GI PRACTICE REVIEW

Second Edition

This book complements

ENDOSCOPY and DIAGNOSTIC IMAGING Part I

and

ENDOSCOPY and DIAGNOSTIC IMAGING Part II

A.B.R. Thomson

THE WESTERN WAY

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Parts I and II

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"For the Democratization of Knowledge"
2012

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GI Practice Review 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 GI 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

Like any good story, there is no real beginning or ending, just an in-between glimpse of the passing of time, a peek into a reality of people's minds, thoughts, feelings, and beliefs. The truth as I know it has a personal perspective which drifts into the soul of creation. When does life begin, when does an idea become conceived, when do we see love or touch reality? A caring, supportive, safe, and stimulating environment creates the holding blanket, waiting for the energy and passion of those who dream, invent, create – disrupt the accepted, challenge the conventional, ask the questions with forbidden answers. Be a child of the 60's. Just as each of us is a speck of dust in the greater humanity, the metamorphosis of the idea is but a single sparkle in the limitlessness of the Divine Intelligence. We are the ideas, and they are us. No one of us is truly the only parent of the idea, for in each of us is bestowed the intertwined circle of the external beginning and the end….

….during a visit to the Division of Gastroenterology at the University of Ottawa several years ago, the trainees remarked how useful it would be to have more than two hours of learning exchange, a highly interactive tutorial with concepts, problem solving, collegial discussion, the fun and joys of discovery and successes. Ms. Jane Upshall of BYK Canada (Atlanta, Nycomed), who had sponsored two of these visiting Professorships, encouraged the possibility of the development of a longer program. Her successor, Lynne Jamme-Vachon, supported the initial three day educational event for the trainees enrolled in the GI training program at the University of Ottawa. With her entrepreneurial forsight, wisdom, and enthusiasm, the idea began. Lynne's commitment to an event which benefited many of the future clinicians, who will care for ourselves and our loved ones, took hold. Then, thanks to the GI program directors in Ottawa and the University of Western Ontario, Nav Saloojee and Jamie McGregor, more trainees were exposed, future GI fellows talked with other trainees, and a grass roots initiative began. Had it not been for Nav and Jamie's willingness to take a risk on something new, had they not believed in me, then there would have been no further outreach. Thank you, Lynne, Nav, and Jamie. You were there at the beginning. I needed you.

By 2008, all but one GI program in the country gave their trainees time off work to participate in the three day event, GI Practice Review (GI-PR). The course is 90% unsponsored, and is gratis to the participants, (except for the

cost of their enthusiastic participation!) I am happy to give back to the subspecialty that gave me so much for 33 years. I hope GI-PR is helpful to all trainees. I know that from these future leaders there will arise those who will continue to dedicate and donate their time, energy, and ability to the betterment of those who contribute to the continued improvement of our medical profession. The clinicians, the teachers, the researchers.

In the short span of six years, more than 250 fellows, coming from all the 14 training programs in Canada, have participated in the small group sessions in the GI practice review. I thank the training program directors who have supported GI-PR. Special appreciation as well to their many staff physicians who worked without their trainees for the three days of each program.

The idea for the electronic and hard copy summary of the “list of facts” came from the trainees who wished for an aide memoir. But the GI-PR is about more than lists and facts - it is about problem formulation, case discussions, review of endoscopy, histopathology, motility, diagnostic imaging. It is about having fun working together to learn. The subterfuge to gain interest in the basic sciences is the use of clinical scenarios to show the way to the importance of first principles. While the lists are here, the experience is in the performance.

The child will grow, the images will expand, the learning of all aspects of our craft will develop and flourish amongst persons of good will. Examinations will become second nature, as each clinical encounter, each person, each patient, becomes our test, the determination of clinical competence, of caring, of compassion. May these three C’s become part of each of our live’s narrative. And from this start comes Capstone Academic Publishing, an innovation for the highest quality and value in educational material, made available at cost, speaking in tongues, in the languages of many cultures, with the dialect of the true North strong and free, so that knowledge will be free at last.

Outstanding medical practice and true dedication to those from whom we receive both a privilege and pleasure of care, comes from much more than the GI-PR can give you, much more than Q & As, descriptions of diagnostic imaging or endoscopy stills or videos, histopathology or motility. True, we need all of these to jump over a very high bar. But to be a truly outstanding physician, you need to care for and care about people, and you must respect the dignity and rights of all others. You must strike a balance

between love and justice, and you place your family and friends at the top of your wish-list of lifetime achievements.

For the skeptics who ask “What do you want from me?” I simply say “You are the future; I trust that in time you too will help young people to be the best they can be.”

May good luck, good health, modesty, peace, and understanding be with you always. Through medicine, all persons of the world may come to share caring, respect, dignity, and justice.

Sincerely,

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 behavior and wisdom and art, without those special people who turn our minds to the practical - of getting the job done!

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

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

When Rebecca, Maxwell, Megan Grace, Henry and Felix ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding, generous, kind and forgiving. For what I was trying to say and to do was to make my professional life focused on the four C's and an "H"; competence, caring, compassion, and composure, as well as humour - and to make my very private personal life dedicated to family - to you all.

Dedication

Dedicated to Jeannette Rita Cécile Mineault

My life began when I met you:

Your wit, your charm, your laughter,

Your love for children, your caring, your common sense.

As always, all ways, thank you for saying I do.

– – – – – – – – – –

For the parents who gave us life

For the children who gave us hope

For the teachers who gave us knowledge

For the partners who gave us confidence, encouragement and meaning

ESOPHAGUS

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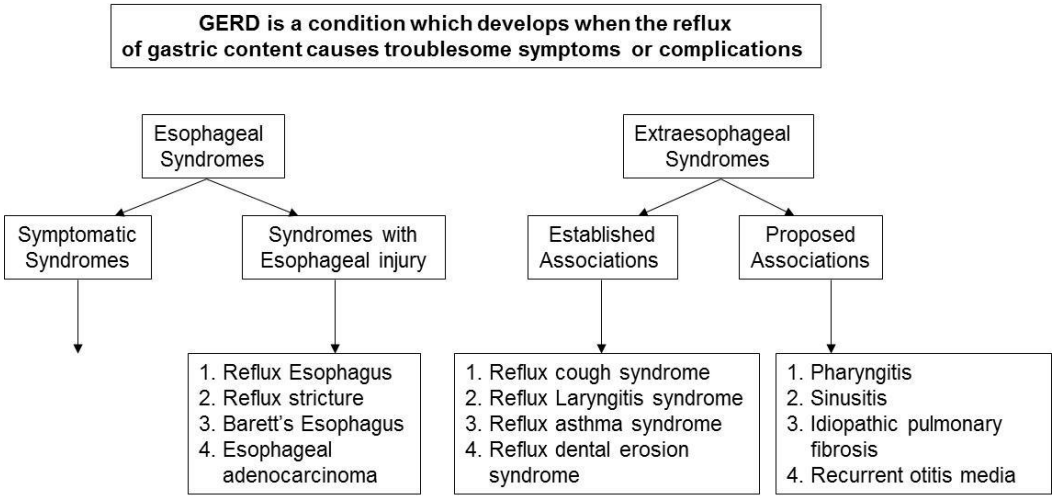
Gastroesophageal reflux disease

1. What is the “Montreal definition” of GERD and its constituent syndromes?



The overall Montreal definition of GERD and its constituent syndromes.

Abbreviation: GERD, gastroesophageal reflux disease

Printed with permission: Vakil N, et al. *Am J Gastroenterology* 2006;101(8):1900-1920.

2. Give 10 non-dietary causes/associations (not pathophysiology) of GERD.

- Hiatal hernia
- Scleroderma, Sjörgren syndrome
- Gastroparesis
- Zollinger-Ellison syndrome, G cell hyperplasia
- Pregnancy, ascites, obesity (increased BMI/ waist girth)
- Smoking, immobility, NG tube
- Medications (calcium channel blockers, theophylline, anticholinergics, nitrates, alpha adrenergic antagonists), Botox injections
- Vagotomy, gastrectomy, post dilation or myotomy for achalasia, bariatric surgery

Abbreviation: GERD, gastroesophageal reflux disease

3. Give a pathophysiological classification of GERD and GERD symptoms, and use this to classify the drugs used to treat persons with GERD.

- Motility disorders
  - Transient lower esophageal relaxations (TLESP)
  - Lower esophageal sphincter
    - Cholinergics (bethanecol)
    - Gaba receptor agonists (baclofen)
    - Hiatus hernia
    - Stomach (gastroparesis), obstructive sleep apnea
    - Prokinetics
  - Weak LES
  - Weak esophageal peristalsis
  - Scleroderma and CREST
  - Delayed gastric emptying

- Damaging factors
  - Normal HCl secretion, but ↑ reflux of acid
    - Alginate, antacids, H_2RAs, PPIs
  - Increased gastric acid production
  - Bile and pancreatic juice
    - Sulcrafate

- Resistance factors
  - Reduced saliva, HCO and EGF production
    - Chewing gum
  - Diminished mucosal blood flow
  - Growth factors, protective mucus
  - Perception
    - TCAs, SSRIs

Abbreviations: GERD, gastroesophageal reflux disease; H2RA, histamine 2 receptor antagonist; LES, lower esophageal sphincter

Printed with permission: Murray JA. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 3.

4. Classify the drugs used to treat GERD.

- ↓TLESP – (gabba receptor agonist (baclofen)
- ↑ LESP – cholinergic (bethanecol)
- ↓ sensation – TCA
- ↓ reflux – alginate
- ↓acid – PPI, H_2RA, antacids

- ↑ gastric emptying – prokinetics (domperidone)
- ↑saliva – chewing gum

5. Give 6 histological abnormalities in GERD.

- Reactive epithelial changes
  - Hyperplasia of the basal zone (3 layers or more)
  - Elongation of papillae (>15% of total epithelial thickness)
  - Increased mitotic figures
  - Increased vascularization of the epithelium
  - Loss of usual longitudinal orientation of the surface epithelium
- Balloon cells
- Erosions
  - Epithelial loss
  - Inflammatory infiltrates – lymphocytes, plasma cells, eosinophils, neutrophils
  - Necrosis
- Barrett's
  - Intestinal metaplasia, dysplasia, adenocarcinoma
  - Goblet cells (shown with combined hematoxyline and eosin-alcian blue PAS stains)
  - Fibrosis

Abbreviation: GERD, gastroesophageal reflux disease

Useful background: The histological grading of GERD

Grade	Inflammatory infiltrates		Basal-cell hyperplasia
	Definition	Cell type	
➢ 0	0-6 cells/HPF	Lymphocytes, plasma cells	3 cell layers or less
➢0.5	Small areas >6 cells/HPF	Lymphocytes, plasma cells	3 cell layers or less
➢ 1	Slight focal infiltration	Lymphocytes, plasma cells	>3 cell layers, less than 1/3 epithelial thickness
➢ 2	Moderate diffuse infiltrate	Lymphocytes, plasma cells, eosinophils	>1/3 and <2/3 of epithelial thickness

➢ 3	Severe inflammation	Lymphocytes, plasma cells, eosinophils, neutrophils	>2/3 of epithelial thickness

Abbreviation: GERD, gastroesophageal reflux disease

Printed with permission: Vieth M. *Best Practice & Research Clinical Gastroenterology* 2008;22(4): pg. 629.

Useful background: The histological grading of GERD

	Length of papillae as % of total epithelial thickness	Thickness of basal cell layer as % of total epithelial thickness
➢ Normal	<15%	1-2%
➢ Grade 1	15-33%	2-20%
➢ Grade 2	34-66%	21-50%
➢ Grade 3	>66%	>50%

Criticisms: Small number of patients; no interobserver variation; questionable control group

Abbreviation: GERD, gastroesophageal reflux disease

Printed with permission: Vieth M. *Best Practice & Research Clinical Gastroenterology* 2008;22(4): pg. 628.

6. Give 8 ENT/pulmonary symptoms and 8 ENT/pulmonary signs of GERD.

Symptoms	Signs
➢ Pharynx, Sinuses--Throat Clearing, Throat Mucus, Globus, Dysphagia, Halitosis, Acid Regurgitation, Waterbrash	○ Sinusitis, Pharyngitis, Lingual Tonsilitis, Halitosis
➢ Larynx--Vocal Fatigue, Hoarseness (dysphonia)	○ Posterior laryngitis, Laryngeal carcinoma, Vocal cord contact ulcers, granulomas, polyps, nodules, subglottic stenosis
➢ Ears--Ear Pain	○ Otitis Media
➢ Lungs—interstitial pulmonary fibrosis (IPF), wheezing, asthma,	○ Signs of pulmonary fibrosis ○ Wheezing

chronic cough, aspiration

- Heart--NCCP, swallowing syncope
  - Sinus arrhythmia
- Teeth--Tooth ache
  - Dental carries
- Neck Pain-- (muscle spasm)
  - Torticollis and muscle spasms

Abbreviations: ENT, ear nost throat; GERD, gastroesophageal reflux disease; IPF, interstitial pulmonary fibrosis

7. Give 10 diagnostic tests for GERD.

- Tests to assess reflux
  - Ambulatory intraesophageal pH monitoring
  - Ambulatory bilirubin monitoring (bile reflux)
  - Ambulatory esophageal impedance and pH monitoring
  - Barium esophagogram, video fluoroscopy swallowing study (VFSS)
  - Optical coherence manometry
  - Scintigraphy
  - Millk scan in infant

- Tests to assess symptoms
  - Empirical trial of acid suppression

		Sensitivity %	Specificity %
- Heartburn and regurgitation	twice daily for 7 days	80	56
- Noncardiac chest pain	twice daily for 14 days	75	85

  - Intraesophageal pH monitoring with symptom association analysis
  - Bernstein test (acid infusion test to reproduce patient's typical symptoms)
  - Cortical sensing and motor control
  - Request® questionnaire

- Tests to assess esophageal damage
  - Endoscopy (optical white light EGD, capsule endoscopy [CE], EUS/FNA narrow band imaging [NBI] with zoom, chromoendoscopy)
  - Esophageal biopsy
  - Contrast radiography

- Tests to assess esophageal function
  - Esophageal manometry (normal or high resolution)
  - Esophageal impedance
  - VFSS

Abbreviations: CE, capsule endoscopy; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GERD, gastroesophageal reflux disease; NBI, narrow band imaging; VFSS, videofluroscopy swallowing study

Adapted from: Richter JE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 916; and 2010, pg. 916.; Printed with permission: Murray JA. *Mayo Clinic Gastroenterology and Hepatology Board Review*: pg. 11.; Thomson ABR. *Clinical Medicine Gastroenterology* 2008;1:pg. 11.; and Spechler SJ. *2008 ACG Annual Postgraduate Course book*: pg. 113.

8. Give 4 uses of ambulatory 24 hr esophageal pH impedence monitoring (EIM).

- Acid reflux
- Non-acid fluid reflux
- Gas reflux (belching)
- Rumination
- Bolus transit
- Dysmotility (spasm)

Abbreviation: EIM, esophageal pH impedence monitoring

Adapted from: Murray JA. *Mayo Clinic Gastroenterology and Hepatology Board Review*: pg. 11.; and Printed with permission: Thomson ABR. *Clinical Medicine Gastroenterology* 2008;1:pg. 11.

9. Give 5 clinical applications of high-resolution narrow band imaging (NBI), along the GI tract, from mouth to anus.

- Oropharynx and hypopharynx
  - Detection of premalignant and early cancer in high-risk individuals

- Esophagus
  - Detection of premalignant (Barrett's esophagus) and early cancer in high-risk individuals
  - Detection of specialized intestinal metaplasia in patients with a short segment of columnar-lined esophagus
  - Detection of flat areas of high-grade intraepithelial neoplasia and early cancer in patients with Barrett's esophagus under surveillance

- Stomach
  - Detection of premalignant and early gastric cancer lesions
  - Delineation of the spread of premalignant and early gastric cancer lesions to facilitate endoscopic mucosal resection and endoscopic submucosal dissection

- Duodenum
  - Detection of foci of adenocarcinoma in patients with ampullary adenomas
  - Diagnosis and classification of villous atrophy in celiac disease

- Colon
  - Detection of flat and depressed lesions
  - Differentiation of neoplastic and non-neoplastic colonic lesions
  - Surveillance of patients with long-standing ulcerative colitis (UC) and hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome)
  - Screening colonoscopy

Abbreviations: NBI, narrow band imaging; UC, ulcerative colitis

Printed with permission: Larghi A., et al. *Gut* 2008;57:pg. 978.

10. Give 10 lifestyle modifications for possible improvement of symptoms of GERD.

- Weight loss if BMI is increased
- Manage ascites
- Smoking cessation
- Elevate head of bed by 15 cm (6 inches)
- Refrain from eating 2 hours before lying down (after meals and at bedtime)
- Avoid a high-fat diet
- Avoid foods that worsen GER symptoms (eg. caffeine, carbonated beverages, chocolate, mint, citrus products, alcohol)
- Avoid (if possible) medications that worsen GER symptoms eg. (anticholinergics, benzodiazepines, beta-agonists, bisphosphonates, calcium-channel blockers, corticosteroids, estrogens, NSAIDs, opiates, progesterone, prostaglandins, theophylline)

- Nasal CPAP if obstructive sleep apnea is present
- Avoid exercise that may increase intra-abdominal pressure

Abbreviations: BMI, body mass index; CPAP, continuous positive airway pressure; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease

11. Give 5 diseases/ conditions associated with a higher risk for sedation-related complications in persons undergoing upper gastrointestinal endoscopy (EGD).

- Morbid obesity
- Short neck
- Alcohol or substance abuse
- Persons on high doses of psychotropic medications
- COPD, asthma
- Cervical neck lesions
- Chronic liver/kidney/heart/ lung disease

12. A 35 year old woman complains of typical GERD symptoms which are poorly responsive to a PPI od. Give 10 potential causes of inadequate PPI response.

- Drugs
  - Non-adherence to PPI
  - PPI not given 30 minutes before breakfast (or first meal of the day if a shift worker)
  - Other medication (nitrites, calcium channel blockers)
  - Rapid metabolism of PPI
  - Reduced bioavailablilty
- Life style (dietary and non-dietary issues, see question #2)
- Large volume regurgitation and need for other drugs (see question #4)
  - Posture (bending, lack of head of bed elevation)
  - Increased BMI / increased waist girth
  - Previous myotomy, hemigastrectomy/ vagometry
  - Delayed gastric emptying
  - Other causes of esophagitis
    - Non-acid GERD

- Motility disorders; DES; achalasia, NCCP
- Functional, hypersensitive esophagus pill esophagitis, NERD, esophageal cancer, skin disease with esophagitis (Epidermolysis dissecans, Mucocutaneous candidiasis), eosinophilic esophagitis, infectious esophagitis (candida, HSV, CMV)

- Other causes of esophageal-like symptoms
  - Stomach-- hypersecretory state, nocturnal acid breakthrough, gastroparesis
  - Small intestine-- bile reflux
  - Colon – GERD associated with IBS
  - Other diagnoses (ie. heart disease)

Abbreviations: CMV, cytomegalovirus; DES, diffuse esophageal spasm; GERD, gastroesophageal reflux disease; HSV, herpes simplex virus; IBS, irritable bowel syndrome; NCCP, non-cardiac chest pain; NERD, normal esophagus reflux disease; PPI, proton pump inhibitor

What's new: NERD

- Persons with typical symptoms of gastroesophageal reflux disease (GERD) may have an endoscopically normal mucosa and be diagnosed as having nonerosive reflux disease (NERD).

- This is sufficient for clinical practice, but in a research setting, NERD may be classified into three groups:
  - Abnormal esophageal acid exposure (41% of NERD subjects)
  - Hypersensitive esophagus: normal esophafeal acid exposure, positive symptom associated with acid or non-acird reflux (32% of NERD patients)
  - Functional heartburn: normal esophageal acid exposure; negative symptom association with acid or non-acid reflux (27% of NERD patients).

<u>Thoughtful reflections</u>

Discuss the ethical considerations relating to a nurse-based triage system for consultations from family physicians asking to see a gastroenterologist, using a protocol denying prompt access to persons with functional disorders or requesting a second opinion.

13. Give 8 potential risks of long-term PPI therapy.

	Risk magnitude/possible consequence
➢ Hypergastrinemia-induced carcinoid tumours	○ Not demonstrated in humans
➢ Accelerated progression of atrophic gastritis/gastric cancer with concomitant *H. pylori* gastritis	○ No documentation of an increase in atrophic gastritis and no basis to recommend testing or treatment for *H Pylori* before long-term PP use
➢ Formation of gastric fundic gland polyps	○ Odds ratio of 2.2 for developing Fundic gland polyps within 1-5 years, negligible, if any, risk of dysplasia ○ Some patients show decreased vitamin B_{12} levels after years of acid inhibition, case reports (2) of clear deficiency
➢ Vitamin B_{12} malabsorption	○ Nested case-control study of UK patients older than 50 years; adjusted odds ration of 1.44 (95% confidence interval, 1.30-1.59) of hip fracture with PPI use longer than 1 year
➢ Calcium malabsorption	○ Poor response to oral iron supplement absorption in 2 iron-deficient individuals improved after cessation of Omeprazole; no clear clinical relevance ○ PPI use is independent risk of *C difficile* diarrhea in antibiotic users, odds ratio of 2.1 (95% confidence interval, 1.2-3.5)
➢ Iron malabsorption	○ Nested case-control analysis, adjusted odds ratio for pneumonia with PPI use of 1.73 (95% confidence interval, 1.33-2.25)
➢ Increased risk of *C difficile* colitis	○ Data on PPI use and increased gastric *N*-nitrosamine remain uncertain and the risk of cancer is speculative ○ Based on 345 accidental exposures compared with 787 controls, no observed increased teratogenecity
➢ Increased risk of community-acquired or nosocomial pneumonia (presumably aspiration)	○ Clinically significant PPI drug-drug interactions are rare (<1/million prescriptions); clinical significance of some PPIs reducing effectiveness of Plavix is uncertain

➢ Gastric colonization with bacteria that convert nitrates to carcinogenic *N*-nitroso compounds that then reflux	○ One case report with lansoprazole ○ 64 cases worldwide, partially reversible (one case requires dialysis, no deaths), estimated risk 1/12,500 patient-years of therapy)
	Risk magnitude/possible consequence
➢ Safety in pregnancy (Omeprazole crosses placenta and is pregnancy safety category C; other PPIs are category B)	○ Population-based case-control study adjusted odds ration of 3.2 (95% confidence interval, 1.4-7.4)

- ➢ Drug-drug interactions; PPIs metabolized by cytochrome P450 and may induce or inhibit drug metabolism (phenytoin, warfarin, Plavix®)
- ➢ Anaphylaxis
- ➢ Acute interstitial nephritis
- ➢ Pancreatitis

Printed with permission: AGA Technical Review. *GE* 2008;135: pg. 1392-1413.

14. Give the FDA category for the safety of drugs used to treat GERD in pregnancy and recommendations for breast-feeding.

Drugs	FDA category	Recommendations for breast-feeding
➢ *Antacids* ○ Aluminum-, calcium or magnesium-containing antacids	None	Most are safe for use during pregnancy and for aspiration prophylaxis during labour because of minimal absorption Avoid long-term, high-dose therapy in pregnancy

○ Magnesium trisilicates	None	Not safe for use in pregnancy as cause fluid overload and metabolic alkalosis
○ Sodium bicarbonates	None	No teratogenecity in animals. Generally regarded as acceptable for human use because of minimal absorption
➢ *Mucosal protectant*		
○ Sucralfate	B	A prospective, controlled study suggests acceptable for use in humans
➢ *Histamine2-receptor antagonist (H2RA)*		
○ Cimetidine	B	Same as above. Ranitidine is the only H2RA whose efficacy during pregnancy has been established
○ Ranitidine	B	Same as cimetidine, but paucity of safety data in humans

Drugs	FDA category	Recommendations for breast-feeding
○ Famotidine	B	Not recommended during pregnancy. In animals, spontaneous abortion, congenital malformations, low birth weight and fewer live births have been reported. Little data in humans.
○ Nizatidine	B	
➢ *Promotility agents*		
○ Cisapride	**C**	Embryotoxic and fetotoxic in animals. Prospective controlled study in human suggest acceptable in pregnancy, but was removed because of cardiac arrhythmias
○ Metoclopramide	B	No teratogenic effects in animals or humans reported Embryotoxic and fetotoxic in animals. Case reports in human suggest similar concerns. Possible cardiac damage.

- *Proton-pump inhibitors*

○ Omeprazole	**C**	No teratogenecity or harm. Limited
○ Lansoprazole	B	human pregnancy data
○ Rabeprazole	B	No teratogenecity or harm. Limited
○ Pantoprazole	B	human pregnancy data
○ Esomeprazole	B	No teratogenecity or harm. Limited human pregnancy data
		No teratogenecity or harm. Limited human pregnancy data

Printed with permission: Ali RAR, and Egan LJ. *Best Practice & Research Clinical Gastroenterology* 2007;21(5): pg. 799-803.

15. GER-related cough may be a diagnosis of exclusion. Name 6 conditions that must be excluded before considering the diagnosis of GER-related cough.

- No exposure to environmental irritants
- Not a present smoker
- Not on an ACE inhibitor
- Normal or stable chest radiograph
- No symptomatic asthma (i.e. cough not improved on therapy, or negative methacholine inhalation challenge test)
- No upper airway cough syndrome due to rhinosinus diseases ruled out (i.e. cough not improved by first generation H_1-receptor antagonists and 'silent' sinusitis ruled out)
- No non-asthmatic eosinophilic bronchitis (i.e. sputum studies negative or cough not improved by inhaled/systemic corticosteroids)

Abbreviations: ACE, angiotensin-converting enzyme; GER, gastroesophageal reflux

Printed with permission: Chandra KM and Harding SM. *Nature Clinical Practice Gastroenterology & Hepatology* November 2007;4(11): pg 606.

16. Outline the possible empiric medical trial for GER-related cough.

- Medications
  - Twice daily PPIs 30-60 minutes before breakfast and dinner
  - Consider adding a prokinetic agent initially if dysphagia is present or if cough does not improve with PPI
  - Assess response to therapy within 1-3 months

- Lifestyle modifications (please see question 10, page 20)

- Further testing

Abbreviations: GER, gastroesophageal reflux; PPI, proton pump inhibitor

Adapted from: Chandra KM and Harding SM. *Nature Clinical Practice Gastroenterology & Hepatology* November 2007; 4(11): pg 606.

17. Give 5 indications for open or laparoscopic surgical fundoplication in the patient with GERD.

- GERD symptoms responding to PPI, (penalty for failure of PPI as an indication)
- Intolerance to PPIs
- Cost of PPIs
- Patient preference, desire for a "cure"
- Persistent large volume regurgitation
- Large symptomatic hiatus hernia
- Respiratory complications from recurrent aspiration
- Recurrent peptic strictures in a young person

Abbreviations: GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor

18. Give 5 etiologies of benign, non-GERD related esophageal strictures.

- Congenital—strictures, atresia
- Drugs and chemicals—radiation, caustic, chemical, thermal, quinidine gluconate
- Webs, rings
- Sclerotherapy
- Acid and non-acid causes of esophagitis
- Surgery--complicated reflux strictures (NG tube, ZE syndrome), ischemia, anastomotic (staples)
- Iatrogenic - EMR for BE, prolonged NG tube, therapy, PDT

Abbreviations: BE, Barrett's epithelium; EMR, endoscopic mucosal resection; NG, nasogastric tube; PDT, photodynamic therapy; ZE, Zollinger-Ellison syndrome

19. Give 4 predictors of initial therapeutic failure of pneumatic dilation of benign esophageal strictures (i.e. repeated dilations required).

- Related to patient
  - Age <40 years
  - Male sex
  - Dilated esophagus

- Related to procedure
  - Inadequate dilation
    - Small size balloon (30 mm)
    - LES pressure >10 mm Hg post-treatment
  - Poor esophageal emptying post-treatment

Abbreviation: LES, lower esophageal sphincter

Adapted from: Boeckxstaens GEE. *Best Practice & Research Clinical Gastroenterology* 2007;21(4): pg. 595.

Barrett's epithelium

20. Barrett's epithelium (BE) is suspected. Give 4 molecular tests which may suggest the presence of dysplasia.

- DNA aneuploidy
- Ki67 (proliferation) – increased expression on immunohistochemistry
- Oncogenes – cyclin D1, TGFα, EGFR, Rus, B-catenin
- Tumour suppressors genes
- Anti-apoptosis genes
- Anti-senescence markers - telomerase

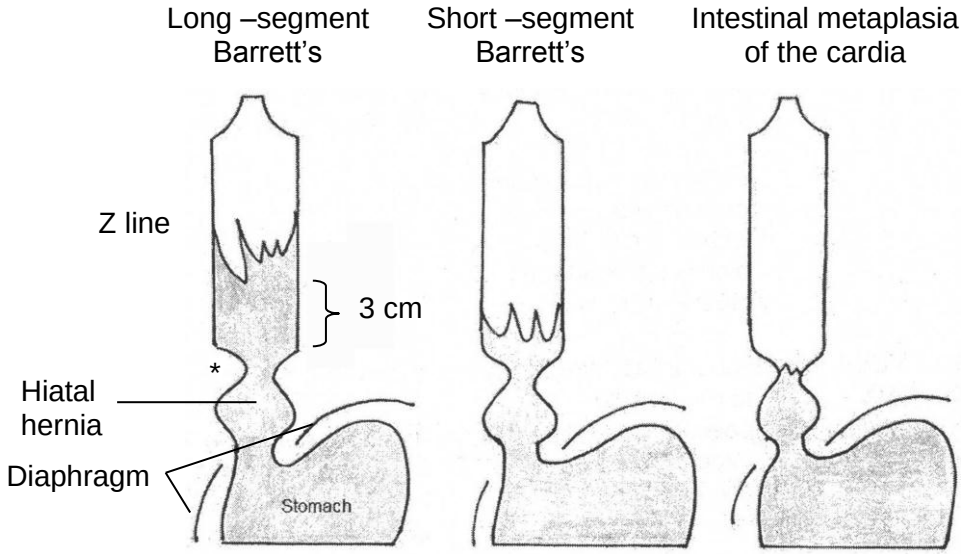
Printed with permission: Flejou JF. *Best Practice & Research Clinical Gastroenterology* 2008; 22(4): pg. 680.

"Because Justice is so rare,

it's such a delight."

John Irving. The last Night in Twisted River, 2009

Useful background: Barrett's epithelium



- Patients with long segment or short segment Barrett's esophagus have salmon-coloured mucosa extending up into the tubular esophagus
- Biopsy shows intestinal metaplasia with goblet cells
- If intestinal metaplasia with goblet cells is found at a normally located zig zag line (Z line), the patients has intestinal metaplasia of the cardia, which confers a lower cancer risk.

*End of tubular esophagus and beginning of stomach.

Adapted from: Mayo GI page 23.

21. Outline suggested recommendations for endoscopic surveillance of persons with Barrett's esophagus (BE).

- Who
  - GERD symptoms > 10yrs, 3 times per week, severe symptoms

- Family history of BE
  - American College of Gastroenterology recommendations for surveillance by esophageal gastroduodenoscopy (EGD)

Dysplasia	Documentation	Follow-up EGD
○ None (metaplasia)	2 EGDs with biopsy (4 quadrant, q 2 cm), confirm by two expert pathologists	3 - 5 years

○ LGD	Repeat EGD with biopsy, when erosive esophagitis healed, confirm by two expert pathologists, confirm with #3 EGD plus biopsies to exclude HED/EMC	q 1 year until no dysplasia

Dysplasia	Documentation	Follow-up EGD
○ HGD – Focal (<5 crypts)	Repeat EGD with biopsy to rule out cancer/document HGD expert pathologist confirmation	q 3 months
○ HGD – Multifocal (>5 crypts)	Radiofrequency ablation, PDT, cryosurgery, EMR, esophagectomy in surgical candidate	

Abbreviations: BE, Barrett's epithelium; EGD, esophageal gastroduodenoscopy; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; GERD, gastroesophageal reflux disease; HGD, high grade dysplasia; LGD, low grade dysplasia; PDT, photodynamic therapy

22. Give 4 endoscopic therapies for Barrett's esophagus (BE) with high grade dysplasia (HGD) or early mucosal cancer (EMC).

- Nd: YAG laser
- Argon plasma coagulation (APC)
- Photodynamic therapy (PDT) with porfimer or 5-aminolevulinic acid (5-ALA)
- Radiofrequency ablation (RFA)
- Cryotherapy
- Endoscopic mucosal resection (EMR)
- Esophagectomy in surgical candidate

Abbreviations: 5-ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; BE, Barrett's esophagus; EMC, early mucosal cancer; HGD, high grade dysplasia.

Printed with permission: Curvers WL, Kiesslich R, Bergman JJ. *Best Prac Res Clin Gastroenterol* 2008; 22(4):687-720.

Useful background: Endoscopic mucosal resection and anticoagulation

Management of antiplatelets and anticoagulant use after EMR

- General
  - Avoid aspirin and all nonsteroidal anti inflammatory medications for the next 2 weeks
  - Advise patients to monitor for symptoms of overt gastrointestinal bleeding, consider prophylactic deployment of hemostatic clips to secure hemostasis, although this is unproven.
- Warfarin
  - Stop Warfarin 5 days before the EMR
  - An INR level less than 1.5 is used as an arbitrary cut off value to proceed with EMR
  - Resume Warfarin 24 hours after the procedure with the usual daily dose
  - Check INR levels 1 week later to ensure adequate anticoagulation
  - In patients deemed to be at high risk of thrombosis, Warfarin cessation is bridged with low molecular weight heparin
- Clopidogrel
  - Discontinue Clopidogrel 7 days before endoscopy
    In patients with high risk cardiac conditions, cessation of Clopidogrel is performed after discussion with the cardiologist; this may entail deferring the EMR, where feasible, until a suitable time period after the insertion of coronary stents

Abbreviation: INR, international normalized ratio

Printed with permission: Namasivayam et al. Clin Gastro Hep 2010;8:743-754.

Useful background: Differences in the genetics of Familial Barrett's esophagus (BE), hereditary diffuse gastric cancer (HDGC) and Tylosis Palmaris

Genetics	Familial Barrett's esophagus	Hereditary diffuse gastric cancer	Tylosis Palmaris
➢ Pattern of inheritance	Proposed autosomal dominant with incomplete penetrance	Autosomal dominant	Autosomal dominant
➢ Chromosome	Unknown	Chromosome16q22	Chromosome 17q25
➢ Genetic	Linkage analyses	Mutations in E-	Downregulati

basis	ongoing	cadherin/CDH1 gene	on of cytoglobin gene
➢ Cancer risk	Up to 31% risk of adenocarcinoma	70% of lifetime risk of diffuse gastric cancer	40-95% lifetime risk of squamous esophageal cancer
➢ Clinical strategies	Consider family history in assessment of GERD	Genetic testing for CDH1 -Endoscopic surveillance -Prophylactic gastrectomy	Endoscopic surveillance

Abbreviations: BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; HDGC, hereditary diffuse gastric cancer

Printed with permission: Robertson E, and Jankowski J. *Am J Gastroenterol* 2008;103: pg 445.

Useful background: The terminology of early neoplastic lesions in Barrett's esophagus (BE), using Riddell's and Vienna classification, and clinical consequences

	Terminology
➢Category 1	Negative for dysplasia
➢Category 2	Indefinite for dysplasia
➢Category 3	Low grade dysplasia
➢Category 4	4.1 High grade dysplasia; 4.2 Non-invasive carcinoma (carcinoma in situ) ; 4.3 Suspicion of invasive carcinoma
➢Category 5	Invasive neoplasia; intramucosal carcinoma; Submucosal carcinoma or beyond

Abbreviation : BE, Barrett's esophagus

Adapted from: Flejou JF. *Best Practice & Research Clinical Gastroenterology* 2008; 22(4): pg. 679.

Useful background: Endoscopy – Barrett's esophagus

- Even with the new high-frequency mini-probes, the accuracy of endoscopic ultrasound (EUS) in distinguishing T1sm (submucosal disease) is only 75-85% (Scotiniotis IA, et al. *Gastrointest Endosc* 2001:689-96.)
- The multiband mucosectomy devise may be superior to the injection/CAP EMR (endoscopic mucosal resection) method for high grade dysplasia in Barrett's epithelium, in terms of procedure time and cost (Pouw RE, et al. *Gastrointest Endosc* 200:AB75).
- Radiofrequency ablation (RF) with the Hab ablation system give a >90% cure rate for low and high grade dysplasia (LGD, HGD), in flat, non-nodular BE tissue (Waye JD, et al. Gastrointest Endosc 2009;In press.)
- Low pressure spray cryoablation using liquid nitrogen gives premise for modular and non-nodular HGD and early esophageal cancer (Johnston MH, et al. *Gastrointest Endosc* 2005:842-8.)
- The morbidity of esophagectomy includes strictures (20-40%), leaks (3-39%), left recurrent laryngeal nerve paralysis (3-16%), gastroparesis, regurgitation of gastric contents, and mortality of 2-10% (Sharma 09).
- Photodynamic therapy (PDT) with porfimer-Na, when exposed to non-thermal red laser light, yields siglet oxygen which resuls in ischemic necrosis in metaplastic and dysplastic BE
- The complications of PDT include stricture in 40% (8% severe), chest pain, mediastinitis, pleural effusion, chest pain and vomiting
- The 5 year survival rate for EMR alone, or EMR plus PDT for early stage esophageal cancer is 97%, and minimally invasive endoscopic therapies may be comparable to esophagectomy for early stage esophageal cancer (ASGE Technology Committee. *Gastrointest Endosc* 2008: 11-18.; Das A, et al. *Am J Gastroenterol* 2008:1340-5.)

Abbreviations: EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; HGD, high grade dysplasia; LGD, low grade dysplasia; PDT, photodynamic therapy; RF, radiofrequency ablation

Esophageal motility disorders (EMD)

Useful background: A simple classification of esophageal motility disorders (EMD)

Primary EMD	Second EMD	Manometric variants
➢ Achalasia (three subtypes)	○ Pseudoachalasia	- Hypertensive peristalsis
➢ Diffuse esophageal spasm	○ Chagas disease	- Hypertensive LES
➢ Nutcracker	○ Scleroderma esophagus	- Ineffective esophageal motility
➢ Absent peristalsis	○ Parkinson's disease	
➢ Gastroesophageal reflux disease (GERD)	○ Infiltrative disorders	

23. Classify esophageal motor abnormalities, and give the qualitative changes in motility in the upper esophageal sphincter (UES), esophageal body (EB) and lower esophageal sphincter (LES) of 4 conventional manometric (dysmotility) syndromes.

Upper esophageal sphincter (UES)	Esophageal body (EB)	Lower esophageal sphincter (LES)
↑ Contraction ○ Zenker's diverticulum	↑ Contraction ○ Nutcracker esophagus ○ Achalasia (compartmentalized pressurization)	↑ Pressure ○ Isolated hypertensive LES ○ Achalasia
↓ Contraction ○ MCTD (e.g. scleroderma) ○ Oculopharyngeal dystrophy	↓ Contraction* ○ Ineffective esophageal motility (IEM) ○ Aperistalsis (e.g. scleroderma)	↓ Pressure ○ Hypotensive LES ○ GERD (↑ tLESR) ○ Scleroderma
↓ Co-ordination ○ Achalasia (complicated) ○ Parkinson's disease	↓ Co-ordination ○ Diffuse esophageal spasm (DES) ○ Achalasia (absent or	↓ Co-ordination ○ (relaxation**) ○ Achalasia, type I ○ Atypical LES

○ Cricopharyngeal bar ○ Belch dysfunction	simultaneous contractions)	relaxation (pseudo-achalasia) ○ Post-fundoplication gas-bloat syndrome

contraction, or impaired retrograde inhibition
** relaxation, or inadequate swallow-induced inhibition

Abbreviations: EB, esophageal body; IEM, ineffective esophageal motility; LES, lower esophageal sphincter; UES, upper esophageal sphincter

Useful background:

- Normal: Normal velocity, <8 cm/s in > 90% of swallows; normal peristaltic amplitude; (≥7 peristaltic contractions with an intact wave progression [amplitude >30 mmHg])
- Aperistalsis: Absent or simultaneous contractions (<30 mmHg)
- Ineffective esophageal motility (IEM): ≥3 peristaltic contractions with failure of wave progression due to an ineffective distal contraction amplitude (<30 mmHg) or failed peristalsis over a segment of the distal esophagus
- Nutcracker esophagus: average peristaltic amplitude >180 mmHg over pressure sensors 3 and 8 cm above LES
- Distal esophageal spasm (DES): contractile velocity >8 cm/s mmHg over pressure sensors 3 and 8 cm above LES in ≥2 swallows
- Isolated hypertensive LES: basal LES pressure greater than 45 mmHg (mid-respiratory pressure)
- Achalasia: abnormal LES relaxation; absent or simultaneous contractions
- Atypical disorders of LES relaxation: abnormal LES relaxation, with some normal, may have simultaneous or absent peristalsis.

Abbreviations: LES, lower esophageal sphincter; MCTD, mixed connective tissue diseases; tLESR, transient lower esophageal sphincter relaxation

Adapted from: Pandolfino et al. *AJP* 2008;103: pp 28.; and Printed with permission: Sifrim D and Fornari F. *Best Practice & Research Clinical Gastroenterology* 2007;21(4): pg. 575-576.

Useful background: The advantage of high resolution esophageal manometry (HREM), and high resolution esophageal pressure topography (HREPT) include:

- High quality, uniform format
- Greater reproducibility
- Viewing simultaneous contractions of the entire esophagus
- Standardized objective metrics
- Topographic patterns easily learned and recognized
- Allows for subclassification of achalasia, and of DES.

Useful background: Esophageal motor abnormalities based on high-resolution manometry.

Diagnostic criteria for esophageal motility

- Normal
  - Normal EGJ pressure (10-35 mm Hg) and relaxation (see below)
  - Peristaltic velocity <8 cm/s in >90% of swallows
  - Normal elevation of intra-bolus pressure at <8 cm/s to <30 mm Hg in > 90% of swallows
  - Mean distal contractile index (DCI) <5000 mm Hg·s·cm**

- Peristaltic dysfunction
  - Mild: 3-6 swallows with failed peristalsis or a >2 cm defect in the 30 mm Hg isobaric contour of the distal esophageal peristalsis (15 mm Hg in proximal-mid esophagus)
  - Severe: $\underline{\geq}$ 7 swallows with either failed peristalsis or a >2 cm defect in the 30 mm Hg isobaric contour of distal esophageal peristalsis (15 mm Hg in proximal-mid esophagus)
  - Aperistalsis: Contractile pressure <30 mm Hg throughout mid-distal esophagus in all swallows (*Scleroderma* pattern: aperistalsis with LES pressure <10 mm Hg)

- Hypertensive dysfunction
  - Peristaltic velocity <8 cm/s in >80% of swallows
  - Mean distal contractile index (DCI) >5000 mm Hg·s·cm**
    - *Hypertensive peristalsis*: mean DCI >5000-8000 mm Hg·s·cm
    - *Segmental hypertensive peristalsis*: hypertensive contraction restricted to mid- or distal esophagus or LOS after-contraction: mean DCI 5000-8000 mm Hg·s·cm
    - Hypertensive peristalsis $\underline{+}$ repetitive or prolonged contraction: DCI >8000 mm Hg·s·cm

- Esophageal spasm (rapidly propagated contractile wavefront)
  - Peristaltic velocity >8cm/s in ≥20% of swallows ± raised DCI
    - *Diffuse esophageal spasm:* rapid contractile wavefront throughout the distal esophagus
    - *Segmental esophageal spasm*: rapid contractile wavefront limited to mid or distal esophageal segment

- Rapid elevation of intra-bolus pressure *(*increased resistance to flow due to functional or structural obstruction in the esophagus or at the esophago-gastric junction [e.g. stricture, post-fundoplication, eosinophilic oesophagitis, poorly coordinated contractions])
  - Rapid elevation of intra-bolus pressure to >15 mm Hg in >8 cm/s in ≥20% of swallows
    - Mild: Intra-esophageal bolus pressure (15 to 30 mm Hg) with ≥80% preserved peristalsis
    - *Severe*: Intra-esophageal bolus pressure (>30 mm Hg) with ≥20% failed peristalsis

- Achalasia
  - Impaired deglutative EGJ relaxation and/or opening
  - Elevation of intra-esophageal bolus pressure due to resistance to flow at EGJ
    - *Classic*: aperistalsis with no identifiable contractile activity
    - *Vigorous*: with persistent contractile activity (spasm) or gross elevation of intra-esophageal bolus pressure with or without esophageal shortening
    - *Variant*: with preserved peristalsis in the distal esophagus in ≥20% swallows

- Abnormal LES tone
  - Hypotensive: 10 s mean <10 mm Hg, with normal peristaltic function
  - Hypertensive: 10 s mean >35 mm Hg, with normal peristaltic function and EGJ relaxation

Abbreviations: DCI, distal contractile index; EGJ, esophagogastric junction; LES, lower esophageal sphincter

Printed with permission: Fox MR, and Bredenoord AJ. *GUT* 2008;57: pg. 419.

Useful background:

- One peristaltic contraction rules out achalasia (Katz 09). The motility changes of achlasia include
  - ↑ LES pressure
  - ↑ residual pressure of LES (incomplete relaxation)
  - Complete absence of peristalsis

- In DES (distal or diffuse esophageal spasm), there is an uncertain relationship between symptoms and the DES motility changes
- The nutcracker esophagus and a hypertensive LES may be seen in persons with GERD
- A video barium examination may be normal even when UES manometry is abnormal
- It is useful to perform provocative testing (intraesophageal acid infusion, balloon distention, edrophonium injection) to attempt to reproduce the patient's symptoms in the setting of NCCP (non cardiac chest pain)
- Combined multichannel intraluminal impedence (MII) and pH testing detects impedence data at 3, 5, 7, 9 and 15 and 17 cm above the LES, and 5 cm above the LES

Abbreviations: DES, distal or diffuse esophageal spasm; DSRS, distal splenerenal shunt; EHT, endoscopic hemostatic therapy; MII, multichannel intraluminal impedence; TIPS, transjugular intrahepatic postoperative shunt

24. Give 15 causes of secondary (pseudoachalasia) achalasia.

- Infection/Infiltration
  - Sarcoidosis
  - Sjogren's syndrome
  - Amyloidosis
  - Fabry's disease
  - Chagas disease (Trypanosoma cruzi)

- Cancer (GI)
  - Squamous cell carcinoma of the esophagus
  - Adenocarcinoma of the esophagus
  - Hepatocellular carcinoma
  - Pancreatic adenocarcinoma

- Cancer (Non-GI) (Paraneoplastic syndrome)
  - Lung carcinoma (non-small cell)
  - Metastatic prostate carcinoma
  - Metastatic renal cell carcinoma

- Breast adenocarcinoma
- Leiomyoma
- Lymphoma
- Reticulal cell sarcoma
- Lymphangioma
- Mesothelioma

➢ Motility
- Parkinson's disease
- Achalasia with associated Hirchsprung's disease
- Hereditary hollow visceral myopathy
- Familial achalasia
- Fundoplication

➢ Surgical
- Post-fundoplication
- Post-vagotomy

➢ Miscellaneous
- Allgrove's syndrome (AAA syndrome) – (Alacidygia; Addisons; Achalasia)
- Hereditary cerebellar ataxia
- Autoimmune polyglandular syndrome type II
- MEN IIb (Sipple's Syndrome)

Adapted from: Clouse RE, and Diamant NE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:871.

