidine – ASA – NSAIDs (e.g. sulindac)
o Ascites	– Furosemide – Thiazides
o IBD	– Azathioprine, 6–MP – Sulfasalazine – Metronidazole
o Tropical sprue	– Tetracycline

  - 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

- Why is there an elevation in serum ALT or AST followed by elevation of ALP?
    - 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.

➢ Laboratory

- Normal serum amylase or lipase do not R/O chronic pancreatitis.
- In a patient with acute pancreatitis, suspect biliary tract gallstones if
    - Bilirubin > 4 mg/dL
    - ALT, AST > 1000 U/mL

But if a patient with acute pancreatitis has also been drinking recently, the ALT, AST may be > 1000 U/mL, and the bilirubin may be increased (true, often > 15 mg/dL). Alcoholics have an ↑ risk of developing gallstones.

➢ Differential

- Identify the differences on diagnostic imaging alcoholic pancreatitis and biliary tract stones.
    - Abdominal ultrasound
        - Not sensitive for bile duct (BD) stones
        - May show indirect evidences of
            - Stones
                - Dilated BD or cystic duct
            - Cholecystitis
                - Gallbladder wall > 4 mm
                - ↑ pericholecystic fluid

➢ Treatment

- In a patient with acute pancreatitis, the best management steps are:
    - Large volume IV infusion
    - Risk stratification for necrotizing pancreatitis
    - Evaluation for cause
        - Alcohol
        - Gallstones
        - Drugs
        - ↑ TG (> 1000 mg/dL)
        - ↑ Ca^{2+}
        - Post ERCP

  - Caution: for mild (interstitial) pancreatitis, do not choose
    - EN / TPN
    - Antibiotics
    - Necrosectomy
- In a patient with acute pancreatitis, suspect severe pancreatitis (necrosis) if the MCQ stem provides:
  - History and signs
    - Fever, hypotension, tachycardia, dyspnea, oliguria
    - Abdominal guarding, rebound tenderness, ileus
    - Hemorrhage
    - Persisting or non–responsive pain
  - Abnormal blood tests
    - Abnormal CT scan (e.g., hematocrit or WBC, but not the level of the elevation of a non–enhancing areas of large portions (> 50%) of pancreas

CHRONIC PANCREATITIS

- Give the causes or associations of chronic pancreatitis.

  - Idiopathic
  - Immune
  - Infection
    - Mumps
    - Sepsis
    - Syphilis
    - *H. pylori* – peptic ulcer disease
  - Infiltration
    - Hemochromatosis
  - Iatrogenic
    - Drug
    - Alcohol
  - Inherited
    - Cystic fibrosis
  - Ischemic
    - Atheroma
  - Endocrine
    - Hypercalcemia
    - Hypertriglyceridemia

CLINICAL VIGNETTE: Give the likely diagnosis.

- Case: Recurrent abdominal pain, ↑ serum lipase and ↑ IgG–4
  - Autoimmune pancreatitis

➢ Clinical

- In the absence of a CT scan of the abdomen, give the clinical findings that suggests necrotizing rather than interstitial (non–necrotizing) pancreatitis.
  - Fever
  - Abdominal tenderness
  - ↓ or absent bowel sounds
  - Bleeding

- Give the diagnostic imaging features in autoimmune pancreatitis.
  - Diffuse pancreatic enlargement
  - Mass or lesion
  - Main pancreatic duct: irregular or multiple strictures

➢ Diagnosis

- The patient is suspected as having chronic pancreatitis. If the MCQ mentions:
  - Family history is positive, think cystic fibrosis
  - ↑ serum immunoglobulins, think autoimmune pancreatitis

MCQ ALERT

A young person, with a mass seen in pancreas, or pancreas diffusely enlarged on diagnostic imaging, or an irregular main pancreatic duct.

- They are going to test for **autoimmune pancreatitis** one way or another: too young an age for pancreatic cancer; chronic pancreatitis with no alcohol, drugs, stones or trauma; may be a family history – make sure that you check whether IgG measurement is a possible choice.

ABDOMINAL X–RAY

- Perform a directed examination of the abdomen and an 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
            - Portal–venous gas
            - Abscess

Adapted from: Jugovic PJ, *et al*. *Saunders/ Elsevier* 2004, pages 191 and 192.

- Give the causes of calcification on abdominal X–ray.

    - Lumen of bowel – Fecaliths
    - Vein – Phleboliths
    - Nodes – Calcified lymph nodes
    - Stones – Calculi: renal, gallbladder, prostatic
    - Glands – Calcified pancreas, adrenal, liver, 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 the causes of radiologic 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.

CYSTIC TUMORS

- Give the clinical, diagnostic imaging and laboratory features that distinguish pseudocysts from cystic neoplasms of the pancreas.

Features	Pseudocyst	Cystic neoplasm
➢ Clinical		
○ Gender	- More commonly male	- Usually female
○ Age	- 30–40 years	- 60–70 years
○ Alcohol abuse	- Common	- Uncommon
○ History of acute or chronic pancreatitis	- Common	- Uncommon
○ Diagnostic imaging (ultrasonography [US], endoscopic US [EUS], or computed tomography [CT])	- Unilocular - No solid component - Associated gland calcification	- Unilocular or multilocular - Solid component - Rim calcification of cyst - Mural nodules of wall
○ Communication between cyst and pancreatic duct on ERCP	- 70%	- Rare (except for IPMN)
➢ Cyst fluid		
○ Amylase	- High	- Low
○ Carcinoembryonic antigen	- Low	- High
○ 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.

➢ Surgery

Intraductal papillary mucinous neoplasm (IPMN) may occur in the main pancreatic duct (MD–IPMN) or branch duct (BD–IPMN).

- Give the **Sendai guidelines** which help to distinguish low from high risk of malignancy developing in IPMN, and therefore the criteria for surgical resection.
    - 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- and BD-IPMN with nodules or thickening on EUS CEA > 192

- A high amylase concentration in the aspirated mucus from an IPMN does not fit with Sendai guidelines or resection of the tumor. Give the reasons why.
    - 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 or MRCP, EUS).

PANCREATIC NEUROENDOCRINE TUMORS (PNET)

➢ Pathology

- The terms PET and carcinoid tumors should be replaced by the term pancreatic neuroendocrine tumor (P–NET)
- Origin from:
    - Pancreatic–islet cells
    - Ducts

- P–NET may be called “functional” when a tumor releases hormone that causes a clinical syndrome, or may be called non–functional because either a hormone is released but there is no clinical syndrome (eg., release of pancreatic polypeptide, ghrelin, neurotensin) or no hormone is released.

- Give the features which distinguish P–NET from other GI–NET.
  - 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%)

➢ Clinical

- Give the most common clinical presentations of the pancreatic neuroendocrine tumors, VIPoma (Verner-Morrison syndrome), glucagonoma, and somatostatinoma and insulinoma. The approximate frequencies are given in brackets.
  - VIPoma
  - Watery diarrhea and dehydration (100%)
  - Hypokalemia (95%)
  - Achlorhydria (30%)

➢ Diagnostic imaging

- Give the approximate sensitivity (%) of diagnostic imaging methods for the localization of primary pancreatic NET.

Tests	Sensitivity (%)
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.

*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.

➢ Prognosis

- Give any 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
  - Flow cytometric features (i.e. aneuploidy)
  - Laboratory findings
    - Elevated serum chromogranin A (in some studies)
    - Elevated serum gastrin level (gastrinomas)
    - Lack of progesterone receptors
  - *Ha–Ras* oncogene or *p53* overexpression

- 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, page 520.

- Therapy of P-NETs
  - Chemotherapy
    - Streptozotocin plus doxorubicin; etoposide plus ciplatin
    - Hepatic artery emboization +/- post–occlusion chemotherapy
  - RTA radiofrequency ablation
  - Somatostatin analogs (all PETs except insulinoma)
  - Interferon–α
    - ↓ symptoms
    - ↑ bcl–2 expression (Tumorostatic)
    - May be combined with somatostatin analogs
  - Surgery
    - Debulking and Liver transplantation (strict selection process)

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, page 509.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

The VIPoma syndrome is characterized by secretory diarrhea, hypochlorhydria and hypokalemia. About half of patients will also have hyperglycemia and hypercalcemia and a third will have flushing. This syndrome is associated with elevated levels of VIP as well as in some patients PNM–27 (peptide histidine methionine), PP, glucagon, insulin and somatostatin.

- Give the pathophysiological basis of the clinical features, based on the action of VIP.
    - Diarrhea
        - ↑ actuates adenylate cyclase, ↑ cAMP → secretory diarrhea
    - Hypochlorhydria
        - ↓ gastric acid secretion
    - Hypokalemia
        - ↑ release of renin, leading to secondary hyperaldosteronism
    - Hyperglycemia
        - ↑ hepatic glycogenolytic activity
    - Hypercalcemia
        - ↑ bone osteolytic activity
    - Flushing
        - VIP is a vasodilator

GLUCAGONOMA

- In the context of glucagonoma, give two other conditions causing necrolytic migratory erythema (NME) and hyperglucagonemia.

➢ 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

- Clinical

o Skin	– Migratory necrolytic erythema (85%) (red macules–bullae: bullae with central necrosis, scaly eczematoid lesions, central clearing, scaling: face, hands, exposed areas, intertriginous areas
o GI	– Weight loss (85%) – Chelitis (15%) – Diarrhea (15%) – Abdominal
o GU	– Hypoaminoacidemia (85%) – Renal glycosuria
o Endocrine	– Diabetes (85%) – Glucose intolerance – Hypocholesterolemia – Renal glycosuria
o Blood	- Anemia (85%)

- Lung
  - Thromboembolic pneumonia (20%)
  - Venous thrombosis
  - Pulmonary emboli
- Psychiatric symptoms (10%)

SOMATOSTATINOMA

- GI
  - Diarrhea (95%)
  - Gallstones (95%)
  - Weight loss (90%)
  - Hypochlorhydria (85%)
  - Steatorrhea (80%)
- Metabolic
  - Diabetes (95%)

Adapted from: Feldman M, *et al*. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, Table 32-7, page 506.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

The Somatostatinoma Syndrome is a complex of 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).
  - Diarrhea
    - ↓ pancreatic secretion
    - ↓ lipid digestion
    - ↓ lipid absorption
  - Weight loss
    - Steatorrhea
  - Diabetes
    - ↓ insulin release
  - Gallbladder disease
    - ↓ gallbladder motility → ↑ biliary sludge / stones
  - Hypochlorhydria
    - ↓ gastric acid secretion

CLINICAL VIGNETTE: Give the likely diagnosis.

- Case: Diarrhea glossitis, angular stomatitis, dystrophic nails, marked weight loss, red patches on skin in buttocks, thighs, groin. Give the likely diagnosis.
  - Necrolytic migratory erythema from NET tumor (glucagonoma) of pancreatic head

GASTRINOMA

- Pathology
  - 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
- Clinical

- Give the clinical features that suggest the **Zollinger–Ellison Syndrome** (ZES).
  - 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
    - Endocrinopathy
  - Associations
    - Diarrhea
    - Weight loss
    - Endocrinopathy
      - Pancreas
      - Parathyroid

Abbreviations: GERD, gastroesophageal reflux disease; PUD, peptic ulcer disease; UGI, upper gastrointestinal; ZES, Zollinger–Ellison syndrome.

- Causative associations
  - Genetic
    - BRCA2
    - Hereditary Non-Polyposis Colon Cancer (HNPCC)
    - PJS (Peutz-Jeghers syndrome)
  - Environmental (possible)
    - Chronic pancreatitis
    - Diabetes
    - Obesity
    - Diet, e.g. ↑ red meat
- Treatment
  - Pre– and post–operative chemotherapy for resectable disease
  - For metastatic disease
    - Gemcitabine plus cisplatin or oxaliplatin
    - Folfirinox (5–FU, leucovorin, irenotecan and oxaliplatin chemotherapy)

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.