Useful background: Radiographic and manometric diagnosis of achalasia

➢ Radiographic
- Esophageal dilatation
- Poor esophageal emptying
- Bird-beak deformity of EGJ
- Absent gastric air bubble

➢ Manometric
- Impaired deglutitive relaxation
- Absent peristalsis (but can have spasm or pressurization)
- Increased LES pressure
- Increased esophageal pressure

➢ Chicago classification of achalasia.

➢ Distal segment, impaired EGJ relaxation
- Achalasia

- Classic achalasia (Type I)
- Achalasia with esophageal compression (Type II)
- ≥ 20% test swallows with esophageal compression (Type III)

Abbreviation: EGJ, esophagogastric junction

Printed with permission: Pandolfino JE, et al. *Gastroenterology* 2008;135:1526.

25. Classify the 3 types of achalasia made by high-resolution manometry, and compare the treatment responses with each type.

	Type I	Type II	Type III
➢ Peristalsis			
○ Absent peristalsis	+		
○ Compartmentalized pressurization		+	
○ Spastic contraction			+
➢ Response to treatment			
○ Heller myotomy	67	100%	0
○ Pneumatic dilation	38	73%	9
○ Botulinim toxin	0	86%	22
➢ Subsequent interventions			
○ Number of interventions	1.6 ± 1.5	1.2 ± 0.4	2.4 + 1.0	1.8 ± 0.7
○ Successful last intervention	56%	96%	29%	71%

Printed with permission: Pandolfino et al. *Gastroenterology* 2008;135: pg. 1526-33.

"Play a crucial role in finding your own humility and humanity"

Grandad

26. Compare the primary treatments for idiopathic achalasia under the headings: response (early, late) morbidity (minor, major).

MECHANICAL

Comparative Feature	Smooth Muscle Relaxants	Botulinum Toxin Injection
➢ Response		
○ Early (<1 yr)	- 50%-70%	- 90% at 1 mo
○ Late (>1-5 yr)	- <50%	- 60% at 1 yr
➢ Morbidity		
○ Minor	- Headache, hypotension (30%)	- Rash, transient chest pain (20%)
○ Major	- NR	- NR
➢ Advantage	- Rapidly initiated, well accepted	- Low morbidity, modest - response durability, well accepted
➢ Disadvantage	- Inconvenient side effects, tachyphylaxis; - poor effect on esophageal emptying	- Repeat injection often required within 1 yr - fibroinflammatory reaction at LES

ENDOSCOPIC		SURGICAL
➢ Pneumatic Dilation	➢ Open Myotomy	➢ Laparoscopic/ Myotomy
○ 60%-90%	○ >90%	○ >90%
○ 60%	○ 75% (at 20 yrs)	○ 85%
○ Rare	○ <10% at 1 yr	○ Symptomatic reflux (10%)
○ echinique-related complications	○ Symptomatic reflux (<10 % at 1 yr)	○
○ 3%-5% perforation (4%)	○ Dysphagia (10%) Mortality (<2%)	○ NR
○ Good response durability	○ Best response rate and	○ Avoids thoracotomy,

	durability		result is likely equivalent to open technique
○ See Morbidity	○ Thoracotomy required	○	Long-term outcome unknown, small conversion to open procedure
	○ severe reflux may develop		

Abbreviations: LES, lower esophageal sphincter; NR, not reported

Adapted from: Clouse RE, and Diamant NE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:pg. 879.

Eosinophilic esophagitis (EoE)

27. Give the typical presentation of eosinophilic esophagitis.

- Young adult
- Male to female ration of 3:1
- Intermittent dysphagia, sometimes severe; food impaction
- Failed treatment with proton pump inhibitor (PPI) therapy for presumed GERD
- Chest pain with odynophagia
- Peripheral eosinophilia is common
- Atopic diseases

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28. Give 5 changes on EGD in the patient with eosinophilic esophagitis (EE).

- Corrugation (multiple rings)
- Longitudinal furrows
- Mucosa: featureless, fragile (crepe paper)
- White surface vesicles (eosinophilic microabscess)
- Proximal or mid-esophageal stenosis/stricture
- Small caliber esophagus

- Food impaction
  - May be normal

Abbreviations: EE, eosinophilic esophagitis; EGD, esophago-gastroduodenoscopy

29. A 30 year old patient with solid food dysphagia presents for an upper endoscopy. There is no history of heartburn or regurgitation, and no family history of esophageal disease. A benign appearing stricture is seen. You suspect eosinophilic esophagitis (EE). Give the steps in management.

- Exclude eosinophilic esophagitis (EE) by biopsy of mid esophagus, >15 eosinophils
- If positive for EE, treat for 4 weeks with PPI, before specific Rx for EE.
- Do not do initial empiric dilation of stricture until EE disproven, or proven by biopsy and treated
- Dilate gently and progressively only after treatment of EE
- Use generous sedation
- If perforation occurs, try to avoid surgery, since wall does not hold sutures well; may need to do Esophagectomy
- Dietary elimination in children

Abbreviation: EE, eosinophilic esophagitis

30. Eosinophilic esophagitis is a high risk disease. Give 4 complications.

- Dysphagia
- Food impaction
- Stricture
- Sloughing of mucosa (mucosal eosinophils)
- Mucosal tear
- Perforation
  - EGD
  - Spontaneous (Boerhave syndrome) (transmural inflammation)

Abbreviation: EGD, esophagogastroduodenoscopy

31. Give 8 causes/associations of eosinophilic gastrointestinal diseases (EGIDs).

- Idiopathic
  - Eosinophilic syndromes
- Infection
  - Fungal, parasitic and non-parasitic
- Inflammation
  - GSE
  - IBD
  - MC
  - GERD
- Neoplasia
  - Hodgkin's lymphoma
  - Esophageal
  - Lleiomyomatosis
- Immune
  - Autoimmune
  - GVH disease
  - Connective tissue disease (e.g. scleroderma)
  - Hypersensitivity
  - Allergy (e.g. foods)
  - Allergic vasculitis
  - Post-transplant
- Iatrogenic
  - Drugs (e.g. gold, azathioprine)

Abbreviations: EGID, eosinophilic gastrointestinal diseases; GERD, gastroesophageal reflux disease; GSE, gluten-sensitive enteropathy; GVH, graft-versus-host disease; IBD, inflammatory bowel disease; MC, microscopic colitis

Adapted from: Mueller S. *Best Practice & Research Clinical Gastroenterology* 2008;22(3): pg. 427.; and Atkins D, et al. *Nat Rev Gastroentol Hepatol* 2009;6(5): 267-278.

Useful background: Comparison of current medical and nutritional treatment strategies for eosinophilic esophagitis

Treatment	Advantages	Disadvantages
➢ Oral steroids (1-2 mg/kg/day: maximum 60 mg)	○ Rapid relief of symptoms	○ Significant systemic side effects ○ Prompt recurrence when discontinued
➢ Swallowed fluticasone (children 440-880 ug/day; adolescents/adults, 880-1769 u.g/day)	○ Minimal systemic steroid absorption ○ Shown to relieve symptoms ○ Normalizes esophageal mucosa	○ Risk of candidal esophagitis ○ Small amount systemically absorbed ○ Long term efficacy unknown, but prompt recurrence when discontinued ○ Difficult for small children and developmentally delayed patients to swallow
➢ Viscous budesonide (<10 y, 1 mg daily; >10 y, 2 mg daily)	○ Easier to swallow ○ Theoretically can reach more distal areas of esophagus ○ Shown to reduce symptoms and normalize esophageal mucosa	○ Cumbersome to mix ○ Theoretical risk of candidal esophagitis ○ Long term efficacy unknown
➢ Monteleukast (20-40 mg daily)	○ Symptomatic relief has been shown at high doses (100mg) ○ No significant adverse effects	○ Not clear whether it improve esophageal eosinophilia ○ Inadequate studies
➢ Cromolyn sodium (100 mg 4 times a day)	○ No significant adverse effects	○ Inadequate studies
➢ Mepolizumab	○ Phase II trials in adults show that it is safe	○ Did not induce significant histologic remission in adult study

	○ Promising preliminary data in pediatric studies	
➢ Elemental diet	○ 92%-98% effective ○ Resolution of symptoms in 7-10 days ○ Histologic remission within 4-5 weeks	○ Poor palatability ○ Usually requires nasogastric or gastrostomy tube ○ Very expensive ○ Socially isolating

Printed with permission: Hait et al. *Clinical Gastroenterology and Hepatology* 2009;7:721-724.

Useful background:

- PPI plus dilations
  - Symptoms, endoscopic and histology changes may improve (Ngo P, et al. *Am J Gastroenterol* 2006: 1666-1670)
  - Dilation
    - Associated perforations are mild (pneumomediastinum)
    - NT free perforations requiring surgery (Richter 09) (Cohen et al. *Clin Gastroenterol and Hepatol* 2007:1149-53)

- Steroids
  - Tablets, 20-40 mg prednisone po for 4-6 weeks, followed by slow taper. Indicated in EOE persons with acute dysphagia, high risk for esophageal perforation while undergoing repeated dilations, severe weight loss, or refractory to other symptoms (Furuta GT, et al. *Gastroenterology* 2007:1342-63).
  - Swallowed fluticasone, 1-2 puffs qid for 6-8 weeks for short-term therapy, but not for maintenance
  - 70% recurrence rate after initial steroid use, and esophageal dilations may still be necessary (Helou EF, et al. *Am J Gastroenterol* 2008:2194-9).

- Montelukast (leukotriene D4 receptor inhibitor)
  - Not recommended because of lack of reduction of eosinophilic infiltration in the esophageal mucosa (Furuta GT, et al. *Gastroenterology* 2007:1342-63; Helou EF, et al. *Am J Gastroenterol* 2008:2194-9)

- Meplizumab (humanized monoclonal IgG antibody to IL-5)
  - Poor response in placebo-controlled study

Adapted from: Richter 09; and Bohm M, Richter JE. *Am J Gastroenterol* 2008:1-10.

- Elimination diets (especially in children) reduce symptoms and mucosal eosinophilia (Liacouras CA, et al. *Clin Gastroenterol and Hepatol* 2005:1198-1206).
  - Use skin prick testing to diagnose Type 1 IgE-mediated sensitivity, and skin patch testing for Type IV Th-2 delayed hypersensitivity reactions
  - Most common food allergies are dairy, eggs, wheat, soy, peanuts, fish/shellfish (Richter 09).

Abbreviations: EE/EOE, eosinophilic esophagitis; PPI, proton pump inhibitor

Useful background: Limitations to medications currently used for EE

- Only one randomised, blinded, placebo-controlled trial and it was conducted with pediatric patients.

- Few trials in adults, especially those with dysphagia and anatomic narrowing of the esophagus.

- Trials only examine short-term treatment (four months or shorter); trials need to be at least one year on and off therapy.

- None of the trials address maintenance or pulse therapy, which may be critical as relapses are common.

- No validated dysphagia or quality of life questionnaires used to quantify patients symptoms resulting in patient and investigator variability.

- Diagnostic criteria and clinical endpoints vary across most studies.

- Numerous confounding variables, which may effect study outcome including acid suppression, dietary restriction and allergy testing.

Useful background: The diagnostic work-up for eosinophilic gastrointestinal diseases (EGIDs)

- General
  - Infection evaluation (stool, intestinal aspirates, and blood analyses)
  - Total and allergen-specific IgE (immunoassays and skin tests)
  - Differential blood cell count
  - Microscopic evaluation of biopsy samples from the affected and non-affected gastrointestinal parts (histological and immunohistological analysis) T-cells , mast cells

- Granule protein and cytokine measurements (immunoassays using blood, feces, or urine)
- Immunophenotyping of blood cells (surface marker staining and subsequent flow cytometric analysis)

- In the presence of hypereosinophila, in addition
  - Immunophenotyping of blood cells (in particular T cells and eosinophils)
  - Bone marrow analysis (cellularity, dysplastic eosinophils, spindle-shaped mast cells, cytogenetic abnormalities, etc.)
  - Measurements of vitamin B12, tryptase, IL-5, and TARC in blood
  - Genetic analysis for the presence of a FIPILI-PDGFRA gene fusion
  - Eosinophil granule protein measurements

Abbreviation: EGID, eosinophilic gastrointestinal diseases

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Dysphagia

32. Give 15 causes of oropharyngeal (transfer) dysphagia.

- Peripheral and central nervous system (PNS and CNS)
- Skeletal, muscular or neuromuscular
- ENT
  - Xerostomin
  - Cancer, radiation to, or surgery on, cricopharynx or larynx
  - Tonsillar abscess
  - Foreign body

- Esophagus
  - Intrinsic
    - Achalasia of UES
    - High esophageal rings, webs
    - Zenker's diverticulum
  - Extrinsic
    - Thyromegaly
    - Spinal osteophytes
    - Senile Ankylosing hyperostosis
    - Rheumatoid cricoarytenoid arthritis
    - Cervical lymphadenopathy
    - Vascular abnormalties

- Drugs
  - Anticholinergics
  - Antihistamines
  - Phenothiazine

Abbreviations: CNS, central nervous system; PNS, peripheral nervous system; UES, upper esophageal sphincter

Adapted from: Cook IJ, and Shaker R. *2006 AGA Institute Postgraduate Course*: pg. 651.

33. Give 10 symptoms of oro-pharyngeal dysphagia.

- ENT
  - Difficulty in gathering or keeping bolus at the back of the tongue
  - Hoarse voice
  - Halitosis
  - Nasal regurgitation
  - Nasal speech and dysarthria
  - Swallow-related cough
  - Recurrent pneumonia

- Esophageal
  - Food sticking in the throat (hesitation or inability to initiate swallowing; inability to propel food bolus caudad into pharynx)
  - Difficulty in swallowing solids
  - Frequent repetitive swallowing in attempts to clear the pharynx

- General
  - Avoidance of social dining
  - Weight loss

34. Give 8 causes of dysphagia/odynophagia in patients with HIV/AIDS, which one related to their infection.

- Infections
  - Candida albicans
  - Cytomegalovirus (CMV)
  - Herpes simplex (HSV)
  - Histoplasma
  - Mycobacterium avium complex (MAC)
  - Cryptosporidium spp.
  - PCP

- Neoplasm
  - Kaposi's sarcoma
  - Lymphoma
  - Squamous cell carcinoma
  - Adenocarcinoma

- Gastroesophageal reflux disease (increased frequency)

- Pill-induced esophagitis

- Idiopathic ulcerations

Esophageal tumours

35. Give the differential diagnosis of benign and malignant esophageal epithelial and non-epithelial tumours.

Epithelial Tumours

- Malignant
  - Squamous cell
  - Adenocarcinoma of the esophagus and esophagogastric junctrion
  - Verrucuos carcinoma
  - Carcinosarcoma
  - Small cell carcinoma
  - Malignant melanoma
- Benign
  - Squamous papilloma (2%)
  - Adenoma (1%)
  - Inflammatory fibroid polyp (20%)

Nonepithelial Tumours

- Malignant
  - Lymphoma
  - Sarcoma
  - Gastrointestinal stromal tumour
  - Metastatic carcinoma
- Benign
  - Leiomyoma (50%)
  - Granular cell tumour
  - Fibrovascular tumour* (3%)
  - Hemangioma (2%)
  - Hamartoma
  - Lipoma (2%)
  - Cyst (10%)
  - Neurofibroma (1%)

*also known as fibrovascular polyp, myxoma, angiofibroma, fibrolipoma, pedunculated lipoma, fibroepithelial polyp.

Adapted from: Ginsberg G and Fleischer DE. *Sleisenger & Fordtran's gastrointestinal and liver disease: 2*006: pg. 969; and 2010, pg. 946.

36. Give 4 causes of multiple filling defects in the esophagus seen on barium swallow.

- Foreign body
  - Effervescent granules
- Infection
  - Candidiasis
- Tumour
  - Squamous cell cancer
  - Candidiasis
  - Papillomatosis
- Blood vessels
  - Varices

37. Give 10 presenting symptoms for esophageal cancer.

- Esophagus
  - Dysphagia, odynophagia
  - Back or chest pain with/without swallowing
  - Halitosis
  - Tracheoesophageal fistula
- Nerves
  - Hoarseness from recurrent laryngeal nerve involvement
  - Horner syndrome (miosis, ptosis, absence of sweating on ipsilateral face and neck)
  - Phrenic nerve involvement from hiccups
- Nodes
  - Supraclavicular adenopathy
- Systemic
  - Weight loss
  - Clubbing
  - Signs/ symptoms of metastases

38. List 10 risk factors for esophageal squamous cancer and for adenocarcinoma.

	Adenocarcinoma	Squamous cell carcinoma
➢ Age	>50	>60
➢ Gender	M	M
➢ Alcohol	-	+
➢ Smoking	-	+
➢ GERD	+	-
➢ BE	+	-
➢ HIV	+	+

- Also, for squamous cell carcinoma
- Previous head and neck squamous cell carcinoma
- Radiation therapy
- Lye ingestion
- Plummer-Vinson (Paterson-Kelly) syndrome
- Achalasia, Tylosis palmaris
- Nutritional deficiencies– riboflavin, niacin; high-starch diet without fruits and vegetables
- Nitrosamines; "bush teas" (diterpene phorbol esters)
- Gluten sensitive enteropathy (GSE)

Abbreviations: BE, Barrett's epithelium; GERD, gastroesophageal reflux disease

39. Give 8 differential diagnoses of dysphagia and odynophagia in persons with HIV/AIDS.

➢ Infection
- Candida albicans (CMV)
- Herpes simplex (HSV)
- Histoplasma capsulatum
- Myocobacterium avium complex (MAC)
- Cryptosporidium spp.
- PCP

➢ Malignancy
- Adenocarcinoma
- Lymphoma
- Kaposi's sarcoma
- Squamous cell carcinoma

- Treatment
  - Pill-induced esophagitis
  - HAART-associated mucositis
  - GERD (idiopathic may be more common)
  - Idiopathic

- Idiopathic ulceration

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; MAC, myocobacterium avium complex

40. List 6 endoscopic imaging modalities for detecting/ staging esophageal neoplasia.

- High resolution/high-definition/magnification endoscopy – white light high resolution endoscopy (HRHDME)

- Chromendoscopy (CE) (combined with HRHDME) – Lugal's sphincter, toludine blue, methylene blue, indigo carmine, acectic acid, crystal violet

- Narrow band imaging (NBI)

- FICE (Fuijnon intelligent chromendoscopy; computed interval chromendoscopy)

- Point spectroscopy – fluorescence, elastic scattering, RAMAN, multimedial

- Autofluorescence imaging (LIFE, light -induced fluorescence endoscopy [FE]), drug-induced FE, video autofluorescence imaging)

- Optical coherence tomography (OCT; micro CT)

- Confocal endomicroscopy

- EUS

Abbreviations: CE, chromendoscopy; CIC, computed interval chromendoscopy; EUS, endoscopic ultrasound; FE, fluorescence endoscopy; FICE, Fuijnon intelligent chromendoscopy; HRHDME, white light high resolution endoscopy; LIFE, light -induced fluorescence endoscopy; OCT, optical coherence tomography

Printed with permission: Curvers WL, Kiesslich R, Bergman JJ. *Best Prac Res Clin Gastroenterol* 2008; 22(4):687-720.

41. Give 6 palliative treatments for the care of the patient with esophageal carcinoma.

- Palliative care

- Non-endoscopic techniques
  - Surgery
  - Radiation therapy
    - External beam radiotherapy
    - Intraluminal radiotherapy (brachytherapy)
  - Chemotherapy

- Endoscopic techniques
  - Laser therapy
    - Thermal (Nd:YAG)
    - Photodynamic therapy
  - Dilation
  - Electrocoagulation (BICAP probe)
  - Chemical injection therapy
  - Stent placement

- Nutritional support
  - Nasoenteric feeding tube
  - Percutaneous endoscopic gastrostomy (PEG)

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Useful background: Main classifications used in esophageal cancer

- PRE-OPERATIVE CLASSIFCATIONS

- Ultrasound (us TNM) classification for esophageal cancers

uT1 Tumour invading the mucosa and the submucosa
uT2 Tumour invading the mucosa without going beyond
uT3 Tumour invading the tunica adventitia (or the serous membrane)
uT4 Tumour invading the adjacent structures

uN0 No lymph node invasion
uN1 Lymph nodes invaded around tumour; round, same echogenicity as
uN2 the tumour
Lymph nodes invaded distant from the tumour (5 cm above or below the upper or lower pole of the tumour)

- CT scan (CT) TNM classification for thoracic esophageal cancers

ctT1 Non-visibility or mass <10 mm in diameter
ctT2 Mass 10-30 mm in diameter
ctT3 Mass >30 mm in diameter with no sign of invasion t mediastinal
ctT4 structures
Idem + sign of spread to mediastinal structures

- Lymph nodes (N)*

ctN0 No detectable adenopathy
ctN1 Regional adenopathy (mediastinal and/or perigastric)

- Distant metastases

ctM0 No distant metastasis
ctM1 Presence of distant metastases (including celiac and cervical adenopathies)

- *Definition of us and ct stages*

Us or I TI N0 M0
ct IIa T2 N0 M0; T3 N0 M0
stage Iib T1 T2 N1 M0

* lymph nodes >10 mm are considered to be high risk of being metastatic

➢ POST-OPERATIVE CLASSIFICATIONS:
- TNM classification

T-Primary tumour
T0 No sign of primary tumour
Tis Carcinoma in situ
T1 Tumour invading the lamina propria or the submucosa
T2 Tumour invading the muscularis
T3 Tumour invading the tunica adventitia
T4 Tumour invading the adjacent structures

- N-Regional adenopathy

Nx Lymph nodes not evaluated
N0 No sign of regional lymph node involvement
N1 Regional lymph node metastases

- Cervical esophagus: cervical lymph nodes, internal jugular, peri-esophageal and supraclavicular nodes

Printed with permission: Veuillez V, et al. *Best Practice & Research Clinical Gastroenterology* 2007;21(6): pg. 949.

Esophageal motility (manometry) cases

Desribe the manometric findings, and give a differential diagnosis.

Case 1: Clinical history: Presenting symptom of heartburn

- Describe the following esophageal motility studies; give the differential diagnosis, and state the most likely manometric diagnosis.

Lower esophageal sphincter (Normal values in brackets):	Esophageal body (Normal values in brackets):
Resting pressure: 21 mmHg (16-30) Relaxation duration: 5.3 seconds (>2) % Relaxation: 93% (80-100%) Residual Pressure: 1.5 mmHg (<8)	Peristaltic contractions: 100% (>80%) Simultaneous contractions: 0% (<20%) Mean contraction amplitude: 73 mmHg (30-180) Mean contraction duration: 2.5 sec (<5.8) Lower amplitude contractions: 0% (<30%) Spontaneous activity between swallows: none

Acid infusion test: Not done
Pharyngo-esophageal sphincter (PE): Not done

Case 2
Clinical history: Presenting with dysphagia

Lower esophageal sphincter (Normal values in brackets):	Esophageal body (Normal values in brackets):
Resting pressure: 23 mmHg (16-30) Relaxation duration: 13 seconds (>2) % Relaxation: 92% (80-100%) Residual Pressure: 3.3 mmHg (<8)	Peristaltic contractions: 20% (>80%) Simultaneous contractions: 80% (<20%) Mean contraction amplitude: 128 mmHg (30-180) Mean contraction duration: 8.1 sec (<5.8) Lower amplitude contractions: 0% (<30%) Spontaneous activity between swallows: none

Acid infusion test: Not done
Pharyngo-esophageal sphincter (PE):
Resting Pressure: 26.5 mmHg (40-150)
Pharyngeal contraction pressure: 48.4 mmHg (40-150)
Coordination: Yes

Case 3

Clinical history: Presenting with heartburn

Lower esophageal sphincter (Normal values in brackets):	Esophageal body (Normal values in brackets):
Resting pressure: 34 mmHg (16-30) Relaxation duration: 10.3 seconds (>2) % Relaxation: 98% (80-100%) Residual Pressure: 0.5 mmHg (<8)	Peristaltic contractions: 100% (>80%) Simultaneous contractions: 0% (<20%) Mean contraction amplitude: 241 mmHg (30-180) Mean contraction duration: 6.1 sec (<5.8) Lower amplitude contractions: 0% (<30%) Spontaneous activity between swallows: none

Acid infusion test: Felt pharyngeal burning by two minutes of infusion, which became stronger by three minutes and radiated to epigastric area. With water, all symptoms gone by six minutes.
Pharyngo-esophageal sphincter (PE): Not done

Case 4
Clinical history: Presenting with chest pain, heartburn, regurgitation and dysphagia

Lower esophageal sphincter (Normal values in brackets):	Esophageal body (Normal values in brackets):
Resting pressure: 1 mmHg (16-30) Relaxation duration: ? seconds (>2) % Relaxation: ?% (80-100%) Residual Pressure: ? mmHg (<8) Difficult to assess relaxation due to low LES pressure	Peristaltic contractions: 0% (>80%) Simultaneous contractions: 0% (<20%) Mean contraction amplitude: ? mmHg (30-180) Mean contraction duration: ? sec (<5.8) Lower amplitude contractions: 0% (<30%) Spontaneous activity between swallows: none

Acid infusion test: Not done
Pharyngo- esophageal sphincter (PE):
Resting pressure: 44.8 mmHg (40-150)
Pharyngeal contraction pressure: 54.3 (40-150)
Coordination: Yes

Case 5
Clinical history: Presenting with dysphagia, heartburn, regurgitation, chest pain, vomiting

Lower esophageal sphincter (Normal values in brackets):	Esophageal body (Normal values in brackets):
Resting pressure: 23 mmHg (16-30) Relaxation duration: 6 seconds (>2) % Relaxation: 58.5% (80-100%) Residual Pressure: 9.3 mmHg (<8)	Peristaltic contractions: 0% (>80%) Simultaneous contractions: 100% (<20%) Mean contraction amplitude: 16 mmHg (30-180) Mean contraction duration: 2.7 sec (<5.8) Lower amplitude contractions: 100% (<30%) Spontaneous activity between swallows: none

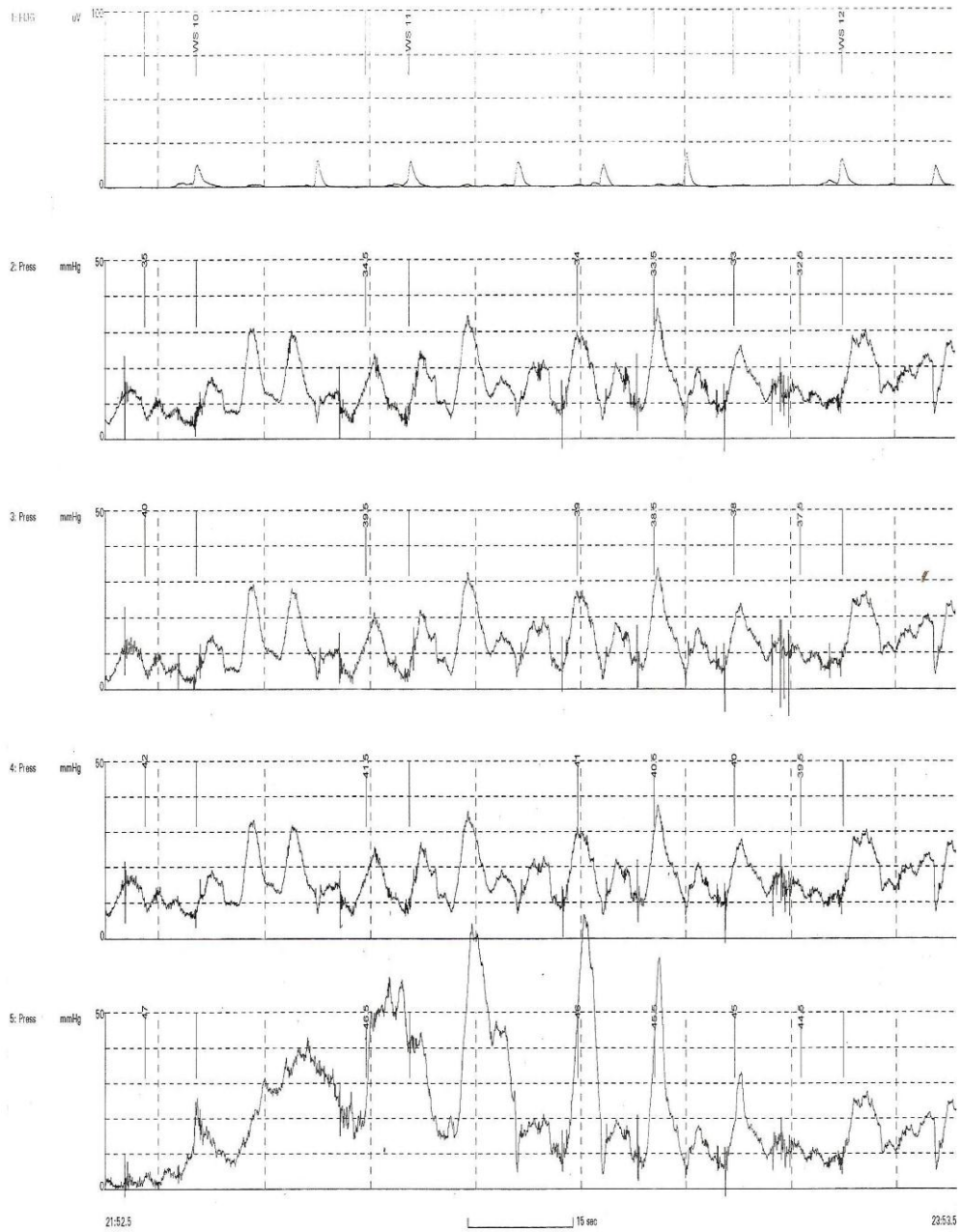
Acid infusion Test: Not done
Pharyngo-esophageal sphincter (PE): Not done

"Don't worry about the neurobiological mechanisms of motivated learning – just provide a safe, stimulating and welcoming environment."

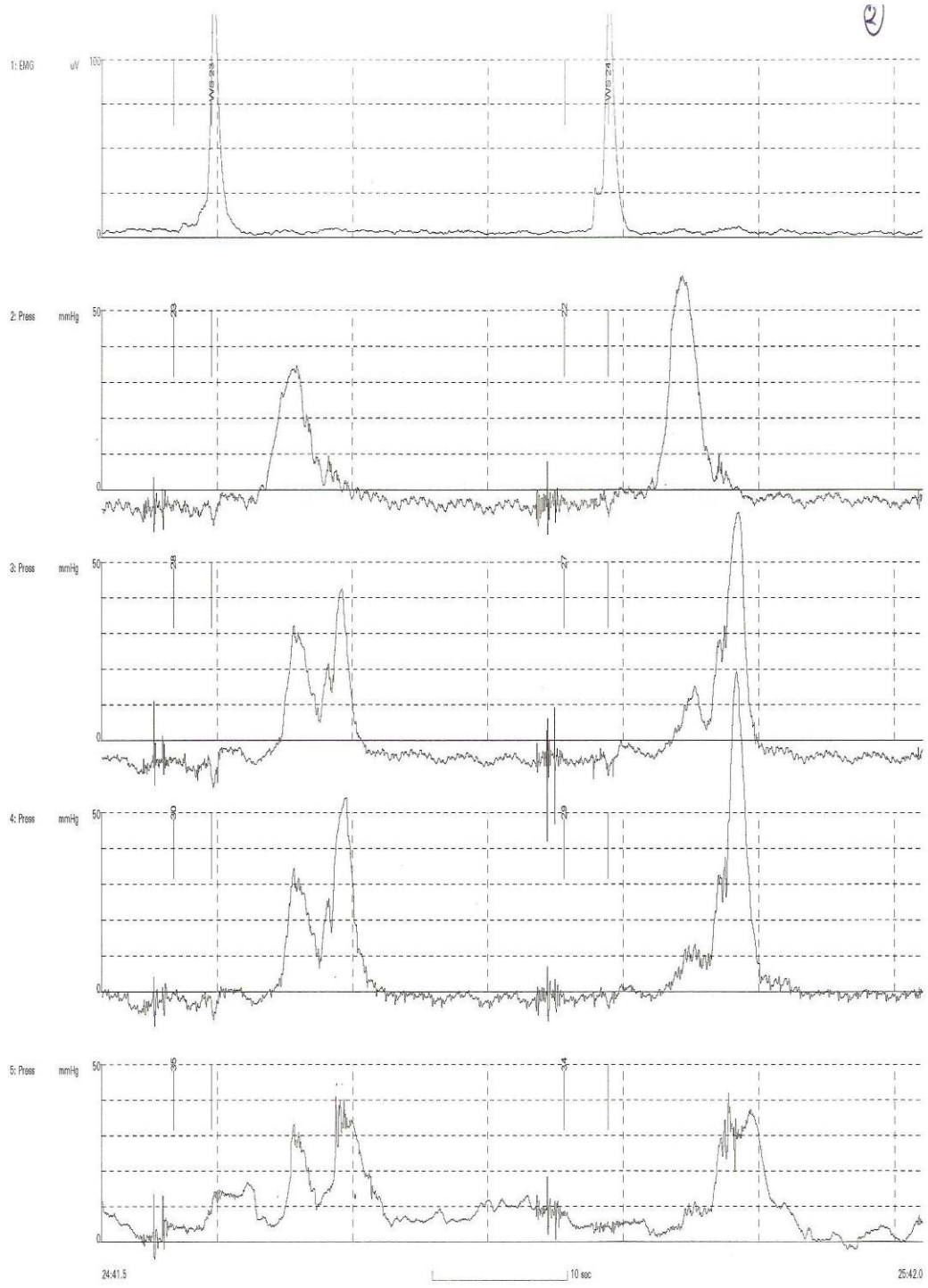
Grandad

Cases 6 to 10 were kindly provided by Dr. Dan Sadowski (University of Alberta)

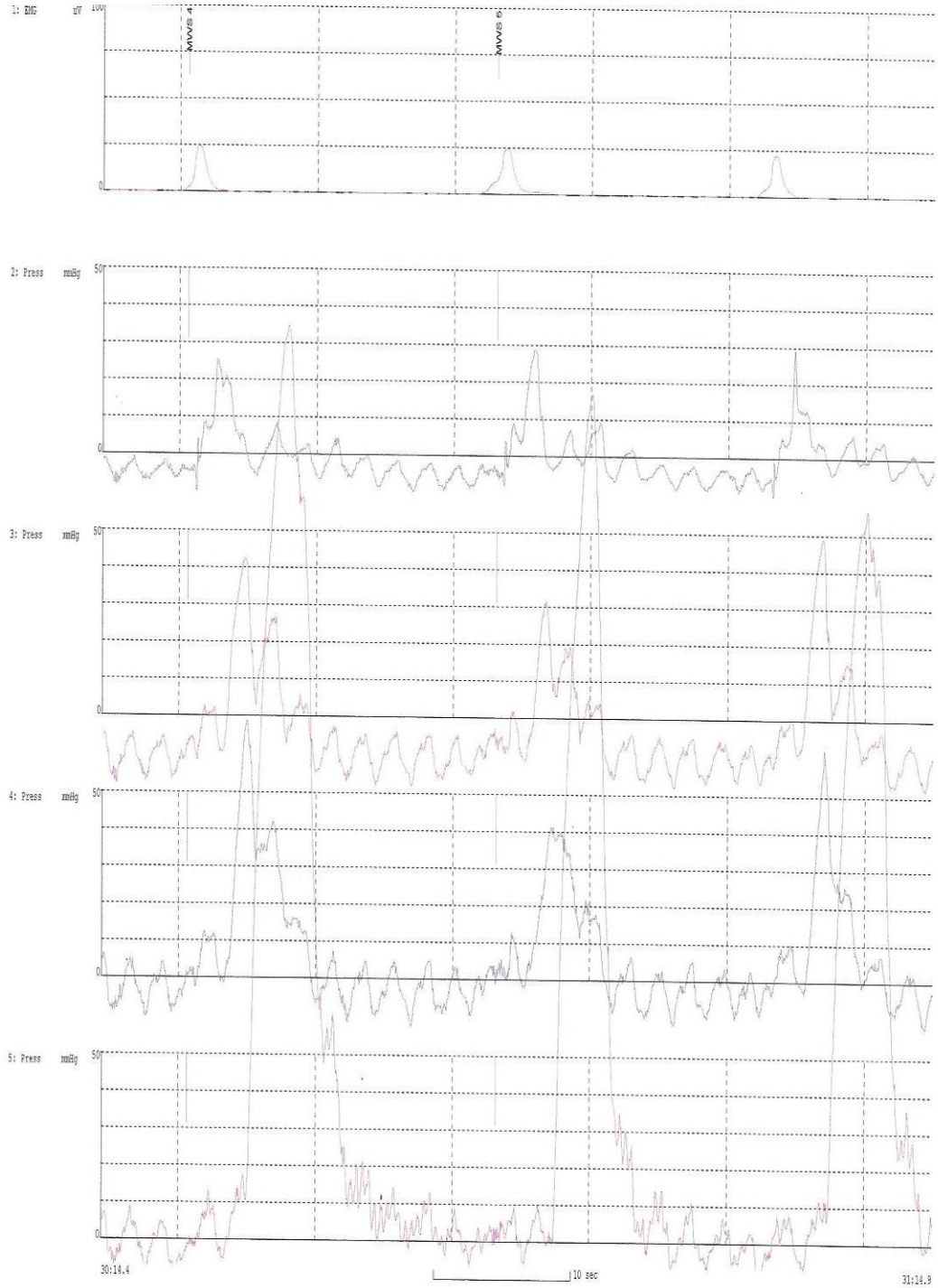
Case 6 – Channel water perfused esophageal manometry



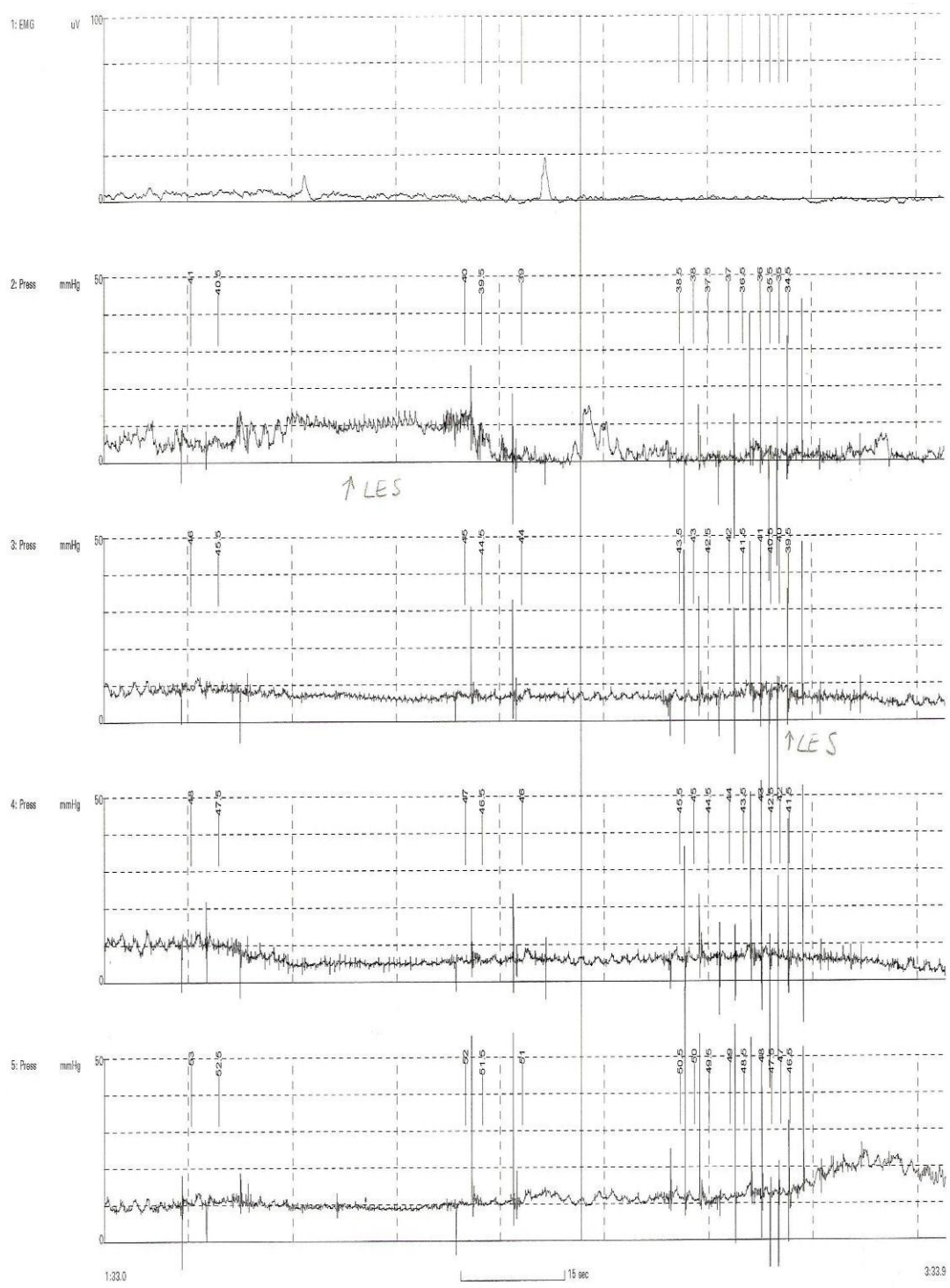
Case 7 – Channel water perfused esophageal manometry



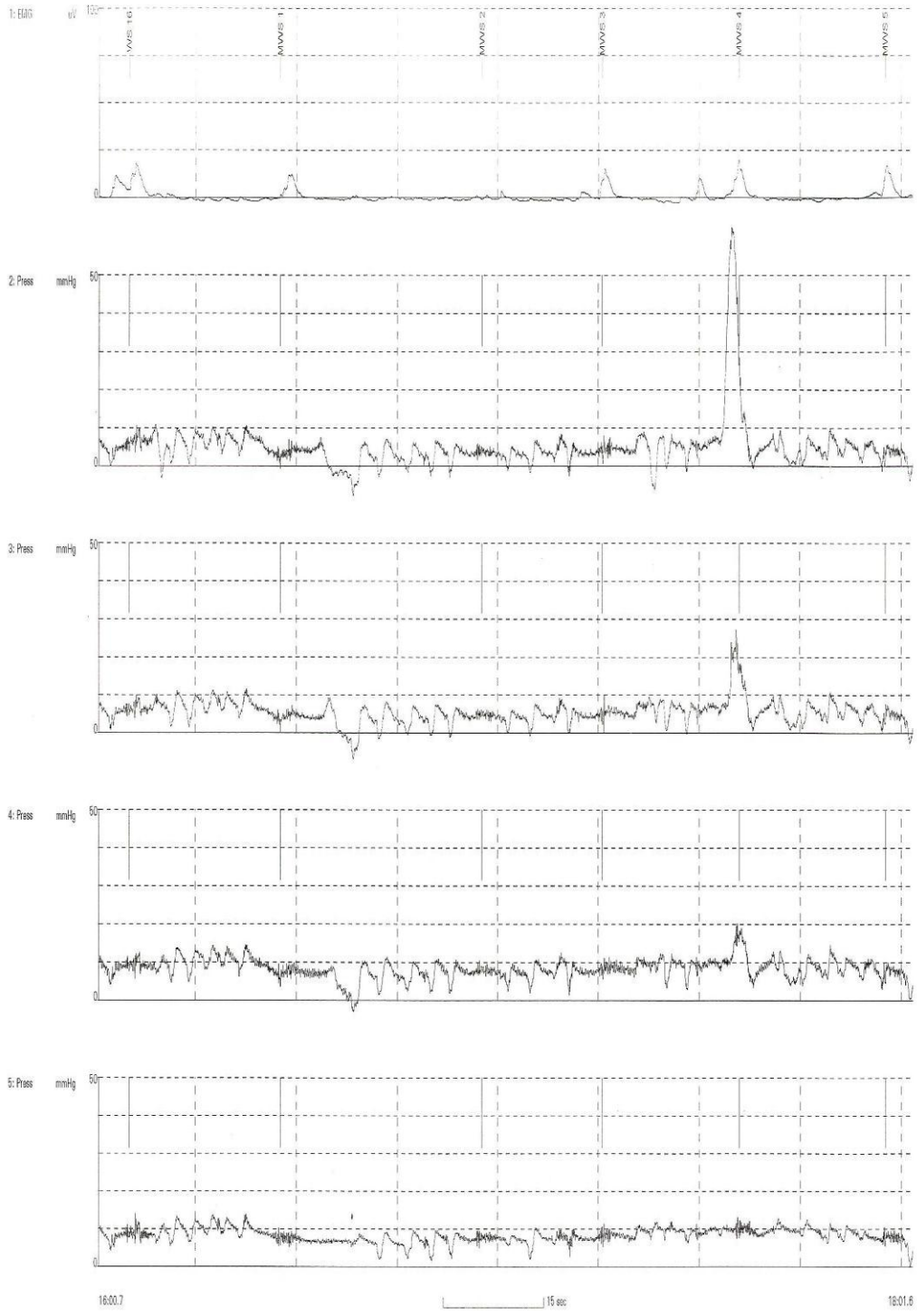
Case 8 – Channel water perfused esophageal manometry



Case 9 – Channel water perfused esophageal manometry



Case 10 – Channel water perfused esophageal manometry



Abbreviations

5-ALA	5-aminolevulinic acid
ACE	Angiotensin-converting enzyme
APC	Argon plasma coagulation
BE	Barrett's epithelium
BID	Twice a day
BMI	Body mass index
CE	Chromendoscopy
CE	Capsule endoscopy
CIC	Computed interval chromendoscopy
CMV	Cytomegalovirus
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DCI	Distal contractile index
DES	Diffuse esophageal spasm
DSRS	Distal splenerenal shunt
EB	Esophageal body
EE	Eosinophilic esophagitis
EGD	Esophageal gastroduodenoscopy
EGJ	Esophagogastric junction
EGD	Esophagogastroduodenoscopy
EGID	Eosinophilic gastrointestinal diseases
EHT	Endoscopic hemostatic therapy
EIM	Esophageal pH impedence monitoring
EMC	Early mucosal cancer
EMR	Endoscopic mucosal resection
ENT	Ear nose throat
EOE	Eosinophilic esophagitis
EUS	Endoscopic ultrasound
FE	Fluoresence endoscopy

FICE	Fuijnon intelligent chromendoscopy
FNA	Fine needle aspiration
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
GIST	Gastrointestinal stromal tumour
GSE	Gluten sensitive enteropathy
GVH	Graft-versus-host disease
H2RA	Histamine2-receptor antagonist
HDGC	Hereditary diffuse gastric cancer
HGD	High grade dysplasia
HREPT	High resolution esophageal pressure topography
HRHDME	White light high resolution endoscopy
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IEM	Inefective esophageal motility
IPF	Interstitial pulmonary fibrosis
LES	Lower esophageal sphincter
LGD	Low grade dysplasia
LIFE	Light induced fluorescence endoscopy [FE]
LES	Lower esophageal sphincter
MAC	Mycobacterium avium complex
MC	Microscopic colitis
MCTD	Mixed connective tissue diseases
MII	Multichannel intraluminal impedence
NBI	Narrow band imaging
NCCP	Non-cardiac chest pain
NERD	Normal esophageal reflux disease
NG	Nasogastric tube
NR	Not reported

OCT	Optical coherence tomography
PDT	Photodynamic therapy
PEG	Percutaneous endoscopic gastrostomy
PNS	Peripheral nervous system
PPI	Proton Pump Inhibitor
RF	Radiofrequency ablation
TIPS	Transjugular intrahepatic postoperative shunt
tLESR	Transient LES relaxation
UC	Ulcerative colitis
UES	Upper esophageal sphincter
VFSS	Videofluroscopy swallowing study
ZES	Zollinger-Ellison syndrome

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STOMACH

TABLE of CONTENTS

Dyspepsia

1. Give the benefits and limitations associated with 5 interventional/ diagnostic approaches to the patient with dyspepsia who is under 50 years of age and who has no alarm symptoms.