SO YOU WANT TO BE A GASTROENTEROLOGIST OR HEMATOLOGIST!

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 a patient with acute or chronic leukemia who present with an acute abdomen, what are the most common disease related to the leukemia?
  - Acute appendicits
  - Intra–abdominal abscess
  - Perforation
  - Necrotizing enterocolitis (ileum and cecum)
  - Typhlitis (inflammation of cecum, often in the presence of neutropenia)

PANCREATIC CARCINOMA

➢ Clinical

- In the context of pancreatic cancer, give the meaning of the Trousseau syndrome.
  - Trousseau syndrome is a vascular thrombosis in patients with pancreatic cancer.

CLINICAL VIGNETTE

- Give the likely diagnosis.

  Case: Abdominal pain, progressive weight loss in an alcoholic; glucose intolerance; mental depression; skin rash (superficial migratory thrombophlebitis; abnormal ultrasound).
  - Pancreatic cancer

  Case: Isolated gastric fundic varices; chronic pancreatitis
  - Splenic vein thrombosis

- Give the stages of pancreatic ductular adenocarcinoma.

Stage	Localization
I	Pancreas
II	Extension into – Duodenum – Bile duct – Peripancreatic tissue
III	Extension into – Regional lymph nodes
IV	Extension into – Stomach – Spleen – Colon – Large nearby vessels – Metastases

➢ Treatment

- Give the nonsurgical treatment of non–resectable pancreatic cancer.
  - Pain control
    - Analgesics
    - Radiation therapy
    - Chemical celiac nerve block
    - Chemical splanchnicectomy
  - Non-resectable
    - Radiation therapy
    - Radiation therapy plus 5–FU
    - Gemcitabine
  - Palliation of biliary obstruction
    - Biliary stent
      - Percutaneous
      - Endoscopic
    - Surgical bypass

The cancer patient may develop side effects from their analgesics, such as constipation or pruritus, and these can be treated or prevented by anticipatory medication. A patient is on meperidine and develops neuroexcitability.

- Give the options for pain control in a cancer patient who develops CNS toxicity with meperidine.
  - Do not use meperidine.
  - Do not try to treat the meperidine–associated neuroexcitability with naloxone (may ↑ AE [adverse effect]).
  - Use maximum doses of

	mg/day
Acetaminophen	4000
Aspirin	4000
Ibuprofen	2400
Naproxen	1250

  - Use increasing doses of morphine, as needed; consider patent–controlled dosing
  - Consider adjuvant therapy
    - Tricyclic Antidepressants (TCA)
    - Anti–convulsants
    - Local analgesics
    - Corticosteroids
    - IV bisphosphonate (for painful bone lesion)

BILIARY TREE

CHOLANGITIS

➢ Clinical

What is the examiner thinking?

Stem	Added information	Think of
• RUQ pain	○ Treatment with NSAIDs	– Biliary colic
	○ Mildly ↑ ALT, AST, bilirubin; fever, leukocytosis	– Acute cholecystitis
	○ Bilirubin > 4 mg/dL, ALT, AST > 1000 U/L, systemic symptoms	– Acute cholangitis
	○ ICU patient, diabetic, non–contributory abdominal ultrasound, negative HIDA scan	– Acalculous cholecystitis
	○ Young women, tender in pelvic adnexia	– Gonococcal or chlamydial perihepatitis (Fitz–Hugh–Curtis syndrome)
	○ Dilated CBD, no stones seen on MRI, EUS, ERCP	– Enlarged gallbladder non–visualized stone impacted in cystic duct, gallbladder externally compressing CBD (Mirizzi syndrome)
	○ Small bowel obstruction, air in biliary tree	– Cholecystoenteric fistula, causing "gallstone ileus"
	○ Immunosuppressed; should inform patient he has *Cryptosporidium* or CMV infection	– AIDs cholangiopathy (CD < 100/μL)

➢ Diagnostics

If US is not diagnostic of gallstones in the bile duct causing cholangitis, the next test to do would be MRI, EUS or ERCP ± sphincterotomy not HIDA scan.

- Explain why.
    - The HIDA scan is "positive when it's supposedly negative"!
    - In order for a selective cholescintigraphy to show the gallbladder, it requires a normal liver and normal serum bilirubin concentration. If the patient has alcoholic hepatitis and mild hyperbilirubinemia, the HIDA scan may not show the gallbladder (non–visualization represents a positive HIDA scan), even though there is no cholecystitis or cystic duct obstruction.
    - We don't want to misdiagnose acalculous cholescystitis on the basis of a non–visualizing gallbladder.
    - When is the patient with RUQ pain +/- tenderness treated with NSAIDs?
        - If there are no ↑ WBC or fever, the biliary cholic may be prevented from progressing to acute cholecystitis (minimally ↑ ALT, AST, bilirubin).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- What is Reynold Pentad modification of Charcot Triad (ChTri) in cholangiohepatitis?
    - Charcot Triad (ChTri)
        - RUQ pain
        - Jaundice
        - Fever
    - Reynold Pentad: ChTri plus
        - Hypotension
        - Altered mental status

➢ Laboratory

- Give the laboratory features which help **distinguish** acute cholecystitis from acute cholangitis.

Lab' Findings	Acute cholecystitis	Acute cholangitis
○ AST, ALT	Minimal ↑	>1000 U/L
○ Bilirubin	< 4	< 4

➢ Treatment

- Give the differences in the treatment (antibiotics and endoscopic surgical intervention) of acute cholecystitis and acute cholangitis.

Treatment	Acute cholecystitis	Acute cholangitis
○ Antibiotic	– Monotherapy ▪ Piperacillin–tazobactam or ▪ Ampicillin–sulbactam or ▪ Ticarcillin–clavulanic acid – Dual therapy ▪ Ceftazidime plus metronidazole – Triple therapy ▪ Ampicillin, gentamicin and metronidazole	– Fluoroquinolone
○ Surgery	– Cholecystectomy for 24–48 hours.	– ERCP drainage – Avoid cholecystectomy until later to avoid ↑mortality

CLINICAL VIGNETTES: Give the likely diagnosis.

- Case: RUQ / RLQ pain, fever, diarrhea, CD4 count < 180
  - *Cryptosporidium* of
    - Biliary tree
    - Terminal ileum
- Case: Intermittent abdominal pain, on ERCP, Bulb–like dilation of ampulla
  - Choledochal cyst, type III ("choledochocele")

  Mucinous discharge from papilla
  - IPMN, main duct (MD–IPMN)

  Blood from ampulla
  - Hemosuccus pancreaticus
- Case: Recurrent RUQ pain, with ↑ AST, ↑ serum amylase; abdominal ultrasound shows dilated common bile duct (CBD) without lithiasis
  - Sphincter of Oddi (SOD) spasm, type I (moderate benefit from sphincterotomy)

CHOLEDOCHAL CYST

- Definition
  - Choledochal cysts are congenital "segmental dilations of the biliary tree that can lead to complications including strictures, 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
  - Types I CBD diffusely enlarged, with tapered ends ("fusiform")
  - Type II CBD diverticula
  - Type III Dilation of intraduodenal portion of CBD ("choledochocele")
  - Type IV Multiple intra– and extra–hepatic cysts of the bile ducts
  - Type V Diffuse intrahepatic cysts

- Usual treatment
  - Surgery – I, II
  - Sphincterotomy – III

NUTRITION

MALNUTRITION

➢ Diagnosis

- What are the factors that cause increase in the pretest probability for the presence of malnutrition?

  - ↓ Intake
    - ↓ appetite
    - Psychiatric illness
    - Conditions requiring a change to suboptimal solid diet (eg liquid diets, tube diets)
    - Elderly patients
  - ↓ digestion or absorption
    - Gastrointestinal tract illness
  - ↑ requirements
    - Malignancy
    - Disorders affecting metabolism
  - ↑ losses
    - Patients with unintentional weight loss of more than 5%, a major category of individuals who need of additional testing

Adapted from: Simel DL, *et al*. *McGraw-Hill Medical* 2009, page 381.

- Give the likelihood ratio 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

	Item score
○ 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: many historical points, symptoms and signs on PE have a PLR <2

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.

REFEEDING SYNDROME

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of gastrointestinal diseases, give the major complications arising from deficiencies of 6 of the following micronutrients and vitamins:
  - Copper – anemia, altered taste
  - Iodine – hypothyroidism
  - Manganese – thin, light hair
  - Selenium – myositis, cardiomyopathy, collagen vascular disease
  - Zinc – acrodermatitis enterohepatica, impaired taste, glucose intolerance, slow wound healing, alopecia, depression, diarrhea
  - Chromium – glucose intolerance
  - Thiamine (B1) – beriberi, wernicke encephalopathy, polyneuritis, anorexia, anemia, ataxia
  - Riboflavin – sore mouth & lips, swollen tongue, photophobia
  - Niacin – pellagra, glossitis, dermatitis, mental confusion
  - Pantothenic acid – poor wound healing

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Define "refeeding syndrome" and outline its pathophysiology.
  - If glucose is fed rapidly, insulin is released, phosphate is rapidly taken up into the cells, and serum PO_4^- falls.
    - Complications to develop include:
      - Neurological (seizures, paresthesias, hyperosmolar coma) and cardiovascular (CCF, death)
      - GI – diarrhea
      - RBC fail to release O_2 normally → Ventricular Tachycardia (VT)
      - 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 or AA shifts these back into the cells, and 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.

EATING DISORDERS

- What is bulimia nervosa ("BLW")
  - **B**inging ≥ 2 times per week of 3 months
  - Attempts to **L**ose weight
    - Vomiting
    - Abuse of laxatives
    - Abuse of diuretics
    - Fasting
    - Excess exercise
  - **W**eight usually normal (anorexia plus bulima may co–exist in a patient)

- Define the restricting type of anorexia nervosa ("WAIF").
  - **W**eight not maintained within 15% of lower limit of normal (LLN)
  - **A**menorrhea (depending on age, failure of menses to begin)
  - **I**mage of body is distorted
  - **F**ear of eating and weight gain

Anorexia nervosa

- Disturbed perception of body image and weight
- Fear to gain weight
- Deliberate loss of weight
- Amenorrhea
- In contract to restricting anorexia nervosa (AN), the binge-eating or 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
  - Fasting
  - Exercise

COBALAMIN (VITAMIN B12)

- What mineral mimics cobalamin deficiency, which is a result from bariatric surgery, or the intake of large amounts of zinc?

  - Copper deficiency may damage posterior columns and be associated with sensory ataxia and anemia.

Cobalamin deficiency is not always associated with anemia or reduced serum levels of the vitamin.

- What metabolites are used to measure to exclude cobalamin deficiency?

  - Methylmalonic acid and homocysteine concentrations in the blood will be elevated in early cobalamin deficiency.

OBESITY

- Definition:
  - "Obesity is a complex heterogeneous disorder that places individuals at increased risk for adverse mental and 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 the mechanisms explaining alterations in serum vitamin levels in obesity.
  - ↓ intake
  - ↓ transport proteins (chronic inflammation in obesity → ↑ proinflammatory cytokines
  - ↑ turnover
  - Shift in tissue distribution

It is often surprising to the physician to learn that protein and calorie malnutrition (PCM) may occur in individuals who are obese.

- Give the symptoms and signs of protein and calorie malnutrition (PCM) which may occur in obesity.
  - General
    - Fatigue
    - Weakness
  - Hair
    - Brittle
    - Loss of hair
    - Altered colour
  - Skin
    - Edema
    - Pressure sores
    - Dry and scaly skin
    - Slow wound–healing
  - CVS
    - Tachycardia

MISCELLANEOUS

HIV INFECTION AND THE GI TRACT IN THE HAART ERA

- Highly active antiretroviral therapy (HAART) may lower HIV viral load to undetectable levels, making opportunistic infections very much less common.
- In some HAART–treated patients, the HIV viral load may be zero, and the CD4 count < 200 mm^3 level lowers.
- A symptom–based diagnostic approach remains reasonable.