Diagnostic approach	Benefits	Limitations
○ "Watchful waiting" only	-Patients with mild and transient symptoms are not prescribed medication or investigated	No clinical studies.
○ Empirical Antisecretory therapy (PPI or H2RA)	-Addresses symptoms immediately -Documented effect on reflux symptoms and ulcer-related symptoms	Recurrence after therapy is the rule. EGD is often only postponed, and may be false negative.
○ Treat based on clinical diagnosis	-Clinically meaningful. Low costs	Unreliable.
○ Treat based on subgrouping and computer-based algorithms	-Clinically attractive. Low costs	Does not reliably predict EGD diagnosis or response to therapy
○ H.*pylori* test-and-treat	-Infected patients with ulcer disease will have symptomatic benefits. Reduces endoscopy rates. Safe and cost-effective compared with endoscopy. Possible reduced risk of later ulcer development.	Low benefit in those without peptic ulcer disease will not benefit. Continuing or recurrent symptoms may frustrate patients and clinician
○ H.*pylori* test-and-scope	- Potential to reduce upper EGD rates in H. pylori low-prevalence areas	Only meaningful if a decision about eradication therapy in infected patients is influenced by endoscopy result. Increases endoscopy demands. Not applicable in H. pylori-high prevalence areas

○ Early endoscopy	-Diagnostic "gold standard". Might lead to reduced medication in patients with normal findings. Increased patient satisfaction in some trials.	Invasive. Costly. About half of EGDs will be normal. Long waiting lists may lead to false negative results. Not the preferred option for many patients. Does not diagnose non-erosive reflux disease (NERD).

Abbreviations: EGD, esophagogastroduodenoscopy; H2RA, H2 receptor antagonist; NERD, non-erosive reflux disease; PPI, proton pump inhibitor.

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What's new: Barrett's epithelium

- Barrett's persons with a high pre-test probability of Barrett's epithelium include middle-aged Caucasian males, or a person with a long (>5 year) history of moderate/severe heartburn occurring more than 3 times per week).
- The presence of alarm symptoms/signs such as vomiting, anemia/bleeding, dysphasia or weight loss have a relatively low sensitivity and specificity to identify the persons with a high probability of having dysplasia or cancer, and therefore requiring an EGD in the management of their symptoms.
- About two-thirds of persons with alarm symptoms/signs have a normal EGD, and less than 10% of dyspeptic persons with alarm symptoms will have a neoplasia (Zoggari et al., AJG 2010; 105; 105; 565-71).

What's new: Dyspepsia - when to perform EGD

- There is a poor correlation between dyspeptic symptoms and findings at EGD (Zagari et al., 2010; Thomson et al., APT 2003; 17: 1481-91; Vakil, AJG 2010; 105: 512-4).
- Attempts to predict the pre-EGD probability of finding a serious lesion have included the patient's age, the presence of "red flags", a family history of esophageal/ gastric cancer, or belonging to a demographic group with such as high risk (eg. in Canada, persons with a high risk of an H.Pylori infection, "new Canadian" from a high endemic area).

Foreign body

2. On a very bizarre night on call, you are called by the Emergency physician with 4 different foreign bodies found by x-ray to be in 4 adult patients' stomachs. The patients are all adults who are asymptomatic. Which of these objects will you come in and retrieve? (write YES for those you would come in for, and NO for those you wouldn't).

   a) A quarter (25 cent piece) – *no*
   b) A toothpick – *yes*
   c) The plastic cap of a pen (2.0 cm long by 4 mm wide) – *no*
   d) A razor blade – *yes [General rule of thumb: long objects (>5cm), wide objects (>3cm), or particularly sharp objects should be retrieved.]*

Bariatric surgery

3. Name 3 bariatric procedures, and list 3 complications for each, and give 5 complications common to all bariatric surgical procedures.

- Specific procedures
  - Gastric bypass (Roux-en-Y)
    - Anastomotic leak with peritonitis
    - Stomal stenosis
    - Marginal ulcers (ischemia)
    - Staple line disruption
    - Internal and incisional hernias
    - Nutrient deficiencies (usually iron, calcium, folic acid, vitamin B12)
    - Dumping syndrome
  - Gastroplasty
    - GERD
    - Stomal stenosis
    - Staple line disruption
    - Band erosion
  - Gastric banding
    - Band slippage
    - Erosion
    - Esophageal dilation
    - Band infections
  - Biliopancreatic diversion
    - Anastomotic leak with peritonitis
    - Protein-energy malnutrition
    - Vitamin and mineral deficiencies
    - Dehydration

- Complications common to all bariatric surgical procedures
  - CNS
    - Psychiatric disturbance
  - Lung
    - Atelectasis and pneumonia
    - Deep vein thrombosis
    - Pulmonary embolism
  - CVS
  - GI
    - Anemia
    - Diarrhea
    - Ulceration
    - GI bleeding
    - Stenosis
    - Gallstones
  - Metabolic
    - Bone disease
    - Too rapid weight loss
  - Surgical
    - Wound infection
    - Failure to lose weight
    - Mortality (0.5-1%)

Abbreviation: CNS, central nervous system

Adapted from: Klein S. *2006 AGA Institute Post Graduate Course*: pg. 175.

4. Give 6 mechanisms or causes of iron- and B12-deficiency associated anemia, diarrhea, metabolic bone disease, and recurrent gastric ulceration in a patient having had a Billroth II partial gastrectomy for peptic ulcer disease (PUD), gastric cancer (GCA) or morbid obesity (bariatric surgery) and Roux-en-Y.

- Iron
  - Pre-surgery iron deficiency
  - Decreased intake from post-op symptoms (anorexia, early satiety)
  - Decreased acid leads to decreased pepsin and decreased meat (iron) digestion
  - Decreased acid: inhibits the acid-mediated solubilizing and reducing of inorganic dietary iron (Fe^{3+} .[ferric] .. Fe^{2+})ferrous])
  - Decreased absorption of Fe^{2+}, Ca^{2+}, BII, bypassing site of maximal absorption (duodenum)
  - Can be slow bleeding at surgical site
  - Bile gastritis
  - Gastric stump cancer

- B12

- Pre-surgery deficiency
- Decreased intake
- Loss of stimulated and co-ordinated release of "R" factor
- Decreased intrinsic factor
- Loss of HCl/pepsinogen to liberate food B12
- Bacterial overgrowth syndrome

- Metabolic bone disease
  - Pre-existing osteoporosis ↓ Ca^{2+} solubilization
  - ↓ vitamin D or Ca^{2+} intake
  - Bypass of site of maximal absorption of Ca^{2+} (duodenum)
  - Binding Ca^{+2} (unabsorbed fatty acids)

- Diarrhea
  - Magnesium-containing antacids, PPI's
  - Early dumping syndrome
  - Retained antrum (↑ gastrin)
  - Hypergastrinemia → HCL hypersecretion (↑ volume, mucosal damage); loss of PPY from ileum, loss of inhibition of gastrin → ↑s. gastrin
  - Bypassed duodenum
  - Unmasked celiac disease
  - Unmasked lactose intolerance
  - Unmasked bile acid wastage
  - Primary or secondary (unmasked) pancreatic insufficiency
  - Bacterial overgrowth syndrome (BOS)

- Peptic ulceration (previous peptic ulcer disease [PUD])
  - ↑ gastrin – ZES, incomplete vagotomy, gastric retention, afferent loop syndrome
  - H. pylori infection
  - NSAIDs, ASA use
  - "Stump" Cancer
  - Ischemia at anastomosis
  - Bile gastritis

- Presentations of ZES (Zollinger Ellison Syndrome) (see Question #16)
  - PUD – severe, multiple, unusual sites; GERD-like symptoms
  - Diarrhea
  - Recurrent ulceration (with or without gastric surgery)
  - Associated MEN I syndrome
  - Thick gastric folds
  - Fundic gland polyps

Abbreviations: BOM, bacterial overgrowth syndrome; GCa, gastric cancer; MEN, multiple endocrine neoplasia ; PPIs, proton pump inhibitor; PUD, peptic ulcer disease; ZES, Zollinger-Ellison syndrome

Gastric dysmotility

5. Give the mechanism (s) of action of 6 prokinetic drugs used for the treatment of symptoms of gastroparesis.

Metoclopramide	-Central/peripheral dopamine receptor antagonist (D_2) -5-HT3 receptor antagonist -5-HT4 receptor agonist
Domperidone	-peripheral D_2 antagonist
Cisapride	-muscarinic (acetylcholine) receptor agonist -5-HT3 receptor antagonist -5-HT4 receptor agonist
Ondansatron	-5-HT3 receptor antagonist
Erythromycin	-motilin receptor agonist
Tegaserod	-Cholinergic 5-HT4 partial agonist
Bethanechol	-muscarinic receptor agonist
Anticholinergic (buscopan, for tachygastria)	
α-adrenergic antagonists	-α-adrenergic antagonist
Botulism toxin injection	-acetycholine esterase inhibitor
Octreotide injection	-phosphodiesterase inhibitors -Viagra® -somatostatin receptor agonist

Adapted from: Quigley EMM. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1007; and 2010, pg. 813.

6. Give 10 therapeutic options for the treatment of nausea and vomiting during pregnancy, including dietary and lifestyle modifications, and medical therapy.

- Dietary and lifestyle modifications (see Question #7)
  - Avoidance of precipitating factors
  - Frequent, small meals high in carbohydrate and low in fat
  - Stimulation of P6 acupuncture point
  - Ginger
  - Vitamin B6 (thiamine

Printed with permission: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): pg. 433.

7. Give 3 mechanisms for the development of post-operative nausea and vomiting (PONV). Give 5 risk factors and 5 methods to reduce PONV.

- Mechanism
  - Release of serotonin from bowel handling tstimulates $5HT_3$ receptors on afferent serotonergic pathways that stimulate the brainstem
  - Reduced blood flow to brainstem during surgery
  - Activated cerebral cortical pathways

- Risk factors for PONV
  - Post Puberty females
  - Non-smokers
  - Previous PONV
  - Use of volatile anesthetics
  - Intra-operative use of opiates
  - High dose neostigmine
  - Prolonged surgery
  - Intra-abdominal surgery
  - Major gynecological surgery

- Methods to reduce the risk of PONV
  - Avoid opioids
  - Avoid nitrous oxide
  - Avoid high-dose reversal agent
  - Adequate hydration
  - High oxygen concentration
  - Propofol anesthetic

Abbreviation: PONV, post-operative nausea & vomiting

Printed with permission: Gan TJ, et al. *Anesth Analg* 2003;97(1):62-71.; and Williams KS. *Surg Clin North Am* 2005;85(6):1229-41.; and adapted from: Kovac AL. *J Clin Anesth* 2006 Jun;18(4):304-18.

8. Give 8 non-pharmaceutical maneuvers that may be used to speed the rate of gastric emptying and be potentially useful for the treatment of the patient with gastroparesis.

- Meal Factors
  - Small, frequent, fluid, neutral pH and temperature, isotonic, low energy density, low fat meals
  - Certain amino acids (e.g. L-tryptophan – [cheese])
  - Avoid offending foods and beverages
  - Vitamin B6 (thiamine) (FDA A)

- Ginger
- Soda crackers (unproven benefit)
- Avoid offending foods/beverages
- Frequent, small meals, low in fat

- Treat other factors
  - Underlying disease/ condition causing/ aggravating gastroparesis
  - Rectal/colonic distention
  - Pregnancy
  - Ascites
  - Hyperglycemia
  - Avoid circular vectoral motion
  - Avoid medications which may relax smooth muscle and thereby aggravate gastroparesis

- Gastric electrical stimulation

- Treat complications
  - GERD, esophagitis
  - Dehydration, electrolyte disturbances
  - Malnutrition

- Miscellaneous
  - Acupuncture – "P6" acupuncture point
  - Gastric electrical stimulation

Adapted from: Quigley EMM. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1007.

9. Classify the causes of nausea and vomiting, and give 20 examples.

   Please see Malagelada JR, and Malagelada C. Nausea and vomiting. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006:pg.145.

10. Give the smooth muscle as well as the CNS receptors which are responsible for the mechanism (s) of action for 12 drugs used for the treatment of refractory nausea and vomiting.

- GI receptors

- Central
  - H-1 receptor antagonists (inner ear) – diphenohydramine, promethazine
  - Cannabinoids – dronabinol, nabilone

- Neurokinin (NK)-1-antagonist – aprepitant, talnetant, osanetant
- Neuroleptic – chlorpromazine, haloperidol
- Benzodiazepines
- 5 HT3 antagonist – Ondansatron
- Metocloprimide
  - D2 antagonist
  - 5HT3/ 5HT4
- Tricylic antidepressants
- Steroids (e.g. dexamethasone and Mannitol) (nausea and vomiting due to increased intracranial pressure)

➢ Gastroparesis
- The vomiting center is on the blood side of the blood-brain barrier
- Some persons with severe, intractable gastroparesis, such as may occur with severe type I diabetes, may improve with near-total gastrectomy and Roux-en-Y anastomosis
- Slowed gastric emptying and delayed small intestinal transit occur in persons with cirrhosis

11. Give 4 drugs that may be used for nausea and vomiting in pregnancy and give the FDA pregnancy use category.

Drug	FDA category	Usual dosage
○ Vitamin B_6 (thiamine)	A	10-25mg three times daily
○ Doxylamine	B	12.5 mg twice daily
○ Erythromycin	Erythromycin (rarely used to treat hyperemesis)	250-500 mg tid
○ Prochlorperazine	C	5-10 mg tid
○ Metoclopramide	B	10-20 mg four times daily (qid)

○ Domperidone, cisapride	C	1-20 mg tid or qid
○ Ondansetron	B	4-8 mg tid
○ Promethazine	C	12.5-25.0 mg qid

Adapted from: Thukral C, and Wolf JL. *Nature Clinical Practice Gastroenterology & Hepatology* 2006; 3(5): pg. 258; and Printed with permission: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): pg. 433.

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Peptic ulcer disease (PUD), H. pylori

12. Name 6 secretory cells of the stomach, and give one chemical/ peptide/ hormone which the cell secretes.

- Goblet cell – mucus
- Parietal cell – HCl, intrinsic factor
- Chief cells – pepsinogen, gastric lipase
- D cells – somatostatin
- G cells – gastrin
- Mast cells – histamine
- Enterochromaffin-like cells – histamine

13. Give 6 causes of thick gastric folds seen on an upper GI series or EGD.

- Infiltration
  - Folds not actually thickened (eg. barium study is wrong – ie. varices)
  - Malignant – adenocarcinoma, lymphoma
  - Benign infiltration -granulomas:e.g. sarcoidosis, TB, Crohn's severe gastritis (ethanol, H. pylori), Menetrier's disease (hyperplasia) eosinophilic gastritis
  - Multiple gastric polyps (HNPCC, FAP, fundic glands)
  - Hypersecretion (Zollinger-Ellison Syndrome)
  - Fundal varices
  - Worms

Abbreviations: EGD, esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; GI, gastrointestinal; TB, tuberculosis

14. Give 4 clinical situations/syndromes which can be associated with fundic gland polyps.

- Hypergastrinemia
- H. Pylori infection
- PPI use
- Familial adenomatous polyposis (FAP; Attenuated FAP, 0.5-1.0% lifetime risk of gastric cancer)
- Cowden's syndrome
- Idiopathic

Useful background: Dyspepsia and pregnancy

- Upper GI symptoms are common in pregnant women, and when EGD has been performed the findings are esophagitis (34%) and gastritis (25%).

- Predictors of heartburn during pregnancy include young age of the mother, her parity, increasing gestational age, and the presence of heartburn before pregnancy (which occurs in 14% of mothers) (Marrero JM, et al. *Br J Obstet Gynaecol* 1992:731-4).

- Only calcium-containing antacids should be used for GERD symptoms, since aluminum-containing antacids may cause fetal neurotoxicity, alginic acid (Gaviscon, sucralfate) may cause fetal distress, and magnesium-containing antacids may cause a number of fetal disorders (renal stones, respiratory distress and cardiovascular impairment, and hypotemia, especially when used in higher doses for longer intervals) (Katz 09).

- Nizatidine is not recommended for lactating mothers (FDA C, due to report of growth retardation of rodent pups)

"There's always a taller mountain."

Grandad

Useful background: Pregnancy and the upper GI tract

- Upper GI symptoms are common in pregnant women, and when EGD has been performed the findings are esophagitis (34%) and gastritis (25%)

- Predictors of heartburn during pregnancy include young age of the mother, her parity, increasing gestational age, and the presence of heartburn before pregnancy (which occurs in 14% of mothers) (Marrero JM, et al. *Br J Obstet Gynaecol* 1992:731-4)

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- Nizatidine is not recommended for lactating mothers (FDA C, due to report of growth retardation of rodent pups)

Abbreviation: EGD, esophagogastroduodenoscopy

15. Give 6 factors to consider when performing endoscopy in pregnant women.

- A strong indication is always needed, particularly in high-risk pregnancies

- Whenever possible, endoscopy should be deferred until the second trimester

- The lowest possible dose of sedative medication should be used (wherever possible FDA category A or B drugs)

- Procedure time should be short

- To avoid inferior venal cava or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position

- Presence of fetal heart sounds should be confirmed before sedation and after the procedure

- Obstetric support should be immediately available

- No endoscopy should be performed in patients with obstetric

complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)

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16. Give a differential diagnosis of vomiting in a newborn.

- Gastroenteritis, gastroesophageal reflux, overfeeding, food allergy, milk protein intolerance, congenital duodenal atresia, pyloric stenosis, volvulus, meconium ileus, Hirschsprung's disease

H. Pylori

17.

a) Give the modes of transmission of H. pylori (Hp), and the impact of one person in the family being positive for H. pylori on the rate of H. pylori infection by others in the family.

- Modes of transmission of Hp
  - Gastro-oral vomitus-oral, fecal-oral

b) Give the impact of an infected family member on others in the family group
  - Hp positive parent
    - Spouse 68% Hp^+
    - Children 40% Hp^+
  - Hp negative parent
    - Spouse 9% Hp^+
    - Children 3%Hp^+
  - Community Risk
    - Adults - approximately 25-30% (depends on person's age)
    - Higher (30%) in older persons
    - >50% First Nations Canadians, new Canadians from high Hp prevalence areas
    - New Canadians from high prevalence countries

18. Give 8 GI and 8 non-GI conditions which may be associated with H. pylori (Hp) infection.

- Hp-associated GI diseases
  - Non-ulcer dyspepsia
  - Acute/chronic gastritis

- Atrophic gastritis (AG) – acceleration with PPI of AG-IM-Dys-GCa → intestinal metaplasia (IM) → dysplasia (Dys) → GCa (non-cardia gastric cancer)
- Duodenal and gastric ulcer (DU and GU) (only ~20% of Hp^+ persons develop clinical disease)
- Accentation of effect of smoking on PUD
- Accentuation of ASA/NSAID effects on peptic PUD
- Maltoma
- Fundic gland polyps
- Hypertrophic gastric folds
- Protective against GERD (possible)
- Halitosis
- Carcinoid tumours
- Colorectal cancer (possible association, due to hypergastrinemia)
- Pancreatic cancer (possible)

➢ Possible Hp-associated non-GI diseases
- Head –otitis media, migraines, headaches
- CNS – Parkinsonism, CVA
- Heart – atherosclerotic diseases
- Lung – chronic bronchitis, COPD, SIDS
- Blood – ITP, iron deficiency
- Skin – idiopathic chronic urticaria, acne, rosacea; Rosacea's
- Growth retardation in children
- Vomiting in pregnancy

Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DU, duodenal ulcer; GCa, gastric cancer; GERD, gastroesophgeal reflux disease; GU, gastric ulcer; ITP, idiopathic thrombocytopenic purpura; PUD, peptic ulcer disease; SIDS, sudden infant death syndrome.

Adapted from: Hunt R. *AGA Institute Post Graduate Course* 2006; pg. 333-342.; and adapted from Graham DY. and Sung JJY. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/ Management* 2006. pg. 1054; and 2010, pg. 839.

19. Give 3 recommended indications for *H. pylori* eradication therapy (ET) in the patient taking NSAIDs or ASA.

➢ Reduce PUD formation

➢ Reduce recurrent PUD

- Reduce recurrent PUD bleeding (in ASA or NSAID high risk users) (ET does not prevent further PUD bleeding in high risk ASA/NSAID users on PPI)

Abbreviation: ET, eradication therapy

Adapted from: Lai LH, and Sung JJY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(2): pg. 270.

Useful background: H. pylori

- Recent meta-analysis does not show a statistical difference in H. pylori eradication rates using either triple or quadruple therapy (RR = 1.002; 95% CI 0.936-1.073) (Luther J Schoenfeld P, et al. *Am J Gastroenterol* 2008:S397.)

- None of the H. pylori treatment guidelines endorse sequential therapy (Chey 09). Another meta-analysis showed 93% eradication rate with sequential therapy versus 74% for clarithromycin-based triple therapy (Jafri N, et al. *Ann Intern Med* 2008:2220-2223), particularly in persons with clarithromycin-resistant strains of H. pylori.

- Meta-analysis has shown superiority of a 10-day course of levofloxacin-based triple therapy vs a 7 day course of bismuth-based quadruple therapy (rr = 0.51; 95% CI: 0.34-0.75) for persistent H. pylori infection (Saad R Schoenfeld P, et al. *Am J Gastroenterol* 2006:488-96.)

- Rifampin has been used as an alternative to clarithromycin, with eradication rates of 38-91% (Chey WD, Wong BC. *Am J Gastroenterol* 2007:1808-1825). There may be rare but serious adverse effects (myelotoxicity and ocular toxicity)

- Furazolide used in place of clarithromycin, metronidazole or amoxicillin gives eradication rates of 52-90% (Chey WD, Wong BC. *Am J Gastroenterol* 2007:1808-1825)

Non-steroidal anti-inflammatory drugs (NSAIDs)

20. Give the recommendations for avoiding peptic ulcers (gastric or duodenal) associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a function of low, moderate and high gastrointestinal, as well as low and significant cardiovascular risk (CV) (e.g. required use of ASA plus NSAID).

	Low GI Risk	Moderate GI Risk	High GI Risk
Low CV Risk (no ASA)	○ An NSAID with a low ulcerogenic potential at the lowest effective dose ○ Consider testing/ treating for H. pylori if starting NSAIDs ○ Avoid multiple or high dose NSAIDs	○ NSAID plus PPI ○ Misoprostol ○ COXIB	○ COXIB plus PPI ○ Misoprostol
Significant CV Risk (requires ASA)	○ NSAID plus a PPI	○ NSAID and a PPI	○ Avoid NSAIDs and COXIB, if at all possible

Abbreviations: COXIB, COX-2 inhibitor; CV, cardiovascular risk; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

*these recommendations did not embrace the patients who required antiplatelet therapy, but the same principle is likely to apply.

Printed with permission: Lanza FL, et al. *Am J Gastroenterol* 2009; 104: pg 728-38.

21. Compare and contrast the endoscopic findings and treatment of portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE).

➢ Feature findings	PHG	GAVE
○ Site	Fundus	Antrum
○ Mosaic pattern	Yes	No

○ Red colour signs	Yes	Yes
○ Findings on gastric mucosal biopsy		
- Thrombi	No	+++
- Spindle cell proliferation	Sparse	++
- Fibrohyalinosis	No	+++

➢ Management	○ ↓ portal hypertension	○ Estrogens
	○ β adrenergic blockers	○ Antrectomy
	○ TIPS	○ (TIPS doesn't help) Endoscopic laser therapy
	○ Liver transplantation	○ Liver transplantation

22. Give the annual risk for an adverse effect in a 70 year old man on a high dose of NSAIDs, who has a history of a prior bleeding peptic ulcer, and is on maintenance PPI - his H. pylori status unknown (baseline absolute risk, 2.5%).

Risk characteristic		RR
➢ Baseline absolute risk for GI event, 2.5%		
➢ Increase in risk	○ Age > 65 years	2.5
	○ Use of anticoagulants	2.5
	○ Use of steroids	2.0
	○ History of peptic ulcer disease	5.0
	○ High dose of NSAIDS	2.0
	○ Presence of Helicobacter pylori	1.5
➢ Reduction in risk	○ Therapy with proton pump inhibitors	0.5

(2.5 x 5 x 2 x 0.5) 12.5 x 2.5%= 31.3%

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; RR, relative risk.

Useful background: Key points to consider regarding NSAIDs and gastroprotection

- Concomitant PPI use reduces the risk of development of NSAID induced endoscopic lesions such as ulcers
- Concomitant PPI use is strongly recommended for high risk NSAID users
- It is not known whether concomitant PPI use reduces the risk of clinically significant GI events such as hemorrhage and perforation
- PPI co therapy in high risk NSAID users is equivalent to COX-2 therapy in preventing NSID induced endoscopic lesions
- PPI use is effective as secondary prevention of ulcer complications in patients needing antithrombotic therapy with aspirin or clopidogrel
- As alternatives to PPIs, misoprostol and H_2RAs can be used in the prevention of NSAID related ulcers and their complications, and their use is cost effective
- PPI co therapy is effective in the healing and prevention of recurrence of ulcers in patients maintained on long term NSAID therapy

Adapted from: Arora et al. *Clinical Gastroenterology and Hepatology* 2009;7: 725-735

Printed with permission: Lanza FL, et al. *AM J Gastroenterology* 2009; 104: 734.

Useful background: Odds ratios (ORs) and *P* values for comparisons between gastroprotective strategies for persons using NSAIDs or COXIBs (COX-2 inhibitors).

A. For all upper GI complications.

NSAID + low dose misoprostol (0.74)					
NSAID + PPI (0.67)	0.88 (0.52-1.49) *P* > .20				
NSAID + PPI + low-dose misoprostol	0.78 (0.46-1.34) *P*	0.86 (0.47-1.57) *P* > .20			

(0.58)	>.20				
COXIB (0.51)	0.68 (0.56-0.85) *P* = .0006[a]	0.75 (0.53-1.06) *P* = .11	0.87 (0.52-1.49) *P* >.20		
COXIB + PPI (0.36)	0.48 (0.36-0.65) *P* < .0001 [a]	0.53 (0.36-0.79) *P* = .0018 [a]	0.62 (0.35-1.09) *P* = .093	0.70 (0.55-0.91) *P* = .0068 [a]	
	NSAID + low-dose misoprostol	NSAID + PPI	NSAID + PPI + low-dose misoprostol	COXIB alone	COXIB + PPI
NOTE: Those shown in bold are statistically significant.					

B. For all upper GI complications secondary to peptic ulcer disease.

NSAID + low dose misoprostol (0.61)					
NSAID + PPI (0.50)	0.81 (0.48-1.38) *P* > .20				
COXIB (0.46)	0.74 (0.55-1.00) ***P*** = .050	0.91 (0.55-1.50) *P* > .20			
NSAID + PPI + low-dose misoprostol (0.29)	0.46 (0.18-1.21) *P* = .117	0.58 (0.21-1.60) *P* > .20	0.63 (0.25-1.60) *P* >.20		
COXIB + PPI (0.23)	0.37 (0.23-0.57) ***P*** < .001 [a]	0.49 (0.25-0.82) ***P*** =.0084 [a]	0.50 (0.34-0.73) ***P*** < .001 [a]	0.79 (0.29-2.09) *P* > .20	
	NSAID + low-dose misoprostol	NSAID + PPI	COXIB alone	NSAID + PPI + low-dose misoprostol	COXIB + PPI

NOTE: ORs for relative risk reduction versus nsNSAID users alone shown in parentheses.

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What's new: Gastroprotection

- Persons with cardiovascular disease (CV) may be on aspirin (ASA) when they develop a NVUGIB.
- The reflex action may be to stop the ASA to reduce the risk of recurrent ASA-associated bleeding.
- This is successful from the GI perspective (recurrent bleeding is higher in patients on rather than off ASA, 10.3% vs 5.4%).
- However, this discontinuation of ASA in the high CV-risk patient leads to a higher CV mortality rate (12.9% vs 1.3%) (Sung et al., Ann. Int. Med.; 2010 152: 1-9).
- This person with both high CV and GI risk be kept on ASA and that gastroprotective therapy with a PPI be used.

Acute non-variceal upper GI bleeding (NVUGIB; UGIB)

23. Give 6 patient-related adverse prognostic variables in persons with acute NVUGIB.

- Increasing age
- Increasing number of comorbid conditions (especially renal failure, liver failure, heart failure, cardiovascular disease, disseminated malignancy)
- Shock – hypotension, tachycardia, tachypnea, oliguria on presentation
- Red blood in the emesis or stool
- Increasing number of units of blood transfused
- Onset of bleeding in the hospital
- Need for emergency surgery
- Anticoagulant use, glucocorticosteroids

Abbreviations: NVUGIB, non-variceal upper GI bleeding

24. Give the rates (%) of rebleeding, surgery and mortality, without and with endoscopic hemostatic therapy (ET), using the Forrest classification of bleeding peptic ulcers.

EGD appearance	Prevalence	Rebleeding Rate (%) No EHT		Surgery Rate (%) No EHT		Mortality rate (%) No EHT	
		EHT(~70%↓)		EHT (~80 %↓)		EHT (~50%↓)	
		EHT°	EHT^{+}	EHT°	EHT^{+}	EHT°	EHT^{+}
Active Bleeding (Ib, ouzing)*	18	55	20	35	7	11	<5
Visible vessel (IIa); not bleeding	17	43	15	34	6	11	<5
Adherent clot (IIb)	15	22	5	10	2	7	<3
Flat pigmented spot (IIc)	15	10	<1	6	<1	3	<1
Clean ulcer base (III)	35	<5	<1	<1	<1	<1	<1

*Forrest 1a, active bleeding (spurting)

Abbreviation: EHT, endoscopic hemostatic therapy

Printed with permission: Atkinson RJ and Hurlstone DP. *Best Practice & Research Clinical Gastroenterology* 2008; 22(2): pg. 235.

Useful background: The Rockall Risk Score Scheme for assessing prognosis in patients with NVUGIB (PUD), using clinical and endoscopic considerations

Variable	0	1	2	3
Age (years)	< 60	60-79	$\geq$ 80	$\geq$ 80
Shock	SBP $\geq$ 100, PR < 100/min	SBP $\geq$ 100, PR $\geq$ 100	SBP < 100 mm, PR $\geq$ 100	SBP < 100, PR $\geq$ 100
Comorbidity	None	None	Cardiac failure, ischemic heart disease, any major comorbidity	Renal failure, liver failure, disseminat

				ed malignancy
Diagnosis at time of endoscopy	Mallory-Weiss tear, or no lesion identified and no stigmata of recent hemorrhage	All diagnoses except malignancy	Malignancy of the upper GI tract	-
Stigmata of recent hemorrhage	None, or dark spot only		-Blood in upper GI tract -Adherent clot -Visible or spurting vessel	-

Maximum score prior to endoscopic diagnosis=7, maximum score following diagnosis=11

Abbreviations: GI, gastrointestinal; NVUGIB, non-variceal upper GI bleeding; PUD, peptic ulcer disease; PR, pulse rate

Useful background: UGIB

- A negative NG aspirate in the patient who presents with melanoma or hematoschezia reduces the likelihood of an upper GI source of the bleeding, but because of curling of the tube or duodenal bleeding which does not relux into the stomach, 15-18% of persons with an upper GI source for bleeding will have a non-bloody aspirate.
- The distribution of the endoscopic type of bleeding ulcers is: clear-based, 55%; a flat pigmented spot, 16%; a clot, 8%; a visible vessel, 8%; and active bleeding, 12% (Enestvedt BK, et al. *Gastrointest Endosc* 2008:422-9.)
- RCTs show that adding bolus plus infusion of PPI to endoscopic hemostatic therapy (EHT) significantly decreased bleeding (NNT, 12) surgery (NNT, 28) and death (NNT, 45) (Laine L, et al. *Clin Gastroenterol Hepatol* 2009:33-47).
- In the patient with UGIB due to esophageal varices (5-30% of all cases of UGIB), adding octreotide plus infusion for 2-5 days for EHT improves the control of bleeding. A;so, adding ceftriaxone or quinolones reduces bacterial infection and mortality (DeFranchis R. *J Hepatol* 2005:167-76.)
- Recurrent esophageal variceal bleeding in the Child-Pugh class A or B cirrhotic, which occurs despite repeated endoscopic variceal banding or maintenance use of nonselective beta blocker may require the

placement of TIPS (transjugular intrahepatic postoperative shunt) or a distal splenerenal shunt (DSRS). The reintervention rate is much lower with DSRS than TIPS (82% vs 11%, likely due to the TIPS shunt stenosis), with no difference in rebleeding, hepatic encephalopathy or death (Henderson JM, et al. *Gastroenterology* 2006:1643-51.)

- Gastric varices due to splenic vein thrombosis can be cured by splenectomy
- In the ICU patient on a mechanical ventilator, IV H2-receptor blocker or PPI through the nasogastric tube is superior to sucralfate to reduce stress when bleeding (Cook DJ, et al. *N Engl J Med* 1998:791-7.; Conrad SA, et al. *Crit Care Med* 2005;33:760-5.

Abbreviations: NNT, number needed to treat; TIPS, transjugular intrahepatic portosystemic shunt; UGIB, upper GI bleeding

Useful background: Recent update of upper gastrointestinal bleeding incidence and mortality

- The overall incidence of hospitalisation for UGIB was 134 per 100,000 population; incidence was higher among men than women (153 vs. 117 per 100,000)
- UGIB incidence, but not mortality was associated with socio-economic status
- Overall case fatality rates at 30 days after hospital admission was 10.0%; fatality rates rose with age and were higher for men than women and for those with (vs. without) comorbid illnesses.
- Adjusted fatality rates are 13% higher for patients admitted on weekends than on weekdays, and 41% higher for patients admitted on holidays than on weekdays (this difference in mortality could be attributed to reduced staffing and lack of availability of endoscopy on weekends and holidays in some hospitals)
- Patients admitted on weekends or holidays suffered higher mortality than those admitted on weekdays (13% higher on weekends, and 41% higher on holidays)
- Fatality rates decreased from 11.4% to 8.6% during the study period.

What's new: Non-variceal upper GI bleeding

- A methodology has been recommended for all the future RCTs in persons with nonvariceal gastrointestinal bleeding (NVUGIB) (Laine et al., 2010).
- No scoring system has been validated to use to predict when rebleeding will occur after endoscopic hemostatic therapy (El munzer et al., 2008). Thus it is not recommended to routinely undertake a second-look EGD.
- Individualize such 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, or a high risk bleeding lesion seen at the index of EGD.

Useful background: A clinical method to estimate volume depletion

Clinical	Class I	Class II	Class III	Class IV
○ Blood loss (mL)	<750	750-1500	1500-2000	>2000
○ Blood loss (% blood volume)	<15	15-30	30-40	>40
○ Heart (beats/min)	<100	>100	>120	>140
○ Blood pressure	Normal	Normal	Decreased	Decreased
○ Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
○ Ventilatory rate (breaths/min)	14-20	20-30	30-40	>35
○ Urine output (mL/h)	>30	20-30	5-15	Negligible
○ Mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic
○ Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Printed with permission: Atkinson RJ and Hurlston DP. *Best Practice & Research Clinical Gastroenterology* 2008; 22(2): pg. 234.

Useful background: Vital signs and acute blood loss

Physical Finding	Sensitivity (%)		Specificity (%)
	Moderate Blood Loss	Large Blood Loss	
➢ Postural pulse increment ≥30/min or severe postural dizziness	7-57	98	99
➢ Postural hypotension (≥ 20 mm Hg decrease in SBP)	9	...	90-98
➢ Supine tachycardia (pulse >100/min)	1	10	99
➢ Supine hypotension (SBP <95 MM Hg)	13	31	98

Adapted from: McGee S. R. Evidence Based Physical Diagnosis. 2nd Edition. *Saunders/Elsevier,* St.Louis, Missouri, 2007, Table 15.2 pg. 167

Useful background: Performance characteristics of hypotension and its prognosis

Finding	PLR
➢ Systolic blood pressure <90 mm Hg	
○ 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 mm Hg	
○ Predicting mortality in patients with acute myocardial infarction	15.5

Abbreviation: PLR, positive likelihood ratio

Source: McGee S. R. Evidence Based Physical Diagnosis. 2nd Edition. *Saunders/Elsevier*, St.Louis, Missouri, 2007, Box 15.1 page 161.

Thoughtful reflections

- Discuss the *ethical considerations relating to liver transplantation for persons with alcoholic liver disease.*
- *Discuss the ethical considerations of offering screenting colonoscopy for persons with average risk of developing colorectal* cancer.

25. Give the similarities and differences in the clinical features of NVUGIB in elderly versus younger persons.

- Similarities
  - Presenting manifestations of bleedings: hematemesis (50%); melena (30%); hematemesis and melena (20%)
  - Peptic ulcer disease most common etiology
  - Safety and efficacy of endoscopic therapy

- Differences (in elderly patients)
  - ↓ Antecedent symptoms (abdominal pain, dyspepsia, heartburn)
  - ↑Prior aspirin and NSAID use
  - ↑ Presence of comorbid conditions
  - ↑ Hospitalization, rebleeding, death

Abbreviation: NVUGIB, non-variceal upper GI bleeding

Printed with permission: Yachimski PS and Friedman LS. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(2): pg. 81.

26. What are the clinical features of upper gastrointestinal bleeding elderly versus younger patients?

- Similarities
  - Presenting manifestations of bleeding: hematemesis (50%); melena (30%); hematemesis and melena (20%)
  - Peptic ulcer disease most common etiology
  - Safety and efficacy of endoscopic therapy

- Differences (in elderly patients)
  - Fewer antecedent symptoms (abdominal pain, dyspepsia, heartburn)
  - Prior aspirin and NSAID use
  - Presence of comorbid conditions
  - Higher rates of hospitalization
  - Higher rates of rebleeding Higher mortality rate

Adapted from: Farrell JJ, and Friedman LS. *Gastroenterol Clin North Am*. 2001;30(2):377-407, viii.

27. Give 10 diagnostic methods for determining the cause of obscure GI bleeding.

Method

➢ Endoscopy	○ Capsule endoscopy (CE) ○ Double balloon enteroscopy (DBE) ○ Push enteroscopy (PE) ○ Intraoperative endoscopy ○ Repeat endoscopy ○ Repeat colonoscopy
➢ Small bowel contrast X-ray	○ Small bowel single contrast ○ Small bowel double contrast (enteroclysis)
➢ CT/MRI	○ CT angiography ○ CT/MRI enteroscopy ○ CT-enterocylsis
➢ Angiography	○ In the presence or absence of acute bleeding
➢ Scintigraphy	○ Erythrocyte scintigraphy (RBC scan) ○ Meckel's scintigraphy

Abbreviations: CE, capsule endoscopy; DBE, double balloon enteroscopy; EGD, esophagogastroduodenoscopy; PE, push enteroscopy

Adapted from: Heil U. and Jung M. *Best Practice & Research Clinical Gastroenterology* 2007;21(3): pg. 402.

Useful background: Obscure GI bleeding (OGIB)

- In persons with OGIB, 35-75% of the causes are revealed by second-leak EGD, and 6% by second-leak colonoscopy (Leighton 09). Small bowel lesions account for only 5% of OGIB, and most of these (70%) are vascular lesions (Cellier C. *Best Pract Res Clin Gastroenterol* 2008:329-40).
- Most of the lesions diagnosed by push enterstomy in persons with OGIB are within the reach of standard EGD.

- The diagnostic yield of capsule endoscopy (CE) in the patient with OGIB ranges from 38-83% (Rondonotti E, et al. *World J Gastroenterol* 2007:6140-9).
- CE is more likely to give a positive yield when there has been more than one episode of bleeding, the bleeding is overt rather than occult (60% vs 46%), CE is performed within 2 weeks of the bleeding episode (91% vs 34%), the bleeding has occurred over more than the 6 months, and the bleeding has resulted in the hemoglobin concentration being < 10 g/dl (Carey EJ, et al. *Am J Gastroenterol* 2007;102:89-95).
- The false negative rate for CE is 19% for tumours, and 11% overall.
- CE cannot be performed in persons with a structure or obstruction, since this would require that the capsule be removed surgically.
- Double balloon enteroscopy (DBE) is superior to single balloon enteroscopy (SBE). DBE can be performed in an oral/antegrade, or anal/ retrograde manner.
- Approximate depth of endoscopic penetration of small bowel
  - Push enteroscopy 90-150 cm
  - Ileoscopy 50-80 cm
  - DBE,
    - Oral 240-360 cm
    - Rectal 102-140 cm
- DBE has a diagnostic yield of 60-80% in persons with OGIB suspected to be from the small intestine, with therapeutic intervention being possible in 40-73%.
- Meta-analysis has shown comparable diagnostic yield for DBE and CE (57-60%), with therapeutic potential with DBE (Pasha SF, et al. *Clin Gastroenterol* Heptaol 2008:671-6.; Chen X, et al. *World J Gastroenterol* 2007;13:4372-8.).
- Meckel scan for a Meckel's diverticulum is performed with technetium 99 m pertechnetate, and has a sensitivity of 64-100% for bleeding from ectopic gastric mucosa.
- A false negative Meckel scan may be the result of a recent barium X-ray obscuring the area of uptake, too small a diverticulum, too small a vascular supply to the diverticulum, or too rapid bleeding from the diverticulum washing out the technetium (Leighton 09).
- The technetium 99 m labeled RBC scan can show slow bleeding, (0.1-0.4 ml/min), whereas angiography needs higher rates of bleeding (>0.5 ml/ min) in order to be positive. With active bleeding, the bleeding site may be localized in 50-75% of patients, but the sensitivity rate falls below 50% with slower rates of bleeding.

- An angiography suggests angioectasia from a vascular tuft or slow filling of a vein. Therapeutic embolization may be performed with gelfoam or coils. Pipaverine may be infused at the time of angiography.
- For CTE (CT enterography), oral contract is given by mouth and by nasojejeunal tube for CT enterocyclis. The diagnostic yield of CTE in OGIB is 45% (Huprich JE, et al. *Radiology* 2008:562-71.), and may be useful to distinguish fibrostenotic from inflammatory Crohn's disease (Paulsen SR, et al. *Radiol Clin North Am* 2007:303-15.; Horsthuis K, et al. *Radiology* 2008:64-79.).
- Hormonal therapy use is controversial in persons with bleeding from angiodysplasia, but may be of use in persons with angiodysplastic bleeding and HHT (hereditary hemorrhagic telegangiectasia), van Willebrand disease, or renal failure.

Abbreviations: CE, capsule endoscopy; CTE, CT enterography; DBE, double balloon enteroscopy; HHT, hereditary hemorrhagic telegangiectasia; OGIB, obscure GI bleeding; SBE, single balloon enteroscopy

28. Give the EGD characteristics and pathological features for 8 types of benign gastric polyps.

Polyp type	Location	Size	EGD	Pathological features	Comments
➢ Fundic gland (75%)	Fundus and upper body	<1 cm	○ Smooth, glassy, transparent; usually multiple polyps are found	○ *Helicobacter pylori*-associated gastritis is rare	○ Associated with PPI use, may regress ○ Dysplasia found in patients with FAP ○ Fundic gland polyp: distorted glands and microcysts lined by parietal and chief cells; no or minimal inflammation

➢ Hyper-plastic (20%)	Random, adjacent to ulcers or stoma sites, or in the cardia if related to acid reflux	Generally <1 cm	○ Small polyps have a smooth dome; large polyps are lobulated, and erosions are common	○ Atrophic gastritis with intestinal metaplasia ○ *Helicobacter pylori*-associated gastritis (25%), dysplasia is rare (<3%) and found in polyps <2 cm	○ *Hyperplastic* elongated, cystic, and distorted foveolar epithelium, marked regeneration; stroma with inflammation, edema, and smooth muscle hyperplasia
➢ Adeno ma	*Incisura angularis*, found in the antrum than fundus	<2 cm	○ Velvety, lobular surface; exophytic, sessile or pedunculated; usually solitary (82%)	○ Atrophic gastritis with intestinal metaplasia ○ May be accompanied by coexistent carcinoma	○ *Adenoma* dysplastic intestinal- or gastric-type epithelium with variable architecture
➢ Inflam-matory fibroid	Submuco-sal, found near the pyloric sphincter	Median 1.5 cm; generally <3 cm	○ Single, firm, sessiole, well-circumscribed, ulceration is common	○ Pernicious anemia commonly found; atrophic gastritis ○ Genetic mutations are common	○ CD34+ spindled stromal cells, inflammatory cells, and thin-walled vessels in a myxoid stroma
➢ Peutz-Jeghers	Random	<1 cm	○ Pedunculated with a velvety or papillary surface	○ Normal ○ Risk of adenocarcinoma rare in gastric polyps	
➢ Juvenile	Found more in the body than in the antrum	Variable	○ More rounded than hyperplastic polyps; superficial erosions; multiple polyps are usually found	○ Normal ○ Polyps may exclusively involve stomach risk of adenocarcinoma but rare in gastric polyps	

Polyp type	Location	Size	EGD	Pathological features	Comments
➢ Polypoid lesion	Gastric location	Size	Endoscopic appearance	Pathological features	Comments
➢ Xan-thoma	Antrum, lesser curvature, prepyloric	<3 mm	○ Can be multiple in groups; sessile, pale-yellow nodule or plaque	○ Chronic gastritis ○ No association with hyperlipidemia	○ Xanthoma aggregates of lipid-laden macrophages in the lamina propria
➢ Pancreatic hetero-topias	Antrum, prepyloric	0.2-4.0 cm	○ Solitary; dome-shaped with central dimple; smooth surface	○ Normal ○ Very rare instances of associated pancreatitis, islet-cell tumours, adenocarcinoma	○ *Pancreatic heteropia* normal components of pancreatic parenchyma
➢ Gastro-intes-tinal stromal tumour	Random, submuco-sal	Variable (median 6 cm)	○ Well-circumscribed; overlying mucosa may be ulcerated	○ Normal ○ 25% are malignant; risk of aggressive behaviour depends on size and mitotic count	○ CD117+, CD34+ spindle cell or epitheliod cell tumour with variable pattern, mitoses, and stroma
➢ Carci-noid	Body and fundus	<2 cm, larger if sporadic	○ Hypergastri-nemic lesions: firm, yellow, broad-based and multiple. Sporadic lesions: large and single	○ Autoimmune atrophic gastritis with intestinal metaplasia parietal cell hyperplasia in ZES normal mucosa if lesion is sporadic ○ Associated with hypergastrinemia, autoimmune atrophic gastritis, ZES or MEN	○ *Carcinoid* nodular proliferation of neuroendocrine cells >500 µm in diameter

Abbreviations: EGD, esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; MEN, multiple endocrine neoplasia; ZES, Zollinger-Ellison syndrome

Adapted from: Carmack SW, et al. *Am J Gastroenterol* 2009;104(6): 524-532.; and Carmack SW, et al. *Nat Rev Gastroenterol Hepatol* 2009;6(6): 331-341.

Gastritis

29. Give 15 causes of histologically diagnosed gastritis.

- Drugs, chemicals, radiation
  - Medications
    - Asprin, NSAIDs, COXIBs
    - Bisphosphonates, K^+ tablets
  - Drugs, chemicals
    - Alcohol, bile, cocaine, chemotherapy, radiotherapy, red peppers, pickles

- Infection
  - Bacterial - H. pylori, Mycobacteria
  - Viral-CMV, HSV
  - Fungal
  - Parasitic

- Graft-versus-host disease (GVHD)

- Autoimmune gastritis (pernicious anemia)

- Ischemia
  - Atherosclerosis
  - Sepsis
  - Burns
  - Shock
  - Mechanical ventilation

- Associated with liver disease – GAVE, PHG

- Trauma/foreign body
  - Nasogastric or gastrostomy tubes
  - Bezoar
  - Prolapse/ sliding hiatal hernia/paraesophageal hernia
  - Cameron ulcer (ulcer in hiatus hernia)

- Infiltration/ tumour
  - Lymphocytic/ collagenous
  - Granulomatous
  - Eosinophilic
  - Tumour

- Miscellaneous
  - Gastritis cystica profunda
  - Ménétrier's disease (hyperplastic, hypersecretory gastropathy)

Abbreviations: CMV, cytomegalovirus; GAVE, gastric antral vascular ectasia; GVHD, graft-versus-host disease; HSV,herpes simplex virus; PHG, portal hypertensive gastropathy

Adapted from: Lee EL, and Feldman M. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1068.; and Printed with permission: Francis DL. *Mayo Clinic Gastroenterology and Hepatology Board Review*; 2008:67.

Gastric polyps and cancer

30. Give 8 risk factors associated with the development of gastric adenocarcinoma.

- Genetic--First degree relative with gastric cancer (hereditary diffuse gastric cancer; 2-3 fold increased risk with mutations in E-cadherin CDH1 gene)

- HNPCC >> FAP

- Polyps--adenomatous gastric polyps (HNPCC, FAP), Peutz-Jeghers syndrome (PJS), hamartomas, Menetrier's syndrome

- *Gastric atrophy--H.pylori* infection, pernicious anemia, chronic atrophic gastritis, subtotal surgical resection with vagotomy for benign gastric ulcer disease

- Diet-- salted, pickled or smoked foods, low intake of fruits and vegetables
- Life Style--Smoking (EtOH is not an independent risk factor)
- Esophageal --Barrett's esophagus (cancer of cardia)

Abbreviation: HNPCC, hereditary nonpolyposis colon cancer

Adapted from: Houghton JM and Wang TC. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006*:* pg 1149.

31. For premalignant lesions on biopsy, give the approximate annual risk of developing gastric cancer (GC).

Pathology	Annual risk	Recommended EGD/biopsy follow-up
➢ Atrophic gastritis (AG)	○ 0.1%	- None
➢ Intestinal metaplasia (IM)	○ 0.25%	- 2-3 years
➢ Mild to moderate dysplasia (MMD)	○ 0.6%	- 1 year
➢ Severe dysplasia (SD)	○ 6.0%	- Definitive therapy (EMR)

Abbreviation: EGD, esophagogastroduodenoscopy

Adapted from: De Vries AC, et al. *Gastroenterology* 2008;134:945-52.

Useful background: Macroscopic types of gastric cancer

Type	Japanese classification	Paris classification
0	Superficial, flat tumours with or without minimal elevation or depression	Superficial polypoid, flat/depressed, or excavated tumours
0I	Protruded 	Polypoid
0IIa	Superficial and elevated 	Non-polypoid and nonexcavated, slightly elevated
0IIb		

0IIc	Flat 	Non-polypoid and nonexcavated, completely flat
0III	Superficial and depressed 	Non-polypoid and nonexcavated, slightly depressed without ulcer
1	Excavated 	Nonpolypoid with a frank ulcer
2	Polypoid tumours that are sharply demarcated from the surrounding mucosa and are usually attached on a wide base	Polypoid carcinomas that are usually attached on a wide base
3	Ulcerated carcinomas that have sharply demarcated and raised margins	Ulcerated carcinomas that have sharply demarcated and raised margins
4	Ulcerated carcinomas that have no definite limits and infiltrate into the surrounding wall	Ulcerated, infiltrating carcinomas that have no definite limits
5	Diffusely infiltrating carcinomas in which ulceration is not usually a marked feature	Nonulcerated, diffusely infiltrating carcinomas
	Carcinomas that cannot be classified into any of the above types	Unclassifiable advanced carcinomas

According to Japanese classification of gastric carcinoma, for the combined superficial types, the type occupying the largest area should be described first, followed by the next type (e.g. IIc+III). Types 0 I and 0 IIa are distinguished from each other by lesion thickness: type 0 I lesions have thickness more than twice that of the normal mucosa and type 0 IIa lesions have a thickness up to twice that of the normal mucosa. Modified from data presented in the Japanese classification of gastric carcinoma and the Paris endoscopic classification of superficial neoplastic lesions.

Printed with permission: Yamamoto H. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(9): pg. 513.

What's new: Genetic abnormalities in gastric adenocarcinoma

	Gene	Approx Frequency (%)
➢ Abnormalities: Amplification/over-expression	COX-2	70
	HGH/SF	60
	VEGF	50
	C-met	45
	AIB-1	40 [363]
	B-catenin	25
	K-sam	20
	Ras	10-15 [60]
	C-erb B-2	5-7 [364]

Zollinger-Ellison syndrome (ZES)

32. Give the tumours found in patients with multiple endocrine neoplasia-type I (MEN-1), and their approximate frequency % is shown.

➢ Tumours	Approximate frequency (%)
○ Parathyroid	90 (78-97)
○ Pancreatic endocrine tumour	80 (81-82)
- Gastrinoma	54
- Insulinoma	21
- Glucagonoma	3
- VIPoma	1
○ Pituitary tumours	40 (21-65)
- Prolactin-secreting	30 (15-46)
- Growth-hormone secreting	16 (6-20)
- Cushing's syndrome	16
○ Adrenal cortical adenoma	30 (27-36)
○ Thyroid adenoma	20 (5-30)

33. Give the presenting features of ZES, and their approximate frequency.

➢ Presenting features of ZES
- ○ Abdominal pain (75%-100%)
- ○ Diarrhea (35%--73%) (isolated presentation in up to 35%)
- ○ Pain and diarrhea (55%-60%)
- ○ Heartburn (44%-64%)

- Duodenal and prepyloric ulcers (71%-91%)
- Multiple ulcers in unusual places
- Stomal ulcers
- PUD refractory to treatment
- Ulcer complications (bleeding, 1%-17%; perforation, 0%-5%, or obstruction, 0%-5%)
- Associated with MEN1 (22%-24%)

Abbreviations: MEN, multiple endocrine neoplasia; PUD, peptic ulcer disease; ZES, Zollinger-Ellison syndrome

Adapted from: Metz DC, and Jensen RT. *Gastroenterology* 2008;135: pg. 1469.

34. Give the investigation of the patient with fasting hypergastrinemia, performed after a detailed history and physical examination.

- Laboratory tests
  - Confirm fasting state for gastrin measurement
  - Calcium, PTH, TSH
  - Creatinine (exclude renal failure)
  - Chromogranin A)
  - Urinary metanephrins
  - Schillings test, serum B_{12}

- Provocative tests
  - Secretin infusion (increases gastrin paradoxically in ZES)
  - Ca^{+2} infusion (marked increase in serum gastrin)
  - Basal and pentagastrin stimulated acid secretion (↑↑ BAO), BAO/MAO>60% (ZES)
  - Food-stimulated acid secretin (G-cell hyperplasia/ hyperfunction)

- Endoscopy
  - EGD
    - Multiple ulcers in unusual sites
    - Biopsy antrum for G-cell number (to distinguish between G-cell hyperplasia [↑G-cell number] vs G-cell hyperfunction (normal G-cell number); H. pylori
    - Thick gastric folds
  - EUS for possible tumour localization

- Diagnostic imaging
  - Abdominal ultrasound
  - CT/ MRI, head (pituitary fossa, tumour in MEN I)
  - Ostreotide scan
  - MBIG scan

- CT scan of abdomen
- MRI of abdomen
- Parathyroid scan

Abbreviations: EUS, endoscopic ultrasound; ZES, Zollinger-Ellison syndrome

Gastroscopy findings in liver disease

35. Give 15 differential diagnoses of bleeding from the upper and from the lower GI tract in persons suffering from HIV/AIDS, excluding non-AIDS-related diagnoses.

Infection	Esophagus	Stomach	Small bowel	Colon
Candida	+			
Cytomegalovirus	+	+	+	+
Herpes simplex	+			
Idiopathic ulcer	+			+
Cryptosporidiosis		+	+	
Salmonella sp.			+	
Entamoeba histolytica				+
Campylbacter				+
Clostridium difficile				+
Shigella sp				+
Kaposi's sarcoma		+	+	+
Lymphoma		+	+	+

Adapted from: Wilcox, C. Mel. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 676.

36. Give the relative risk (RR) of 7 clinical factors associated with upper gastrointestinal clinical events in the person taking NSAIDs.

Clinical features	Relative Risk*
➢ Age >60 – 75 years	2.5
➢ History of upper gastrointestinal symptoms	2.5
➢ History of peptic ulcer	2.5
➢ Severe rheumatoid arthritis disability	2.5
➢ History of cardiovascular disease	2.5

➢ *Helicobacter pylori* positive	2.0
➢ History of gastrointestinal bleeding	5
o High dose NSAID	7
o Multiple NSAIDs	10
o Concomitant low dose ASA	10
o Concomitant anticoagulants	10
o Concomitant corticosteroids	1.5
o Concomitant selective serotonin reuptake inhibitors	2.0

Abbreviations: ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drug

*RR, relative risks associated with various risk factors. As these studies included differing patient populations and not all studies considered all risk factors, direct comparisons of the magnitudes of the risks (i.e. rows of the table) should be avoided.

Adapted from: Rostom et al. *Alim.Pharm.Therapeutics* 2009; 29:481-496.

"The man who follows the crowd will usually get no further than the crowd. The man who walks alone is likely to find himself in places no one has ever been"

Alan Ashley-Pitt

Abbreviations

ASA	Acetylsalicylic acid
BOM	Bacterial overgrowth syndrome
CE	Capsule endoscopy
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COXIBs	COX-2 inhibitors
CMV	Cytomegalovirus
CTE	CT enterography
CV	Cardiovascular risk
CVA	Cerebrovascular accident
DBE	Double balloon enteroscopy
DU	Duodenal ulcer
ECL	Enterochromaffin- like
EGD	Esophagogastroduodenoscopy
ET	Endoscopic hemostatic therapy
ET	Eradication therapy
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
GAVE	Gastric antral vascular ectasia
GCa	Gastric cancer
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GU	Gastric ulcer
GVHD	Graft-versus-host-disease
H2RA	H2 receptor antagonist
HHT	Hereditary hemorrhagic telegangiectasia
HNPCC	Hereditary nonpolyposis colon cancer
HSV	Herpes simplex virus
ITP	Idiopathic thrombocytopenic purpura
MEN	Multiple endocrine neoplasia
NERD	Non-erosive reflux disease
NNT	Number needed to treat
NSAIDs	Non-steroidal anti-inflammatory drugs
NVUGIB	Non-variceal upper GI bleeding
OGIB	Obscure GI bleeding
PE	Push enteroscopy
PHG	Portal hypertensive gastropathy
PONV	Post-operative nausea & vomitting
PPIs	Proton pump inhibitors

PR	Pulse rate
PUD	Peptic ulcer disease
RR	Relative risk
SBE	Single balloon enteroscopy
SBP	Systolic blood pressure
SHR	Endoscopic stigamata of recent hemorrhage.
SIDS	Sudden infant death syndrome
TB	Tuberculosis
TIPS	Transjugular intrahepatic portosystemic shunt
UGIB	Upper GI bleeding
ZES	Zollinger Ellison syndrome

Suggested reading list and references

1. Dysmotility

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8. Useful websites

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American Gastroenterological Association : http://www.gastro.org/

American Gastroenterological Association Position Statements: http://journals.elsevierhealth.com/periodicals/ygast/content /agai

American Society for Gastrointestinal Endoscopy: http://www.asge.org/

American Society for Parenteral and Enteral Nutrition: http://www.clinnutr.org/

ASGE Award-winning website: http://www.gastrointestinalatlas.com/English/english.html

ASGE Guidelines for Biliary and Pancreatic Endoscopy: http://www.asge.org/nspages/practice/patientcare/biliary.cfm

ASGE Guidelines for Endoscopic Training: http://www.asge.org/nspages/education/training/trainingguidelines.cfm

ASGE Guidelines for Lower Gastrointestinal Endoscopy: http://www.asge.org/nspages/practice/patientcare/lgeindex.cfm

ASGE Guidelines for Preparation for Endoscopy: http://www.asge.org/nspages/practice/patientcare/preparation.cfm

ASGE Guidelines for Upper Gastrointestinal Endoscopy:
http://www.asge.org/nspages/practice/management/ugeindex.cfm

Atlas of Gastrointestinal Endoscopy: http://www.endoatlas.com/

Canadian Association of Gastroenterology: http://www.cag-acg.org/

Clinical Trials: www.clinicaltrials.gov

Gastrolab: http://www.gastrolab.net/welcome.htm
International Foundation for Functional Gastrointestinal Disorders:
http://www.iffgd.org/about/about.htm

National Digestive Diseases Information Clearinghouse:
http://digestive.niddk.nih.gov/index.htm
Rome criteria: http://www.romecriteria.org/

Society for Surgery of the Alimentary Tract: http://www.ssat.com/

Society of American Gastrointestinal Endoscopic Surgeons:
http://www.sages.org/

The International Society for Diseases of the Esophagus:
http://www.isde.net/

SMALL BOWEL

TABLE of CONTENTS

Small bowel bacterial overgrowth syndrome (SBBO)

1. Give the usual bacterial presence (10^x/ml) of different sites along the gastrointestinal tract.

- Stomach – 10^3/mL
- Jejunum – 10^4/mL
- Ileum – 10^{6-8}/mL (gram-positive)
- Colon – 10^{10-12}/mL (gram-negative, anaerobic, facultative aerobic)

*note that > 10^5/mL in the proximal small intestine is considered to be abnormal, and is compatible with the diagnosis of SBBO.

2. Secretory IgA is the predominant immunoglobulin found in intestinal secretions.

- List two functions of Secretory IgA.
  - Binds bacteria and dietary antigens (thus limiting absorption/immune response)
  - Phagocytosis

- What immunologic characteristic makes this immunoglobulin ideal for its function in the GI tract?
  - Resistant to digestion
  - Secreted
  - Does not activate complement cascade
  - Does not participate in antibody-dependant cytotoxicity.

3. Give 8 components of the GI mucosal barrier, and for each give their function to protect against enteric infection.

Components	Function
➢ Epithelium: glycocalyx, villi	○ Innate immune response ○ Antigen presentation ○ Block penetration of ingested antigens (tight junctions)
➢ Defensins	○ Antimicrobial peptides
➢ Trefoil factors	○ Protection from a variety of deleterious agents (bacterial toxins, chemicals and drugs); provide restitution after mucosal injury

➢ Mucus/mucins	○ Block penetration of ingested antigens
➢ Proteases: pepsins, pancreatic enzymes	○ Breakdown of ingested antigens
➢ Gastric acid (pH)	○ Breakdown of ingested antigens
➢ Bile acids	○ Breakdown of ingested antigens
➢ Intestinal peristalsis	○ Block penetration of ingested antigens

Components	Function
➢ Indigenous microflora (microbiotica)	○ Competitive inhibition ○ *Direct:* competition for essential nutrients and bacterial receptor sites; creation of restrictive physiological environments; secretion of antibiotic-like substances ○ *Indirect:* chemical modification of bile salts and dietary fats, induction of protective Ig responses, stimulation of peristalsis
➢ Secretory-IgA (s-IgA)	○ Binds bacteria and dietary antigens ○ Phagocytosis
➢ GALT-associated IgA, IgG[a], IgM[a] (serum)	○ Clear antigens penetrating gastrointestinal barrier/systemic immunity ○ Assist in opsonization and phagocytosis of antigens
➢ Lymphoid follicles in lamina propria	○ Clear antigens penetrating gastrointestinal barrier
➢ Intraepithelial lymphocytes (IEL)	○ Innate and acquired immune responses
➢ Mesenteric lymph nodes	○ Phagocytosis and antigen presentation

Printed with permission: Acheson DWK. *Best Practice & Research Clinical Gastroenterology* 2004;18(2):pp 389.

4. Give 5 tests to diagnose small intestinal bacterial overgrowth (SIBO), and give the principal of their use.

- Jejunal aspiration ($>10^5$/mL)
- Jejunal luminal bile acids (deconjugated and dehydroxylated)
- H2 – breath test with lactulose
- C^{13} glycocholic acid, D-xylose
- Schilling test
- Trial of appropriate antibiotic

Abbreviation: SIBO, small intestinal bacterial overgrowth syndrome

5. Describe the enterohepatic circulation of bile acid and describe the defects which occur with SIBO ileal resection, and hepatic cholestasis disease.

6. Give 15 conditions that cause SIBO.

- Reduced gastric acid
  - Atrophic gastritis, pernicious anemia
  - Medications (H2 receptor antagonists, proton-pump inhibitors)
  - Gastric surgery

- Reduced pancreatic and biliary secretion
  - Pancreatic insufficiency
  - Cholestasis

- Structural abnormalities (neoresevoirs, fistulae)
  - Small bowel diverticulae (not colonic diverticulae)
  - Adhesions
  - Surgical anastomosis and diversions
  - Fistulae (colo-enteric, gastrocolonic)
  - Strictures, webs
  - Absent or incompetent ileocecal valve

- Dysmotility syndromes
  - Diabetes
  - Drugs
  - Acute enteric infection
  - Scleroderma
  - Intestinal pseudo-obstruction syndromes
  - IBS-D association, IBS-C association

- Decreased host defence (decreased immune function)
  - Undernutrition
  - Immune deficiencies particularly absence of secretory immunoglobulin A (IgA)

Abbreviation: SIBO, small intestinal bacterial overgrowth syndrome

7. Outline the treatment of the patient with SIBO.

- Correct any predisposing condition, if possible

- Nutrition (correction of SIBO complications)
  - Lactose-free, low-residue diet
  - Increase calories/ protein if malnourished
  - Micronutrient supplementation -vitamin B12, fat soluble vitamins (A, D, E and K), calcium, magnesium
- Drugs
  - Antibiotics (gram-neg anaerobes), prebiotics, probiotics
  - Prokinetics
  - Interval or maintenance therapy, where appropriate

Abbreviation: SIBO, small intestinal bacterial overgrowth syndrome

Gluten sensitive enteropathy (celiac disease, CD)

8. Give three possible factors which may be useful in the prevention of celiac disease (CD).

- Breast-feeding
  - CD prevalence is significantly reduced (~50%) when infants are breast fed at the time of gluten introduction
  - The risk of developing CD decreases by 63% in children breast fed for > 2 months
  - The mechanism of protection is not yet elucidated.
  - Long-term prospective studies are required to assess this protection from breast feeding is permanent.

- Timing of gluten introduction
  - Age at first gluten exposure appears to affect CD onset.
  - Continuing breast-feeding with slow gluten introduction could be beneficial.
  - Avoiding early (<4 months) and late (>7 months) introduction of gluten is recommended.

- Viral infections
  - High frequency of rotavirus infection may be correlated with increased risk of CD in predisposed individuals.
  - A peptide recognised by immunoglobulin of CD patient's shares homology with a rotavirus protein (VP-7).
  - A seasonal pattern of CD is observed, with an increased risk of CD in summer- born children.

- Microflora and probiotics
  - CD patients have modified intestinal microflora
    - Probiotics may have a minor effect to balance microbiota composition and modulate the immune response

Printed with permission: Macmillan Publishers Ltd: Pinier M. et al. *Am J Gastroenterol* 2010; 105:2551–2561, Box 1, page 2554.

9. Give 10 clinical conditions which are associated with false positive or false negative, serologic testing for CD.

- False negative
  - True false negative
  - IgA deficiency
  - Children < 2 years
  - Recent gluten free diet
  - TPN (NPS, with no gluten taken by mouth)
  - Current or recent use of steroids, immunosuppressives, anti-TNFs
  - Previous hematopoietic stem cell transplantation

- False positive
  - Congestive heart failure (New York class 3 or 4)
  - Autoimmune diseases (may be associated with CD which is in a latent phase)
  - Liver diseases
  - Inflammatory bowel disease
  - Silent (occult), or potential (latent) celiac disease

Adapted from: Green PHR, Rostami K, Marsh MN. *Best Practice & Research Clinical Gastroenterology* 2005; 19(3): pg 391.

10. Give the clinical presentations of celiac disease, and the extent of the associated enteropathy.

Symptoms	Symptoms	Celiac* HLA	Anti-tTG	Enteropathy
➢ Classical (symptomatic)	+	+	+	Yes
○ GI symptoms	+/-	+	+	Yes
○ Extra-intestinal symptoms	-	+	+	Yes
➢ Silent (occult) ○ None, or minimal symptoms	-	+	+	Normal, or minimal change
➢ Potential (latent)*				

Abbreviation: tTG, tissue transglutaminase

*On first biopsy, small mucosa may be normal or with minimal changes, but on rebiopsy some time later, the fully expressed enteropathy may be seen

Adapted from: Crowe SE. *2007 AGA Institute Postgraduate Course*: pg. 24; and Printed with permission: Fasano A and Catassi C. *Best Practice & Research Clinical Gastroenterology* 2005;19(3): pg. 468.

11. Give 20 intestinal and extraintestinal conditions associated with celiac disease.

- Intestinal
  - Esophagus – squamous cell Ca, adenocarcinoma, Eosinophilic esophagitis
  - Stomach – lymphocytic gastritis; pernicious anemia, atrophic gastritis
  - Small bowel
    - Celiac disease (classical, silent, potential)
    - Ulcerative ileojejunitis
    - Collagenous sprue
    - Diffuse small intestinal lymphoma
    - Early aberrant T-cell lymphoma (EATL)
    - Refractory sprue, types 1 and 2
    - Unclassified sprue (sprue-like intestinal disease)

- Colon – microscopic colitis, IBS
- Liver – AIH, AIC, PBC, PSC, ideopathic transaminitis, fatty liver
- Pancreas – 2° insufficiency, diabetes, autoimmune pancreatitis
- Nutritional abnormalities - short stature, osteopenic bone disease, iron and vitamin deficiencies, unexplained weight loss

- Extra-intestinal
  - Neuropsychiatric and CNS
    - Chronic fatigue syndrome
    - Irritability, depression
    - Peripheral neuropathy
    - Epilepsy (with intracranial calcifications)
    - Gluten ataxia syndrome (gait and limb ataxia), paresthesia
    - Night blindness
    - Autism (controversial)
  - Teeth
    - Dental enamel defects
  - Lung
    - Fibrosing alveolitis
    - Bird fancier's lung
  - Hematopoietic
    - Iron deficiency anemia, hemorrhage, ↓ intake
    - Thromobocytosis
    - Howell-Jolly bodies
    - IgA deficiency
  - Musculoskeletal
    - Atrophy, tetany, weakness, myalgias, osteoporosis
    - Autoimmune connective tissue disorders: Sjorgren's syndrome, RA, lupus
    - Osteoporosis
  - Endocrine - secondary hyperparathyroidism, insulin-dependent DM, (T, DM), autoimmune thyroid disease, autoimmune adrenal disease
  - Integument
    - Follicular hyperkeratosis, dermatitis
    - Petechiae, ecchymoses
    - Dermatitis herpetiformis
    - Edema
    - Acrodermatitis enterohepatica
  - Obstetrical - infertility, obstetrical complications (miscarriage), amenorrhea
  - Renal – IgA nephropathy
  - Miscellaneous - Downs syndrome, Turners syndrome
  - Pediatrics - delayed puberty, slow growth

Abbreviations: AIC, autoimmune cholangitis; AIH, autoimmune hepatitis; CD, celiac disease; DM, diabetes mellitus; IBS, irritable bowel syndrome; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis.

Adapted from: Green PHR, Rostami K, Marsh MN. *Best Practice & Research Clinical Gastroenterology* 2005;19(3): pg 39.; and Crowe SE. *2007 AGA Institute Postgraduate Course*: pg. 25.

12. Give 20 clinical indications for serological testing for CD.

- Positive family history

- Autoimmune endocrine disorders
  - Insulin-dependent diabetes mellitus
  - Autoimmune thyroid disease
  - Autoimmune adrenal disease

- Autoimmune connective tissue disorders
  - Sjogren's syndrome
  - Rheumatoid arthritis
  - Systemic lupus erythematosis

- Hepatobiliary conditions
  - Primary sclerosing cholangitis
  - Primary biliary cirrhosis
  - Autoimmune cholangitis
  - Elevated transaminases

- Other gastrointestinal disorders
  - Lymphocytic gastritis
  - Microscopic colitis

- Miscellaneous conditions
  - IgA deficiency, IgA nephropathy
  - Down syndrome, Turner's syndrome

Printed with permission: Crowe SE. *2007 AGA Institute Postgraduate Course*: pg. 25.

13. Give the acceptable foods, and the foods to avoid for CD patients.

- Acceptable foods
  - Corn, rice, buckwheat products, potatoes
  - Wine, and distilled alcoholic beverages

- Fruit and vegetables
- Meat
- Nuts
- Dairy products (unless lactose-intolerant)

- Foods to avoid (also see b, below)
  - Wheat, rye, barley
  - Triticale (wheat-rye hybrid)
  - Millet and sorghum
  - Oat products (if there is cross-contamination)
  - Hydrolyzed vegetable protein
  - Beer, lager, stout, malt

b) Give 10 common sources of hidden gluten.

- Foods and beverages
  - Bouillon/soups
  - Candy
  - Communion wafers
  - Drink mixes/herbal tea
  - Gravy/sauces
  - Imitation meat/seafood
  - Salad dressings/marinades
  - Nutritional supplements
  - Self-basting turkeys
  - Soy sauce
  - Fat replacers
  - Contamination
  - Malt alcohol/vinegar

- Medications
  - Medications (pills and capsules)

- Contamination
  - Play-Doh®
  - Lipstick/lip balms
  - Airborne flour
  - Glues and pastes
  - Chewing gum

Abbreviation: CD, celiac disease

Adapted from: Farrell RJ, and Kelly CP. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg 2295; and 2010, pg. 1813.

14. Give conditions other than celiac disease where there may be an increased density of small intestinal intraepithelial lymphocytes (IELs), on the small bowel mucosal biopsy.

No villous shortening, ↑ IELs	Villous shortening, ↑ IELs
➢ Celiac disease	➢ Celiac disease
➢ Tropical sprue	➢ Tropical sprue
➢ Autoimmune diseases/ conditions	➢ Collagenous sprue
➢ Non-steroidal anti-inflammatory drugs	➢ Protein intolerance (cow's milk or soya milk)
➢ Crohn's colitis	➢ Post-infectious diarrhea
➢ Microscopic colitis	
➢ Bacterial overgrowth syndrome	

Abbreviations: CD, celiac disease; IELs, intestinal intraepithelial lymphocytes

Printed with permission: Collins P, Wahab PJ, Murray JA. *Best Practice & Research Clinical Gastroenterology* 2005;19(3): pg 344.; and Daum S, Cellier C, Mulder CJJM. *Best Practice & Research Clinical Gastroenterology* 2005;19(3):pg. 415.

15. Give 10 causes other than refractory CD for persisting villous atrophy in the presence of normal numbers of IELs (villous shortening, N-IELs).

- ➢ Tuberculosis (including atypical)
- ➢ HIV/AIDS
- ➢ Common variable immunodeficiency syndrome
- ➢ Whipple's disease
- ➢ Radiation enteritis
- ➢ Immunoproliferative small intestinal disease
- ➢ Crohn's disease
- ➢ Eosinophilic gastroenteritis
- ➢ Autoimmune enteropathy
- ➢ TPN (total parental nutrition)

Printed with permission: Daum S, Cellier C, Mulder CJJM. *Best Practice & Research Clinical Gastroenterology* 2005; 19(3): pg. 415.

16. Give 4 factors which support the diagnosis of CD in patients with an increased density of intraepithelial lymphocytes (IELs) but no villous shortening, on the small bowel mucosal biopsy.

- Family history of celiac disease
  - At least 15% of first-degree relatives are affected (1/100 → 15/100)
- Concomitant autoimmune conditions
  - Risk of CD approximately 5-fold increased (1/100 → 5/20)
- HLA DQ2 or DQ8 positive
  - Sensitivity 0.84, specificity 0.91
- Increased density of villous tip IELs
  - Sensitivity 0.84, specificity 0.95
- Increased density of $\gamma\delta$ + IELs
  - High sensitivity, low specificity, high negative predictive value
- Gluten dependence/ response
  - Should be ascertained by gluten challenge or gluten-free diet

Printed with permission: Collins P, Wahab PJ, Murray JA. *Best Practice & Research Clinical Gastroenterology* 2005; 19(3): pg 347.

17. An abnormal small bowel biopsy stains positive on PAS. What is the differential diagnosis?

- α_1 antitrypsin deficiency
- Whipples disease (diastase resistant)
- MAC (Mycobacterium-avium complex infection)
- Lymphany ectasia

18. Outline the diagnosis of celiac disease in a person with a GFD.

19. Give 15 differential diagnoses of a “sprue-like” small bowel biopsy in a patient suspected of having CD.

- Celiac disease and its variants
- Infection
  - post viral gastroenteritis
  - giardiasis
  - small intestinal bacterial overgrowth (stasis syndrome)

- HIV (immunodeficiency syndromes)
- MAC (Mycobacterium-avium complex infection)
- cryptococcus, giardia lamblia, strongyloides
- topical sprue (infections agent suspected)
- Whipple's disease
- Crohn's disease
- Amyloidosis
- Mastocytosis
- Histoplasmosis
- Eosinophilic enteritis
- xanthelasma
- Waldenstroms macroglobulinemia

- Infiltration
  - Benign
  - Malignant immunoproliferative small intestinal disease (IPSID, ie alpha chain disease), lymphoma

- Immune
  - graft-versus-host disease
  - hypogammaglobulinemia

- Food
  - food protein hypersensitivity (rye, barley, egg, fish, rice, poultry, cow's milk, soy, other proteins)
  - oats-induced villous atrophy
  - folate, cobalamin, zinc deficiency
  - protein-calorie malnutrition

- Drugs, radiation
  - NSAIDs, colchicines, neomycin, chemotherapy
  - radiation

- Miscellaneous
  - Zollinger-Ellison syndrome
  - mesenteric lymph node cavitation syndrome
  - α-β-Lipoproteinemia
  - lymphangiectasia
  - microvillus inclusion disease (children)
  - Waldenstroms macroglobulinemia

Abbreviations: CD, celiac disease; IPSID, immunoproliferative small intestinal disease

Adapted from: Freeman HJ. *Can J Gastroenterol* 2008;22(3): pg 277.

20. For the following conditions which may be associated with a “sprue-like” lesion, indicate the histological features which may be used to distinguish the condition from celiac disease.

Cause of malabsorption	Histological features
➢ Collagenous sprue	- Collagenous band below atrophic epithelium
➢ Mycobacterium-avium complex infection (MAC)	- Acid-fast bacilli, foam cells, PAS positive macrophages
➢ Amyloidosis	- Congo red-stained deposits with apple-green birefringence in polarized light
➢ Crohn’s disease	- Epitheloid granulomas and characteristic focal inflammation
➢ Eosinophilic gastroenteritis	- Eosinophilic infiltration
➢ Lymphangiectasia	- Ectatic lymph vessels, fat in lymphatics
➢ Lymphoma	- Clonal expansion of lymphocytes
➢ Mastocytosis	- Diffuse infiltration with mast cells
➢ Infection	- Organism seen on histologi cal examination (eg. giardia lamblia, strongyloides, TB, HIV)
➢ Whipples	- Acid-fast bacilli, foam cells, PAS positive, diastase resistant staining in macrophages
➢ Abeta-lipoproteinemia	- Large lipid droplets

Abbreviation: MAC, mycobacterium-avium complex infection

Adapted from*:* Freeman HJ. *Can J Gastroenterol* 2008; 22(3): pg. 277.

21. Give 3 conditions causing malabsorption that are usually excluded by a normal small bowel biopsy.

- ➢ Sprue (actually, not always – patchy, treated, immunosuppression, potential – anti tTG positive, but small bowel biopsy histologicaly normal)
- ➢ Hypogammaglobulinemia
- ➢ α-β-Lipoproteinemia
- ➢ Whipples (except in very rare circumstances with only CNS Whipples)

22. A patient with previously well-controlled biopsy-proven CD while on a gluten-free diet (GFD), develops recurrent diarrhea, still while on a GFD. List 15 causes or conditions specific to CD that could explain this clinical scenario.

- Diet
  - Non-adherence to GFD
  - IUnintentional gluten intake
  - Zinc deficiency, folate/B12 deficiency
  - Primary lactose intolerance (lactase deficiency)
  - Severe malnutrition

- Intestinal complications of sprue
  - Refractory celiac disease*
  - Collagenous colitis
  - Small bowel adenocarcinomans
  - Early abberant T cell lymphoma (EATL)
  - Lymphoma of small bowel
  - Ulcerative jejunoileitis
  - Lactose/fructose malabsorption

- Other GI complications of CD
  - Primary pancreatic deficiency
  - Loss of stimulus for pancreatic enzyme secretion; unmasked pancreatic insufficiency
  - Cholestatic liver disease
  - Small bacterial overgrowth (SIBO)
  - Diarrhea – predominant irritable bowel syndrome (IBS-D)
  - Microscopic colitis

- Non-intestinal complications
  - Diabetes
  - Thyroid disease (hypo- [SIBO] or hyperthyroidism[rapid transit])
  - Adrenal insufficiency

- A second disease or wrong initial diagnosis (including unclassified sprue**)

**refractory celiac disease requires evidence of an initial response to a gluten-free diet. **with unclassified sprue (or sprue-like intestinal disease), no initial response to a gluten-free diet was documented.*

Abbreviation: CD, celiac disease; EATL, early abberant T cell lymphoma; GFD, gluten-free diet; IBS-D, predominant irritable bowel syndrome

Adapted from: Freeman HJ. *Can J Gastroenterol* 2008; 22(3): pg. 277.

Useful background: Celiac disease (CD)

- The HLA close II molecules DQ2 and DQ8 are required for but are not sufficient by themselves for the development of CD: 50% of Americans are positive for one of these molecules, but only 1% develop CD. However negative HLA DQ2 or DQ8 rule out CD as a cause of the enteropathy (high negative predictive value).
- IgA tTG (tissue transglutamase) serology is >95% sensitive for CD, especially when there is a high titre
- Anti-gliadin antibodies have a relatively high false negative rate, and have been replaced by IgG DPG (deamidated gliadin peptide) assays that have a sensitivity comparable to anti-tTG
- The endoscopic features of CD (scalloping of the muscosal folds, less prominent folds, fissules, and a nodular/ mosaic pattern) are only 59% sensitive but 92% specific for CD
- Prevalence of conditions associated with CD, which may result in an apparent complete response to gluten-free diet; IBS (18%); lactose intolerance (9%); microscopic colitis (7%); or bacterial overgrowth syndrome (6%)

Abbreviations: CD, celiac disease ; DPG, deamidated gliadin peptide; NRCD, non-responsive CD; tTG, transglutamase

Useful background: Non-responsive CD (NRCD is the continuation of the symptoms and signs of CD despite at least 6 months of adherence to a gluten free diet [GFD])

- Definitions
  - Refractory celiac disease (RCD) is symptomatic severe small intestinal villous atrophy micking celiac disease but not responding primarily or secondary to at least 6 months of a strict gluten-free diet and not accounted for by other causes of villous atrophy or overt intestinal lymphoma
- 10% of CD patients develop 1˚ or 2˚ NRCD, usually due to non-adherance to the receommended GFD (36%)
- After instituting a gluten-free diet, 90% of CD patients lose their symptoms and signs, and anti-tTG normalizes, even with low level or episodic intake of gluten
- 10% of those with NRCD, and 1% of those with CD, develop refractory celiac disease (RCD)
- Type I RCD: absence of abnormal intra-epithelial T cell lymphocytes (IELs); 5 year survival rate, 90%

- Type II RCD: clonal T cell expansion, with presence of abnormal intra-epithelial IELs which lack the usual T cell markers (CD4, CD8, IL-2R). Associated with ulcerative ileo jejunitis, necrotizing mesenteric lymphodenopathy and T-cell enteropathy; 5 year survival rate <50%, despite nutritional support, steroids (including budesonide), immunosuppressants, anti-TNF or stem cell transplantation

Abbreviations: GFD, gluten free diet; IELs, intra-epithelial T cell lymphocytes; NRCD, non-responsive CD; RCD, refractory celiac disease

What's new: Enteroscopy

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

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 dignosed celiac youths (30% high and 70% low titer of APA), and may also be associated with low level of IGF-1 (Devecchio et al, AJG 2010; 105: 691-6).
- In Europe, the standard mortality rate of persons with symptomatic celiac disease is increased and varies from 1.26 in Finland to 3.6 in Sicily (Biagi & Corazza, 2010).

23. Give 4 benefits for using 5-ASA (Mesalazine) for IBS.

- Clinical
  - Observational data suggests clinical benefits of mesalazine
  - Randomized, placebo controlled pilot study in IBS patients from Italy showed clinical benefit

- Compared to placebo
  - Mesalazine ↓ mast cell infiltration
  - ↓ mast cell histamine release
  - ↓ abdominal pain intensity scores
  - ↑ general well being

Crohn's disease (see Colon chapter, ulcerative colitis)

Useful background: Clinical manifestations in CD

- Diarrhea 90%
- Pain 90%
- Bleeding 50%
- Weight Loss 85%
- Fever 60%
- Malaise 40%

- Natural History of Crohn's Disease in North America
  - At any given point in time following the first year of the disease
    - Activity
      - High 10%
      - Low 25%
    - Remission
      - 65%

- Natural History of Corticosteroid Therapy for IBD (approximate percentages)

	30 Day	1 Year
Failure of steroid withdrawal (relapse at dose reduction or within 30 days after end of treatment)	25	-
Prolonged Response	~32	49
GCS Dependence	28	22
Surgery	38	29
Induction of clinical remission (4-16 wk)	75%	

What's new: Predictors of future severe Crohn's disease

- Clinical: the presence of perianal disease at the time of diagnosis, the need to use steroids, and age under 40 years all suggested a future severe course of CD (Beaneugerie et al, 2006)

- Mutation in NOD_2/CARD 15 (ileal stricture, future need for surgical resection)

- HLA-DRB1* 0103 allele
- Increasing number of abnormal serological markers (such as pANCA, ASCA, AMCA, ALCA, anti-omp-c, anti-CB_{1R1}, anti-I_2

24. A 25 year old female has had ileal Crohn's disease for 3 years and has been taking no medications for the past 2 years. She smokes 1 pack of cigarettes per day. She presents to your office with 1 month of abdominal pain and diarrhea.You get a small bowel follow through and it reveals a short segment of ileal disease. You prescribe entocort 9 mg/day. You see her again in 1 month and she feels completely well and you begin tapering her entocort. Give 5 options for further therapy at this time.

- Taper entocort to 6 mg/day, then to 3 mg then stop before 12 months
- Taper entocort completely off and leave her on no medications
- Taper entocort off and use Pentasa® 4 gm/day
- Start azathioprine or 6-mercaptopurine as maintenance agents
- Start methotrexate as a maintenance agent (advise contraception)
- Start anti-TNF, with or without immune suppression (controversial)
- Stop smoking (equivalent to immunosuppression)
- Discuss contraception, pregnancy planning
- Antibiotics, probiotics
- Surgery
- Symptom control
- Education, including Crohn's and Colitis Foundation (CCFC)

25. Give 6 treatments for confirmed duodenal Crohn's disease.

- "Who is the patient?"
  - Age, other disease sites; NSAIDs and smoking
  - Nutrition
  - Education re induction, maintenence
- PPIs
- H_2-blockers
- Sulcrafate
- Oral small bowel released 5-ASA (Pentasa®; not well supported by data)
- Oral intake of 5-ASA enema

- Systemic corticosteroids
- Immune suppression
- Anti-TNF
- Endoscopic dilation of associated stricture
- Surgery
- Treat associated nutrient deficiency, fluid and electrolyte imbalance

26. Compare and contrast the medicines available in Canada for the treatment of Crohn's disease.

27. Give the anatomical location of the release in the GI tract of 5 of the orally administered 5-ASA products.

- Mesalsal®/Salofalk®: terminal ileum (pH > 6)
- Asacol®: terminal ileum; cecum (pH > 7)
- Pentasa®: release begins in jejunum
- Dipentum® and sulfasalazine: colon (requires colonic bacteria to cleave the diazo bond in the drug)
- Balsalazide® (available only in the US): colon
- MMX – colon
- Generic 5-ASA (modeled after Asacol): terminal ileum, but may be released at pH 5.5 (in proximal GI tract which is the potential problem with it)
- Sulfasalazine

Note: Meta-analyses of 5-ASA in active CD: statistically superior to placebo, but 18 CDAI unit difference is not clinically meaningful. (Hanauer SB, Stromberg U. *Clin Gastroenterol Hepatol* 2004;2:379-88)

28. Give 5 immunosuppressive agents commonly used in gastroenterology or hepatology (for example for Crohn'sdisease, ulcerative colitis, autoimmune hepatitis, liver), and for each give their mode of action, common toxic effects, and recommended monitoring.

Agent	Mode of action	Monitoring	Toxic effects
○ Cyclosporine (CyA), tacrolimus	Calcineurin inhibitor: which suppresses IL-2-dependent T cell proliferation	Blood level of CyA, cholesterol, magnesium, Creatinine, BP, BS	Renal, neurologic, hyperlipidemic, hypertension, hirsutism
○ Sirolimus (Rapamycin)	Inhibition of MTOR, which disrupts IL-2 induced intracellular signalling in lymphocytes	Blood level	Neutropenia, thrombocytopenia, hyperlipidemia
○ Prednisone	Alter gene transcritption of steroid response elements (SRE); cytokine inhibitor (IL-1, IL-2, IL-6, TNF, and IFN gamma)	BP, BS, annual eye exam, DEXA scan	(see previous question)
○ Azathioprine	Inhibition of T and B cell proliferation by interfering with purine synthesis (↓DNA/RNA)	White blood cell count, liver enzymes	Bone marrow suppression, hepatotoxicity
Agent	Mode of action	Monitoring	Toxic effects
○ Mycophenolate mofetil (Cellsept)	Inhibition of T and B cell proliferation by interfering with purine synthesis	White blood cell count	Diarrhea, bone marrow suppression
○ Methotrexate	Folate antimetabolite (↓DNA)	Liver biopsy after 1,500 mg (only 2 years maintenance therapy)	Hepatic fibrosis Bone marrow suppression

Agent	Mode of action	Monitoring	Toxic effects
○ OKT3	Blocking of T cell CD3 receptor, depletion of effector T cells and T regs, preventing stimulation by antigen	$CD3^+$ count	Cytokine release syndrome, pulmonary edema, increased risk of infections
○ IL-2 receptor blocker	Competitive inhibition of IL-2 receptor on activated lymphocytes	None	Hypersensitivity reactions with basiliximab

Abbreviations: BP, blood pressure; BS, blood sugar; DEXA, DEXA scan for bone mineral density; IFN, interferon; IL, interleukin; LEs, liver enzymes; MTOR, mammalian target of rapamyacin; TNF, tumour necrosis factor.

Adapted from: Martin P, and Rosen HR. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2049.

Useful background:

- In persons with reduced TDMT activity, the risk of myelotoxicity when using the standard rather than a reduced dose of AZA/6-MP is increased 4-fold (Gisbert JP, Nino P, Rodrigo L et al. *Am J Gastroenterol* 2006;101:2769-76.)

- In support of measuring AZA metabolites (such as 6-TG), weight-based dosing of AZA/6-MP still underestimates the dose 50% of the time (Morales A, Salguti S, Miao CL, et al. *Inflamm Bowel Dis* 2007;13:380-5

29. Give 15 gastrointestinal complications of immunosuppression with azathioprine or methotrexate (<u>not</u> including glucocorticosteroids).

- Infection
  - CMV, HBV, HSV, EBV (PTLD)
  - Candida albicans, tropicalis
  - Yersinia enterocolitica
  - *C. difficile*
  - Microsposidia

- Strongyloides stercoralis
  - H. pylori

- TB

- Mucosal injury
  - Diarrhea
  - Ulceration (AZA or MMF-induced slowing of intestinal cell turnover); may also result of cocomitant intake of other medications, e.g. NSAIDs, steroids,

- Colon: diverticular disease → diverticulitis

- Perforations (upper or lower GI tract)

- Liver
  - Hepatitis
  - Methotrexate-associated fibrosis

- Biliary tract
  - Thickened gallbladder wall
  - Sludge
  - Stones
  - Dilated ducts
  - Hydrops

- Pancreatitis
  - Acute (AZA, CyA; may also be from complications of CMV, hypercalcemia, cholelithiasis)

- GI malignancy
  - Lymphomas (including Malt lymphoma, hepatosplenic lymphoma)
  - Kaposi sarcoma
  - Colorectal cancer
  - Post-transplant lymphoproliferative disorder (PTLD) (EBV)

Abbreviations: AZA, azathioprine; CyA, cyclosporin A; EBV, Ebstein Barr virus; PTLD, post-transplant lymphoproliferative disorder.

Adapted from: Helderman J, and Goral S. *J Am Soc Nephrol* 2002; 13: pg. 277-287.

What's new: Mutations in Crohn's disease

- Intestinal macrophages secrete cytokines and chemokines in response to intestinal bacteria. This process of post-translational modification may be impaired in some persons with CD, as well as there being a reduced recruitment of neutrophils to the tissue for destruction and removal of the organisms in the autophage lysosomes.
- This may possibly be associated with NOD_2 receptor mutations which reduce the acute inflammatory response to enteric organisms, and thereby exacerbating and amplifying the chronic response (Fava Dannese, Nat Rev. 61; GI/Hep 2010; 7: 126-128).
    - The NOD2 mutations are associated with reduced transcription of IL-10, leading to an enhancement of the granulomatous reaction, which in course is a feature of CD.
    - This defect in the transport of vesicles in the macrophage may be linked to mutations in IREM and ATE 16L1, autophagy related genes which may be abnormal in CD.
    - NOD_2 mutations are also associated with higher loads of bacteria colonization of the crypts, and thereby higher bacterial loads.