➢ Differential Diagnosis

- Give the causes of dysphagia and odynophagia in patients with AIDS.

  - Infection
    - *Candida albicans*
    - Cytomegalovirus (CMV)
    - *Herpes simplex*
    - *Histoplasma capsulatum*
    - *Mycobacterium avium* complex
    - *Cryptosporidium* spp.
  - Neoplasm
    - Kaposi's sarcoma
    - Lymphoma
    - Squamous cell carcinoma
    - Adenocarcinoma
  - Gastroesophageal reflux disease (GERD)
  - Pill–induced esophagitis
  - Idiopathic ulcerations

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.

Idiopathic Esophageal Ulcers

- Multiple ulcers
- Well–circumscribed
- Punched–out
- Normal intervening mucosa

- Give the viral infection associated with condyloma acuminata and squamous cell carcinoid of the anorectal area in HIV/AIDS?
  - Human papilloma virus (HPV)

- Give the screening method to detect this infection, and what they predict.
  - Cytological specimens of the anal canal are used to screen for HPV (type 16 and 18), and have a high predictive value for dysplasia.

- 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.

- Give the causes of **upper GI bleeding** (UGIB) that are most frequently involved in HIV/AIDS patients in the HAART era.
  - The causes of UGIB that are not related to HIV/AIDS are the most common cause in the HAART–treated patient.

- Give the most common cause of **lower GI bleeding** in HIV/AIDS patients in the HAART era.
  - CMV colitis

- **Name the three common** infections in HIV / AIDs which do not cause **colitis** and rectal bleeding in HIV/AIDS.
  - Pathogens which do not cause mucosal ulcerations such as MAC, microsporidia and cryptosporidia, do not cause bleeding.

- Give the infectious agents which are most commonly induced in the immune reconstitution syndrome following the introduction of HAART therapy.
    - Mycobacteria, e.g. MAC lymphadenitis
    - CMV, e.g. CMV uveitis

Infections by enteric bacteria such as *Salmonella*, *Shigella* and *Campylobacter* are common and virulent in HIV/AIDS.

- Give their characteristic features of infection.
    - High rates of bacteremia
    - High rates of antibiotic resistance
    - May need to be treated with IV ciprofloxacin

- 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.

- 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.

- Give the most common infectious cause of diarrhea in HIV/AIDS patients with HAART era.
    - *C. difficile*
    - "punishment marks" if you said *Giardia lamblia* or *Entamoeba histolytica*

- Give the most common cause of drug–induced diarrhea in HIV/AIDS.
    - The most common cause of drug–induced diarrhea in HIV/AIDS is HAART therapy (protease inhibitors).
    - The most common HAART drug causing diarrhea is Nelfinavir.

An HIV/AIDS patient develops bloody diarrhea, fever and a raised serum LDH concentration.

- Give the most likely infectious cause.
  - Histoplasmosis causing diffuse colitis with ulceration.

- For differential diagnoses for 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.

- Give the dermatological conditions in GI disorders.
  - Acanthosis nigricans
    - Definition
      - Black, velvety skin growth specifically in axilla
    - Causes
      - Benign
        - T2DM
        - Cushing syndrome
        - Acromegaly
        - Polycystic ovarian syndrome(Stein–Leventhal syndrome)
      - Malignant
        - Adenocarcinoma, specially of stomach or other parts of GI tract; uterus or ovary; lungs, breast, prostate
        - Lymphoma

- In the context of HIV/AIDS, give the infectious agents that cause Kaposi's sarcoma, and bacillary peliosis hepatis.
  - Kaposi's sarcoma – HHV–8 (human herpes virus–8)
  - Bacillary peliosis hepatis
  - *Bartonella henselae*, or *B. quintana*

GASTROINTESTINAL MANIFESTATIONS OF SYSTEMIC DISEASE

Scleroderma (progressive systemic sclerosis [PSS])

GI complications occur in > 80% of patients with PSS, and may affect all parts of the GI tract.

- Give the examples.

- Mouth
  - Perioral skin
  - Xerostoma
- Esophagus
  - ↓ LES pressure
  - ↓ motility → ↓ acid clearance
  - GERD (100% in those with severe cutaneous PSS)
  - Strictures and Barrett epithelium (BE)
  - ↑ risk of candidiasis
  - ↑ risk of esophageal adenocarcinoma
- Stomach
  - Gastroparesis
  - Gastric antral vascular ectasia (GAVE)
- Small bowel (SB)
  - ↓ motility (↓ IMCC [interdigestive migrating motor complex])
  - Duodenum
    - Dilated
    - Pseudo–obstruction, malabsorption, intussusception, volvulus, pneumatosis intestinalis
  - Jejunum
    - Dilated
    - Shortened
    - Accordion–like
    - Pneumatosis cystoides intestinalis (PCI)
    - Pseudo–obstruction
    - Pseudo–diverticula
    - Sacculations
    - SB volvulus
    - Small intestinal bacterial overgrowth (SIBO)
    - Arteritis (rare)
      - Mesenteric thrombosis
      - Infarction

- Colon
  - Constipation
  - Wide–mouthed diverticula (actually, pseudodiverticulae on the antimesenteric side, transverse and descending colon)
  - Telangiectasia – 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

Rheumatoid Arthritis

- Give the gastrointestinal and hepatobiliary manifestations of rheumatoid arthritis.

Temporomandibular arthritis	- Impaired mastication
Esophageal dysmotility	- Dysphagia, GERD
Visceral vasculitis	- Abdominal pain, cholecystitis, intestinal ulceration and infarction
Amyloidosis	- Pseudo–obstruction, malabsorption, protein–losing enteropathy, intestinal ulceration and infarction, gastric outlet obstruction
Portal hypertension (Felty syndrome)	- Variceal haemorrhage
Gold enterocolitis	- Enteritis, diarrhea, fever, eosinophilia, megacolon

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

About 15% of patients with rheumatoid arthritis (RA) have positive biochemical markers for liver disease.