30. Give 10 risk factors for the development of osteopenia/osteoporosis in inflammatory bowel disease (IBD).

- Demographics
    - Low bone mineral intensity peak in patients with pediatric onset of IBD
    - Increasing age
    - Female gender
    - Immobilization
    - Smoking
    - Family history of osteoporosis
- Nutrition
    - Malnutrition
    - Malabsorption of vitamin D, calcium and Vitamin K
    - Low body mass index
- Drugs
    - Use of corticosteroids
- Inflammation
    - Chronic inflammatory state

- Type of IBD (CD vs. UC, small intestinal involvement)

- Metabolic
  - Previous fragility fracture
  - Hypogonadism

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

Adapted from: Ghishan FR & Kiela PR. *AJP-Gastrointest Liver Physiol* • 2011;300: G191-G201 Table 1, page G192.

Useful background: IBD drug interactions

- 5-ASAs-increase INR, 6-TG and methotrexate (MTX); decreases digitalis levels
- Allopurinal-increases 6-TG
- ACE inhibitors-increase 6-MP-associated risk of anemia, leucopenia
- Methotrexate (MTX) levels are reduced by tetracycline, and increased by penicillin 5-ASAs and NSAIDs; folic acid deficiency worsens MTX toxicity
- Metronidazole increases the effect of statins, sildenafil, calcium channel blockers, and ↑ INR
- Anti-TNF therapy causes 6.4 fold increase in mortality rate in persons with pre-existing pulmonary disease
- Steroids cause osteoporosis by changing the optimal ratio of Rankl relative to OPG/ OCIF; this effect of steroids is greatest in the first 6 months of their use

Abbreviations: MTX, methotrexate; OCIF, osteoclastogenesis inhibitory factor; OPG, osteoprotegerin

31. Give the mechanism of action of 4 treatments for calcium oxalate kidney stones.

- Fluid
  - Adequate intake of water by mouth

- Reduce oxalate absorption
  - Reduce intake of oxalate (cranberry juice, chocolate, etc)
  - Oral calcium supplements to bind oxalates in the gut lumen
  - Colectomy, if indicated for other reasons
- Increase renal excretion

- Correct metabolic acidosis

- Bind luminal bile acids binding agents

32. Give the relative contraindications to anti-TNF therapy.

- Pre=existing severe immunosuppression
- Allergy to anti-TNF
- Intestinal stenosis
- Fistulizing disease with abscess
- Fistulae to bladder
- Untreated active infection (TB, HBV, HCV)
- Multiple sclerosis (MS), optic neuritis
- Congestive cardiac failure (New York grade III, IV)
- Lymphoma
- Acute liver failure
- Cancer in the past

Abbreviations: HBV, hepatitis B viral infection; HCV, hepatitis C viral infection; MS, multiple sclerosis; TB, tuberculosis.

33. Give a definition for primary and secondary infliximab failures (IFX) in patients with inflammatory bowel disease (IBD); outline their proposed mechanisms.

- Primary – No response to induction therapy, possibly due to high pre-treatment TNF-α levels, inadequate dose of IFX (low trough IFX concentration), or TNF-α independent inflammatory pathways
- Secondary (Loss of symptomatic response after initial successful induction therapy)
  - Mechanisms
    - Antibody to IFX (especially with on-demand IFX infusions)
    - Increased clearance (rapid metabolism) of IFX
    - Inadequate dose of IFX (low trough IFX concentration) non-TNFα dependent inflammatory pathways
    - Development of IBD-related complications e.g. stricture, abscess

- Non-IBD related symptoms e.g IBS, SIBO, bile acid wastage, c. difficile infection

34. Classify the medications used in patients with IBD. For 5 of these, give the FDA category for pregnancy, and recommendations for breast feeding.

Drug	FDA category	Recommendations for breast feeding
Balsalazide	B	Yes
Mesalamine	B	Yes
Sulfasalazine	B	Yes
Olsalazine	C	LHD
Rifaximin	C	LHD
Amoxicillin/clavulinic acid	B	Probably compatible
Metronidazole	B	**No**
Ciprofloxacin	C	LHD
Corticosteroids	C	Yes
Cyclosporin	C	**No**
Tacrolimus	C	LHD
Thalidomide	X	**No**
AZA/6-MP	D	LHD
Methotrexate	X	**No**
Adalimumab	B	LHD
Infliximab	B	LHD
Loperamide	B	Yes
Diphenoxylate	C	**No**

During **pregnancy, No** thalidomide, or methotrexate

During **breastfeeding, No** metronidazole, cyclosporine, thalidomide, methotrexate or dephenoxylate

Abbreviation: LHD, limited human data

Printed with permission: Kane SV. *2008 ACG Annual Postgraduate course book*: pg. 27.

Useful background: IBD and pregnancy

- Colectomy and ileoanal anastamosis increases infertility 3-fold (Waljee A, al. *Gut* 2006:1575-80.)

- The incidence of abnormal PAP smears is increased in women with IBD (Kane S, et al. *Am J Gastroenterol* 2008:631-6).

- The transmission of IBD from parent to child is low
  - One parent with IBD; transmission risk is 7%
  - Both parents have IBD, 37% risk of transmission (Yang H, et al. *Gut* 1993:517-24.)

- While earlier studies have suggested poor outcome of pregnancy in IBD patients with active disease (Miller J. *J R Soc Med* 1986:221-5.), this has not been confirmed more recently (Mahadevan U, et al. *Gastroenterology* 2007:1106-12)
- In a community based study from northern California, the activity of IBD at conception usually carries through the pregnancy as well as post-partum period (Young 09).
- Although the only contraindications to vaginal delivery in Crohn's disease is active perianal disease, the likelihood of having a Caesarean section is increased 1.5 times above that of non-IBD women (Cornish J, et al. *Gut* 2007:830-7).
- Having an extensive episiotomy at delivery may contribute to the 18% risk of a woman developing perianal disease after childbirth (Iinyckyj A, et al. *Am J Gastroenterol* 1999:3274-8).
- Breast feeding may or may not be a risk factor for the development of Crohn's disease in the infant (Klement E, et al. *Am J Clin Nutr* 2000:1342-52.; Jantchou P, Turck D. *Am J Clin Nutr* 2005:485-6)
- Flexible sigmoidoscopy during pregnancy does not increase the risk of premature labour (Cappell M, Colon V, Sidhim O. *Dig Dis Sci* 1996;41:2353-61.)
- Only 29-44% of IBD patients breast feed their infant (compared to an American standard of 60%), and 43% of those mothers who breast feed their babies flared, possibly because 74% of those who flared had stopped maintenenace medications (Kane S, Lemieus N. *Am J Gastroenterol* 2005:102-5).
- There have been no reports of hepatosplenic T-cell lymphoma in IBD patients on monotherapy with anti-TNF therapy, or a combination of infliximab or adalimumab with methotrexate

- If anti-TNF therapy is added to AZA or MTX because of failure to respond to these immunosuppressants, then it would appear to be reasonable to stop immunosuppressant once the anti-TNF therapy has been started, especially since withdrawal of aziothioprine and continuation of the inflixumab (IFX) alone has no effect on the continued response to IFX, as compared to patients on both IFX and AZA (Van Assche G, et al. *Gastroenterology* 2008:1861-8.) This issue remains controversial.
- For patients with secondary loss of response to IFX, switching to ADA gives "recapture" remission rates of 21% at 4 weeks and 40% at one year (Panaccione R, et al., DDW 2008, #920); switching from IFX to certolizumab pegol at 6 weeks gives a "recapture" response of 60% and remission of 40% (Reinisch W, et al. DDW 2008: #494)

Abbreviations: IBD, inflammatory bowel disease; IFX, inflixumab

35. In the patient with Crohn's disease (CD) who presents with sub-acute, small bowel obstruction (SBO), give the causes, diagnostic procedures, and the managements.

- Causes
  - Active CD
  - Stricture
  - Fruit pits
  - Gallstone ileus
  - Enterolith

- Diagnostic procedures
  - Plain abdominal films
  - Conventional CT
  - CT enterography
  - MRI enterography
  - Small bowel (gastrograffin) x-ray
  - Abdominal ultrasound
  - Doppler ultrasound
  - FDG-PGT (18F- flurodeoxyglucose positron emission tomography [PET])
  - Capsule endoscopy (penalty, because of suspected stricture)

- Management
  - Treatment of inflammatory CD (avoid anti-TNF)
  - Through-the-scope balloon dilation
  - Adjuvent steroid injection into inflammatory narrowing
  - Expandable metal stents
  - Stricturoplasty
  - Open or laparoscopic surgical resection

Abbreviations: PET, positron emission tomography

36. Outline the features used to make a distinction between ulcerative colitis (UC) and Crohn's disease (CD).

- Clinical Features

Feature	Ulcerative colitis	Crohn's Disease
Malaise, fever	+	+++
Abdominal pain	+	+++
Diarrhea	+	+++
Rectal bleeding	+++	+
Weight loss	+	++
Signs of malnutrition	+	++
Perianal disease	+	++
Abdominal mass	o	++
Risk of colorectal cancer	+++	++
Lymphoma	-	+

- Intestinal Complications

Stricture	Rare (exclude CRC)	Common
Fistulas	Very Rare	Common
Sepsis	Uncommon	Common
Toxic Megacolon	May occur	Uncommon
Perforation	Uncommon	Uncommon
Hemorrhage	Common	Uncommon
Rate of malignancy	Increased	Increased

- Radiological Features

Mucosal Ulceration	Superficial	Superficial
Fissures	Never	Characteristic
Strictures or fistulas	Rare	Common
Ileal involvement	Never ("backwash ileitis")	Narrowed/common
Distribution	Continuous, Symmetric	Discontinuous, Asymmetric

- Endoscopic Features

Aphthous and linear ulcers	Rare	Common
Cobblestone appearance	Never	Common
Pseudopolyps	Common	May Occur
Distribution	Continuous	Discontinuous (skip lesions)
Rectal Involvement	Characteristic	Occasionally occurs

	UC	CD
➢ Histopathology of ulcerative colitis (UC) and Crohn disease (CD)		
○ Crypt	-Distorted -Abscesses	-Normal or focally distorted abcesses
○ Inflammation type	-Acute and chronic	-Normal or chronic
	-Continuous between and within biopsies	-Patchy between and within biopsies
○ Depth	-Superficial	-Transmural
○ Granuloma	-No	-Yes

Useful background: Reasons for failure of AZA/6-MP (possible Reasons to measure metabolites of AZA/6-MP)

- 70% - ↓ 6-TG: too low a dose
- 25% - ↓ 6-TG + ↑ 6 MMP: predominant metabolism by TPMT
- 5% - ↓ 6-TG + ↓6-MMP; poor adherence

➢ Step Away from Step-Up Therapy in Crohn's Disease: Suggestions
- Less use of 5-ASA, glucocorticosteroids
- More use of immunosuppressants, biologies

37. Give 3 different schemes for the classification of gastrointestinal fistulae, based on anatomy, output volume, and etiology.

Scheme	Classification
➢ Anatomical location	Internal, external Low, high Simple, complex
➢ Output volume	Pancreatic Low (<200 ml/day) High (≥200 ml/day) Intestinal Low (<500 ml/day) High (≥500 ml/day)
➢ Etiological	Underlying disease

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38. In the patient with Crohn's disease and perianal fistulae (PF), give a classification, 6 diagnostic tests, and medical and/or surgical treatments.

- Classification – low, high; simple, complex; anatomical location

- Diagnostic tests
  - Digital rectal examination (DRE)
  - EUA (examination under general anaesthesia)
  - Pelvic ultrasound
  - Pelvic CT
  - Pelvic MRI
  - Sigmoidoscopy/colonoscopy
  - EUS
  - Barium studies (fistulogram, sinogram)
  - Cystoscopy

- Treatments
  - Medical
    - Drugs used to treat Crohn's disease
    - CO_2 laser ablation
    - Hyperbaric O_2
    - Injection of silver microspheres with antibiotic
  - Surgery
    - Seton placement
    - Glue
    - Fistulotomy
    - Endorectal advancement flap
    - Fecal diversion
    - Proctocolectomy

Abbreviations: DRE, digital rectal examination; EUA, examination under general anaesthesia; EUS, endoscopic ultrasound; PF, perianal fistulae

39. Give the patient-related and fistula-related characteristics associated with spontaneous closure of gastrointesinal fistulae.

- Patient characteristics
  - Low output (mL/day) <500
  - Young (<40 years)
  - Well nourished
  - Cause of fistulae
  - Anastamosis characteristics – anastamotic breakdown

- Fistula characteristics
  - Lateral fistula

- No incomplete disruption
- No abscess near leakage
- No distal obstruction
- Fistula tract >2 cm
- Non-epithelialised fistula tract
- Enteral defect <1 cm
- Fistula site: Oropharyngeal, esophageal, duodenal stump, pancreatobiliary, jejunal
- Late post-operative leakage
- Adjacent bowel healthy
- No severe systemic diseases

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40. Give 15 causes of malnutrition in persons with IBD.

- Reduced oral intake
  - Disease-induced (e.g., postprandial abdominal pain and diarrhea, sitophobia, anorexia (↑TNF), nausea and vomiting)
  - Iatrogenic (e.g., restrictive diets, "fad" diets)

- Malabsorption
  - Reduced absorptive surface (e.g., shortened small intestine due to prior resection, diseased segments)
  - Bacterial overgrowth (e.g., associated with strictures and bypassed loops, stasis)
  - Bile salt deficiency after ileal resection (e.g., impaired micelle formation and steatorrhea)
  - Lactase deficiency (e.g., associated with small bowel disease)
  - Drug-induced malabsorption
    - Cholestyramine (e.g., bile acids; fat; fat-soluble vitamins, including vitamin D and K)
    - Sulfasalazine (e.g., folic deficiency associated with reduced absorption and increased requirement related to hemolysis)
    - Steroids (e.g.. calcium absorption, and patient mobilization)
    - Methotrexate (e.g. nausea/vomiting)

- Increased nutrient loss
  - Protein-losing enteropathy
  - Diarrhea fistula losses of electrolytes, minerals and trace elements zinc, iron, calcium, magnesium, selenium
  - Gastrointestinal blood loss (e.g., iron loss)

- Increased requirements
  - Chronic inflammatory disease, fever, abscess, superimposed infection, surgery

Printed with permission: Griffiths AM. *Best Practice & Research Clinical Gastroenterology* 2004;18(3): pg.519.

Useful background: Obscure GI bleeding: Where in the small bowel are the lesions?

- AVM's
  - Jejunum-36%
  - Ileum-34%
  - Jejunum and ileum-30%

- Polyps
  - Jejunum-70% (36% proximal jejunum)
  - Ileum-30% (16% terminal ileum)

- Endoscopic therapy for AVMs (AV malformations, angiodysplasia, angioectasia, angioma, venous ectasia): less than 10% of persons with angioectasia ever bleed, and 50% will never rebleed.
- Cessation rates from AVM using push enteroscopy (PE), 57-85% (*AGA technical review, 2007*)
- One year after double-balloon enteroscopy for AVM, 57% required retransfusion, or are bleeding-free (Gerson LB. *Gastrointest Endosc Clin N Am*. 2009 Jul;19(3):481-96); other studies have shown rebleeding rates ranging from 20-63% (Viazis N, et al. *Gastrointest Endosc*. 2009 Apr;69(4):850-6.; Kafes AJ, et al. *Gastrointest Endosc*. 2007 Aug;66(2):304-9.; de Leusse A, et al. *Gastroenterology* 2007 Mar;132(3):855-6.).

Printed with permission: Feagins LA, and Kane SV. *The American Journal of Gastroenterology* 2009;104:770.

Miscellaneous

41. Give a classification of drugs used in gastroenterology which are associated with diarrhea.

- Esophagus/stomach
  - Magnesium-containing antacids, PPIs, H2RAs
  - Misoprostol

- Small bowel
  - Prokinetics
  - Antiabsorptives
  - 5-ASA, immunosuppressants

- Colon
  - Laxatives osmotic
  - Magnesium citrate
  - Antibiotics
  - Cholinergics
- Liver
  - Lactulose (PSE)
  - Herbs

- Heart
  - Beta blockers

- Chemotherapy

Useful background: Give the physiological pathways that stimulate net NaCl/water secretion and absorption. For each pathway, give 2 examples of signalling molecules that modify these physiological pathways

- Agents that stimulate net secretion
  - Increase cAMP
    - Vasoactive intestinal polypeptide
    - Adenosine
    - Prostaglandins
    - Histamine
    - Bradykinin

  - Increase cGMP
    - Nitric oxide
    - Guanylin
    - Uroguanylin

  - Increase Ca_i, and/or active protein kinase C
    - Acetylcholine
    - Serotonin
    - Substance P
    - Histamine
    - Bradykinin
    - ATP
    - Adenosine

    - Neurotensin
  - Other pathways
    - Interferon-γ
    - TNF-α
    - Interleukin-1 (IL-1)
    - Interleukin-6 (IL-6)
    - Epidemal growth factor (EGF)

- Agents that stimulate net absorption
  - Decreases cAMP
    - Norepinephrine
    - Epinephrine
    - Dopamine
    - Enkephalins
    - Neuropeptide Y
    - Somatostatin

  - Coupled transport
    - Glucose, galactose, fructose
    - Amino acids, dipeptides/tripeptides
    - Short-chain fatty acids

  - Other pathways
    - Aldosterone
    - Glucocorticosteroids
    - Somatostatin
    - GLP-2

Adapted from: Freeman HJ, and Thomson ABR. *First Principles of Gastroenterology* 2005. pg. 190.

42. Give 4 symptoms or signs that would confirm your suspicion of dehydration from diarrhea.

- Dry mucous membranes (eyes and mouth, etc)
- Thirst
- Sunken eyes
- Tachypnea
- Tachycardia, decreased jugular venous pressure, decreased skin turgor, decreased urination, decreased weight, irritability/lethargy, low blood pressure
- Postural hypotension.

43. Give 10 causes of prolonged diarrheal illness after travel ("prolonged traveller's diarrhea").

- Infection
  - Persistent bacterial infection
  - Missed second infection
  - Aeromonas
  - Escherichia coli (enteroinvasive)
  - Persistent protozoal infection
  - Giardia
  - Entamoeba histolytica
  - Cryptosporidium
  - Antibiotic-associated diarrhea (AAD), Cl. difficile infection
  - Onset of chronic (presumably viral) enteritis/colitis

- Diet/Drugs
  - Change in diet
  - Excess alcohol intake
  - Drugs

- Other Diseases
  - Unmasked lastase deficiency, GSE, IBD, lymphocytic/collagenous colitis
  - Tropical sprue
  - Post-infectious diarrhea-predominant IBS (D-IBS)

Abbreviations: AAD, antibiotic-associated diarrhea; D-IBS, diarrhea-predominant IBS; GSE, gluten sensitive enteropathy; IBD, inflammatory bowel disease.

44. Give 10 causes of protein-losing enteropathies.

- Increased lymphatic pressure
  - Congestive heart failure
  - Constrictive pericarditis
  - Primary, secondary lymphangiectasia

- Ulcerating intestinal disease
  - IBD (Crohn's disease, ulcerative colitis)
  - Colon cancer

- "Leaky gut"
  - Celiac disease
  - Small intestinal bacterial overgrowth
  - Whipple's disease
  - Vasculitides

45. Give the dietary therapy during the 3 intestinal adaptive phases which occur after extensive small intestinal resection in the patient with Crohn's disease who develops short bowel syndrome.

- Acute phase
  - Starts immediately after intestinal resection
  - Lasts less than 4 weeks
  - Infusion therapy using Ringer's solution, glucose and amino acid solutions, substitution of water soluble vitamins and trace elements
  - Start parenteral nutrition

- Adaptation phase
  - Lasts from less than 4 weeks to 2 years
  - Maximal stimulation of intestinal adaptation is achieved by gradually increasing intestinal nutrient exposure
  - Oral/enteral nutrition with gradually increasing nutrient loads: isosmolar salt–glucose-solutions, tea, carbohydrate solutions, medium chain triglycerides, amino acids
  - Predominantly long chain triglycerides, free fatty acids, small amounts of medium chain triglycerides in patients with preserved colon; saccharose, maltose, glutamine, pectin; addition of vitamins and minerals as needed, in particular calcium

- Maintenance phase
  - Permanent dietetic treatment must be individualized
  - Frequent small meals, high fat diet, small amounts of medium chain triglycerides in patients with preserved colon; fluids can usually be taken with meals, addition of vitamins and minerals as needed, in particular calcium
  - Avoidance of nutrients rich in oxalate if distal small intestinal resection
  - Effective therapy of acute exacerbations and optimal maintenance therapy of Crohn's disease are of pivotal importance.

Printed with permission: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2004; 18(5): pg. 978-982.

46.
a) Give 7 causes of small bowel obstruction, and 7 causes of large bowel obstruction.

- Adhesions, hernias, strictures from IBD, gallstone ileus, mesenteric artery syndrome, small bowel tumours, metastatic cancer, cystic fibrosis, volvulus, Crohn's disease

- Colon cancer, volvulus, diverticulitis, ileus, narcotics ileus, mesenteric ischemia, IBD with stricture, Ogilvie's syndrome, adhesions, intussusception, endometriosis

b) Identify three potential complications of bowel obstruction

- Perforation, septicemia, hypovolemia

47. Give 4 common causes of infertility in men with inflammatory bowel disease.

- Medications; sulfasalazine, 5-ASAs, methotrexate (see question #41)
- Active inflammatory bowel disease
- Poor nutritional status
- Tobacco use
- Alcohol use
- Postsurgical complications

Printed with permission: Feagins LA, and Kane SV. *The American Journal of Gastroenterology* 2009;104(3):773.

48. Give the recommended dosing for adalimumab or certolizumab pegol, in patients with Crohn's disease.

- Adalimumab
  - 160 mg subcutaneously (SC) on day 1 of week 0, followed by 80 mg SC on day 1 of week 2.
  - Patients who respond to this two week induction regimen should continue on a maintenance regimen of 40 mg SC every other week.
  - Patients who have suboptimal response to 40 mg SC every other week may increase frequency of dosing to 40 mg SC weekly, or increase their dose to 80 mg every other week.
    - Subsequent response in 4-week nonresponders has not been established.
  - Episodic dosing has not been evaluated, and may increase Immunogenicity

- Certolizumab pegol
  - Recommended dosing is 400 mg SC at weeks 0, 2, and 4 and then end 4.

- No evidence of benefit for additional treatment at week 6 for nonresponders
- Patients who respond to the induction regimen should continue on maintenance dosing with 400 mg SC every 4 weeks.
  - Additional dosing schedules have not been evaluated in IBD but anticipate similar recommendations to other anti-TNFs regarding higher dose/reduced interval treatment. In patients with rheumatoid arthritis, changing the maintenance dosing schedule to 200 mg SC every 2 weeks increases drug exposure by approximately 50%

49. In any patient, and not necessarily one with Crohn's disease, give 10 major causes of small or large intestinal ileus.

- Infection
  - Intra-abdominal or systemic sepsis
- Inflammation
  - Appendicitis, diverticulitis, perforated duodenal mation
  - Lower lobe pneumonia
- Ischemia
  - Mesenteric arterial embolus or thrombosis, mesenteric venous thrombosis, chronic mesenteric ischemia
- Metabolic
  - Hypokalemia, hyponatremia, hypomagnesemia, hypermagnesemia, hypocalcemia, hypercalcemia
- Trauma
  - Laparotomy, laparoscopy, lower rib fractures
  - Lumbar compression fracture
- Drugs
  - Narcotics, phenothiazines, diltiazem, anticholinergic agents, clozapine
- Electrolytes

Adapted from*:* Turnage, Richard H., Heldmann, Maureen.,and Cole, Philip. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2671.

50. Give a classification of benign and malignant small intestinal tumours.

- Epithelium
  - Adenoma
  - Adenocarcinoma

- Vascular
  - Angiosarcoma

- Neural
  - Neurofibroma
  - Neurofibrosarcoma
  - Neruilemmoma
    Spinal cells (Interstitial cells of Cajal)

- Muscle
  - Leiomyoma
  - Leiomyosarcoma

- Fat
  - Lipoma
  - Liposarcoma

- WBC
  - Lymphoma
    Low-grade B cell lymphoma
    Immunoproliferative small intestinal
    Enteropathy-associated T-cell lymphoma
    (EATL)

- Carcinoid
- Lymphatic-lymphangioma
- Fibrous
  - Fibroma
  - Fibrosarcoma

51. Give the meaning of 7 of the following terms for adults with Crohn's disease.

Term	Definition
○ Active disease	- CDAI >150
○ Remission	- Change in CDAI $\geq$ -100, CDA1$\leq$150
○ Relapse	- CDAI > 150 & ↑ CDAI by 70

○ Early relapse		- Relapse < 3 months after achieving remission on previous therapy
○ Pattern of relapse		- Infrequent ≤ 1 relapse/year - Frequent ≥ 2/year
○ GCS refractory disease*		- Active disease despite full dose GCS for 4 weeks
○ GCS dependent disease*		- Unable to reduce GCS below the equivalent of prednisone of 10 mg/day (budesonide 3 mg/d) with 3 months of starting GCS, without recurrent active disease - Relapse within 3 months of stopping GCS (early relapse)
○ Morphological recurrence†	0	No lesions
	1	<5 aphthous ulcers
	2	>5 aphthous ulcers with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolonic anastomotic lining (< 1 cm)
	3	Diffuse aphthous ileitis with diffusely inflamed mucosa
	4	Diffuse ileal inflammation with larger ulcers, nodules or narrowing

Term	Definition
○ Extent of:	- Localized: < 30 cm in extent - Extensive: >100 cm in total extent
○ Colitis unclassified	- (do not use the term “indeterminate colitis” which is used for operative specimens) A change in diagnosis from Crohn’s colitis to UC during the first year; occurs in 10-15% of cases.
○ Risk factors for recurrence	- Smoking, prior appendectomy, family history of IBD, perhaps the use of OCA, NSAIDs, antibiotics, pregnancy, ± stress

* *assumes exclusion of disease-specific complications.*
† *hyperemia and edema alone are not signs of recurrence*

Abbreviations: CDAI, Crohn’s disease activity index; GCS: glucoscorticosteroids; NSAIDs, non-steroidal anti-inflammatory drug; OCA, oral contraceptive agent; UC, ulcerative colitis

52. Give 7 macroscopic features suggesting the diagnosis of Crohn's disease.

- Colonoscopy
  - Confluent deep linear ulcers, aphthoid ulcers
  - Deep fissures
  - Fistulas
  - Cobblestoning
  - Skip lesions (segmental disease)
  - Strictures
  - Rectum typically spared

- Pathology
  - Thickening of the intestinal wall
  - Fat wrapping of mesentery

53. Give 5 blood, stool, or urine tests in Crohn's disease which suggest the possibility of a higher risk of symptomatic relapse.

- Blood
  - CRP
    - ↑ CRP (> 20 mg/L), ↑ ESR (> 15), (8X ↑ risk of relapse if both markers positive: negative predictive value 97%)
    - ↑↑↑ CRP – suspect abscess
    - CRP may be used to guide therapy and follow-up
  - ↑ α_2 globulin, α glycoprotein, ↑ TNF

- Stool markers (calprotectin, lactoferrin, TNF – related to extent and degree of ulcerated intestinal surface, with high predictive value for colonic inflammation, and for upcoming clinical relapse

- ↑Urine lactulose/mannitol excretion ratio (intestinal permeability test)

Useful background: Response and secondary failure after anti TNF-α therapy

- Approximately 1/3 of primary responders lose response over course of 6-12 months
  - Change in behavior of disease
  - Development of antibodies to therapy
  - Loss of response to anti-TNF mechanism of action

➢ Opportunistic infections in IBD

	Odds Ratio
Any medication (5-ASA, AZA/6MP, Steroids, MTX, Infliximab)	3.50
5-ASA	0.98
Corticosteroids	3.4
AZA/6MP	3.1
MTX	4.0
Infliximab	4.4
One medication	2.7
Two medications	9.4

Adapted from: Toruner M, et al. Presented at DDW 2006; andvan Asche et al. *Gastroenterology* 2007; 132:A-103.

54. Give the factors affecting adherence to 5-ASAs in patients with ulcerative colitis.

➢ Risk factors that are difficult to modify
  - Age
  - Gender
  - Patient agreeableness
  - Education level
  - Recent disease course
  - Immunomodulator use (if required for remission)
  - Previous adverse events attributed to medication

➢ Potentially modifiable risk factors
  - Cost of co pay and other barriers to refilling medications
  - Treatable depression
  - Physician- patient relationship
  - Dosing regimen

Printed with permission: Higgins PD, Rubin DT, Kaulback K, et al. Aliment Pharmacol Ther. Systematic Review: Adherence to 5- ASA, flares and costs in UC. *Journal Compilation* 2009;29:255.

55. Give 6 host mechanisms present in a lactating infant which help her/him to protect against acute infectious diarrhea. Include substances present in the mother's milk which help to protect against acute infectious diarrhea.

- Gastric acidity
- Mucins
- Normal microbiotica
- Motility
- Secretory IgA
- Toll-like receptors
- Defensins
- Systemic immune responses
- Milk - IgA antibodies, lactoferrin, lysozyme, lactoperoxidase, peptides inhibiting bacterial adherence

Printed with permission: Navaneethan, U. and Giannella, R.D. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 15: pg. 637-647.

56. Give 5 carbohydrate-containing foods that may be absorbed incompletely in the healthy human small intestine, and provide the name of the substrate responsible for colonic gas production.

Food carbohydrate	Malabsorbed
Dairy products (milk, ice cream, cottage cheese, yogurt)	-Lactose
Soft drinks, honey	-Fructose
Legumes (baked beans, soy beans)	-Stachyose, raffinose
Dietetic candies and chewing gum	-Mannitol, sorbitol, xylitol
Complex carbohydrates (wheat, corn, retrograded starch	-Resistant and
potatoes)	
Grains, fruits, vegetables	-Fibre (hemicellulose,
pectin, gums) mucilage	

Adapted from: Oghe, Hiroki and Levitt, Michael D. Intestinal gas. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006: pg. 187-198.

57. Give a classification of major types of therapies or approaches used to treat persons with excessive abdominal bloating or flatus.

- Diet
  - Eat small, non-fatty meals slowly (reduce aerophagia)
  - Reduce poorly digested carbohydrates (beans, legumes etc)
  - Avoid carbohydrate beverages
  - Take liquids at end rather than during a meal
  - Avoid chewing gum or chewing tobacco
  - Treat underlying conditions e.g. celiac disease, IBS, bacterial overgrowth, heightened emotional awareness
  - Reduce surface tension
    - Simethicone
    - Activated charcoal
    - Bismuth subsalicylate

- Stomach
  - Treat gastroparesis

- Small bowel
  - Lactase: for lactose intolerance
  - α-galactosidase: effective for legume-rich meals
  - pancreatic enzymes: uncertain efficacy for gas and bloating of any cause
  - Modify gut flora
    - Antibiotics
    - Probiotics
    - Prebiotics

- Colon
  - Treat associated constipation
  - Visceral hypersensitivity (↑ perception): TCAP, SSRIs, SNRIs

Adapted from: Farthing, Michael J.G. Tropical *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006*:* pg 2308.

58. Give 6 accepted indications for the use of capsule endoscopy (CE).

- Occult gastrointestinal bleeding
- Suspected Crohn's disease (unless stricture may be present)
- Suspected small bowel tumour
- Surveillance of inherited polyposis syndromes
- Evaluation of drug induced small bowel injury
- Partially responsive celiac disease

Adapted from: Eliakim, R. *Curr Opin Gastroenterol* 2008(2): g. 161.

59. Give 20 differential diagnoses of small bowel and colonic Crohn's disease.

Small Bowel

- Backwash ileitis in ulcerative colitis
- Iatrogenic (drugs)
  - Ischemic (oral contraceptives, ergotamine, amphetamines, phenylephrine, cocaine)
  - NSAID-related ulcer or stricture
- Gynecological disorders
  - Ectopic pregnancy
  - Endometriosis
  - Ovarian cyst or tumour
  - Ovarian torsion
  - Pelvic inflammatory disease
  - Tubo-ovarian abscess
- Ileitis associated with spondyloarthropathy
- Infection
  - *Actinomycosis israelii*
  - *Anisakis simplex*
  - Cryptococcosis
  - Cytomegalovirus
  - *Histoplasma capsulatum*
  - *Mycobacterium avium* complex
  - *Mycobacterium tuberculosis*
  - Neutropenic enterocolitis
  - *Salmonella*
  - *Yersinia enterocolitica*
  - *Yersinia pseudotuberculosis*
- Infiltrative disorders
  - Amyloidosis
  - Eosinophilic gastroenteritis
- Other inflammatory disorders
  - Appendiceal abscess
  - Appendicitis
  - Cecal diverticulitis

Colon

Acute self-limited colitis

Indeterminate colitis
Ulcerative colitis
Behçet's disease
Microscopic colitis
Collagenous colitis
Lymphocytic colitis

Diversion colitis
Pouchitis
Diverticular disease associated segmental colitis
Graft-vs.-host disease
Solitary rectal ulcer syndrome

- Infection
  - Viral
    - Cytomegalovirus (CMV)
    - Herpes (HSV)
  - Bacterial
    - Clostridium difficile
    - Salmonella species
    - Shigella species
    - Yersinia enterocolitica
    - Campylobacter jejuni
    - Vibrio perahaemolyticus
    - Aeromonas hydrophila
    - Neisseria gonorrhoeae
    - Listeria monocytogenes
    - Chlamydia trachomatis
    - Syphilis
    - Staphylococcus aureus
    - Escherichia coli (0157:H7)
  - Protozoan
    - Amebiasis (ENT amoeba histolytica)
    - Balantidiasis
    - Schistosomiasis

- Neoplasms
  - Fungal
    - Histoplasmosis
    - Candidiasis

Small bowel

- Lymphoid nodular hyperplasia
  - Carcinoid tumour
  - Cecal or ileal adenocarcinoma
  - Lymphoma
  - Lymphosarcoma
  - Metastatic cancer
- Torsion of the appendiceal epiploica
- Vascular disorders
  - Behçet's syndrome
- Ischemia (radiation, drugs); acute enteritis, chronic enteritis, stricture; chronic mesenteric ischemia); focal segmental ischemia
- Henoch-Schönlein purpura
- Vasculitis (polyarteritis nodosa, Churg-Strauss syndrome, systemic lupus erythematosus, Takayasu's arteritis, Wegener's granulomatosis, lymphomatoid granulomatosis, giant cell Arteritis, rheumatoid vasculitis, Thromboangiitis obliterans)

Colon

- Iatrogenic (drugs)
  - Enemas
  - Laxatives
  - OCA
  - Ergotamine
  - Amphetamines
  - Phenylephrine
  - Cocaine
  - Nonsteroidal anti-inflammatory drugs (NASIDs)
  - Penicillamine
  - Gold
  - Methyldopa
- Ischemia (radiation, drugs)
- Infiltration
  - Amyloidosis
  - Eosinophilic colitis
  - Chronic granulomatous disease
  - Sarcoidosis
  - Neutropenic colitis
- Neoplasms
- Lymphoid nodular hyperplasia
  - Carcinoid tumour
  - Cecal or ileal adenocarcinoma
  - Lymphoma
  - Lymphosarcoma
  - Metastatic cancer

Abbreviation: CMV, cytomegalovirus; HSV, herpes simplex virus; NSAID, nonsteroidal inflammatory drug

Printed with permission: Sands, B. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006*:* pg. 2475.; and Su, Chinyu and Lichtenstion, Gary R. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/*Management 2006: pg. 2514.

60. In discussing with a patient the risk of starting azathioprine.

- Give 3 potential risks and their likelihood of occurrence.
  - 3% of allergic reaction including pancreatitis and hepatitis, usually within the first month intolerance to medication (ie headache, nausea, malaise) that requires drug withdrawal in 10%
  - 20-25 % risk of leucopenia
  - Drug interaction: allopurimol, 5-ASA
  - Increase levels of 6-TG; possible increased immunosuppression ad risk of malignancy when given with anti-TNF therapy
  - Increase in relative risk of small bowel lymphoma (controversial)
  - Lack of response

- Give different ways of monitoring during azathioprine therapy to reduce these risks.
  - Gene assay that measures the thiopurine methyl transferase (TPMT) genotype(mutation)
  - TPMT enzyme assay
  - 6-TGN (metabolic products) (6-thio guanine nucleotides, active metabolite)
  - Access CBC, liver enzymes

- Give the clinical interpretations of the following blood concentrations of azathiopurine metabolites.

6-TGN	6-MMP	Clinical interpretations
➢ Low	➢ Low	○ Non-compliance, or ○ Sub-therapeutic dosing
➢ Low/ normal	➢ High	○ MP resistant
➢ Normal	➢ Low	○ High risk for increased liver enzymes
➢ High	➢ Low	○ Responder or refractory
➢ High	➢ High	○ Responder, refractory or risk of leucopenia ○ Over-dosed

Abbreviations: 6-TGN, 6-Thioguanine nucleotides; 6-MMP, 6-methyl Mercaptopurine; MP, Mercaptopurine

Useful background:

- Meta-analysis has shown that the rate of non-Hodgkins lymphoma (NHL) is $61/10^5$ patient years in persons on anti-TNF therapy plus immunomodulators, a rate similar to that from the use of immunomodulators (Siegel CA, et al. *Clin Gastroenterol Hepatol* 2009;in press.)

Serious side effects of anti TNF agents in Crohn's disease

Event	Estimated frequency per 10^5
○ NHL (baseline)	20
- Also on IM	40
- Also on anti TNF in perspective	60
○ Death from sepsis	400
○ Tuberculosis	50

*Data on file, Centocor, Inc. TNF= Tumour necrosis factor; NHL= no Hodgkins lymphoma; IM= immunomodulator (azathioprine/6-mercaptopurine); HSTCL= hepatosplenic T cell lymphoma

Adapted from: Siegal, Corey A. *2009 ACG Annual Postgraduate Course* 2009:267-9.

- Surgery is commonly needed in persons with Crohn's disease' 18% in the first year after diagnosis, and 80% after 20 years. The operative mortality is $80/10^5$, compared with a $40/10^5$ mortality rate for dying of sepsis from anti-TNF therapy (Siegel CA, et al. *Clin Gastroenterol Hepatol* 2006:1017-24.)

- Elemental, hydrolyzed and polymeric formulas are equally effective in the treatment of IBD (Zachos M, et al *Cochrane Database Syst Rev* 2007:CD000542.) (Or, 0, 33)

Abbreviation: NHL, non-Hodgkins lymphoma

61. Give 6 factors/approaches that have been shown to enhance recovery from postoperative ileus.

- Surgery
  - Thoracic epidural local anesthetics
  - Intravenous or wound local anesthetics
  - Goal-directed fluid therapy and avoiding fluid excess
  - Laparoscopic surgery
  - Avoid NG tubes
- Patient
  - Laxatives
  - Peripheral opiod antagonists
  - Early oral feeding
  - Chewing gum
  - Minimize opiod use

Adapted from: Kehlet, H. *Nature Clinical Practice Gastroenterology & Hepatology* 2008 ;5: pg 552-558.

Useful background: Nutrition in IBD (Nguyen GC, et al. *Inflamm Bowel Dis* 2008:1105-11)

- Approximate frequency of nutritional deficiencies in IBD (Crohn's disease and ulcerative colitis)

- High (~ 70%)
  - Weight loss

- Medium (~ 40%)
  - Hypoalbuminemia
  - Anemia
  - Iron
  - Folic acid
  - Vitamin B12
  - Vitamin D
  - Zinc

- Low (~ 25%)
  - Calcium
  - Magnesium

- Vitamin A
- Vitamin E
- Vitamin K
- Selenium

Adapted from: Seidner, Douglas L. *2009 ACG Annual Postgraduate Course*: 271-276.

- Steroids are more effective than enteral nutrition in the treatment of active Crohn's disease (Zachos M, et al. *Cochrane Database Syst Rev* 2007:CD000542.)

- The prevalence of malnutrition is increased in IBD: 6.1% in Crohn's disease, 7.2% in ulcerative colitis, vs 1.8% in non-IBD controls (275-5). the adjusted odds ratio for malnutrition in IBD was 5.57 (95% CI 5.29-5.86), with a greater risk of malnutrition in those with fistulizing CD (or 1.65; 95% CI: 1.50-1.82), and in IBD patients who had undergone bowel surgery (or 1.37; 95% CI: 1.27-1.48). Importantly, malnutrition was also associated with a longer length of hospital stay, increased hospital mortality (or 3.49: 95% CI: 2.89-4.23) and double to hospital costs.

- There is no benefit of fish oil in Crohn's disease (Turner D, et al. *Cochrane Database Syst Rev* 2009;CD006320.; Feagan BG, et al. *JAMA* 2008:1690-7.)

62. Give 8 factors contributing to the increased risk of osteoporosis in persons with IBD.

- Disease
  - Type of IBD (malabsorption of calcium, vitamin D)
  - Chronic inflammatory activity
  - Chronic/recurrent corticosteroid use

- Patient
  - Increasing age
  - Female gender
  - Hypogonadism
  - Low BMI
  - Smoking
  - Family history

- Non-IBD factors
  - Previous fragility fracture

63. Give 10 genetic, microbiome and mucosal epithelial defense mechanisms which may have therapeutic implication in IBD.

- Genetic changes
  - "It is estimated that known genetic associations account for only about 20% of the genetic variance underlying, susceptibility to inflammatory bowel disease" (Abraham & Cho, NEJM 2009;361: 2066-78)
  - Familial clustering of cases of IBD
  - Twin studies
  - NOD2 (Nucleotide Oligomerization Domain 2) (host- microbiome interactions)
  - Components of the IL-23 type 17 helper T cell (Th 17) pathway
  - ATG 16 G1, the autophagy gene, as well as the immunity- related GTPase M protein (IRGM) intracellular components such as organelles, apoptotic bodies, and microbes

- Mucosal repair and barrier function
  - Polymorphisms in proximity to the gene encoding EP_4 ($PTGE_4$) in Crohn's disease (CD).

- Microbiome (microorganisms which inhabit the GI tract)
  - Persons with CD and UC have a reduced number and diversity, as compared with controls, of the mucosa-associatd phyla Firmicutes and Bacteroidetes

- Defense of the epithelium
  - Lumen
    - Acid
    - Blie
    - Pancreatic enzymes
    - Mucus
  - Motility
  - BBM
    - Tight junctions
    - a-defensins
    - Toll like receptors
    - Cell matrix adhesion
    - Epithelial cell development or proliferation
    - Restitution of epithelial cells after injury
    - Stress of the endoplasmic reticulum
  - MALT/GALT
    - B cells secretory immunoglobulins
    - Dendritic cells

- T cells (Peyer's patches, mesenteric lymph nodes, lymphoid follicles) when activated produce integrin a4B7 and CCR9 (a chemokine receptor)
- Pattern recognition receptors (innate immune cells) Intestinal vasculature-adhesion molecules (selections, integrins) and chemokines (secreted cell attractants)
- Leukocyte migration

- Major SB parasites
  - Giardia
  - Cryptosporidia
  - Cyclosporia

- Factitious diarrhea anthraquinone

- Anti-reflex surgery associate with diarrhea – 20%

Acute infectious diarrhea

64. Compare and contrast the clinical presentation, causes, site of involvement, and fecal leukocytes of persons with inflammatory versus non-inflammatory infections.

Characteristic	Inflammatory diarrhea	Non-inflammatory diarrhea
➢ Clinical presentation	-Bloody, mucoid small-volume diarrhea, tenesmus lower left quadrant abdominal cramps -May be febrile and toxic	Large-volume, watery diarrhea; no blood, pus or tenesmus. May have nausea, vomiting, cramps but no fever
➢ Causes	*Shigella* spp., *Salmonella* spp., amebic colitis, *campylobacter* spp., EAEC, EHEC, EIEC, *Yersinia* spp., *Clostridium difficile*	Norovirus, rotavirus, *Vibrio cholerae*, *Giardia lamblia*, ETEC, enterotoxin-producing bacteria, *Staphylococcus aureus, Cryptosporidium parvum, Clostridium perfringens*
➢ Site of involvement	Colon	Small intestine
➢ Fecal leukocytes	Positive	Negative

Abbreviations: EAEC, Enteroaggregative *Escherichia coli*; EHEC,

Enterohemorrhagic *Escherichia coli*; EIEC, Enteroinvasive *Escherichia coli*; ETEC, Enterotoxigenic *Escherichia coli*

Printed with permission: Navaneethan U. and Giannella R. *Nature Reviews Gastroenterology and Hepatology* 2008(5): 637-647, Table 1.

65. Give 5 foods and/or beverages which are generally safe, often safe and often unsafe with respect to the risk for developing traveller's diarrhea.

Generally safe	Often safe	Often unsafe
➢ Food and beverages served steaming (>59^{o}C) hot	➢ Tortillas and breads or toast containing butter or sauces	➢ Fruits and vegetables with intact skins: berries, tomatoes
➢ Bottled carbonated drinks including soft drinks and beer	➢ Fruit juices which may have been augmented with tap water	➢ Hot sauces on tabletop
➢ Bottled water with intact seal apparent on opening	➢ Use of tap water to rinse mouth and toothbrush without swallowing it	➢ Moist foods served at room temperature including vegetables and meats
➢ Syrups, jellies, jams, honey	➢ Foods serviced on airplanes in developing regions	➢ Any food served buffet-style that is maintained at room temperature
➢ Fruits that are peeled	➢ Few ice cubes	➢ Tap water even at hotels claiming filtration systems
➢ Dry items such as bread an rolls		➢ Large quantities of ice
➢ Any foods carefully prepared in one's own apartment or hotel		➢ Hamburgers not served hot or at fast food service restaurants with rapid turnover of prepared hamburgers

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66. Give 15 of the major enteropathogens causing “traveller’s diarrhea”.

- Bacteria
  - Enterotoxigenic Eschenchia coli (ETEC)
  - Enteropathogenic E. coli (EPEC)
  - Enteroaggregative E. coli (EAggEC)
  - Enteroinvasive E. coli (EIEC)
  - Salmonella
  - Campylobacter jejuni
  - Mycobacterium tuberculosis (and Mycobacterium bovis)
  - Aeromonas and Plesiomonas

- Viruses
  - Rotavirus
  - Enteric adenoviruses (types 40, 41)
  - Measles virus
  - Human immunodeficiency virus

- Protozoa
  - Ciliophora
    - Balantidium coli
  - Mastigophora
    - Giardia lamblia
  - Coccidia
    - Cryptosporidium parvum
    - Isosprora belli
  - Microspora
    - Enterocytozoon bieneusi
    - Encephalitozoon intestinalis
  - Cyclospora – Cyclospora cayetanensis

- Helminths
  - Strongyloides stercoralis
    - Schistosoma
    -

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67. Give the advantages and disadvantages of adding concomitant immunomodulators to anti-TNF therapy in Crohn disease (CD).

Advantages	Disadvantages
➢ ↓ Antibodies (at least to infliximab) ➢ Benefit in steroid-dependent CD (SONIC) ➢ ↓ acute/delayed infusion reactions ➢ ↓ immunogenecity	○ ↓ duration of response (with episodic therapy) ○ No difference in short- or long-term responses to induction + maintenance therapy in refractory CD (ACCENT, CHARM, PREcISE) ○ No benefit with steroid-induction (COMMIT) ○ ↑ long-term toxicity - Serious infections - Risk of infections

68. Give 6 features differentiating organic diarrhea from functional diarrhea.

Feature	Organic diarrhea	Functional diarrhea
➢ Weight loss	○ Often present	○ Absent
➢ Duration of illness	○ Variable (weeks to years)	○ Usually long (>6 mo)
➢ Quantity of stool	○ Variable but usually large (>200 g in 24 h)	○ Usually small (<200 g I n 24 h)
➢ Blood in stool	○ May be present	○ Absent (unless from hemorrhoids)
➢ Timing of diarrhea	○ No special pattern	○ Usually in the morning or after meals
➢ Nocturnal symptoms	○ May be present	○ Absent
➢ Fever, arthritis, skin lesions	○ May be present	○ Absent
➢ Emotional stress	○ No relation to symptoms	○ Usually precedes or coincides with symptoms
➢ Cramping abdominal pain	○ Often present	○ May be present

69. Give 7 signs and symptoms of systemic illnesses to be considered in the person with diarrhea.

Sign or symptom	Diagnosis to be considered
➢ Systemic ○ Marked weight loss	○ Malabsorption, inflammatory bowel disease, cancer, thyrotoxicosis
➢ Joint ○ Arthritis	○ Ulcerative colitis, Crohn's disease, Whipple disease, *Yersinia* infection
➢ CNS ○ Neuropathy	
➢ CVS ○ Postural hypotension	○ Diabetic diarrhea, Addison disease, idiopathic orthostatic hypotension, autonomic dysfunction

Sign or symptom	Diagnosis to be considered
➢ Hematology ○ Eosinophilia ○ Lymphadenopathy	 ○ Eosinophilic gastroenteritis, parasitic disease ○ Lymphoma, Whipple disease
➢ Skin ○ Flushing ○ Hyperpigmentation	○ Malignant carcinoid syndrome ○ Amyloidosis
➢ GU ○ Proteinuria	
➢ GI ○ Peptic ulcers	○ Diabetic diarrhea, amyloidosis ○ Zollinger-Ellison syndrome ○ Whipple disease, celiac disease, Addison disease, pancreatic cholera, eosinophilic gastroenteritis

Abbreviations

AAD	Antibiotic-associated diarrhea
AIC	Autoimmune cholangitis
AIH	Autoimmune hepatitis
AZA	Azathioprine
BP	Blood pressure
BS	Blood sugar
CD	Celiac disease
CD	Crohn's disease
CDAI	Crohn's disease activity index
CE	Capsule endoscopy
CMV	Cytomegalovirus
CTE	CT enterography
CyA	Cyclosporin A
DBE	Double balloon enteroscopy
DEXA	DEXA scan for bone mineral density
D-IBS	Diarrhea predominant IBS
DM	Diabetes mellitus
DPG	Deamidated gliadin peptide
DRE	Digital rectal examination
EAEC	Enteroaggregative escherichia coli
EATL	Early aberrant T cell lymphoma
EBV	Ebstein Barr virus
EHEC	Enterohemorrhagic escherichia
EIEC	Enteroinvasive escherichia coli
ETEC	Enterotoxigenic escherichia coli
EUA	Examination under general anaesthesia
EUS	Endoscopic ultrasound
GCS	Glucoscorticosteroids
GFD	Gluten-free diet

GSE	Gluten sensitive enteropathy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHT	Hereditary hemorrhagic telegangiectasia
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-D	Predominant irritable bowel syndrome
IEL	Intraepithelial T-cells lymphocytes
IFN	Interferon
IFX	Inflixumab failures
IL	Interleukin
IPSID	Immunoproliferative small intestinal disease
LE	Liver enzymes
LHD	Limited human data
MAC	Mycobacterium-avium complex infection
MS	Multiple sclerosis
MTOR	Mammalian target of rapamyacin
MTX	Methotrexate
NHL	Non Hodgkins lymphoma
NRCD	Non-responsive CD
NSAIDs	Non-steroidal anti-inflammatory drugs
OCA	Oral contraceptive agent
OCIF	Osteoclasto genesis inhibitory factor
OGIB	Obscure GI bleeding
OPG	Osteoprotegerin
PBC	Primary biliary cirrhosis
PET	Positron emission tomography
PF	Perianal fistulae
PSC	Primary sclerosing cholangitis

PTLD	Post-transplant lymphoproliferative disorder
RA	Rheumatoid arthritis
RCD	Refractory celiac disease
SBBO	Small bowel bacterial overgrowth syndrome
SBE	Single balloon enteroscopy
SBO	Small bowel obstruction
SIBO	Small intestinal bacterial overgrowth syndrome
TB	Tuberculosis
TNF	Tumour-necrosis factor-α
TPN	Total parental nutrition
TTG	Tissue transglutamase
UC	Ulcerative colitis

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COLON

TABLE of CONTENTS

Perianal disease

- Fissures

1. A 78 year old female with severe, poorly controlled Parkinson's disease is admitted to a geriatric unit. She has decompensated over the holidays with dysphagia. A gastroscopy was unremarkable. Plans are underway regarding a percutaneous gastrostomy for feeding. In the interim, you are called due sudden onset rectal pain and bleeding. On examination you diagnose an acute anal fissure, in the posterior midline (6 o'clock position).

a) Give 3 other causes of bright red rectal bleeding that this patient is specifically at risk for in relation to her underlying disease process (Parkinson's disease).
   - Hemorrhoid
   - Stercoral (ischemic) ulcer
   - Solitary rectal ulcer syndrome

b) List 4 risk factors that this patient has for developing an anal fissure.
   - Age
   - Immobility
   - Constipation
   - Parkinson's Disease related decreased colonic activity
   - Antiparkinsonian drugs L-DOPA, anticholinergics (cogentin)
   - Dehydration/electrolyte imbalance
   - Fecal incontinence (overflow diarrhea)
   - Manual stool extraction
   - Enemas

2. Give 3 treatments and their major side-effects or complications of management of a chronic anal fissure.

- General
  - Treat underlying cause(s)
  - Supportive therapy

- Medical
  - Stool softeners, bulk, sitz bath, diet, fluids
  - Topical nitroglycerin(0.2% t.i.d)
    - Hypotension, headache, flushing
  - Diltiazem (calcium channel blocker [CCB]) cream (2%, t.i.d)
    - Flushing, headache, hypotension, bradycardia
  - Botulin toxin injection into the sphincter
    - Fecal incontinence, flatus incontinence (7%); effect wears off

- Surgical
  - Lateral sphincterotomy
    - Fecal incontinence
    - Recurrence (10%)
  - Diverting colostomy

Adapted from: Hull S. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2892; and 2010, pg. 2265.

3. Give 3 anatomical structures and the mechanisms by which they contribute to normal fecal continence.

- Nerves – pudenal nerve/sacral segments S2 – S4/brain: The pudenal nerve has both afferent and efferent limbs, sensing stool entry into the rectum and delivering the impulse through the sacral nerves, spinal cord, to the brain. The efferent limb carries the sensation of distension which causes central pathways to send signals via the afferent limb to allow for conscious contraction of external sphincter to maintain continence.

- Muscles
  - Internal anal sphincter (IAS)
  - External anal sphincter (EAS)
  - Levator ani complex: The internal anal sphincter is tonically contracted providing continence at rest. When stool enters the rectum the IAS relaxes, however, continence is maintained if consciously desired by contraction of the EAS. The IAS returns to resting tone, the rectum demonstrates compliance allowing intrarectal pressure to decrease and the urge to defecate to pass. The levator ani muscles provide additional support to the EAS. As well, they form a sling around the anal canal, forming an acute angle during rest, creating a mechanical barrier for continence. Inability to distend without substantial rise in pressure thus not overwhelming resting anal tone.
  - Rectum - reservoir

Abbreviations: EAS, external anal sphincter; IAS, internal anal sphincter

Adapted from: Schiller LR. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 200-201.

4. Give 5 tests/procedures which are useful to investigate the patient with fecal incontinence.

- Clinical
  - History, physical examination
  - Sensory and motor (DRE) testing
  - Perianal descent (normally 1.5-3.0 cm)

- Mucosa
  - Endoscopy

- Muscle
  - Structure
    - EUS
    - MRI/ CT
  - Function
    - Colon transit study
    - Contraction pressure: pellet retention test
    - Expulsion pressure: balloon expulsion test
    - Co-ordination: anorectal manometry “defecography”

- Nerve
  - Pundendal nerve terminal latency

Abbreviations: DRE, digital rectal examination; EUS, endoscopic ultrasound

5. Give 15 medical and surgical treatments of fecal incontinence.

- Treat underlying cause (s)

- Supportive therapy (the patient)
  - Education/counseling/habit training
  - Trained defecation
  - Diet (fiber; lactose, fructose, reduce caffeine intake)
  - Incontinence pad
  - Perianal hygiene/skin care

- Pharmacological (the stool)
  - Fiber
  - loperamide
  - lomotil
  - Codeine
  - Cholestyramine/colestipol
  - Estrogen
  - Phenylephrine

- Sodium valproate

- Biofeedback therapy
  - Anal sphincter muscle strengthening
  - Rectal sensory conditioning
  - Recto-anal coordination training

- Perianal
  - Anal plugs
  - Pessary
  - Kegal exercises
  - Sphincter bulking (collagen, silicone)
  - Anal electrical stimulation
  - Injection sclerotherapy
  - Sacral nerve stimulation

- Surgery
  - Artificial anal sphincter
  - Sphincteroplasty
  - Anterior repair (rectocele)
  - Gracilis/gluteus muscle transposition +/- stimulation
  - Colostomy
  - Pelvic reconstruction
  - Options: rubber band ligation
  - Surgical excision
  - PPH-Stapled Hemorrhoidopexy

Adapted from: Schiller L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 207.

Useful background: Fecal incontinence

- Definition: The recurrent uncontrolled passage of fecal material for at least one month duration (Rao 09)

- Subtypes
  - Passive – involuntary release of stool or flatus
  - Urge – release of fecal contents despite voluntary attempts to retain contents
  - Seepage – leakage of small amounts of stool following an evacuation

- Value of rectal examination in the person with fecal incontinence
  - Perianal sensation
  - Sphincter tone at rest or voluntary contraction, and election of perineum

- Sphincter tone
- Length of anal canal
- Anorectal angle

- Psyllium has been shown in a RCT to reduce the number of episodes of fecal incontinence by 50%; uncontrolled studies suggest a benefit for cholesylamine or amitriptyline (Rao 09)

- The operant conditioning techniques of biofeedback training using visual, auditory or verbal feedback, are meant to improve the strength of the anal sphincter muscles, anorectal sensory perception, and coordination of anal sphincter, gluteal and abdominal muscles following rectal balloon dilation or voluntary squeeze

- Both biofeedback training and Kegal exercises each produce a 50% reduction in fecal incontinence. One study has shown superior improvement with biofeedback as compared to exercises, on a per protocol but not an intention-to-treat basis. Another study (Hegmen et al, GE 2007;132:A-83) showed 77% of persons with fecal incontinence showing improvement versus 40% treated with Kegal exercises with 66% versus 48%, respectively, being totally content.

- RCTs have shown a benefit for sacral nerve stimulation for fecal incontinence when the anal sphincter is intact

- The Malone procedure (antegrade continent enema procedure – cecostomy or appendicostomy for antegrade washing of the colon) gives a 61% success rate for fecal incontinence over 39 months

- Biofeedback defecation is also of benefit for dyssynergic defecation, providing sustained 12 month improvement in 80% as compared with 22% in the standard care (laxative [PEG] and counseling group), with improved ability to expel a test balloon, and standard care correction of dysynergy in 79% of the active biofeedback group versus 4% in the sham group (Rao SSC, et al. *Clin Gastroenterol Hepatol* 2007:331-8.) In a second study, there was 70% improvement at 3 months, with biofeedback vs 23% with diazepan and 28% with placebo (Heymen S, et al. *Gastroenterology* 2007:A-83.)

- Biofeedback is also of benefit in persons with solitary rectal ulcer syndrome (Rao SSC, et al. *Clin Gastroenterol Hepatol* 2007:331-8.)

6. Give the diagnostic imaging findings suggestive of intestinal ischemia.

- Bowel lumen
  - Caliber
  - Content
  - Transition point if associated obstruction
  - Inraluminal hemorrhage
  - Small bowel feces sign

- Bowel wall
  - Thickness
  - Homogeneity
  - Enhancement pattern
  - Length of involvement
  - Pneumatosis

- Mesentery
  - Edema
  - Hemorrhage
  - Patency of mesenteric vessels
  - Mesenteric vascular engorgement
  - Ascites
  - Volvulus
  - Intussusception

Printed with permission: Gore, et al. *Clinical Gastroenterology and Hepatology* 2008; 6: 849-859.

7. Give the affected structure and pathophysiology of 4 disorders causing functional anorectal outlet obstruction.

Affected structure	Pathophysiology
○ Internal sphincter- Hirschsprung's disease	– No relaxation
○ External sphincter- Pelvic floor dyssynergia ('anismus')	- Paradoxical contraction
○ Pelvic floor- pelvic floor descent	– Loss of pressure
○ Rectal wall -Intussusception	– Luminal obstruction
○ Rectal wall –Anterior, rectocele	– Loss of pressure

Printed with permission: Müller-Lissner S. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 474.

8. Give the medical and surgical treatment of chronic internal hemorrhoids.

- Treat underlying associated causes
  - Diarrhea/constipation, prolapse, bleeding, deficient intake of fibre and fluids

- Supportive therapy
  - Avoid straining and limit time on commode

- Pharmacological
  - Barrier creams: zinc oxide, lanolin (limit contact of stool and mucus with sensitive anoderm)

- Surgery
  - Repair fissures to limit further trauma
  - Surgery – rubber band ligation, injection sclerotherapy, surgical excision, PPH-stapled hemorrhoidopexy

Adapted from: Hull T L. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2836-2839; and 2010, pg. 2263.

Mesenteric ischemia

9. Give 20 causes of acute and chronic mesenteric ischemia.

- Superior mesenteric artery (SMA) embolism 50%
  - Atrial fibrillation, left ventricle thrombosis, ulcerated aortic plaque

- Superior mesenteric artery thrombosis 15%

- Non-occlusive mesenteric ischemia 25%
  - Vasospasm, shock, congestive cardiac failure, cardiac dysrythmias

- Medications
  - 5-HT3 antagonist
  - 5-HT4 agonist
  - Cocaine
  - Digitalis
  - Dopamine
  - OCA

- Mesenteric venous thrombus (10%)
  - Hypercoagulable conditions
    - Primary

        - Secondary
            - Cirrhosis, diabetes, hyperlipidemia, IBD, inflammation , intra-abdominal sepsis, paraneoplastic, perforation, postoperative, smoking, trauma
    - Portal hypertension
    - Oral contraceptive agent
    - Perforated viscous
    - Pancreatitis
    - Trauma
    - Inflammatory bowel disease

- Focal segmental ischemia (5%)
    - Mechanical
        - Trauma
        - Radiation
    - Localized small vessel occulsion
        - Cholesterol emboli
        - Strangulated hernias
        - Vasculitis
        - Volvulus
        - Sickle cell disease

- Irritable bowel syndrome (IBS), and its treatment (5-HT3 antagonists, 5-AT4 agonists)

- Chronic mesenteric ischemia
    - Vessel lumen
        - Atherosclerosis and atheroma
        - Diabetes, hyperlipidemia, smoking
    - Vessel wall
        - Celiac artery compression syndrome
        - Fibrovascular dysplasia
        - Mesenteric venous thrombosis
        - Takayasu's arteritis
        - Thromboangiitis obliterans

Abbreviations: IBS, irritable bowel syndrome; OCA, oral contraceptive agent; SMA, superior mesenteric artery

Adapted from: Brandt L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2566.; and 2010, pg. 2036 and 2039; and Printed with permission: Sreenarasimhaiah J. *Best Practice & Research Clinical Gastroenterology* 2005;19 (2): pg 285-286.

10. Give 10 endoscopic and microscopic pathological changes in acute mesenteric ischemia.

- Colonoscopic
  - Superficial half of colonic mucosa preferentially affected
  - Hemorrhagic streaking (mucosal and submucosal hemorrhage)
  - Superficial ulceration
  - Deep ulcers
  - UC-like colitis
  - Liquification necrosis
  - Perforation
  - Stricture (reversible, irreversible, saccular stricture)
  - Pneumatosis linearis (colonic gangrene, HIV disease)
  - Carcinoma (pressure of CRC produces local ischemia)
  - Diverticulosis-associated ischemia
  - Isolated R-colon ischemia (IRCI) may be heralding a SMA occlusion

- Microscopic
  - Fibrin plugs in capillaries
  - Partial necrosis and ulceration
  - Crypt abscesses
  - Iron-laden macrophages in submucosa

Abbreviation: IRCI, isolated R-colon ischemia

Adapted from: Brandt L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2566.; and Printed with permission: Sreenarasimhaiah J. *Best Practice & Research Clinical Gastroenterology* 2005;19(2): 285-286.

11. Give 10 clinical presentations of acute and chronic mesenteric ischemia.

- Acute
  - Background clinical picture of underlying disease
  - Acute onset of pain out of proportion to benign abdominal examination
  - Rectal bleeding
  - Urge to defecate/diarrhea
  - Abdominal tenderness
  - Confusion, sepsis, hypertension, fever, post prandial pain
  - Rebound guarding
  - Consider risk factors (DM, AF, etc.), including drugs e.g alosetron, tegaserod, cocaine, digitalis
  - Association with IBS (irritable bowel syndrome)

- Chronic
  - Symptoms
    - Post-prandial intestinal angina
    - Fear of eating (sitophobia)
    - Weight loss
    - Nausea and vomiting
  - Signs
    - Abdominal tenderness out of proportion to benign abdominal examination
    - Epigastric bruit (non-specific)
    - Gastric ulceration
    - Gastroparesis
    - Gallbladder dyskinesia

Adapted from: Brandt L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2566.; and Printed with permission: Sreenarasimhaiah J. *Best Practice & Research Clinical Gastroenterology* 2005;19(2): pg 285-286.

12. Give 5 investigations for, and the treatment of acute mesenteric ischemia.

- Investigations
  - Colonoscopy or flexible sigmoidoscopy, with mucosal biopsy
  - Abdominal film
  - Angiography
  - CT angiography
  - MRI
  - 'Doppler ultrasound (shows only proximal vessels)
  - Lab' – lactic acidosis, ion gap metabolic acidosis, hypercoagulopathy work up, anemia, leucocytosis
  - Laproscopy, if high index of clinical suspicion of infarction

- Treatment
  - Supportive
  - Treat associated, underlying conditions
  - Early surgery with resection for infarction/gangrene/perforation
  - Embolectomy
  - Papaverine
  - Thrombolectomy
  - Broad spectrum antibiotics if micro-perforation is suspected

Adapted from: Brandt L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2566.; and Printed with permission: Sreenarasimhaiah J. *Best Practice & Research Clinical Gastroenterology* 2005;19 (2): pg 285-286.

Ulcerative colitis (UC)

13. A patient with severe UC is hospitalized, placed on oral glucocorticosteroids (GCS), but does not respond.

a) Give 5 molecular mechanisms of steroid resistance.

- Abnormalities in absorption/metabolism (liver disease)
- Altered number of GCS receptors, or altered numbers of isoforms (α, β, δ)
- Altered affinity of GCS for GCS receptors
- Reduced affinity of the GCS receptor ligands to bind to DNA
- Altered expression of transcription factors (AP-1, NF-k B) and/or cytokines (IL-2, IL-4, p38 activated MAP kinase)
- Genetic factors (primary steroid resistance, MDR-1 [P-glycoprotein 170], HLA class II allele DRB1*0103)

Adapted from: Farrell RJ, and Kelleher D. *J Endocrinol* 2003; 178(3): 339-46.

b) Give 5 clinical causes of "steroid resistance" in patients with "colitis" (factors causing persistence of symptoms).

- Infection - C. difficile, CMV
- NSAIDs
- Smoking discontinuation
- Drug interactions
- UC with CD-like features – discontinuous disease, superficial fissuring ulcers, aphthous ulcers, ileal involvement, involvement of the upper GI tract, granulomas
- CD with UC-like features – pancolitis, superficial colitis
- Other forms of "colitis" that may mimic UC
- Development of colorectal cancer (CRC)

c) Give a clinical strategy for dealing with steroid resistance in patients with IBD, in whom the above factors causing persistence of symptoms have been excluded.

- Adjust dose, change to IV
- Higher dose of 5-ASA (controversial), or 5-ASA enemas
- Cyclosporine
- Azathioprine, 6-MP
- Methotrexate
- Biologics – anti TNF
- Probiotics
- Fish oil, nicotine patch
- Colectomy

Adapted from: Mayer LF. *AGA Institute post graduate course book* 2007. pg. 109.

Useful background: Mayo Score for ulcerative colitis

Mayo Index	0	1	2	3
○ Stool frequency	Normal	1-2/day >normal	3-4/day >normal	5/day >normal
○ Rectal Bleeding	None	Streaks	Obvious	Mostly blood
○ Mucosa	Normal	Mild friability	Moderate friability	Spontaneous bleeding
○ Physician's global assessment	Normal	Mild	Moderate	Severe

- Long-term treatment goals of IBD patients
  - Rapidly relieve symptoms
  - Avoid surgery
  - Avoid hospitalisation
  - Improve QoL
  - Heal mucosa

Source: VanAssche G et al. page 139. Insights Into Patient and Physician Communication and Expectations: Results of a Large Pan-European Survey of Physicians and Their Patients With Inflammatory Bowel Disease. ECCO 2008.

14. Give the biopsy features of acute self-limiting colitis (AC) which help to distinguish it from chronic idiopathic ulcerative colitis (UC).

- Crypts are straight, parallel, close
- PML are abundant, and scattered in the lamina propria (LP)
- No lymphoplasmacytosis at base of crypts
- Large, bulging, cystic dilation with a "necklace" of cells around any crypt abscess

Abbreviations: AC, acute self-limiting colitis; LP, lamina propria; PML, polymorphonuclear leucocytes; UC, ulcerative colitis

15. Give 20 conditions that cause "colitis" and may mimic ideopathic ulcerative colitis (UC).

- Infection
  - Viral
    - Cytomegalovirus (CMV)
    - Herpes (HSV)
  - Bacterial
    - Clostridium difficile
    - Salmonella species
    - Shigella species
    - Yersinia enterocolitica
    - Campylobacter jejuni
    - Vibrio perahaemolyticus
    - Aeromonas hydrophila
    - Neisseria gonorrhoeae
    - Listeria monocytogenes
    - Chlamydia trachomatis
    - Syphilis
    - Staphylococcus aureus
    - Escherichia coli 0157:H9
  - Protozoan
    - Amebiasis (amoeba histolytica)
    - Balantidiasis
    - Schistosomiasis
  - Fungal
    - Histoplasmosis
    - Candidiasis

- Iatrogenic (drugs)
  - Enemas
  - Laxatives
  - OCA
  - Ergotamine
  - Amphetamines
  - Phenylephrine
  - Cocaine
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Penicillamine
  - Gold
  - Methyldopa

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; OCA, oral contraceptive agent

Adapted from: Su C et al. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/Management* 2006. pg.2514; and 2010, pg. 1956 and 1990.

16. Give 3 extraintestinal complications of UC that do not improve with colectomy.

- Ankylosing spondylitis
- PSC
- Pyoderma gangrenosa

17. Give 8 "alternative therapies" for UC and CD.

- UC
  - Phosphatidyl choline
  - Curcumin (phytochemical in tumeic)
  - Hypnosis
  - Granulocyte/monocyte apheresis
  - Probiotics

- CD
  - Omega-3 fatty acids (DHA - and EPA-containing fish oil)
  - AST-120 oral spherical absorption carbon (for fistulae)
  - IL-12/IL-23 (ustekinumab)
  - Naltrexone
  - Probiotics

18. Give 6 factors/approaches that have been shown to enhance recovery from postoperative ileus.

- Thoracic epidural local anesthetics
- Intravenous or local anesthetics
- Laxatives
- Peripheral opiod antagonists
- Goal-directed fluid therapy, avoiding fluid excess
- Early feeding
- Laparoscopic surgery
- Chewing gum
- Avoid nasogastric tubes
- Minimize opiod use

Printed with permission: Kehlet, H. *Nature Clinical Practice Gastroenterology & Hepatology* 2008 ;5: pg 552-558.

19. Give the sensitivity, specificity, PPV and NPV of the serological markers ASCA and pANCA in persons with Crohn's disease (CD) and ulcerative colitis (UC).

Marker	Diagnosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ASCA	CD	50-65	70-85	80	64
pANCA	UC	65-80	70-85	64	80

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Adapted from: Targan SR. *AGA Institute PostGraduate Course book*. pg. 47.

20. Give 4 predictive factors for the development of pouchitis.

- Positive association
  - Extraintestinal manifestations
  - Primary sclerosing cholangitis
  - Antineutrophil cytoplasmic antibody with a perinuclear staining pattern (p-ANCA)
  - Extent of pre-roperative UC
- Negative association
  - Smoking

Printed with permission: Gionchetti P, et al. *Best Practice & Research Clinical Gastroenterology* 2004;18(5): pg 995.

21. A patient has an ileoanal pouch (IAPP) after proctocolectomy for UC. Give 8 differential diagnoses for late pouch-related symptoms.

- Cuffitis
- Pouchitis
- Irritable pouch syndrome
- Crohns disease
- NSAID-induced damage (especially with isolated afferent limb ulcers)
- Poor reservoir capacity
- Adhesions

- Stricture
- Abscess
- Pelvic floor dysfunction
- Late anastomotic leak
- Small intestinal bacterial overgrowth syndrome (SIBO)
- Malignancy (squamous cell cancer) of anus, small bowel cancer
- Unmasked celiac disease
- Unrelated conditions, including infections

Useful background: Pouchitis

- The likelihood of developing chronic pouchitis in a UC patient having an IAPP is over 80% if serological testing shows high levels of pANCA (Fleshner P, et al. *Clin Gastroenterol Hepato*l 2008:561-8.)
- Persons who fail to respond to one antibiotic for pouchitis may respond to two antibiotics
- Some persons wilth IAPP require chronic continuous antibiotics to maintain remission (antibiotic-dependent chronic pouchitis)
- For antibiotic-dependent chronic pouchitis, one option is to alternate 3 or 4 antibiotics every week
- The 9 month relapse rate of pouchitis when using VSL #3 is 15%, vs 100% for placebo
- The efficacy of budesonide enemas is comparable with metronidazole tablets
- Topical or oral mesalamine, or anti-TNF therapy, may also be effective for pouchitis

22. Give the indications for the use of infliximab in persons with ulcerative colitis (UC).

- Induction of remission in adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, corticosteroids, or immunomodulators
- Maintenance of remission after infliximab for induction therapy
- Hospitalized patients with severe UC
- Steroid-sparing
- Extraintestinal manifestations of UC

- Spondyloarthropathy
- Pyoderma gangrenosum

- Unresponsive iritis/uveitis

Adapted from: Sandborn W. *AGA Institute PostGraduate Course book* 2007; pg. 138.

Useful background: CRC in IBD

- Meta-analysis shows a role for 5-ASA for chemoprevention of CRC in IBD (OR 0.51, 95% CI 0.29-0.92) (Velayos FS, et al. *Am J Gastroenterol* 2005:1345-53.)
- UDCA has a chemopreventative effect for CRC in ulcerative colitis (UC) patients with primary sclerosing cholangitis (PSC) (Wolf JM, et al. *Aliment Pharmacol Ther* 2005:783-8.)
- The number of UC patients with dysplastic with lesions detected on colonoscopy can be doubled by the use of chromoendoscopy (Fashner 09)

Abbreviations: PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid

Useful background: Traditional serrated adenomas (TSA) and sessile serrated adenomas (SSA)

- TSA
  - Infrequent
  - Dysplastic
  - Often protuberant
  - Distal colon
- SSA
  - Sessile or flat (subtle)
  - Proximal
  - BRAF mutation
  - CpG island methylator phenotype
  - Microsatellite instability

Colonic polyps, and cancer: non-familial forms

Useful background: Approximate incidence of GI cancers (10^5/year)

Years of Age	<49	50-74	>75
Esophagus	<1	12	28
Stomach	<1	22	78
Colon	<1	150	400

Source: Canadian Cancer Surveillance, Health Canada

23. Give 5 factors which must be taken into account when stratifying risk and the need for screening for colorectal cancer (CRC).

- Age >50 yrs
- Personal history of colonic polyps or CRC
- Family history - polyps, CBC, Lynch/FAP-associated tumours
- High risk groups
  - IBD patients
  - African-Canadians
  - Smokers
  - Obesity (BMI>30, waist circumference>32-34")
  - Concurrent PSC (primary sclerosing cholangitis) in conjunction with ulcerative colitis (UC)
  - Dietary risk factors – low daily intake of fresh fruit, vegetables anf fiber (possible); low intake of calcium and vitamin D; high intake of saturated fatty acids (especially red meat)

Useful background:

			(%)
➢ Malignant Potential of Colonic Adenomas			
○	Size	< 1 cm	1
		1-2 cm	10
		>2 cm	45
○	Histology	Tubular	5
		Tubular Villous	25
		Villous	40
○	Dysplasia	Mild	5
		Moderate	20
		Severe	35
➢ Colorectal Cancer			
		M>F	
○	Site	Cecum/Asc. Colon	25

Transverse	15
Descending	5
Sigmold	25
Rectum	20

24. From the following table, calculate the absolute risk (AR) of CRC in a 55 year old patient whose father developed proven CRC at age 59, his 50 year old brother had an adenomatous colonic polyp, and a grandmother and an aunt of unknown age had CRC (baseline absolute risk for 50 year old, 6%).

Familial setting	RR
○ One first-degree relative with CRC	2.3
- < 45 yrs	3.9
- 45 – 59 yrs	2.3
- > 59 yrs	1.8
○ Two first-degree relatives with CRC	3.8
○ More than two first-degree relatives with CRC	4.3
○ One second- or third-degree relative with CRC	1.5
○ Two second-degree relatives with CRC	2.3
○ One first-degree relative < 60 yrs with an adenoma	2.0

Abbreviation: AR, absolute risk; RR, relative risk

RR=(2.3 x 2.0 x 2.3)= 10.5; Absolute risk for average risk person over age 50, 6%; absolute risk for this person, (10.6 x 6%= RRxAR >60%)

Printed with permission: Winawer SJ. *Best Practice & Research Clinical Gastroenterology* 2007; 21(6): pg. 1035.

Useful background: From the “Acrin” trial of CT colography (NEJM 2008;359: pp 1207-1219), give the sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) for detecting colonic polyps ranging from 5 to 10 mm

➢ Efficacy and test performance

	>5mm	>6mm	>7mm	>8mm	>9mm	>1cm
SENS	65%	78%	84%	87%	90%	90%

>5mm	>6mm	>7mm	>8mm	>9mm	>1cm	>5mm
SPEC	89%	88%	87%	87%	86%	86%
PPV	45%	40%	35%	31%	25%	23%
NPV	95%	98%	99%	99%	99%	99%

Source: Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med*. 2008 Sep 18;359(12):1207-17.

25. Give the recommended follow-up interval for post-polypectomy colonoscopic surveillance.

Finding on screening	Follow-up interval
➢ < 10 adenomas	
○ 1-2 tubular adenomas < 1 cm	5-10 yrs
○ 3-10 adenomas, or any adenoma with villous elements, high-grade dysplasia or ≥ 1 cm in size	3 yrs
○ Patients with prior advanced adenomas after normal follow-up examination, or only 1-2 small tubular adenomas	< 3 yrs
➢ >10 adenomas (possible familial syndrome)	2-6 months to confirm complete removal
○ Large sessile adenoma removed piecemeal	10 yrs
○ Small distal hyperplastic polyps without adenomas	Interval uncertain
○ Proximal colon hyperplastic polyps	Same as for adenoma
○ Sessile serrated adenomatous (SSA) polyp	

Adapted from: Rex DK. *2008 ACG Annual Postgraduate course book*: pg. 90; and Printed with permission: Levin B, et al. *Gastroenterology* 2008;134(5): pg. 1588.

26. Give 7 endoscopic techniques or technical improvements which enhance the colonoscopic sensitivity for CRC screening.

- ➢ Improve sedation
- ➢ Improve personal quality assessment
- ➢ Improve performance skills of colonoscopist
  - ○ Documented intubation of cecum (> 90%)

- Withdrawal time > 7 minutes
- Personal detection rate of adenomatous polyps on screening colonolscopy of average risk persons > 50 years of age (males, 25%; females, 15%)

- Improve bowel cleansing

- Improve insertion
  - Cap-fitted colonosocopy
  - Overtubes

- Improve imaging
  - Wide-angle white light colonoscopy
  - Narrow-band imaging
  - Chromoendoscopy
  - Electronic chromoendoscopy
  - Confocal laser microscopy

27. Give the pharmacological or nutritional agents which have been shown to be effective chemoprevention to reduce the risk of development or redevelopment of colorectal adenomas/CRCs.

- Drugs
  - ASA
  - Coxibs
  - 5-ASA in IBD
  - Hormone replacement therapy (HRT) in post menopausal women

- Nutrients
  - Selenium
  - Calcium (+ vitamin D)
  - Non-western diet (low intake of saturated fats in red meat)
  - High intake of green leafy vegetables
  - Possibly folate, vitamins C, E, B-carotene
  - Probably not dietary fiber

- Exercise

Adapted from: Arber N, and Levin B. *Gastroenterology* 2008;134(4): 1224-1237; and Meyerhardt JA, et al. *JAMA* 2007;298(7): 754-764.

Useful background: The TNM staging system for colorectal cancer and published survival rates for different stages

T – Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into subserosa or into non-peritonealised pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum

N – regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

M- Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage	T N	M	5-year overall survival
Stage I	T1, T2 N0	M0	80-95%
Stage IIA	T3 N0	M0	72-75%
Stage IIB	T4 N0	M0	65-66%
Stage IIIA	T1, T2 NI	M0	55-60%
Stage IIIB	T3, T4 NI	M0	35-42%
Stage IIIC	Any T N2	M0	25-27%
Stage IV	Any T Any N	MI	0-7%

Printed with permission: Tejpar S. *Best Practice & Research Clinical Gastroenterology* 2007; 21(6): pg. 1074.

Useful background: Guidelines for screening and surveillance for the early detection of colorectal adenomas and cancer in individuals at increased risk or at high risk

Risk category	Age to begin	Recommendation	Comment
Increased risk – patients with history of polyps at prior colonoscopy			
➢ Patients with small rectal hyperplastic polyps	-	○ Colonoscopy or other screening options at intervals recommended for average-risk individuals	○ An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow-up
➢ Patients with 1 or 2 small tubular adenomas with low-grade dysplasia	○ 5 to 10 years after the initial polypectomy	○ Colonoscopy	○ The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)
➢ Patients with 3 to 10 adenomas, or 1 adenoma > 1 cm, or any adenoma with villous features or high-grade dysplasia	○ 3 years after the initial polypectomy	○ Colonoscopy	○ Adenomas must have been completely removed. If the follow-up colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent

			examination should be 5 years.
➢ Patients with > 10 adenomas on a single examination	○ < 3 years after the initial polypectomy	○ Colonoscopy	○ Consider the possibility of an underlying familial syndrome.
➢ Patients with sessile adenomas that are removed piecemeal	○ 2 to 6 months to verify complete removal	○ Colonoscopy	○ Once complete removal has been established subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments.

Risk category	Age to begin	Recommendation	Comment
Increased risk – patients with colorectal cancer			
➢ Patients with colon and rectal cancer should undergo high-quality perioperative colonoscopy to ensure there is no synchronous CRC	○ 3 to 6 months after cancer resection, if no unresectable metastases are found during surgery: alternatively, colonoscopy 1 year after the	○ Colonoscopy	○ In the case of nonobstructing tumours, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, CTC with intravenous contrast or DCBE can be used to detect synchronous neoplasms in the proximal colon.

	resection, or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease		
➢ Patient undergoing curative resection for colon or rectal cancer		○ Colonoscopy	○ This colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumours. If the examination performed at 1 year is normal, then the interval before the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 years. Following the examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy. Periodic examination of the rectum for the purpose of

Risk category	Age to begin	Recommendation	Comment
Increase risk- patients with a family history			
➢ Either colorectal cancer or adenomatous polyps in a first-	○ Age 40 years, or 10 years before the youngest	○ Colonoscopy	○ Every 5 years

degree relative before age 60 years or in 2 or more first-degree relatives at any age	case in the immediate family		
➢ Either colorectal cancer or adenomatous polyps in a first – degree relative age 60 or older or in 2 second – degree relatives with colorectal cancer	○ Age 40 years	○ Screening options at intervals recommended for average – risk individuals	○ Screening should be at an earlier age, but individuals may choose to be screened with any recommended form of testing
High risk			
➢ Genetic diagnosis of FAP or suspected FAP without genetic testing evidence	○ Age 10 to 12 years	○ Annual FSIG to determine if the individual is expressing the genetic abnormality and counseling to consider genetic testing	○ If the genetic test is positive, colectomy should be considered
➢ Genetic or clinical diagnosis of HNPCC or individual at increased risk of HNPCC	○ Age 20 to 25 years, or 10 years before the youngest case in the immediate family	○ Colonoscopy every 1 to 2 years and counseling to consider genetic testing	○ Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited MMR gene mutation. It should also be offered when the family mutation is not already known, but 1 of the first 3 of the modified

Bethesda criteria is present.

Risk category	Age to begin	Recommendation	Comment
➢ Inflammatory bowel disease, chronic ulcerative colitis and Crohn's colitis	○ Cancer risk begins to be significant 8 years after the onset of pancolitis or 12 to 15 years after the onset of left-sided colitis (UC or CC)	○ Colonoscopy with biopsies for dysplasia	○ Every 1 to 2 years; these patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease

Abbreviations: CC, Crohn's colitis; CRC, colorectal cancer; CTC, computed tomographic colography; DCBE, double-contrast barium enema; FAP, familial adenomatous polyposis; FSIG, flexible sigmoidoscopy; HNPCC, hereditary nonpolyposis colon cancer (Lynch syndrome); MMR, mismatch repair; UC, ulcerative colitis.

Printed with permission: Levin B, et al. *Gastroenterology* 2008;134(5): pg. 1588.

Useful background:

- The guidelines for CRC screening and surveillance are frequently being updated (U.S. Preventive Services Task Force. *Ann Int* Med 2008:627-37.; Rex DK, et al. *Am J Gastroenterol* 2009:739-50.)

- Even following guidelines, CRC may develop in the interval between polypectomies. These "interval cancers" develop in about 0.6% of persons screened, having polypectomy, and then followed with an appropriate surveillance program (Winawer SJ, et al. *CA Cancer J Clin* 2006:143-59.; Rex DK, et al. *Gastroenterology* 2006: 1865-71).

- While a single hyperplastic polyp normally does not have a malignant potential, followup is necessary if it is serrated, > 10 mm in size, or if these are multiple hyperplastic polyps above the rectosigmoid area

- Colonoscopy screening provides its greatest benefit from the detection of left-sided lesions. In fact, the usefulness of colonoscopy to reduce the risk of right-sided CRC has been challenged.

- Newer endoscopy equipment such as high-definition, narrow band imaging, or chromoendoscopy (including FICS [fujinon intelligent chromoendoscopy system], and the Pentax-scan) have yet to be shown to constantly improve polyp detection and CRC mortality

- Persons with CRC associated with K-ras mutations do not respond as well to anti-ECFR therapy (Jiang Y, et al. *Cancer* 2009. In press.)

Abbreviations: EGFR, epidermal growth factor receptor; FICS, fujinon intelligent chromoendoscopy system; FIT, fecal immunochemical test

28. Give the surveillance recommendations after resection of serrated polyps.

Resected polyp	Recommended surveillance interval
➢ Typical hyperplastic polyp	No surveillance recommended, unless multiple, large and proximally located
➢ Sessile serrated adenoma (non dysplastic)	5 years if < 3 lesions, all < 1 cm size; 3 years if ≥ 3 lesions, or any ≥ 1 cm size
➢ Sessile serrated adenoma with dysplasia (SSAD)	3 years after ensuring complete resection
➢ Traditional serrated adenoma (TSA)	
➢ Suspected type I hyperplastic polyposis (serrated adenomatous polyposis)	1-3 years, with resection of polyps > 5 mm

Printed with permission: Huang C.S. Am J Gastroenterol 2011;106:229-240,Table 3, page 237.

Colonic polyps and tumours: familial forms

Useful background: Genetic testing is part of the standard management of families with FAP. What are the methods used for genetic testing in FAP to confirm the diagnosis of FAP in suspected cases, and to determine if a person from a family with FAP is a gene carrier?

- *In vitro* protein truncation in FAP
  - Detects the presence of truncating mutations in vitro
  - Detects a mutation in 80% to 90% of affected families known to have FAP
  - Near 100% effective in family members once the presence of a mutation has been found in an affected person

- Gene sequencing
  - Often preceded by single-strand conformational polymorphism (SSCP) or denaturing gradient gel electrophorsis (DGGE) to narrow the area of the gene where sequencing is to be performed
  - Up to 95% effective in finding a disease-causing mutation if it is present
  - Near 100% effective in family members once the presence of a mutation has been found in an affected person

- Linkage testing
  - Used if other methods unsuccessful
  - Two or more affected persons from two generations must be living for DNA to be obtained
  - Effective in >95% of families, with >98% accuracy with present linkage markers

- Genotype-phenotype correlations:
  - These have not yet been found to be of precise use in the clinical setting
  - The following correlations have been made:
    - CHRPE (congenital hypertrophy of the retinal pigment epithelium): present in families with mutations distal to exon 9 of the APC gene
    - Dense polyposis: present with mutations in the mid portion of exon 15
    - AFAP/AAPC: found with mutation in the extreme proximal or distal end of the gene
    - Osteomas and desmoids (Gardner's syndrome): more commonly found with mutations in the distal portion of exon 15

Abbreviations: CHRPE, congenital hypertrophy of the retinal pigment epithelium; DGGE, denaturing gradient gel electrophorsis; SSCP, single-strand conformational polymorphism

Adapted from: Doxey BW, Kuwada SK, Burt RW. *Clin Gastroenterol Hepatol*. 2005;3(7):633-41; and Burt R, Neklason DW. *Gastroenterology* 2005;128(6):1696-716.

29. Give the median age of onset of CRC in the 4 phenotypes of FAP.

Phenotype	Age, yrs
○ Profuse	39
○ Intermediate	39-50
○ Attenuated (AFAP)	>50 (R colon)
○ MYH (MAP)	>60 (recessive)

30.Give the clinical management of FAP (familial adenomatous polyposis).

- Genetic testing
  - Consider genetic testing between ages 10 to 12 years, as it will first be clinically useful.
  - May need to begin in first decade of life to determine who should be screened for hepatoblastoma

- GI tract screening
  - Colon cancer risk near 100%
  - Sigmoidoscopy in gene carriers every 1 to 2 years, beginning at age 10 years, or in all at-risk persons if genetic testing is not done or not informative.
  - Colonoscopyevery 2 years beginning at age 20 in families with AFAP/AAPC, or sometimes earlier, depending on the age of polyp emergence in other family members
  - Upper GI tract (5-10% cancer risk for duodenal or peri-ampillary, 0.5% for gastric)
  - Upper GI endoscopy
    - Begin when colon polyps emerge or by age 25 years
    - Repeat every 1 to 3 years, depending on the number of polyps, their size and histology
    - Side viewing should be performed as part of the examination to carefully identify and examine the duodenal papilla.
  - Small bowel
    - Diagnostic imaging should be done before colectomy.
    - Should be done if numerous or large adenomas are present in the duodenum

- Frequency determined by number and size of lesions found
- Pancreas (2% cancer risk) -periodic US (abdominal ultrasound) after age 20
- Hepatoblastoma (1.6 % of children <5 yrs) EUS (endoscopic ultrasound), AFP (alpha-fetoprotein) during first decade of life
- Non GI tract screening
  - thyroid (2%) – annual thyroid exam starting age 20
  - cerebellar meduloblastoma (<1%) – possible periodic head CT

Adapted from: Half EE, and Bresalier RS. *Curr Opin Gastroenterol* 2004;20(1):32-42.

31. Give the recommended interval of duodenoscopic screening (visualization and biopsy) of duodenal polyps in FAP, using the Spigelman staging criteria.

Score	1	2	3
○ Polyp count	1-4	5-20	>20
○ Polyp size (mm)	1-4	5-10	>10
○ Histologic type	Tubular	Tubulovillous	Villous
○ Grade of intraepithelial neoplasia	Low-grade	Intermediate*	High-grade

Grade	Surveillance interval (years)
O	5
I, II	3
III	1
IV	3-6 months – pylorus preserving, pancreas sparing duodenectomy

Stage 0: 0 points, Stage I: 1-4 points, Stage II: 5-6 points, Stage III: 7-8 points, and stage IV: 9-12 points

*Intermediate grade is not existent in actualized classifications of intraepithelial neoplasia

Printed with permission: Schulmann K, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 413.

32. Give the recommended method, age to begin, interval of screening, and management of the person with FAP.

Screening method	Age to begin	Interval	Management
➢ Colonoscopy or flexible sigmoidoscopy	- 10-12 years, or late teens if attenuated FAP	- If polyps are detected, screen annually until colectomy	- Colectomy is recommended when polyps become too numerous to monitor safely, or if polyps are ≥1 cm or exhibit advanced histology. Removal of the rectum should be based on polyp burden and family history
➢ Flexible sigmoidoscopy	- Within two years after colectomy	- Every 6 months to 3 years depending on polyp size and number	- Chemoprevention with NSAIDs may be considered
➢ EGD with end and side viewing instrument	- 20-25 years or at the onset of colonic polyps	- 3 yrs if stage[1] 0, II - 2 yrs if stage[1] III - 6-12 months if stage[1] 4	- Chemoprevention with NSAIDs has been shown to be less effective for upper GI adenomas

Screening method	Age to begin	Interval	Management
➢ Physical examination	- 10 to 12 years	- Annually	
➢ Physical exam, hepatic ultrasound, and alphafetoprotein	- 6 months	- Every 6 months during first decade of life	

➢ Determined by location of suspected desmoids, often abdominal CT	-	When palpable mass or relevant symptoms present

[1]Spigelman staging criteria

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- ➢ Improvement in survival from CRC
  10 yr global benefit LC > RC
  - Split dosing of preparation for colonoscopy is best prep'
  - If you find a prox-polyp-look again, because of likely additional missed lesion
  - I serrated adenoma = risk of 3 adenomas
  - "ADR" – adenoma detection rate
  - ADR for second colonoscopy = 9.8% = pick – up for retroflexed view in cecum
  - ADR correlates well with RC serrated lesion detection

- ➢ "FDAs" (Flat & depressed adenomas)
  - Height < ½ of diameter
  - Aggressive biological behaviour
    - ↓ K Ras and ADC mutations
    - Alternate neoplastic pathways
  - More advanced SX ↑ pathology

- ➢ Watch for LST – lateral spreading tumour

- ➢ Serrated polyps
  - sessile or flat
  - Malignant potential is "significant"
    - LC HP (Hyperplastic polyp)
    - RC SSA (Sessile serrated adenoma)
    - LC TSA (traditional serrated adenoma)
    - SSA/P (without/with dysphasia/cancer)

Serrated = distortion of crypts "boot-/bell-shaped"
Abbreviation: LC, left colon; RC, right colon

- Colon appearance
  - Mucus cap
  - Pale
  - Normal Vascular pattern lost
  - Fuzzy edges

Serrated polyposis syndrome = hyperplastic polyposis (5 sen.serrated polyps proximal to sigmoid colon, of which ≥ 2= 10 mm)

33. Give the relative risk (RR) of 3 GI cancers associated with BRCA2 mutations.

Site	RR
➢ GB cholangiocarcinoma	5.0
➢ Pancreatic cancer	3.5
➢ Gastric cancer	2.6

Source*:* The Cancer risks in BRCA2 mutation carriers.The Breast Cancer Linkage Consortium. *J Natl Cancer Inst.* 1999 Aug 4;91(15):1310.