- Give the histologic changes in the liver seen in RA.
  - 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 develop mixed cryoglobulinemia
    - These patients rarely have antibodies to anticyclic citralinated peptide (CCP), they 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 with hepatic toxicity

Systemic Lupus Erythematosus (SLE)

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

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 on CT which help make the diagnosis of bowel ischemia in SLE.
  - 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 (hypoattenuation)
  - Intestinal segments – dilation
  - Mesenteric vessels – engaged
  - Mesenteric fat – hyperattenuation

MISCELLANEOUS MSK DISORDERS

○ Cogan syndrome	– Mesenteric vasculitis (infrequent)	▪ Hemorrhage, ulceration, intestinal infarction, intussusception
	– Crohn's disease	▪ Bloody diarrhea, abdominal pain, fissures, fistulas
○ Familial Mediterranean fever	– Serositis/peritonitis, amyloidosis, PAN, Henoch–Schönlein purpura	▪ Abdominal pain, fever, dysmotility
○ Köhlmeier–Degos disease	– Mesenteric vasculitis	▪ Hemorrhage, ulceration, intestinal infarction, malabsorption
○ Polymyositis–dermatomyositis	– Skeletal muscle dysfunction	▪ Aspiration ▪ ↓ deglutition
	– Dysmotility	▪ Dysphagia, GERD, gastroparesis, constipation, diverticula
	– Mesenteric vasculitis (rare)	▪ GI ulceration, perforation, pneumatosis intestinalis
○ Reactive arthritis	– Ileocolonic inflammation	▪ Usually asymptomatic
○ Sjögren 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
○ Wegener granulomatosis	– Mesenteric vasculitis	▪ Cholecystitis, appendicitis, ileocolitis, intestinal infarction

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

- In SLE, the vasculitis is usually in the small vessels, and visceral angiography is not very useful diagnostically.
- 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.
- In fact, about 80% of PAN patients will have aneurysmal dilations especially in the superior mesenteric artery.
- Thus, bowel ischemia is common.

- Give GI associations of PAN in addition to bowel ischemia, with its complications of infarction and perforation.

Gallbladder / BT	– Acalculous cholecystitis – Hemobilia – Biliary strictures
Pancreas	– Pancreatis
Liver	– Hepatic infarcts – HBV infection

A middle–aged man who moved to Canada 20 years ago from Syria developed acute abdominal pain, fever, and arthralgias. The relapsing and remitting nature of the symptoms led to the consideration of porphyria as the diagnosis, but laboratory investigations for porphyria were negative. CT scan of the abdomen suggested a small bowel obstruction.

- Give the renal conditions could develop.
  - Nephrotic syndrome
  - Amyloidosis
  - Chronic renal failure

- I still do not know the GI diagnosis! This sounds more like a nephrology question.
  - 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 this attacks, he would have developed sterile peritonitis, leading to the symptoms of small bowel obstructions from adhesions.
  - Treatment is colchicine.

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

- Give the GI complications of **systemic lupus erythematosus** (SLE)

○ Mouth	– Oral ulcer
○ Esophagus	– ↓ motility – GERD
○ Stomach	– Hypertrophic gastropathy – Gastritis
○ Small bowel	– Protein–losing enteropathy – Steatorrhea – Pneumatosis cystoides intestinalis (PCI)
○ Colon	– Necrotizing enterocolitis (NEC) – Vasculitis of the small vessels – Ischemic colitis
○ Pancreas	– Pancreatitis
○ Liver	– Lobular hepatitis – Antinuclear antibodies positive but not Autoimmune hepatitis (AIH) – Nodular regenerative hyperplasia (NRH) – Budd–Chiari syndrome ▪ Lupus anticoagulants ▪ Anticardiolipin antibodies – Fatty liver

Mixed Connective Tissue Disease (MCTD)

○ Dysmotility	- Dysphagia, GERD, stricture, gastroparesis, bezoars, pseudo–obstruction

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

- Polymyositis and dermatomyositis have been traditionally considered to represent an inflammatory myopathy of skeletal muscle.
- Other parts of the GI tract have smooth muscle, which are not expected to be affected by disorders in skeletal muscles.
- This would explain transfer dysphagia and nasal regurgitation
- These patients may have other GI complications such as:
  - Disorders of the motility of the lower esophagus
  - Gastroporesis
  - Hypomotility of the small ntestine
  - Pneumatosis intestinalis
  - Colonic dilation
  - Pseudodiverticula

Polymyositis, PSS and SLE may overlap in a syndrome known as Mixed connective tissue disease (MCTD).

- Give the unusual therapeutic feature of esophageal motility complication which occur in MCTD?
  - In MCTD, the esophageal motility disorder responds to glucocorticosteroids.

Polyarteritis Nodosa (PAN)

- Mesenteric vasculitis
  - Appendix
    - Appendicitis
  - Gallbladder
    - Cholecystitis
  - Pancreas
    - Pancreatitis
    - Hemorrhage
    - Obstruction
    - Perforation
    - Infarction
    - Submucosal hematomas
    - Strictures

Churg–Strauss Sydrome (CSS)

- Mesenteric vasculitis - Hemorrhage, ulceration, intestinal infarction, perforation
- Eosinophilic gastritis - Gastric masses

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Churg–Strauss Syndrome (CSS or allergic granulomatous angitis) is characterized by sinusitis, rhinitis, asthma and peripheral eosinophilia. The level of the esosinophilia may be 1500 eosinophils/mm^3 in these CSS patients who have GI complications.

- Give the GI complications seen in Churg-Strauss Syndrome (CSS).

○ Abdominal pain (nausea, vomiting, bleeding)	– Eosinophilic gastroenteritis (diarrhea) – Ulcerations – Perforations
○ Pancreas	– Pancreatis
○ Gallbladder	– Cholecystitis
○ Colon	– Ulceration
○ Peritoneum	– Ascites

"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 decision."