Lynch syndrome

Useful background: FAP, AFAP (attenuated FAP), MAP

- 70% of the germline defects in APC are inherited, while 30% occur spontaneously
- Mutations or deletions in the APC gene are present in 90% of FAP and 30% of aFAP
- 100% will develop CRC by age 40 years
- With aFAP, the adenomas develop later than with FAP, there are fewer polyps (< 100), the polyps tend to be on the right side of the colon, CRC develops at a later age, and 80% rather than 100% develop CRC
- Screening must be done for gastric fundic glad ployps, periampullary polyps and for duodenal and cancer
- Gardner's syndrome is FAP plus extraintestinal lesions: CHRPE (congenital hypertrophy of the retinal epithelium, throid cancer, sebaceous cysts, supernumerary teeth, osteomas, fibromas, lipomas
- MAP was originally considered to be due to bi-allelic mutations in the base excursion repair gene (Y165C, G382D) MYN (recessive

inheritance), but cases of mono-allelic mutations are being now described (autosomal dominant inheritances)

- 10-500 adenomatous polyps, with a 50% risk of CRC

Useful background: In families not meeting the Amsterdam criteria, three approaches have been suggested:

- The frequent presence of micro-satellite errors in tumour tissue is called micro-satellite instability (MSI). MSI is present in >90% of colon cancers in HNPCC. MSI is present in only about 15% of sporadic colon cancers, and occurs usually by a different mechanism. MSI is easily detected in tumour tissue and is often used as a marker that leads to the suspicion of HNPCC. It has been suggested that MSI testing be done on tumours when one of the "Bethesda criteria" are met. They are as follows:
  - Individuals with cancer in families that meet the Amsterdam criteria
  - Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers*

- Apply MSI testing to the colon cancer tissue in the following situations and when positive, perform mutation findings in DNA from peripheral blood:
  - CRC diagnosis <50 yrs
  - CRC plus one first-degree relative with colon or endometrial cancer
  - CRC plus a previous colon or endometrial cancer
  - With this method, 24% of colon cancer cases will undergo MSI testing of the tumour, and 4% of colon cancer cases will have mutation finding in the MMR gene

- Use a specific logistic model applied to an extended family that includes kindred structure and known cancer cases
  - If the model predicts >20% chance of HNPCC, go directly to mutation finding.
  - If the model predicts <20% chance of HNPCC, first do MSI and if positive, go to mutation finding

The Bethesda criteria were developed to identify persons whose tumours should be tested for microsatellite instability, the tumour fingerprint, the DNA MMR gene mutation.

- Go directly to MMR mutation finding if one of the first three Bethesda criteria for testing tumour tissue is positive, but use age <50 years, rather than 45 yrs. In one study this approach gave a sensitivity of 94%, and a specificity of 49%.
  - Over 95% of families in whom mutations have been found have mutations of either the MSH2 or MSH1 genes, which are responsible

for replication error repair. These types of errors usually occur during DNA replication. They are most often one or several base pairs in length. Mutation of the MMR genes leads to rapid accumulation of relocation error, and frequently are found in DNA repeats, singlets, doublets, or triplets, called microsatellites

- Individuals with CRC and a first-degree relative with CRC and/or diagnosed at age <45 yrs, and an adenoma diagnosed at age <45 yrs
- Individuals with CRC or endometrial cancer diagnosed at age <45 yrs
- Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribform) on histopathology diagnosed at age <45 yrs
- Individuals with signet-ring-cell-type colorectal cancer diagnosed at age <45 yrs
- Individuals with adenomas diagnosed at age <40yrs
- Endometrial, ovarian, gastric, hepatobiliary, or small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter
- Genetic errors that accumulate when the MMR genes are mutated and dysfunctional are quite specific and include genes such as TGFbeta and BAX
- Mutations in any one of the MMR genes leads to HNPCC

Adapted from: Bresalier RS, and Schiller, L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2774.; and Printed with permission: Burt R. *2007 AGA Institute Postgraduate course*: 237.

Useful background:

- Bethesda criteria (for testing tumour tissue)
  - Persons who have had 2 Lynch tumours
  - Persons with a Lynch tumour with a first degree relative under 50
  - Persons with a Lynch tumour in at least 2 first- or second-degree relatives at any age
  - CRC diagnosed before age 50
  - CRC with MSI-related histological features diagnosed before age 60

- The revised Bethesda guidelines
  - Colorectal cancer under 50 years of age
  - Synchronous or metachronous Lynch syndrome related cancers[1] regardless of the age at diagnosis
  - Colorectal cancer that exhibits histological features associated with the MSI[2] prior to age 60 years
  - Individuals with colorectal cancer and a first-degree relative with a Lynch syndrome-related tumour[1], and at least one of the two diagnosed under age 50 years

- Individuals with colorectal cancer who have tow or more first- or second-degree relatives affected with Lynch syndrome related cancers[1], regardless of age

[1]Lynch syndrome related cancers for these guidelines include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), sebaceous gland adenomas, and keratoacanthomas.
[2]MSI associated histologic features include tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

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34. Give the cancer risk and the screening recommendations for 6 Lynch syndrome (HNPCC) tumours.

Cancer	Cancer risk	Screening recommendations
○ Colon	80%	- Colonoscopy, every 1-2 years, beginning at age 20-25 yrs or 10 yrs younger than the earliest case in the family, whichever comes first
○ Endometrial*	43-60%	- Pelvic exam, transvaginal ultrasound and/or endometrial aspirate every 1-2 years, starting at age 25-30 yrs
○ Ovarian	9-12%	- Uncertain
○ Gastric	13-19%	- Upper GI endoscopy every 1-2 years, start at 30-35 yrs
○ Urinary tract	4-10%	- Ultrasound and urinalysis (urine cytology) every 1-2 yrs, starting at age 30-35 yrs
○ Renal cell adenocarcinoma	3.3%	- Same as above
○ Biliary tract and gallbladder	2.0-18%	- Uncertain, possible LFTs annually after age 30 yrs
○ Central nervous system, usually glioblastoma (Turcot syndrome)	4%	- Uncertain, possibly annual exam and periodic head CT in affected families

- Small bowel 1-4% - Uncertain, at least small bowel X-ray if symptoms occur

*Guidelines are empiric, except for colon

Adapted from: Burt RW. *2007 AGA Institute Postgraduate Course:*240.

35. Give the 5 characteristic pathologic features of tumours that are highly suggestive of microsatellite instability (MSI) (Lynch syndrome).

- Lymphocytes infiltrating the CRC tumour
- A Crohn's-like lymphocytic reaction
- Mucinous histology
- Poor differentiation
- Lack of "dirty" necrosis

Useful background: CRC

- There are 3-pathways in the adenoma-CRC pathway: chromosomal instability (CIS) pathway, microsatellite instability pathway (MIS), and the epigenetic pathway.
- With the epigenetic pathway, DNA methylation in the promoter region of genes leads to gene silencing, which is essentially equivalent to inactivating metastasis (Ahnen 09). These epigenetic defects in methylation are replicated through cell division and a defective clone of cells is produced.
- One of the methylation-induced inactivations is in MLH-1, one of the mismatch repair genes
- Hyperplastic polyps (HP) are the earliest colonic lesion in the epigastric pathway
- Large hyperplastic polyps (HP) (>10 mm) on the right side of the colon may develop into serrated adenomas, and have a malignant potential
- 15% of all CRCs are thought to develop through this epigastric pathway of serrated adenomas
- Because both Lynch Syndrome cancers and serrated adenoma cancers make a mismatch repair gene (MLH-1), the tumour morphology may be similar.
- Quantitative Systematic Reviews have shown that guaiac-based fecal occult blood testing (FOBT) reduce CRC mortality by 13-16% on an intention-to-treat basis, and a 25% reduction when adjusted for screening attendance (Source: Hewitson P, Glasziou PP, Irwig L et al. Cochrane

systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): an update. *Am J Gastroenterol* 2008;103:1541-9.)

a) Immunochemical FOBT (iFOBT)

Lesion	Sensitivity (%)
➢ Cancer	66
➢ Dukes' A	50
➢ Dukes' B	70
➢ Dukes' C/D	78
➢ HGD	33
➢ Adenoma ≥ 1 cm	20
➢ Advanced neoplasia	27
○ proximal	16
○ distal	31

➢ Specificity for cancer and for advanced neoplasia > 95%

b) Test characteristics: Cancer

Fecal Hb Threshold	Sensitivity (%)	Specificity (%)
≥ 50 ng/ml	100	84
≥ 75 ng/ml	94	88
≥ 100 ng/ml	88	90

➢ Fecal DNA testing
- ○ Basis for Fecal DNA testing (fDNA)
  - Colorectal cancer is a disease of mutated genes
  - Mutations manifest through 3 pathways:
    - Chromosomal Instability
    - Microsomal Instability
    - Hypermethylation of promoter regions
- ○ Neoplasms shed cells that release DNA and have disordered apoptosis

➢ Issues for Fecal DNA Testing
- ○ Performance is no better than iFOBTs or high-sensitivity guaiac-based tests
- ○ Testing interval not established
- ○ Management of positive fDNA test and negative colonoscopy is uncertain
- ○ Cost is greater than other non-invasive tests

- Radiation risk and CTC (CT colography)
  - Average natural background radiation risk in USA is 3 mSv/year; average CTC effective dose, 2-5 mSv/year (Cash BD. CTC: Life after Acrin—is it time to adopt? *ACG Annual Scientific Meeting Symposia Session* 2009;97-100)
  - Primary tumours affected by radiation (thyroid, breast, lung) are shielded with CTC
  - Rates of case induction by radiation fall dramatically after 35 years of age (Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med*. 2007 Nov 29;357(22):2277-84)
- Histological Imaging can be performed with OCT (optical coherence tomography), LCM (laser confocal endomicroscopy), endocytoscopy.

Abbreviations: LCM, laser confocal endomicroscopy; OCT, optical coherence tomography

Useful background: The screening and management guidelines for Lynch syndrome[1]

Cancer	Screening	Age to start	Interval	Treatment
➢ Colon	Colonoscopy	20-25 yrs (or 10 yrs before the earliest diagnosis in the family)	Every 1-2 years	Consider colectomy if cancer or advanced adenoma is found
➢ Endometrial/ Ovarian	Endometrial biopsy (for pre-menopausal women) and transvaginal ultrasound (preferably day 1-10 of cycle) for premenopausal women	30-35 yrs (or 5-10 yrs before the earliest diagnosis in the family)	Annually	Consider prophylactic TAH/BSO after childbearing Consider oral contraceptives for premeno-pausal women
	CA125	30-35 yrs	Every 6-12 months	

Cancer	Screening	Age to start	Interval
➢ Stomach[2]	EGD	30-35 yrs	Every 1-2 yrs

➢ CNS[2]	MRI	Only if CNS	Every 1-2 yrs
➢ Urinary tract[2]	Pelvic and abdominal US Urinalysis with cytology	symptoms 30-35 yrs 30-35 yrs	Annually
➢ Biliary tract, gallbladder[2]	Liver function tests Small bowel	30-35 yrs	Every 1-2 yrs
➢ Small bowel[2]	enteroclysis	30-35 yrs	Every 1-2 yrs

[1]These guidelines are for individuals with known mismatch repair gene mutations or those who have a strong family history of colon cancer and the tumours demonstrate MSI

[2]The risks for these cancers and limitations of current screening methods should be discussed with patients. If the patient and physician agree, screening for these cancers may be undertaken as outlined.

Abbreviations: TAN/BSO, total abdominal hysterectomy, bilateral salpings-opherectomy; CNS, central nevous system; EGD, esophagogastroduodenoscopy.

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"Let's change the interactions between alerting, orienting and executive functions, and control in a standard curing paradigm."

Grandad

Useful background: Characteristics, associated cancers and genetic testing of Lynch syndrome

Genes	Genetic testing	Lifetime Cancer Risks	Other features reported in some case	
➢ MLH1	Full sequence of the coding	Colon	50-80%	-Sebaceous adenomas, epitheliomas and Keratoxanthomas
➢ MSH2	regions of	Endometrium	20-60%	-Café-au-lait spots
➢ MSH6	MLH1, MSH2, and MSH6	Stomach	11-19%	-Brain tumours
➢ PMS2	Large deletion analysis with Southern blot or MLPA[1]	Ovary	9-12%	
		Hepatobiliary tract	2-7%	Hematological malignancies have been reported in individuals with biallelic mismatch repair mutations
	MSI[2] and IHC[3] for the mismatch repair proteins	Upper urinary tract	4-5%	
		Small bowel	1-4%	
	MLH1 methylation and BRAF testing to help differentiate sporadic MSI tumours from those due to Lynch syndrome	Brain/CNS	1-3%	
		Sebaceous carcinoma of the skin	1%	

[1]Microsatellite instability
[2]Immunohistochemistry
[3]Multiplex Ligation-dependent Probe Amplification

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36. List the tumours and other abnormalities involved in Gardner's syndrome.

- Gardner's Syndrome

- CNS
  - Medalloblastoma

- Eye
  - CHRPE (congenital hypertrophy of the retinal pigment epithelium)

- Mouth
  - Supernumerary teeth

- Thyroid
  - Thyroid papillary tumour

- Skin
  - Desmoid tumours
  - Epidermoid cysts

- Bone
  - Osteomas
- GI
  - Colonic polyps, duodenal polyps
  - Fundic gland polyps

  - Genetics
    - Mutation of the tumour suppressor gene on the long arm of chromosome 5
    - MYH is a base-excision-repair gene on chromosome 1

Peutz-jegher syndrome (PJS), Juvenile polyposis syndrome (JPS) and Cowden syndrome (CS)

37. Give the lifetime cancer risk at GI and non-GI sites for FAP, HNPCC (Lynch syndrome) and Peutz-Jegher Syndrome (PJS).

		FAP (%)	HNPCC (%)	PJS (%)
➢ GI	Stomach	<1	11-19	29
	Duodenum	4-12	-	-
	Small bowel	1	1-4	13
	Pancreas	2	-	36
	Hepatobiliary (hepatoblastoma)	<1	2-7	-
	Colon	~100	~100	39
➢ Non-GI	CNS	<1	1-3	-
	Thyroid	(medulob	(glioblastoma	-
	Adrenal	lastoma)	)	-
	Endometrium	2	-	9
	Ovary	<1	-	21
	Upper urinary tract	-	20-60	-
	Skin	-	9-12	-
	Breast	-	4-5	54
	Lung	-		15
	Testicle (Sertoli	-	1	++
	cell)	-	(sebaceous)	

Adapted from: Burt RW. *AGA Institute Postgraduate Course book* 2007: pg. 235, 237 and 241.

38. Give the clinical characteristics and recommended genetics testing, and screening of persons with PJS.

- General
  - Autosomal dominantly inherited syndrome of histologically specific hamartomatous polyps together with characteristic mucocutaneous pigmentation
  - Occurrence estimated to be 1 on 150,000 live births
  - Arises from mutations of the STK11 (also called LKB1)

- Mucocutaneous pigmentation
  - Occur in over 95% of cases
  - Most common in the perioral and buccal areas (94%), but also occurs:

        - Around the eyes
        - On palmar and plantar surfaces
        - On an around the genetalia and anus
    - Appears in infancy and begins to fade at puberty, except on the buccal mucosa, which provides a clinical feature for diagnosis even in adult life

- GI polyps
    - Histology and morphology:
        - Distinctive histology of hamartomatous polyps
        - May be sessile or pedunculated, ranging in size from mm to cm
    - Distribution
        - Stomach, 38%
        - Small bowel, 78%
        - Colon, 42%
        - Rectum, 28%
    - Clinical presentation
        - Benign complications from the polyps (bleeding, obstruction and intussusceptions) predominate in the first three decades of life
        - Cancer may arise in polyps even though they are hamartomas

- Overall malignancy risk:
    - GI and non-GI cancers are common in PJS, with a combined frequency of all cancers being 93% by age 65 yrs
    - Cancer risks and screening recommendations, which are all empiric, are given under management

- Juvenile polyposis syndrome (JPS) (1/100,000)
    - Multiple juvenile polyps in colon (98%), stomach (14%), duodenum (2%), jejunum and ileum (7%)

- Genetics and recommended genetic testing
    - Arises from mutations of the STK11 (also called LKBI)
    - Disease causing mutations found in this gene in about half of families with the clinical disease, suggesting the possibility of other PJS genes
    - Genetic testing is commercially available

- Clinical management
    - Clinical management involves mainly screening for cancer prevention
    - Empiric guidelines have been developed for organs in which cancer develops
    - Cancer of colon (39%), esophagus (0.5%), stomach (29%), pancreas (36%), breast (54%), ovary (21%), lung (15%), uterus (9%)
    - Adenoma malignum of cervix

- Ovarian sex cord tumours with annular tubules (SCTAT)
- Testicular tumours

Adapted from: Itzkowitz SH, and Rochester J. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006. pg. 2746-7; and 2010, pg. 2181 and 2185.

Useful background: PJS

- Germline mutation in the STK II (LKBI) gene, with mutations seen in 90% of persons with PJS
- 50% of mutations are inherited, and 50% are spontaneous, appearing de novo
- Muco-cutaneous macules may be present at birth on buccal mucosa, lips, peroral region, fingertips or toes (Burke 09)
- Polyps occur in small intestine (> 75%), colon (42%), stomach (38%), and rectum (28%) (colon plus rectum, 70%)
- Clinical presentation age 10-20 years from time of initial small bowel obstruction
- Cerebriform polyps on EGD; microscopicaly, smooth muscle arborization
- Cancer risk (hamartoma-carcinoma sequence) is 90% by age 65
- Sites of cancer development include:
  - Intestinal
    - Colon, 39%
    - Pancreas, 36%
    - Stomach, 29%
    - Small bowel, 13%
    - Esophagus, 0.5%
  - Extra-intestinal
    - Breast,, 54%
    - Ovary 21%
    - Lung, 15%
    - Uterus, 9%
    - Rarely cervix, ovary, testicle

- World Heatlh Organization diagnostic criteria for PJS: any one of the following:
  - 3 or more histologically characteristic PJS polyps
  - 1 or more PJS polyp in a person with a family history of PJS
  - Characteristic and prominent mucocutaneous pigment, in a person with a family history of PJS

- 1 or more PJS, plus characteristic and prominent muco-cutaneous pigmentation

Useful background:

- > 5 juvenile polyps of colorectum; and/ or juvenile polyps throughout the GI tract; and/ or 1 or more juvenile polyps in a person with a family history of JPS.

Useful background: The Hamartomatous polyposis syndromes

Syndrome	Gene (% chance of finding a mutation in proband)	Lifetime cancer risk		Other features
➢ Peutz-Jeghers syndrome (PJS)	STK11 (30-70%)	Breast Colon/rectum Pancreas Stomach Ovarian[1] Small bowel Lung Uterine/cervix[2] Testicle	54% 39% 36% 29% 21% 13% 15% 9% Rare	- Mucocutaneous pigmentation - Histologically characteristic gastrointestinal hamartomas, mostly small bowel, but in all areas
➢ Juvenile polyposis syndrome (JPS)	SMAD4 (20%) BMPR1A (20%) ENG (rare)	Colon Upper GI cancers including stomach, pancreas, and small bowel	68% 21%	- GI juvenile polyps - Features of HHT[4] - Digital clubbing - Congenital defects
➢ Cowden syndrome (CS)	PTEN (80-90%)	Breast Thyroid (especially follicular) Endometrium Kidney	25-50% 10% 5% ↑	- Mucocutaneous papules - Macrocephaly - Hamartomas of the

Colon and upper GI tract	CRC may be ↑	gastrointestinal tract, thyroid, and breast - Lhermitte-Duclos disease

[1]Sex cord tumours with annular tubules; [2]Adenoma malignum; [3]Sertoli cell tumours; [4]Hereditary hemorrhagic telangiectasia

Printed with permission: Burt RW. *2007 AGA Institute Postgraduate Course.* pg. 241.

39. Give the clinical characteristics, genetics and clinical management of persons with juvenile polyposis syndrome (JPS).

- General
  - Juvenile polyps occur in 2% of children. The diagnosis of JP is made with the presence of 10 or more juvenile polyps in the GI tract.
  - At least a third of these will be found to have the autosomal dominantly inherited syndrome
  - The incidence of inherited JP is approx. 1 in 100,000 individuals
  - At least half of the affected families are found to have a disease causing mutation of the SMAD4 gene (also called the DPC4 gene) on chromosome 18 or of the BMPRIA gene. Both of these genes are involved in the TGF beta signaling pathway.

- Clinical characteristics
  - Juvenile polyps:
    - The polyps are most commonly found in the colon, but may occur anywhere throughout the GI tract
    - Multiple juvenile polyps in colon (98%), stomach (14%), duodenum (2%), jejunum and ileum (7%)
    - The full-blown syndrome may be characterized by hundreds of polyps
    - Polyps in JP differ from sporadic juvenile polyps in that new polyps almost always recur after polyps are removed and polyps always occur in adults
    - JP polyps have a smooth surface, are often covered by exudates, may be sessile or pedunculated and range in size from mm to cm's
  - Symptoms: colonic bleeding and anemia usually occur in the first decade of life
  - The risk of colon cancer appears to be many-fold increased, and predominates the clinical presentations after the third decade of life
  - The average age of colon cancer diagnosis is approx 34 yrs

- Gastric, duodenal and pancreatic cancers have been reported in JP, but their association is less certain
- Congenital defects have been noted with the non-familial but not the familial form of the disease. These include:
  - Cardiac abnormalities
  - Cranial abnormalities
  - Cleft palate
  - Polydactyly
  - Bowel malrotations

- Genetics
  - Half of the affected families have a disease causing mutation of the SMAD4 gene (also called the DPC4 gene) on chromosome 18
  - Other genes may be involved (BMPRIA on chromosome 10)

- Colon screening
  - This consists mainly of prevention of benign and malignant complications
  - Only empiric guidelines are available
  - CRC
  - Colonoscopy, beginning with symptoms or in early teens, if no symptoms occur. Interval determined by number of polyps but at least every 3 years once begun

Adapted from: Itzkowitz SH, and Rochester J. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006. pg. 2734-2747; and 2010, pg. 2185.

Useful background: Criteria for phenotypic diagnosis of Cowden Syndrome (CS)

- Germline mutations in PTEN gene seen in 85% of CS affected persons

- > 90% of affected persons have mucocutaneous papillomatous papiles (hamartomas), as well as hamartomas of the infundibulum of the hair follicles (trichilemmomas)

- Other important features of CS include hamratomas of GI tract, tumours of breast and thyroid, macrophaly, and mental impairment

- 40% have involvement of esophagus (glycogen acanthosis), stomach and colon (hamartomas)

- Any part of GI tract from stomach to rectum may have hamartomas, juvenile polyps, adenomas, lipomas, inflammatory polyps, ganglioneuromas, or lymphoid hyperplasia

- A juvenile-like polyp which contains neural components is characteristic for CS (Jass JR. *Pathol Res Pract* 2008:431-447.)

Useful background: JPS

- Germline mutation in either the SMAD4 (MADH4) gene (in 35%) or in the BMPRIA gene (in 25%)
- 20-60% have a family history, and the remainder appear de novo
- The juvenile hamartomatous polyps demonstrate dilated cystic glands, columnar lining, abundant lamina propria which may contain an inflammatory infiltrate
- These juvenile polyps may be seen in JPS, CS, and BRRS on Gorlin's syndrome
- Polyps in colon and stomach
- Colorectal cancer (CRC) risk in JPS
  - 20% by age 25 years
  - 68% by age 60
- With the SMAD4 mutation, 23% have AVMs in brain, lung, and liver, consistent with HHT (hereditary hemorrhagic telangiectasia), and are more likely to have gastric polyps, massive gastric polyps, or gastric cancer

Abbreviation: HHT, hereditary hemorrhagic telangiectasia

40. Give the clinical characteristics, genetics and recommended genetics testing and screening of persons with Cowden syndrome (CS).

- General
  - CS occurs in about 1 in 200,000
  - Autosomal dominant
  - Mutations of the PTEN gene on chromosome 10

- Clinical characteristics
  - Multiple hamartomatous polyps occur in the colon and throughout the GI tract. A number of different types of hamartomas occur:
    - Juvenile polyps (by far the most common)
    - Lipomas
    - Esophageal glycogenic acanthosis

- Inflammatory polyps
- Ganglioneuromas
- Lymphoid hyperplasia

- Colon cancer risk is estimated at 17%. Additionally, this condition must be distinguished from other hamartomatous diseases
- Skin lesions (99%)
- Cowden syndrome is the presence of multiple facial trichilemmomas (the hallmark sign, most commonly around the mouth, nose and eyes):
  - Café-au-lait spots
  - Vitiligo
  - Papillomatous papules
  - Acral keratosis
  - Cysts, as well as squamous cell and basal cell carcinomas
- Oral mucosal lesions
  - These are histologically similar to the trichilemmomas
  - They develop a few years after the skin growths and are present in approximately 85% of patients
  - They include pinpoint, red, flat-topped papules on the outer lips and small, flat, papillomatous or verrucous papules of the oral mucosa, gingiva and tongue
- Thyroid abnormalities:
  - Two-thirds of patients have multinodular goiter histologically arising from nodular hyperplasia or follicular adenomas
  - There is an approximate 3-10% risk of thyroid carcinoma
- Breast lesions:
  - 75% of affected females have breast lesions, including fibrocystic disease and fibroadenomas
  - There is a 30-50% incidence of breast carcinoma, with frequent bilateral occurrence, and a median age at diagnosis of 41 yrs
  - Genitourinary abnormalities (44% of affected women)
    - Multiple uterine leiomyomas (fibroids) and/or bicornuate uterus
- Additional benign soft tissue and visceral tumours have been observed:
  - hemangiomas
  - lipomas
  - lymphangiomas
  - neurofibromas
  - uterine leimyomas
  - meningiomas
- Developmental or congenital abnormalities also occur:
  - hypoplastic mandible
  - a prominent forehead
  - a high-arched palate

- Specific clinical diagnostic criteria have been suggested by the *International Cowden Consortium* for the diagnosis of CS:
  - Pathognomonic criteria
    - Mucocutaneous lesions

    1) Trichilemmomas, facial
    2) Acral keratoses
    3) Papillomatous papules
    4) Mucosal lesions
  - Major criteria
    - Breast carcinoma
    - Thyroid carcinoma (non-medullary), especially follicular thyroid carcinoma
    - Macrocephaly (megalencephaly) (≥95th percentile)
    - Lhermitte-Duclos disease (LDD); cerebellar dysplastic gangliocytoma
    - Endometrial carcinoma
  - Minor criteria
    - Other thyroid lesions (eg: adenoma or multinodular goiter)
    - Mental retardation (IQ≤75)
    - GI hamartomas
    - Fibrocystic disease of the breast
    - Lipomas
    - Fibromas
    - GU tumour (eg: renal cell carcinoma, uterine fibroids or malformation

- Operational diagnosis in a person with mucocutaneous lesions alone if:
  - There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
  - Cutaneous facial papules and oral mucosal papillomatosis, or
  - Oral mucosal papillomatosis and acral keratoses, or
  - Palmoplantar keratoses, 6 or more
    - 2 major criteria but one must include macrocephaly or LDD
    - 1 major and 3 minor criteria
    - 4 minor criteria

- Operational diagnosis in a family where one person is diagnosted with CS
  - The pathognomonic criterion
  - Any one major criterion with or without minor criteria
  - Two minor criteria

- A related syndrome, Bannayan-Ruvalcaba-Riley (BRR) syndrome, is now believed to be related to CS.
  - BRR characteristics:

- Macrocephaly
- Lipomas
  - Pigmented macules on the glans penis
  - Other features of Cowden's syndrome

- BRR also arises from mutations of the PTEN gene

- CS and BBR are referred together as the PTEN hamartoma tumour syndromes (PHTS)
- Screening to detect early cancers associated with CS

Cancer	Cancer risk	Screening recommendations
Colon	-About 17%	No recommendations
Thyroid	-3-10%	Annual thyroid exam, startingin teens
Breast	-25-50%	Annual breast exam, starting at age 25 yrs; annual mammography, starting at age 30 yrs
Uterus/ovary	-Possible increase	Uncertain

Printed with permission: Zbuk KM, and Eng C. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(9): pg. 496.

Useful background: The surveillance recommendations for Cowden syndrome

<u>Women</u>

- Training and education in breast self-exam (BSE) and monthly BSE starting at age 18 years
- Semiannual clinical breast exam starting at age 25 years or 5-10 years earlier than earliest known breast cancer in the family
- Annual mammography and breast MRI screening starting at age 30-35 years or 5-10 years earliest known breast cancer in the family (whichever is earlier)
- Blinded endometrial aspiration

<u>Men</u>

- Annual comprehensive physical exam starting at age 18 years or 5 years younger than the youngest age of diagnosis of a CS cancer in the family (whichever is younger), with particular attention to breast and thyroid exam
- Annual urinalysis; consider annual urine cytology and renal ultrasound, if family history of renal cancer
- Baseline thyroid ultrasound at age 18 years, and annual thereafter

biopsies annually for premenopausal women starting at age 35-40 years, or 5 years before earliest diagnosis of endometrial cancer in the family; annual endometrial ultrasound in postmenopausal women

- Discuss options for risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, extent of cancer risk, and reconstruction options
  - Education regarding the signs and symptoms of cancer
  - Annual dermatologic exam
  - Advise about risk to relatives, and possibility of genetic testing for relatives

Printed with permission: Zbuk KM, and Eng C. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(9): pg. 497.

41. Discuss the ethical issues involved in establishing a colorectal cancer screening program for average risk persons (over age 50 years in Canada).

- Gain in performance skills of operator.
- Better bowel cleansing
- Water instillation
- Insertion
  - Cap-fit colonoscopy
  - Overtubes
- Imaging
  - Wide-angle colonoscopy
  - Narrow-band imaging
  - Chromoendoscopy
  - Electronic chromoendoscopy
  - Confocal laser microscopy

Lower GI bleeding (LGIB)

42. A man who has sex with men (MSM) presents with rectal bleeding, urgency, tenesmus – give 10 possible colonic diagnoses related to HIV/AIDS, and state how you would investigate this patient.

- Infections
  - CMV, HSV, C. difficile, Shigella sp., campylobacter, entameoba histolytica
  - Herpes simplex infection involving the distal rectum
  - Infectious ulcerations due to HSV, CMV, tuberculosis, histoplasmosis, HPV, LGV

- Cancer
  - Anorectal carcinomas are more common in homosexual men than in the general population, and the risk increases dramatically with HIV infection
  - CRC – lymphoma, squamous cell carcinoma
  - Kaposi's Sarcoma
  - Lymphoma
  - Perirectal abscesses
  - Anal fissure
  - Trauma
  - Squamous cell Ca, CRC
  - Infections
    - Idiopathic ulcers
    - Perirectal abscess, fistula
  - Local diseases
  - Bowel diseases
  - Investigation
    - Anoscopy and sigmoidoscopy with mucosal biopsy and with evaluation of anorectal pus for PMNs
    - gram stain for gonococci
    - Tzanck prep, and culture for HSV, VDRL and PCR for C. trachomatis. Biopsy should be performed even if visual inspection of the anal canal is normal, since a normal appearance does not exclude high grade dysplasia.

Printed with permission: Yachimski, and Friedman. *Nature Clinical Practice Gastroenterology & Hepatology* February 2008; 5 (2): pg 81.

43. Give the causes of hematochezia in adults.

Causes	Approximate frequency (%)	Comments
➢ Diverticular disease	30	○ Stops spontaneously in 80% of patients ○ In one series, the need for surgery may be unlikely if <4U red cell transfusion given in 24 h, but is required in 60% of patients receiving >4U in 24h

Causes	Approximate frequency (%)	Comments
➢ Colonic vascular ectasia (AV malformation, angiodysplasia)	25	○ Frequency of these lesions vary widely in clinical series ○ Acure bleeding appears to be more frequently due to lesion in proximal colon
➢ Colitis	10	○ Ischemic colitis often presents with pain and self-limited haemotochezia. Colitis is segmental, most often affecting splenic flexure ○ Bleeding may also occur from other types of colitis, such as Crohn's disease or ulcerative colitis (see Small Bowel question 40) ○ Bloody diarrhoea is most frequent symptom of infectious colitis and inflammatory bowel disease of the colon
➢ Colonic neoplasia/post-polypectomy	10	○ Post-polypectomy bleeding is frequency self- limited, amd may occur ≤14 days after polypectomy

➢ Anorectal causes (including hemorrhoids, varices)	5	○ Anoscopy/proctoscopy should be included in the rectal initial evaluation of these patients
➢ Brisk upper GI bleeding	5	○ A negative nasogastric aspirate does not exclude this possibility
➢ Small bowel sites	10	○ Frequency diagnosed by radiologic studies or enteroscopy after the acute bleeding episode has resolved.

Adapted from: Zuccaro G. *Best Practice & Research Clinical Gastroenterology* 2008; 22(2): pg. 227.

Constipation

44. The causes of constipation may be classified as neurogenic, drug-associated, and metabolic. Give 8 causes of constipation in each category.

- Neurogenic
  - Central
    - Multiple sclerosis
    - Parkinson's disease
    - Cerebral infarction (CVA)
    - Medullary trauma
  - Spinal
    - Cognitive challenge
    - Dementia
    - Meningocele
    - Spinal cord lesions (trauma, tumour)
    - Cauda equina lesions
  - Gut
    - Autonomic neuropathy (paraneoplastic, pseudoobstruction, diabetes)
    - Aganglionosis: congenital (Hirschsprung's) or acquired
    - Cathartic colon (laxative abuse)
    - Narcotic bowel syndrome

- Drug-associated
  - Analgesic: narcotics e.g. opiates ("cathartic colon"), non-narcotics
  - Antacid (aluminum)
  - Anticholinergics (dopaminergics)

- Anti-Parkinson drugs
- Antipsychotics
- Antidepressants (tricyclics, but not SSRIs – serotonin reuptake inhibitors)
- Antidiarrheals
- Antihypertensives (calcium channel blockers, clonidine)
- Antiseizure medications
- Bile acid sequestrants
- Chemotherapeutic agents
- Nutrient supplements: calcium, iron
- 5-HT3 antagonists
- Somatostatin analogs

- Metabolic
  - Diabetes mellitus
  - Glucagonoma
  - Hypothyroidism
  - Hypoparathyroidism
  - Hypopituitarism (panhypopituitarism)
  - Hypocalcemia
  - Hypomagnesium
  - Hypokalemia
  - Heavy metal poisoning
  - Pregnancy
  - Progesterone level cyclic fluctuation (just before menses)
  - Porphyria
  - Low intake of water

Printed with permission: Müller-Lissner S. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 475.

45. Give the investigations which are appropriate for the investigation of persons with constipation.

- History and physical– social, laxative and drug use, psychological assessment, stool chart; full examination including digital rectal exam (DRE)
- Lab tests – Ca++, glucose, TSH, electrolytes, CBC, Mg^{++}
- 3 views of the abdomen
- Colonoscopy, defecating proctogram (defecogram), colonic transit study, EUS, colonic manometry
- Diagnostic imaging
- Manometry, anorectal manometry

- Functional testing, balloon expulsion

Abbreviation: DRE, digital rectal exam

46. Give 10 non-pharmacological treatments of constipation.

- Treat underlying conditions
- Bowel management programs
- Psychological management
- Avoid constipating medications
- Exercise
- Adequate water intake
- Dietary measures
- Biofeedback (pelvic floor retraining)
- Total colectomy with ileorectal anastamosis

47. Give the FDA category of laxatives in pregnancy.

Safe (B)	Caution (C)	Unsafe (D)
○ Lactulose ○ Glycerine ○ Polyethylene glycol (PEG) ○ Bulking agents ○ Bisacodyl	– Saline osmotic laxatives – Castor oil – Senna – Docusate sodium	-Anthraquinones -5HT4 agonists -Prostaglandins (misoprostol)

Adapted from: Cullen G, and O'Donoghue D. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 815.; and Thukral C, and Wolf JL. *Nature Clinical Practice Gastroenterology & Hepatology* 2006; 3(5): pg. 260.; Printed with permission: Kane SV. *AGA Institute 2007 Spring Postgraduate Course Syllabus:*511.

48. Give 5 causes of constipation in pregnancy.

- Hormonal – slow transit
- Mechanical
- Medications
- Lifestyle
  - Reduced exercise
  - Dietary changes
- Pre-existing disease:
  - Chronic slow-transit constipation
  - Irritable bowel syndrome
  - Congenital or acquired megacolon
  - Chronic idiopathic intestinal pseudo-obstruction

Adapted from: Quigley EMM. *Best Practice & Research Clinical Gastroenterology* 2007;21(5): pg. 882.; and Cullen G, and O'Donoghue D. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 810.

49. Give 3 risk factors for the development of incontinence post-partum.

- Vaginal delivery
- Instrumental delivery
- Emergency cesarean section
- Epidural anesthesia
- Perineal laceration

Printed with permission: Quigley EMM. *Best Practice & Research Clinical Gastroenterology* 2007;21(5): pg. 885.

50. Give the approximate frequency of 5 undesirable outcomes after colectomy for chronic constipation.

Undesirable outcomes	Approximate frequency (%)
Abdominal pain	40
Small bowel obstruction	15
Reoperation	10
Fecal incontinence	10

Undesirable outcomes	Approximate frequency (%)
➢ Diarrhea	10
➢ Recurrent constipation	10
➢ Stoma dysfunction	5

Printed with permission: Müller-Lissner S. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 476.

Useful background: Constipation

- Slow proximal colonic transit put normal distal transit suggests slow transit constipation. Normal proximal colonic transit but slow distal transit suggests pelvic dyssynergy or anorectal dysfunction

- Only slow transit constipation will respond to subtotal coletomy with ileorectal anastomosis

- With dilation of both the colon and rectum, as well as normal anal sphincter function proctocolorectomy and an ileoanal anastamosis may be suitable; if anal sphincter function is abnormal, an ileostomy needs to be performed

Irritable bowel syndrome (IBS)

51. Give 10 treatments for IBS.

- Treat any other associated symptoms e.g. pain

- Cognitive behavior therapy

- Medications
  - Anticholingergics
  - Peppermint oil
  - Desipramine
  - Amitryptyline
  - Trimipramine
  - Doxepin
  - TCAs, SSRIs
  - Bulking agents – psyllium, methylcellulose, fiber
  - Osmotic laxatives – M of M, lactulose, PEG, sorbilol, mannitol
  - Stimulant laxatives – Senna, Bisacodyl, castor oil
  - Lubricant – mineral oil
  - CFTR stimulants

- Chloride- channel agonists
- Prostaglandins
- Cholinergics: neostigimine, bethanecol
- 5HT4 agonist
- Prokinetics - dopamine
- Motilin agonist
- Colchicine

Abbreviation: IBC-C, constipation-predominant IBS

Adapted from: Connor BA. *Clin Infect Dis* 2005;41 suppl 8:S577-86.; and Spiller RC. *Gastroenterology* 2003;124(6):1662-1671.

52. Give the diagnostic criteria for functional abdominal pain syndrome (FAPS).

- Presence for at least 3 months, with onset of at least 6 months before diagnosis of:
  - Continuous or nearly continuous abdominal pain; and
  - No or only occasional relationship of pain with physiologic events (e.g. eating, defecation, or menses); and
  - Some loss of daily functioning; and
  - The pain is not feigned (e.g. malingering); and
  - Insufficient symptoms to meet criteria for another disorder of gastrointestinal function that would explain the pain

Printed with permission: Drossman D. *Clinical Gastroenterology and Hepatology* 2008;6:pg 979.

53. Give 5 categories/classes of drugs used for pain in functional GI disorders.

Category	Examples/typical doses	Comments
○ Opiate analgesics	Hydrocodone 5-10mg QID	Avoid if possible ; chronic use should be monitored by pain management physician
○ Central opiate agonists	Tramadol 50mg TID-QID	May cause GI side effects: nausea, vomiting, constipation
○ NSAIDS	Ibuprofen 400mg	Beware dyspepsia, ulcer not

	QID	significant
○ Tricyclics SSRI/SNRI	Paroxetine 20mg daily Duloxetine 30-60mg daily	Good choices if coexisting panic disorder or depression
○ Anticonvulsants	Gabapentin 300mg TID	Sleepiness a problem with higher doses
	Pregabalin 50-100mg TID	

Printed with permission: Schiller LR. *2008 ACG What's new in GI pharmacology course book*: pg. 34.

54. Give the ROME III criteria for IBS.

- Symptom onset at least 6 months prior to the diagnosis
- Recurrent abdominal pain or discomfort for at least 3 days of the month in the last 3 months
- Association with at least 2 of the following:
  - Improvement with defecation
  - Onset associated with change in stool frequency
  - Onset associated with change in stool form

Printed with permission : Longstreth GF, Thompson WG, Chey WD, et al. *Gastroenterology* 2006;130(5):1480-1491.

55. Give 3 pathophysical abnormalities associated with post-infectious IBS.

- ↑ intestinal permeability
- ↑ intestinal IL-1b
- ↑ enterochromafin cells
- ↑ serotonin blood levels after food

Adapted from: Connor BA. *Clin Infect Dis* 2005;41suppl 8:S577-86.; and Spiller RC. *Gastroenterology* 2003;124(6):1662-1671.

56. Outline guidelines to enhance the physician-patient relationship.

- Listen actively
  - Focus on the patient's world, ie, "Sit where the patient sits"

- Allow the patient to tell his/her story without interruption
- Seek to understand the symptom experience within a biopsychosocial context

- Identify and respond to the patient's concerns and expectations
  - What do you think is going on?
  - What are your worries and concerns?
  - What are your expectations from me?

- Validate the patient and illness
  - Acknowledge the pain
  - Acknowledge the impact of the illness
  - Provide a physiologic explanation of the symptoms

- Set realistic and consistent limits when ordering tests
  - "Don't just do something, stand there"
  - Order tests on the basis of objective data rather than pain severity

- Psychosocial assessment
  - Why is the patient coming now?
  - Is there a history of traumatic life events?
  - What is the impact of the pain on quality of life?
  - What is the role of family or culture?
  - What are the patient's psychosocial resources?

- Help the patient take on responsibility for the care
  - Involve patient in treatment options
  - "How are you managing with your pain?" rather than "How is your pain?"

- Provide some continuity of care (along with primary care provider)

Printed with permission: Drossman D. *Clinical Gastroenterology and Hepatology* 2008;6:pg 980.

Useful background: IBS, probiotics, and antibiotics

- For benefit, NNT=4 (Moayyeddi P, Ford AC, Talley NJ et al. The efficacy of probiotics in the therapy of irritable bowel syndrome: a systematic review. *Gut* 2008)

- Systematic Review: many sub-optimal study designs; 2 high quality studies suggested that only Bifidobacter infantis 35,624 showed benefit in IBS (Brenner DM, Moeller MJ, Chey WD et al. The utility of probiotics in

the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol* 2009;104(4):1033-49).

- Rifaximin increases IBS improvement from 20% with placebo, to about 40% (Pimentel M, Park S, Mirocha J et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med.* 2006 Oct 17;145(8):557-63).

What's new: Irritable bowel syndrome

- Persons with IBS (particularly diarrhea-predominant or mixed diarrhea/constipation) may have diverticulitisis (9% of males and 17% of females with IBS), but the presence of IBS is not associated with an increased risk of diverticulitis (Jung et al., 2010; 105: 652-661).

- Traditionally, constipation has been classified into normal transit, slow transit, and functional defecatory disorders. This is not an ideal approach, since the changes in slow transit do not necessarily reflect problems with motor function, and colonic tone and compliance (presence-volume relationships) were not taken into account. Addressing these issues, a new mechanistic cliassification is suggested based on 1) fasting phasic activity and tone; 2) phasic activity and tonic postprandial high amplitude contractions, and respomses (Ravi et al., GE 2010; 138: 89-97).

- A number of new features have been suggested in the pathogenesis of IBS (Ohman & Simran, 2010):
  - Innate immunity – increased numbers or altered functions of innate immunity cells (innate cells, monocytes/monocytes/macrophages, CD3+ or CD4+ T cells, CD8+ T cells, or B-cells in the small and/or large intestine, and in the blood).
  - Intestinal permeability – decreased expression in the jejunum of the tight junction protein ZO1 (aka zonula occludins protein)
  - Neuroimmune interactions – increased number of sensory nerve fibres expressing the capsaicin receptor TRPV1
  - Microbiotica – increased risk of IBS after enteric infection, abnormalities in fecal microbiotica

Diverticular disease

57. Describe the stages of diverticular disease.

- Stage 0 — Development of diverticular disease
- Stage I — Asymptomatic disease
- Stage II — Symptomatic disease
  a. Single episode
  b. Recurrent
  c. Chronic (pain, diarrhea, IBD overlap/SCAD)
- Stage III — Complicated
  Abscess
  Phlegmon
  Obstruction
  Fistulization
  Bleeding
  Sepsis
  Stricture

Abbreviation: SCAD, segmented colitis associated with diverticulum

Printed with permission: Sheth AA, Longo W, and Floch MH. *AJG* 2008;103: pp 1551.

"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

58. Give a CT and a clinical classification of diverticulitis (e.g. Hinchey, Buckley, and EAES).

a) Hinchey classification (perforated diverticulitis)

	CT findings
○ Stage I	– Pericolic abscess or phlegmon
○ Stage II	– Pelvic, intra-abdominal or retroperitoneal abscess
○ Stage III	– Generalized purulent peritonitis

- Stage IV – Generalized fecal peritonitis

Printed with permission: Sheth A A, Longo W and Floch MH. *AJG* 2008;103: pp 1551.

b) Buckley classification

	CT findings
Mild	– Bowel wall thickening, fat stranding
Moderate	– Bowel wall thickening >3 mm, phlegmon or small abscess
Severe	– Bowel wall thickening > 5 mm, frank perforation with subdiaphragmatic free air, abscess > 5 cm

c) EAES clinical classification

	Clinical description	Recommended diagnostic testing
➢Grade I ○ Symptomatic, uncomplicated disease	-Fever, crampy abdominal pain	Colonoscopy *vs* barium enema to rule out malignancy, colitis
➢Grade II ○ Recurrent, symptomatic disease	-Recurrence of above	CT scan *vs* barium enema
➢Grade III ○ Complicated disease	-Abscess -Hemorrhage -Stricture -Fistula -Phlegmon -Purulent and fecal peritonitis -Perforation -Obstruction	CT scan

Abbreviation: EAES, European Association for Endoscopic Surgeons

Printed with permission: Sheth AA, Longo W, and Floch MH. *AJG* 2008;103: pp 1551-2.