Henoch–Schönlein purpura

- Mesenteric vasculitis - Intussusception, ulcers, cholecystitis, hemorrhage, intestinal infarction, appendicitis, perforation

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Henoch–Schönlein Purpura (HSP) is characterized by
- Abdominal pain, renal disease, arthralgias
- Non–thrombocytopenic purpura arising from systemic vasculitis
- GI bleeding is also common

- Give GI complications of HSP, other than abdominal pain and bleeding.
  - Small bowel
    - Aphthous ulcers
    - Walll thickening
    - Dilation
    - Protein–losing enteropathy
    - Strictures
    - Intramural hematoma
    - Intussusceptions
  - Colon - Ischemic perforations
  - Appendix - Appendicitis
  - Pancreas - Pancreatits
  - Gallbladder - Cholecystitis

Mixed cryoglobulinemia

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Mixed cryoglobulinemia (raised serum concentration of IgG plus IgM) is characterized by arthralgia, purpura, and asthenia.
- Give the associations of cryoglobulinemia.
  - HCV infection
  - IBD
  - Celiac disease
  - Postintestinal bypass syndrome
  - Small intestinal
    - Colonic vasculitis
    - Ischemia
    - Diarrhea
    - Perforation

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

- **Wegener granulomatosis** (WG) is characterized by vasculitis involving the sinuses, lungs and kidney. When WG involves the GI tract, give the reason why it may be confused with Crohn's disease (CD).
  - Stomach – Granulomas
  - Small bowel – Ileocolitis, with granulomas* – may mimic Crohn's disease (CD)
  - Gallbladder – Gangrenous cholecystitis
  - Cryoglobulinemia – Mesenteric vasculitis (rare)

BEHÇET DISEASE

- Mucosal ulcerations
  - Hemorrhage, perforation, pyloric stenosis
  - Complications as in rheumatoid arthritis

SO YOU WANT TO BE A GASTROENTEROLOGIST OR RHEUMATOLOGIST!

Behçet disease (BD) is characterized by uveitis, aphthous ulcers of the mouth, skin lesions, and genital ulcers. About half of BD patients have GI complications, which may mimic Crohn's disease (CD).

- Give GI complications of BD which reflect why BD needs to be differentiated from CD.
  - 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

DIABETES AND THE GI TRACT

SO YOU WANT TO BE A GASTROENTEROLOGIST OR ENDOCRINOLOGIST!

- Give the role of EMG studies in a diabetic patient with unexplained upper abdominal pain.
  - 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.

Neuromuscular disorders (such as Charcot–Marie–Tooth syndrome, myasthenia gravis, muscular dystrophies, amyotrophic lateral sclerosis) may be associated with motility disorders.

- Esophagus
  - Cervical (oropharyngeal) dysphagia
  - Achalasia Mmitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
- Stomach
  - Gastroparesis
- Small intestine
  - Pseudo–obstruction
- Colon
  - Fecal incontinence

SO YOU WANT TO BE A GASTROENTEROLOGIST OR NEUROLOGIST!

GI symptoms are common (70%) in persons with multiple sclerosis (MS), such as oropharyngeal dysphagia.

- Give causes of constipation related to MS.
  - ↓ activity
  - Rectal intussusception
  - Rectal outlet obstruction
  - Stercoral ulcers
  - Incoordinated relaxation of muscles
    - Puborectalis
    - Internal anal sphincter (IAS)

Neurological Injury

- Give common GI complications after a cardiovascular accident (CVA) or injury to the head or spinal column.

  - 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
    - Duodenitis (8%)

- Spinal cord

  - Esophagus
    - GERD
  - Stomach
    - Gastroparesis
      - ↓ drug absorption
    - Ulceration (GU)
  - Duodenum
    - Ulceration (DU)
      - ↑ risk of
        - Bleeding
        - Asymptomatic perforation
  - Small intestine
    - Amyloidosis (secondary)
  - Pancreas
    - Pancreatitis
  - Colon
    - Constipation
      - Sensation ↓ rectal fullness
      - Motor ↓ control of defecation

Source: Feldman, M., *et al*. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier* 2010, page 579.

- Why is defecation reflex usually intact in patients with spinal cord injury?
  - The defecation reflex is usually intact in spinal cord injury patients because the lower motor neurons nerve roots, from S_2, S_3 and S_4 sacral nerve roots, are not affected.

- Idiopathic autonomic neuropathy affecting the sympathetic and parasympathetic systems (70%) often affects the GI tract. Give the symptoms which suggest autonomic (parasympathetic) neuropathy.
    - Diarrhea
        - Hypersalvation
        - Hyperhydrosis
    - *Note
        - Small intestinal bacterial overgrowth (SIBO) 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 amyloidosis 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 liver biopsy.

- 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
    - Infiltration of amyloid
    - Walls of arteries, arterioles, portal and hepatic veins
        - Extracellular, amorphous, hyaline deposits
    - Three patterns of deposits:
        - Globular deposition in space of Disse
        - Parenchymal and sinusoidal intralobular deposits
        - Mixture of parenchymal and periportal vascular deposits

Useful Pointers

- The liver is 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 include 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:
- Muscularis mucosa – ↓ absorption
- Muscle layer – Dysmotility
- Vessel walls – Ischemia
  – Infarction
- Direct pressure damage to myenteric plexus and visceral nerve trunks

CHRONIC RENAL DISEASE AND THE GI TRACT

Chronic renal disease associated with a plethora of GI complications, especially to patients on hemodialysis (HD) or peritoneal dialysis (PD).

- Give the 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
  - Small bowel
    - Angiodysplasia
      - ↑ risk of bleeding
      - Risk of bleeding related to
        - Duration of renal failure
        - Need for HD
    - Ulcers
    - Ischemia (non–occlusive)
    - Ileus
    - SIBO
    - Choleretic diarrhea

- Duodenum
  - Duodenitis (nodular)
  - Brunner's gland hyperplasia
- Colon
  - ↑ rupture of diverticulae
  - Ileus
  - Intussusception
  - Cecal ulcers
  - Fecalomas
    - ↓ motility
    - Use of barium, aluminium–containing antacids
- Pancreas
  - Pancreatitis

THE ICU 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 of patients in the ICU including post–operative of major surgery.
  - Esophagus
    - GERD, including severe esophagitis
  - Stomach
    - Gastroparesis
    - Stress ulceration
      - Usually seen in ICU patients who are ventilated, or who have coagulopathies
  - Small intestine
    - Diarrhea in half of the hospitalized patients with severe acute respiratory syndrome (SARS)
  - Colon
    - Ischemic colitis
  - Gallbladder
    - Acalculous cholecystitis

SYSTEMIC INFECTION

SO YOU WANT TO BE A GASTROENTEROLOGIST!

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.

Give the changes on liver biopsy of a patient with systemic infection.

- Hepatocytes
  - Little changes, no necrosis
  - Portal area
    - Mild portal infiltrate of mononuclear cells
- Zone 2 and 3
  - Bile stasis
- Cholangitis lenta
  - Dilated
  - Bile thrombi
  - Surrounded by neutrophils
- Mild steatosis

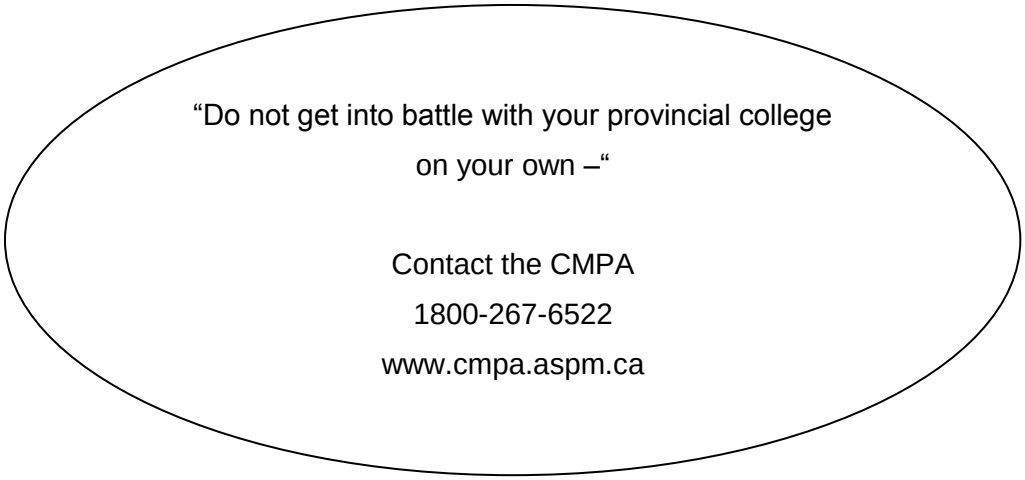
ENDOSCOPY

- What are the complications of intraoperative endoscopy?
  - Gut
    - Tear or perforation
    - Avulsion of superior mesenteric artery
  - Patient
    - Congestive heart failure (CHF)
    - Chronic renal failure (CRF)
    - Ileus

- Capsule endoscopy (CE)
  - Non–progressive obstruction
- Enteroscopy
  - Push (peds colonoscope)
  - Balloon
    - Single balloon (SBE)
    - Double balloon (DBE)

- CT scan
  - Regular
  - CT angiogram
  - CT enterography and enteroclysis

- MRI
  - Regular
  - MR enterography and enteroclysis
  - Problems with MR enterography
    - Patient must sit still for 10 minutes
    - SB peristalsis
    - Claustrophobia



SUGGESTED PRACTICE CASE SCENARIOS FOR OSCE EXAMINATIONS

Primary Stem	Secondary Stem	Diagnosis
➢ Abdominal pain	○ In an alcoholic	- Pancreatitis
	○ With jaundice and RUQ pain	- Acute cholelithiasis
	○ With jaundice and fever in a diabetic	- Ascending cholangitis
	○ Acute epigastric with guarding	- Perforated DU
	○ Chronic epigastric	- DU and *H. pylori*
	○ Acute epigastric with hypotension in elderly male	- Rupture AAA
	○ Diffuse pain with atrial fibrillation and diarrhea	- Intestinal ischemia
	○ Lower abdominal pain and fever in older patients	- Diverticulitis
	○ Lower abdominal pain and fever	- Appendicitis
➢ Hematochezia	○ Massive rectal bleeding in elderly patients	- Diverticulosis
	○ Spotting blood & mucous in young person	- IBD
	○ Blood in stool of older patients	- Rectal CA
➢ Abdominal mass	○ Renal mass	- PKD or Renal cell carcinoma
	○ Cecal mass	- CD, Crohn's disease
	○ Pulsatile midline mass	- Abdominal aortic aneurysm
	○ LUQ mass	- Splenomegaly
➢ Diarrhea	○ Acute following travel	- *Giardia*
	○ In elderly	- Drugs
	○ With blood in stool	- Bacterial
	○ Chronic diarrhea in Asian	- Lactose intolerance
	○ Chronic diarrhea, microcytic anemia & rash in Caucasian	- Celiac
	○ Chronic diarrhea, bronchospasm, murmur & flushing	- Carcinoid
	○ Floating stools, pain, weight loss, alcohol abuse	- Pancreatic insufficiency

Primary Stem	Secondary Stem	Diagnosis
➢ Abnormal lab tests		
➢ Jaundice	○ Painless with pruritus, in older patients	- Pancreatic cancer
	○ Painless with pruritus , fatty diarrhea in middle–aged female	- Primary biliary cirrhosis
	○ Painless with pallor	- Hemolytic anemia
➢ Abdominal distension	○ Signs of portal hypertension	- Pregnancy
	○ Heartbeat	
	○ Android obesity	- Cirrhosis 2° chronic hepatitis
	○ Large kidneys	
	○ Massive splenomegaly	- Syndrome X
		- PKD
➢ Other		

Source: 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

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