Useful background: IBS

- In IBS, hyperanalgesia and/ or the cognitive process of hypervigilance towards adverse events occurring in the viscera alters the perception towards, for example, pain or distention (Naliboff BD, et al. *Gut* 1997:505-12).

- A community-based study has shown that psychological factors, including somatization, are strongly associated with IBS (Choung RS, et al. *Am J Gastroenterol* 2009.).

- Useful psychological therapy includes cognitive behavioural therapy, dynamic psychotherapy, and hypnotherapy (Brandt LJ, et al. *Am J Gastroenterol* 2009:S1-35.; Lackner JM, et al. *Clin Gastroenterol Hepatol* 2008:899-906.; Ford AC, et al. *Gut* 2009:367-78).

- The fecal microbiota is altered in IBS patients, as compared with healthy persons (Kassinen A, et al. G*astroenterology* 2007:24-33).

- A proportion of IBS patients have associated small intestinal bacterial overgrowth (SIBO). Eradication of the SIBO may improve IBS symptoms (Pimental M, et al. *Am J Gastroenterol* 2003:412-9.; Lembo A, et al. *Gastroenterology* 2008;134).

Abbreviation: SIBO, small intestinal bacterial overgrowth

Useful background:

- How does Clostridium difficile cause pseudomembranous colitis in a patient with a history of antibiotic use?
  - Antibiotics deplete regular gut microbiotica, which normally outnumber the C.*difficile* which is present.
  - C.*difficile* can resist antibiotics as a spore and then will outgrow normal microbitica when antibiotics are discontinued.
  - Toxins A and B are produced by the greater numbers of C.*difficile* ,cause diarrhea.

59. For acute post-operative megacolon (Ogilvie Syndrome), and for chronic megacolon, give the causes and the medical management.

- Acute
  - Causes
    - Severe underlying medical or surgical illness

- Increased age
- Increased BMI
- Use of patient-controlled analgesia

- Treatment
  - Neostigmine 2mg IV over 3-5 min with ECG monitoring to detect bradycardia. If no response in 4 minutes, repeat once (response rate>80%); if no response, perform decompression colonoscopy.
  - Contraindications to neostigmine: signs of colonic ischemia or perforation, bronchospasm, bradycardia, creatinine >3mg/dl, pregnancy.
  - Reduce the 35% risk of recurrence of megacolon by using 30g/dayof PEG electrolyte solutions. There is no proven benefit of placement of decompression tube.

- Chronic megacolon
  - Causes
    - Occurs rarely in hospitalized patients with neurological disorders, diseases of intestinal smooth muscle, or may be idiopathic.
    - May be associated with disintegration of enteric nerves, or atrophy of the collagenous connective tissue membrane of the myenteric plexus and muscularis propria
  - Treatment
    - PEG electrolyte solution is useful;neostigmine, fibre and lactulose solution are ineffective.

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  - Causes
    - Severe underlying medical or surgical illness
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    - May be associated with disintegration of enteric nerves, or atrophy of the collagenous connective tissue membrane of the myenteric plexus and muscularis propria
  - Treatment
    - PEG electrolyte solution is useful; neostigmine, fibre and lactulose solution are ineffective.

61. Give 4 proposed pathophysiologic mechanisms for acute intestinal pseudo-obstruction.

- Noxious stimulation cause reflex motor inhibition (through splanchnic afferents)
- ↑ sympathetic motor input to the intestine (↓ contract)
- ↑ or ↓ parasympathetic motor activity to the intestine (↓ relaxation or ↓ contraction)
- ↑ peripheral μ opioid receptors stimulation by endogenous or exogenous opioids (initially intestinal activation, followed by prolonged inhibition preventing contraction)
- ↓ nitric oxide release from inhibitory motoneurons (↓ relaxation)

Adapted from: Camilleri, Michael. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2697.

62. Give the endoscopic differentiation between UC and Crohn's colitis, in terms of distribution, inflammation, ulceration, and appearance of colonic lumen.

Variable	Ulcerative colitis	Crohn's disease
➢ Distribution	○ Diffuse inflammation	- Rectal sparing
	○ Extends proximally in continuity from the anorectal junction	- "skip" lesions

➢ Inflammation	○ Diffuse erythema ○ Loss of vascular markings with ○ Mucosal granularity or friability	- Focal /asymmetric, "cobblestoning" - Granularity and friability
➢ Ulceration	○ Small ulcers in a diffusely inflamed mucosa; deep, ragged ulcers in severe disease	- Aphthoid ulcers - Linear/serpiginous ulceration - Intervening mucosa is often normal
➢ Colonic lumen	○ Narrowed in long-standing chronic disease ○ Strictures are rare	- Strictures are common

Adapted from: Su, Chinyu and Lichtenstion, Gary R. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2514.

63. Give the differential diagnosis of the causes of upper and lower gastrointestinal bleeding in persons with HIV/AIDS (excluding non-AIDS specific diagnoses).

- Esophagus
  - Infection
    - *Candida**
    - Cytomegalovirus*
    - Herpes simplex
    - Idiopathic ulcer

- Stomach
  - Infection
    - Cytomegalovirus*
    - Cryptosporidiosis
  - Infiltration
    - Kaposi's sarcoma*
    - Lymphoma

- Small intestine
  - Infection
    - Cytomegalovirus*
    - *Salmonella* sp.
    - *Cryptosporidium*
  - Infiltration
    - Kaposi's sarcoma*

- Lymphoma

- Colon
  - Infection
    - Cytomegalovirus*
    - *Entamoeba histolytica*
    - *Campylobacter*
    - *Clostridium difficile*
    - *Shigella* sp.
    - Idiopathic ulcerations
  - Infiltration
    - Kaposi's sarcoma*
    - Lymphoma

*More frequent

Adapted from: Wilcox, C. Mel. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg 676.

Radiation damage

64. Give the symptoms associated with 4 types of lesions associated with chronic radiation enteritis.

Lesion (s)	Symptoms
➢ Stricture	○ Obstruction
➢ Abscess	○ Infection
➢ Fistula	○ Fistulization
➢ Ulceration	○ Bleeding
➢ Mucosal damage	○ Malabsorption

Adapted from: Cho, L Chinsoo., and Antoine, John E. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 819.

Intra-abdominal abscesses

65. Give 6 common causes of intra-abdominal abscesses.

- Perforated
  - Stomach/ duodenum - peptric ulcer)
  - Small bowel - Crohn disease
  - Colon - diverticulitis
  - Appendix - appendicitis
  - Gallblasser - cholecystectomy
- Trauma
- Tumour

Adapted from: Minei, Joseph P. and Champine, Julie G. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006; pg. 526.

66. Give 8 clinical risk factors for intra-abdominal abscess formation.

- Systemic factors
  - Increasing age
  - Preexisting organ dysfunction
  - Transfusion
  - Malnutrition
  - Chronic Glucocorticoid use
  - Underlying malignancy

- Local factors
  - Severity of illness/infection
  - Delay to surgery for underlying disease
  - Severity of trauma
  - Formation of an ostomy
  - Nonappendiceal source of infection

Adapted from: Minei, Joseph P. and Champine, Julie G. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006; pg. 526.

67. Give 10 causes of fecal incontinence.

- Rectum
  - Congenital abnormalities of the anorectum
  - Fistula
  - Rectal prolapse
  - Anorectal trauma
  - Fissure – treatment (Botoxin)
  - Childbirth injury
  - Surgery (including hemorrhoidectomy)
  - Sequelae of anorectal infections
  - Crohn's disease

- Diarrhea/overflow from constipation

- Central nervous system processes
  - Dementia
  - Encopresis (childhood)
  - Mental retardation
  - Stroke
  - Brain tumour

- Spinal cord injury
  - Multiple sclerosis
  - Tabes dorsalis
  - Cauda equina lesions

- Pudendal nerve damage
  - Polyneuropathies
  - Diabetes mellitus
  - Shy-Drager syndrome
  - Toxic neuropathy
  - Traumatic neuropathy
  - Perineal descent

Printed with permission: Schiller, L. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 202.

68. Give 20 extraintestinal manifestations of IBD.

- CNS –depression

- Malignancy
  - Colorectal cancer, small bowel adenocarcinoma

- Lymphoma
- Hepatosplenic lymphoma
- Cholangiocarcinoma

- Musculoskeletal
  - Peripheral arthropathy
  - Ankylosing spondylitis
  - Sacroiliitis
  - Clubbing
  - Avascular necrosis (osteonecrosis)
  - Osteopenia, oseoporosis
  - Osteomalacia

- Ophthalmologic
  - Uveitis/iritis
  - Episcleritis
  - Scleritis
  - Conjunctivitis
  - Retinal vascular disease
  - Cataracts, glaucoma (may be related to steroid use)

- Dermatologic
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Angular stomatitis
  - Aphthous stomatitis
  - Pyostomatitis vegetans
  - Psoriasis
  - Metastatic Crohn's
  - Sweet's syndrome

- Hematologic
  - Iron deficiency anemia
  - Autoimmune hemolytic anemia
  - Anemia of chronic disease
  - Leukocytosis or thrombocytosis
  - Leukopenia or thrombocytopenia
  - Hypercoagulable state

- Hepatobiliary
  - Drugs (e.g. azathioprine, methotrexate, α-TNF, salazopyrine)
  - Metastatic malignancy
  - Granulomatous autoimmune hepatitis
  - Primary biliary cirrhosis (PBC)
  - Liver abscess

- Hepatic amyloidosis
- Hepatic granulomas
- Steatosis, (NAFLD, NASH)

- Blood vessels
  - Portal vein thrombosis
  - Budd-chiari syndrome

- Biliary
  - Primary sclerosing cholangitis (PSC – see Hepatobiliary section for discussion of secondary sclerosing cholangitis [SSC])
  - Cholangiocarcinoma
  - Gallstones

- Genitourinary
  - Stones
  - Amyloid
  - Interstitial nephritis
  - Fistulae

- Nutrition/growth defects

- Psychological

- Ob/gyne'
  - Infertility
  - Low birth weight
  - Preterm delivery
  - Drug effects (MTX, thalidomide)
  - Amenorrhea
  - Vaginal fistulae

Permission granted: Su, Chinyu and Lichtenstion, Gary R. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2536.

"It is highly feasible to simplify complex issues."

Grandad

69. Give the lesions, syndromes or diseases associated with four types of vascular malformations, based on the most affected vascular structure.

Most affected vascular structure	Lesions, syndrome, disease
➢ Venous	○ Varices ○ Haemorrhoids
➢ Capillary	○ Gastric antral vascular ectasia ○ Portal gastropathy
➢ Arteriovenous	○ Angiodysplasia ○ Teleangiectasia
➢ Arterial	○ Dieulafoy's lesion ○ Ehlers-Danlos syndrome ○ Pseudoxanthoma elasticum

Printed with permission: Regula, Jaroslaw. et al.*Best Practice & Research Clinical Gastroenterology* 2008;22(2): pg. 314.

70. Give a comparison of the 2 major types of peripheral arthropathy associated with UC.

Feature	Type 1 (Pauciarticular)	Type 2 (Polyarticular)
○ Frequency in UC	35%	24%
○ Number of joints affected	<5	≥5
○ Joints affected	Mainly large joints Knee>ankle>wrist>elbow>MCP>hip>shoulder	Mainly small joints MCP>knee>PIP>wrist>ankle>elbow>shoulder
○ Duration of attacks	<10 wk (median 5 wk)	Months to years (median 3 yr)
○ Association with bowel disease activity	Related	Unrelated

Abbreviation: MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint

Adapted from: Su, Chinyu et al. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2537.

71. Give 8 predictive factors for non-adherence to therapeutic recommendations in patients with UC.

- Predictive factors
  - Patient
    - Depressed
    - New patient status
    - Male gender
    - Single status
    - Younger age
    - Full-time employment
  - Drug
    - Three times daily dosing
    - Four or more concomitant medications
  - Disease
    - Left-sided disease
    - Lower disease duration
  - MD-patient relationship

Adapted from: Hawthorne, A.B., Rubin, G., and Ghosh S. *Aliment Pharmacol Ther* 2008; 27**:** pg 1159.

72. Give 6 medications used for patients with microscopic colitis, and comment.

- Medication
  - Loperamide (or other antidiarrheals)
  - Bismuth subsalicylate
  - Mesalamine
  - Cholestyramine
  - Budesonide
  - Prednisone
  - Azathioprine/6-mercaptopurine
  - Methotrexate

Source: Chande, N. *Canadian Journal of Gastroenterology* 2008; 22: pg 687.

Useful background: Classification of colorectal polyps

- Mucosal lesions
  - Adenoma
    - Tubular
    - Tubulovillous
    - Serrated villous
  - Carcinoma
    - Carcinoma in situ
    - Intramucosal
  - Invasive
  - Hyperplastic
  - Inflammatory
  - Juvenile (retention)
  - Peutz-Jeghers (hamartomas)
  - normal mucosa in a polypoid configuration

- Submucosal Lesions
  - Colitis cystica profunda
  - Pneumatosis cystoides intestinalis
  - Lymphoid polyp (benign and malignant)
  - Lipoma
  - Carcinoid
  - Metastic neoplasms

Adapted from: Itzkowitz, Steven H. and Rochester, Jeremy. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2714.

73. Give the recommended age of onset (years) and interval (every x years) for CRC screening for each of the following.

Group	Age	Interval
➢ Average risk	50	10
➢ Family history:		
○ one first-degree relative (parent, sibling or child) with a CRP or AP (adenomatous colonic polyp) at age < 60 or 10 yr younger than the earliest diagnosis in family	40	5
○ one first-degree relative (parent, sibling or child) with a CRP or AP (adenomatous colonic polyp) at age > 60	40	10

Group	Age	Interval
○ two first-degree relatives with CRC at any age	40	5
○ two second-degree relatives (grandparents, aunt/uncle) with CRC at any age	40	10
○ one second degree or third-degree relative (great-grandparent or cousin) with CRC at any age	40	10
○ Syndromic familial risk:		
familial adenomatous polyposis (FAP): genetic diagnosis, or clinical diagnosis from family history	10	1-2
○ HNPCC: genetic diagnosis, or clinical diagnosis from family history	20, or 10 yr earlier than the youngest age of CRC in the family	1-2

Source: *World Gastroenterology Organization and International Digestive Cancer Alliance, chaired by Professor S. Winawek, USA*.

Useful background: Colorectal cancer

- Three FOBT RCT's performed in 1993 to 1996 demonstrated a 13-21% reduction in CRC mortality (Winawer 09). The performance characteristics (sensitivity and specificity) of FIT (fecal immunochemical test) is comparable to FOBT1, without the need for dietary changes three days before FOBT.

- CRC screening may be stopped at age 70 or 75, or at a time based on serious comorbidities

- Persons of African heritage have a risk of CRC shifted to an earlier age than do Caucasians, and their screening of African Canadians should begin at age 45.

- The performance of screening colonoscopy done by skilled endoscopists or appropriately selected persons detects adenomas in approximately 15% of women and 25% of men, with 5-10% advanced adenomas (> 10 mm, villous, or with high grade dysplasia), < 1 % cancers, and a

complication rate (perforation or bleeding) of about 1 per 1000 colonoscopies

- Post polypectomy, surveillance must be continued.

- Post polypectomy surveillance recommendations:
  - Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years. An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow up.
  - Persons with one or two small tubular adenomas (<1cm) , and with only low grade dysplasia should have their next follow up colonoscopy in 5 to 10 years. The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician).
  - Patients with 3 to 10 adenomas, or any adenoma 1 cm, or any adenoma with villous features, or high grade dysplasia should have their next follow up colonoscopy in 3 years
  - If the follow up colonoscopy is normal or shows only one or two small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years.
  - Persons who have more than 10 adenomas at one examination should be examined at a shorter (<3 years) interval established by clinical judgement, and the clinician should consider the possibility of an underlying familial syndrome.
  - Persons with sessile adenomas that are removed piecemeal should be considered for follow up at short intervals (2 to 6 months) to verify complete removal.
  - Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment.
  - More intensive surveillance is indicated when the family history may indicate hereditary nonpolyposis colorectal cancer.
  - Every 5-10 years, except every 3 years for multiple, large, villous and proximal initial lesions.
  - Number- for each additional adenoma, OR=1.32
  - Size- for each additional 10 mm adenoma size, OR=1.56

- Villous – OR=1.40
- Proximal – OR=1.68

Note: Sessile serrated adenomas and serrated sessile hyperplastic polyps may have malignant potential.

Source: Winawer, Sidney J. Screening and surveillance for colorectal cancer: review and rationale. *2009 ACG Annual Postgraduate Course:*21-25.

74. Give 5 inherited colon cancer syndromes, and for each give the affected gene (s), and the demonstrated mutation frequency (%) in the index case, and the likelihood (%) of finding a mutation in the index case.

Syndrome	Gene(s)	Demonstrated mutation frequency (%) Index Case
○ FAP, AFAP	-APC, attenuated APC (dominant)	90
○ MAP	-MYH (recessive)	100
○ HNPCC	-MLH1, MSH2, MSH6	50-70
○ Peutz-Jegher	-Germline mutation of serine/threonidine kinase gene (STK11) or chromosome 19	50
○ Juvenile polyposis	-SMAD4 on chromosome 8; BMPR1A,on chomrosome 10	50
○ Cowden syndrome	-PTEN	90

Abbreviations: FAP, familial adenomatous polyposis; AFAP, attenuated familial adenomatous polyposis; MAP,modified adenomatous polyposis; HNPCC, hereditary non-polyposis colon cancer (Lynch syndrome)

Source: World Gastroenterology Organization and International Digestive Cancer Alliance, chaired by Professor S. Winawek, USA.

Useful background: Polyposis syndrome

- Polyposis syndromes broken down into the adenomatous and hamartomatous subtypes

Syndrome	Inheritance pattern	Polyp type	Commercial gene Mutation testing	Extra-intestinal tumours
FAP	AD	Adenomatous	APC	Yes
AFAP	AD	Adenomatous	APC	Yes
MAP	AR (AD)	Adenomatous	MYH	Yes
PJS	AD	Hamartomatous: Peutz-Jeghers polyps	STK11	Yes
JPS	AD	Hamartomatous: Hamartomatous: juvenile	SMAD4 or BMPR1A	Yes
CS	AD	Hamartomatous:juvenile, ganglioneuroma, lipoma, hyperplastic	PTEN	Yes

Abbreviations: AD, autosomal dominant; AR, autosomal recessive

- FAP, a FAP, HNPCC and MAP are adenomatous polyp syndromes, PJS and JPS are hemartomatous and CS includes hemartomatous, juvenile, ganglioneuronia, lipoma or hyperplastic polyps
- Gene mutation testing includes: FAP and a FAP, APC gene; HNHCC, mismatch repair gene; MAP, MYN gene; PJS, STKII; JPS, SMAD4 or BMPRIA; CS, PTEN

Abbreviations: CS, Cowden's syndrome; FAP, familial adenomatous polyposis; HNPCC, Lynch syndrome; JPS, juvenile polyposis syndrome ; MAP, MYH-associated polyposis; PJS, Peutz-Jegher's syndrome

Source: Burke, Carol A. Polyposis syndrome: making sense of genetic testing. *2009 ACG Annual Postgraduate Course*: 192-196.

Useful background: Lower GI bleed (LGIB)

The seven most common colonic sources of severe hematochezia (421 colonic cases) (Expressed as percent of colonic sources)

Source	(%)
➢ Diverticulosis*	30
➢ Internal hemorrhoids*	12
➢ Ischemic colitis	12
➢ Rectal ulcers*	9
➢ UC, Crohn's, other colitis	7
➢ Colon, angiomas/XRT*	7
➢ Other LGI sources*	5

Abbreviation: LGIB, lower GI bleed

Source: Jensen DM. Lower GI. *2009 ACG Annual Postgraduate Course*:123-129.

75. Give a summary of drugs commonly used for irritable bowel syndrome and diarrhea during pregnancy.

Drug	Pregnancy use category	Usual dosage	Additional comments
➢ Tegaserod	B	6 mg twice daily	Limited data; should be considered only when other measures fail to control constipation – predominant irritable bowel syndrome
➢ Loperamide	B	2-4 mg daily or after each unformed stool	Antidiarrheal agent of choice during pregnancy
➢ Diphenoxylate with atropine sulphate	C	1-2 tablets four times daily	Should be avoided during pregnancy. Contains 2.5 mg diphenoxylate plus 0.025 mg atropine per tablet
➢ Dicycloverine (dicyclomine)	B	10-20 mg four times daily	Should be reserved for women with refractory symptoms

➢ Hyoscyamine	C	0.125-0.250 mg every 6 h as needed	Should be reserved for women with refractory symptoms
➢ Tricyclic antidepressants	C/D	Dose differs according to retail brand	Questionable safety in pregnancy; use should be limited to the severely symptomatic

Printed with permission: Thukral, Chandrashekhar., and Wolf, Jacqueline L. *Nature Clinical Practice Gastroenterology & Hepatology* 2006; 3(5): pg. 261.

76. Give 4 symptoms and signs of diverticular disease.

Complication	Signs and symptoms	Signs
➢ Diverticulitis	○ Pain, fever & constipation or diarrhea (or both)	○ Palpable tender colon, leukocytosis
➢ Pericolic abscess	○ Pain, fever (with or without tenderness) or pus in stool	○ Tender mass, guarding, leukocytosis, soft tissue mass on abdominal films or ultrasonograms
➢ Fistula	○ Depends on site; dysuria, pneumaturia, fecal discharge on skin or vagina	○ Depends on site; fistulogram, methylene blue
➢ Perforation	○ Sudden severe pain, fever	○ Sepsis, leukocytosis, free air
➢ Liver abscess	○ Right upper quadrant pain, fever, weight loss	○ Tender liver, tender bowel or mass, leukocytosis, increased serum alkaline phosphatase, lumbosacral scan (filling defect)
➢ Bleeding	○ Bright red or maroon blood or clots	○ Blood on rectal examination, sigmoidoscopy, colonoscopy, angiography

77. Give 4 complications for colorectal self-expandable metal stents. The mean % incidence is shown for your interest.

Complication	Mean incidence (%)
➢ Re-obstruction	10
➢ Migration	10
➢ Perforation	4
➢ Bleeding	5
➢ Pain	5
➢ Death	1

Printed with permission: Baron, Todd H., et al. *Best Practice & Research Clinical Gastroenterology* 2004: pg. 220.

What's new: New developments in endoscopic surveillance

New techniques have been introduced that increase the sensitivity and specificity of endoscopic surveillance.

- Chromoendoscopy
  - Dyes to stain the colonic mucosa.
  - Sensitive and so can detect more dysplasia per (targeted) biopsy
  - Effective surveillance method.63-65

- Narrow band imaging
  - Interference filters to illuminate the mucosa in narrow red, green and blue
  - Better visualization of the mucosal structure and vascular networks
  - Improve in the detection of dysplasia

- Autofluorescence imaging
  - Blue light for the excitation of tissue specific autofluorescence.
  - Superior to conventional endoscopy for detecting dysplasia.70

- Endomicroscopy enables
  - Imaging of the microarchitecture of the colonic mucosa and vasculature
  - Using a combination of chromoendoscopy and endomicroscopy, Kiesslich *et al*, reported a 4.75 fold increased detection rate of neoplastic lesions compared with conventional colonscopy alone.72

Source: *Gastroenterology and Hepatology* 2009; 6:672

78. Give the endoscopic and pathological features of five types of dysplasia in patients with IBD.

Lesion	Endoscopic	Pathological features	Approximate risk for CRC
➢ Sporadic adenoma	○Circumscribed polypoid lesion, pedunculated or sessile ○Typically outside the actively or previously inflamed colonic mucosa	- Circumscribed lesion - tubular, tubulovillous or villous architecture - crypts uniformly lined with adenomatous epithelium	5%
➢ DALM, adenoma like	○Circumscribed polypoid lesion ○Mostly sessile ○In (previously) inflamed areas of the colonic mucosa. ○Often undistinguishable from sporadic adenomas	- Tubular, tubulovillous or villous architecture - Dysplastic mucosa - Generally lamina propria inflammation. - Dysplastic crypts may be mixed with normal crypts	5%
➢ DALM, nonadenoma like	○Irregular ○Diffuse ○Masses or plaque like lesions in actively or previously inflamed areas of the colonic mucosa	- Dysplastic mucosa - Crypts lined with dysplastic epithelium - Occasionally admixed with non dysplastic crypts and inflamed lamina propria	60%
➢ LGD in flat mucosa	○No gross abnormality	- Crypts lined with dysplastic epithelium - High ratio of nucleus to cytoplasm - Nuclei remain confined to the basal half of the cell	18%
➢ HGD in flat mucosa	○No gross abnormality	- Nuclei extend into the luminal parts of the dysplastic epithelium	36%

*Risk may apply to HGD in both flat and raised mucosa.

Abbreviation: CRC, colorectal cancer; DALM, dysplasia associated lesions or masses; HGD, high grade dysplasia; LGD, low grade dysplasia

Adapted from: van Schaik FD, et al. *Nature Review Gastroenterology and Hepatology* 2009; 11:671-8, page 674

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

Grandad

Abbreviations

AC	Acute self-limiting colitis
AD	Autosomal dominant
AFAP	Attenuated familial adenomatous polyposis
AR	Autosomal recessive
AR	Absolute risk
CC	Crohn's colitis
CHRPE	Congenital hypertrophy of the retinal pigment epithelium
CMV	Cytomegalovirus
CNS	Central nevous system
CRC	Colorectal cancer
CTC	Computed tomographic colonography
DCBE	Double-contrast barium enema
DGGE	Denaturing gradient gel electrophorsis
DRE	Digital rectal exam
EAES	European Association for Endoscopic Surgeons
EAS	External anal sphincter
EGD	Esophagogastroduodenoscopy
EGFR	Epidermal growth factor receptors
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
FAPS	Functional abdominal pain syndrome
FICS	Fujinon intelligent chromoendoscopy system
FIT	Fecal immunochemical test
FSI	Focal segmental ischemia
FSIG	Flexible sigmoidoscopy
GCS	Glucocorticosteroids
HHT	Hereditary hemorrhagic telangiectasia
HNPCC	Hereditary non-polyposis colorectal cancer (Lynch)

	syndrome
HSV	Herpes simplex virus
IAS	Internal anal sphincter
IBS	Irritable bowel syndrome
IBS-D	Diarrhea-predominant IBS
IBC-C	Constipation-predominant IBS
IRCI	Isolated R-colon ischemia
LCM	Laser confocal endomicroscopy
LGIB	Lower GI bleed
LP	Lamina propria
MAP	Modified adenomatous polyposis
MCP	Meta carpophalangeal joint
MMR	Mismatch repair
MSM	Men who have sex with men
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCA	Oral contraceptive agent
OCT	Optical coherence tomography
Od	Once per day
PIP	Proximal interphalangeal joint
PML	Polymorphonuclear leucocytes
po	By mouth
PSC	Primary sclerosing cholangitis
RR	Relative risk
SCAD	Segmented colitis associated with diverticulum
SIBO	Small bacterial overgrowth
SMA	Superior mesenteric artery
SSCP	Single-strand conformational polymorphism
TAN/BSO	Total abdominal hysterectomy, bilateral salpingo-opherectomy
tid	Three times per day

UC	Ulcerative colitis
UDCA	Ursodeoxycholic acid

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1. Bleeding

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5. IBS

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HEPATOBILIARY

TABLE of CONTENTS

General

1. Give the detailed laboratory and diagnostic imaging investigation of the patient with suspected chronic liver disease.

- History and physical examination
  - Fatigue, malaise, anorexia, fever, weight loss/gain, ankle swelling
  - Following blood donation-positive hepatitis B or C test
  - Blood transfusions
  - Drug abuse
  - MSM (men who have sex with men)
  - Extrahepatic manifestations (see Question 2)
  - Following acute hepatitis-failure of recovery, whether clinical or biochemical or both
  - Abnormal liver enzyme or function tests, or positive hepatitis B or C viral markers at routine check-up
  - Abnormal physical findings
    - Hepatomegaly,
    - Signs of portal hypertension: splenomegaly, jaundice, peripheral edema, ascites, hepatic encephalopathy, renal dysfunction, bleeding (varices, coagulopathy)
    - Liver – big/normal/small

  - Cutaneous and endocrine changes
    - Spider nevi, palmar erythema, Dupuytren's contractures
    - Gynecomastia, testicular atrophy, impotence
    - Amenorrhea
    - Parotid enlargement

  - Coagulopathy
    - Hypoprothrombinemia
    - Thrombocytopenia
    - Dysfibrinogenemia
    - Slit lamp Kayser-Fleisher rings

  - Circulatory changes
    - Hyperdynamic circulation
    - Arterial desaturation, clubbing

- Laboratory tests
  - Liver function tests
    - Bilirubin
  - Liver enzymes
    - Aspartate transaminase (AST; SGOT)
    - Alanine transaminase (ALT; SGPT)

- Gamma-globulin
- Albumin
- Alkaline phosphatase (ALP)
- INR
- Gamma glutamyl transferase (GGT)

- Hematology
  - Hemoglobin
  - White cell count
  - Platelet count
  - PPT
- Special tests
  - Serum antibodies
    - Nuclear
    - Smooth muscle
    - Mitochondrial
    - Liver/kidney microsomal
  - HBsAg
  - HBeAg
  - HBeAb
  - Anti-HCV and HCV RNA
  - Serum iron, transferin, % saturation, genetic testing
  - Serum ferritin
  - Serum ceruloplasmin, as well as blood and urinary copper
  - Alpha-fetoprotein (AFP)
  - Creatine kinase (if smooth muscle disease suspected as cause of ↑ALT/AST, fasting, LDL and HDL cholesterol, triglycerides
  - Protein electrophoresis (polyclonal ↑ gamma globulins in AIH)

- Abdominal ultrasound, CT, fibroscan

- Core liver biopsy
  - Hematoxylin and eosin, connective tissue stains, "special stains" (eg for iron, copper, HBV)

Adapted from: Simon JB. *First Principles of Gastroenterology* 2005. pg. 500-505.

2. List 15 clinically significant extrahepatic manifestations of acute and chronic liver disease.

- CNS: depression, anxiety, hepatic encephalopathy (HE)

- Lung: portopulmonary hypertension, hepatopulmonary syndrome, pleural effusion, congestive heart failure, aspiration

- Heart: prolonged QT (from low Mg 2+); endocarditis; eripheral intravascular vasodilation, ↓ systemic vascular resistance, ↑ HR, ↑ BP, ↑ CO, vitamin K,

- Blood: Coagulopathy (DIC, fibrinolysis), thrombocytopenia, Hypersplenism, ↓ thrombopoetin, immune mediated destruction, ITP (especially with use of interferon for HCV), direct effect of alcohol, cryoglobulinemia

- GI
  - Esophageal ulcers from sclerotherapy, GERD, varices
  - Stomach: delayed gastric emptying, PHG, GAVE
  - Small bowel: slow transit, bacterial overgrowth

- Bone: osteoporosis, osteomalacia: cholestasis, liver Tx, malnutrition, alcohol, tobacco, ↓ motility, hypogonadism, malabsorption

- Renal: hyponatremia, ascites, hepatorenal syndrome, glomerulosclerosis (HCV), nephritioc syndrome, amyloid

- Muscle: spastic paraparesis (from demyelination of corticospinal tracts and posterior columns), wasting; arthritis (hemochromotosis)

- Gonads; hypergonadism, amenorrhea

Abbreviations: GAVE, gastric antral vascular ectasia; PHG, portal hypertensive gastropathy

Adapted from: Simon JB. *First Principles of Gastroenterology* 2005. pg. 502.

3. Give 10 management considerations in the pre- and post-operative care of the patient with advanced liver disease (CHLD score).

- Risk stratification

- Prevention of HE
  - Hepatic encephalopathy
  - Correction of reversible metabolic factors (eg. hyponatremia, hypocalcemia)
  - Oral lactulose administration, titrated to ~3-4 bowel movements per day
  - Administration of nonabsorbable antibiotics
  - Avoidance of nephrotoxic insult (eg. NSA|Ds, narcotics, benzo's))
  - Supportive care
  - Correction of reversible metabolic factors

- Treat complications of portal hypertension (PHT)
  - Ascites, peripheral edema
  - Oral diuretic therapy with spironolactone and/or furesomide
  - Fluid restriction (if sodium concentration is <120 mmol/l)
  - Avoidance of excessive saline administration
  - Albumin infusion (with paracentesis volumes >5 l)
    - Antibiotics for spontaneous bacterial peritonitis
    - Steroids
  - Coagulopathy
    - Vitamin K supplementation (oral or parenteral)
    - Fresh, frozen plasma transfusions
    - Intravenous administration of cryoprecipitate
    - Intravenous administration of recombinant factor VIIa
    - Platelet transfusions
  - Paracentesis with analysis of ascitic fluid for evidence of infection

- Diet
  - Maintenance of an adequate protein intake (1-1.5 g/kg per day)
  - Promotion of a balanced diet
  - Dietary sodium restriction (<2 g daily)

- Pain control
  - Dilaudid
  - Avoid benzodiazepans, NSAIDs, narcotics

- Assess pulmonary function
  - Supplemental oxygen

Adapted from: Hanje AJ, and Pate T. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4: pg. 272.

4. Give the Child-Pugh classification of liver disease.

Parameter	1	2	3
➢ Ascites	None	Slight	Mod/severe
➢ Encephalopathy	None	Slight/mod (1-2)	Mod/severe (3-4)
➢ Bilirubin (mg/ dl)	<2 (<34)	2-3 (34-50)	>3 (>50)
➢ Albumin (mg/ dl)	>3.5 (>35)	2.8-3.5 (28-35)	<2.8 (<28)
➢ PT (INR)	1-3 (<1.7)	4-6 (1.7-2.2)	>6 (>2.2)

Total score	Child-Pugh classification
5-6	A
7-9	B
10-15	C

Adapted from: Kim WR, et al. *Hepatology* 1999;29(6):1643-8.; and Durand F, Valla D. *J Hepatol* 2005;42.

Useful background:

- Direction of flow of blood in veins of abdominal wall
  - Flow below umbilicus is down into saphenous veins.
  - Above umbilicus flow is upwards into veins of thoracic wall.
  - In portal hypertension, dilated veins show normal direction of flow
  - In IVC obstruction, flow in veins below umbilicus is reversed, ie. flows upwards

- Umbilicus is common site of infiltration by cancer metastases

- Spider nevi are telangiectases
  - Leuconchyia-white nails, beginning at the lunula-may be normal; seen in cirrhosis, leprosy, arsenic poisining, vasomotor disturbance of fingers

- Finger clubbing with portal cirrhosis.

- Dupuytren's contracture in alcoholic cirrhosis

- Patients with hemolytic jaundice do not have pruritus or bradycardia

- Biliary cirrhosis-1°, 2°
  - GB disease
  - Methyltestosterone
  - Chlorpromazine
  - Very occasionally due to severe infection, hepatitis

- Parotid enlargement is common in liver disease, as is fever, even in absence of infection (look for spontaneous bacterial peritonitis)
- Knobbly liver with umbilication – pathognomonic of hepatic metastases (2°)
- Jaundice with hepatic 2° is usually due to
  - lesions at hepatic fissure

- ascites due to portal vein obstruction by glands
- peritoneal deposits

Fatty liver diseases

5. Give the molecular mechanisms of fat accumulation in the liver, and the development of non-alcoholic fatty liver disease (NAFLD)/ non-alcoholic steatohepatitis (NASH).

- Hepatic steatosis
  - ↑ dietary fat or delivery of fat to the liver
  - ↑ carbohydrate transport to the liver, with formation of fatty acids (↑ lipogenesis)
  - Bacterial flora
  - Oxidative stress
  - ↑ peripheral insulin resistance (↑ leptin, ↓adiponectin ;↑insulin, ↑TNFα)
  - ↑ mitochondrial synthesis of fatty acids (FA's)
  - ↑ fat synthesis (increased insulin activates SREBP-1, the sterol regulatory element binding protein 1-c, and increase CHREBP, the carbohydrate regulatory element binding protein)
  - ↓ transport of FA's out of the liver (↓β-oxygenation), ↓Apolipoprotein B-100

- Hepatocyte injury, inflammation and fibrosis
  - ↑Oxidative stress
  - ↑Lipotoxicity
  - ↑ Death receptors
  - ↑ apoptosis
  - ↓ DNGA (transcriptonial sensitizer)
  - Stellate cell activation

Adapted from: Pellicoro A, and Faber KN. *APT* 2007; 26 (2): pg. 149-160.

6. Give 15 causes of macrosteatosis.

- Liver – Wilson's disease, alcohol, NAFLD/NASH, HCV-3 (acute fatty liver of pregnancy)
- Infection – HCV-3, bacterial overgrowth, fever, viral infections
- Drugs – corticosteroids, alcohol, estrogen, amiodarone, HAART (for HIV) tetracycline, vitamin A toxicity
- Metabolic – hyperlipidemia, TPN, tyrosinemia, galactosemia, glycogenoses, abetalipoproteinemia, diabetes

- Nutrition – rapid weight loss or gain, obesity, pancreatic insufficiency, Kwashiorkor, TPN, bariatric surgery, short bowel syndrome
- Pediatric conditions - Weber-Christian
- Ideopathic

Adapted from: Oh MK, et al. *Aliment Pharmacol Ther* 2008; 28:pg. 507.

7. Give 5 causes of microvesicular steatosis.

- Pregnancy—Acute fatty liver of pregnancy, HELLP syndrome
- Infection – HBV, HCV, HDV
- Drugs – Reye`s syndrome (salicylates), valoproic acid, amioderone, A2T, DDI, tetracycline
- Metabolic – Jamaican vomiting sickness, urea cycle and mitochondrial defects, carnitine deficiency, Wolfman's disease

Adapted from: Oh, M.K. et al. *Aliment Pharmacol Ther* 2008; 28:pg. 507.

Useful background: Genetic abnormalities may exist in some persons with alcoholic liver disease (ALD), cholethiasis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), alpha1 anti-trypsin deficiency (α1-AT), and polycycstic liver disease (PCLD)

- ALD
  - Genotypes of the aldehyde dehydrogenase (ALDH2-*2 allele) and the P4502EI (C2 allele)
  - Polymorphism of TNF2 at position -238 (G→A)
  - A→ e mutation in exon 1 of the Cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene

- Cholelithiasis
  - ABC B4 gene (PC transporter)
  - ABC B11 gene (bile salt export pump)
  - CYP7AI (cholesterol 7α-hydroxylase)
  - FXR farenesoid x
  - E4 allele of APOE (apolipoprotein E)
  - N TCP (Na+ dependent taurocholate cotransporting peptide)
  - TNF receptor 2
  - SHP (small heterodimer partner)

- PBC (environmental: smoking, HRT (hormone replacement therapy), UTI (urinary tract infection), toxic waste sites, Chlamydia, pneumonia, betaretrovirus, novosphingobium aromaticivorans)

- MHC class II HLA-DR8 allele
- CTLA-4 gene
- IL-I

➢ PSC
- HLA A1-B8-DRB1*0301-DQA-1*0501-DQB1*0201, and DRB*1301-DQA-1*0103-DQB1*0603
- Genetic polymorphisms: TNF α; stromelysin, matrix metallopeptidase 3; MHC class I polypeptide-related sequence A, chemokine C-C motif receptor 5; intracellular adhesion molecule-1, CD54

➢ α 1-AT
- mutation in codon 342 of the 1-AT gene, changing a single amino acid from lysine to glutamate

Abbreviation: HRT, hormone replacement therapy

Printed with permission: Juran BD, and Lazaridis KN. *Clin Gastro Hepat* 2006; 4: pg. 548-557.

8. Give 5 patient-related and 5 laboratory-related predictors of progression of NAFLD (simple steatosis) to NASH.

➢ Patient
- Age > 45 years
- Female
- Ethnicity (Hispanic, Asian >White >Black)
- Type II diabetes mellitus
- BMI > 35 (especially visceral obesity)
- Insulin resistance
- Hypertension
- Metabolic syndrome (insulin resistance), even in young, non-obese persons
- Stigmata of portal hypertension

➢ Laboratory
- ↑ ALT > 2x ULN
- ↑AST:ALT >1 [suggests fibrosis]
- ↑ Triglycerides >1.5
- ↑ INR
- ↑ Bilirubin
- ↓Platelets
- ↓Albumin
- Indexes of insulin resistance (HOMA, QUICKI, OGIS)
- ↑ Elevated ferritin levels

- ↑ Hyaluronic acid*
- Anti-MDA antibodies*

- Imaging biopsy
  - Fibroscan
  - Severe steatosis (centrilobular, macro steatosis)
  - ↑ Stainable iron
  - Signs of cirrhosis

* useful if normal

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HOMA, homeostatic model assessment; MDA, malondialdehyde; OGIS, oral glucose insulin sensitivity index; QUICKI, quantitative insulin-sensitivity check index; ULN, upper limit of normal.

Adapted from: Pinzani, et al. *Nature Clinical Practice Gastroenterology & Hepatology* February 2008; 5(2): pg 102; and Reid AE. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2010, pg 1408.

9. Give 8 liver biopsy criteria for NASH.

- Present in all or most cases
  - Diffuse or centrilobular steatosis, predominantly macrovesicular; degree may correlate with BMI
  - parenchymal inflammation (+/- focal necrosis), neutrophils, macronuclear cells
  - Lobular necrosis

- Features observed with varying frequency
  - Ballooning hepatocyte degeneration
  - Pericellular fibrosis (chicken wire fibrosis) – perivenular* (zone 3), perisinusoidal or periportal (37%-84%)
  - Mallory bodies
  - NAFLD Activity Score (see Useful background which follows)
  - Cirrhosis (7%-16% on index biopsy)
  - Glycogenated nuclei
  - Lipogranulomas
  - Stainable iron

Adapted from: Reid AE. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1796; and 2010, pg 1407.

10. Give the pros and cons of performing a percutaneous liver biopsy in a patient with NAFLD and abnormal liver enzymes.

Issues	Argument in favor of biopsy with acceptable risk	Reasons for not performing a biopsy.
➢ Abnormal hepatic biochemical tests and NAFLD		
○ Elevated ALT	Confirm diagnosis	Cause accurately identified clinically in > 90% cases without biopsy
○ Diagnosis of NAFLD	Patients may not have classic NAFLD risk factors	Accurate diagnosis of NAFLD generally possible without biopsy
○ Identify severity of NAFLD	Only biopsy can distinguish simple steatosis from steatohepatitis	Non-invasive markers may be developed to distinguish the two
○ Treatment of NAFLD	Presence of steatohepatitis or fibrosis may motivate some to undertake risk factor modification	There is no proven therapy for NAFLD. Absence of steatohepatitis or fibrosis may remove motivation for some to undertake risk factor modification

Printed with permission: Reddy K R. *2006 AGA Institute Postgraduate Course Syllabus:* pg. 81.

Useful background: Risk of cirrhosis, hepatocellular carcinoma (HCC) and mortality in hepatitis B and hepatitis C virus (HBV/HCV) monoinfected and coinfected patients

Feature	Cirrhosis	HCC	Mortality
Study	Zarski et al, 1998 33	Shi et al, 2005 Donato et al, 1998	Amin et al, 2006 Di Marco et al, 1999
HBV monoinfection	22%	OR 16-23	SMR 1.4-5.3
HCV monoinfection	30%	OR 8-17	SMR 2.4-3.1
HBV/HCV coinfection	50%	OR 36-165	SMR 5.6-49

Abbreviations: HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; OR, odds ratio; SMR, standard mortality ratio

Printed with permission: Wursthorn, et al. *Best Practice Res Clin Gastroenterol* 2008;22:1063-1079.

Useful background: NAFLD/NASH

- NAFLD and NASH may be distinguished using Kleiner's scoring system, also known as "NAS" (NASH activity score) (Kleiner DE, et al. *Hepatology* 2005;41:1313-21.)

- Based on:
    1. Simple steatosis
    2. Steatosis plus inflammation alone
    3. Steatosis plus ballooning
    4. Steatosis plus fibrosis (Matteoni CA, et al. *Gastroenterology* 1999:1413-9.)

Useful background: Grading and staging of the biopsy lesions of NASH

- Grade I. Mild
    - Steatosis: predominantly macrovesicular, involves <33% or up to 66% of the lobules; increased BMI may correlate with BMI
    - Ballooning: occasionally observed; zone 3 hepatocytes
    - Lobular inflammation: scattered and mild acute (polymorphs) and chronic (mononuclear cells) inflammation
    - Portal inflammation: none or mild

- Grade 2. Moderate
    - Steatosis: any degree and usually mixed macrovesicular and microvesicular
    - Ballooning: present in zone 3
    - Lobular inflammation: polymorphs may be noted associated with ballooned hepatocytes, pericellular fibrosis; mild chronic inflammation may be seen
    - Portal inflammation: Mild to moderate

- Grade 3. Severe
    - Steatosis: typically >66% (panacinar): commonly mixed steatosis
    - Lobular inflammation: scattered acute and chronic inflammation; polymorphs may appear concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
    - Portal inflammation: Mild to moderate

- Staging (fibrosis)
    - Stage 1: zone 3 perivenular perisinusoidal fibrosis, focal or extensive
    - Stage 2: as above plus focal or extensive periportal fibrosis
    - Stage 3: bridging fibrosis, focal or extensive
    - Stage 4: cirrhosis

- Types 3 and 4 of NAFLD commonly occur together, and may be known as NASH, and types 1 and 2 of NAFLD are known as SS (simple steatosis) or non-NASH fatty liver (NNFL) (Matteoni CA, et al. *Gastroenterology* 1999;116:1413-9.)

- About 2/3 of NAFLD are SS (NNFL) and 1/3 are NASH
- Only 10-15% weight reduction reduces hepatic fat (Harrison SA, Day CP. *Gut* 2007:1760-9)
- Agents tested to treat NAFLD, but not being of consistent benefit, include UDCA, vitamins C and E, thiazolidinediones, statins, ARBs (angiotensin receptor blockers), grehlin-leptin modulators, and antioxidants such as SNACS-nitroso-n-acetyl cysteine (Caldwell 09). Vitamin E supplementation shows promise.

- Bariatric surgery achieves weight reduction and benefits many parameters of NASH (Mummadi RR, et al. *Clin Gastroenterol Hepatol* 2008:1396-1402.)

Abbreviations: ARBs, angiotensin receptor blockers; NAS, NASH activity score; NNFL, non-NASH fatty liver; SS, simple steatosis

Printed with permission: Cortez-Pinto H, and Camilo ME. *Best Practice & Research Clinical Gastroenterology* 2004;18(6): pg 1097.

11. Give the treatment of anti-viral resistant HBV.

- Lamivudine or telbuvidine resistance
  - Add adefovir (or tenofovir)
  - (stop lamivudine, switch to Truvada)
  - (Switch to entecavir- pre-existing lamivudine resistant mutations predispose to entecavir resistance)
- Adefovir resistance
  - Add lamivudine
  - (stop adefovir, switch to Truvada)
  - Switch to or add entecavir
- Entecavir resistance
  - Switch to or add tenofovir

*Truvada-combination of emtricitabine and tenofovir
**Emtricitabine, tenofovir, and Truvada

12. Give 5 cutaneous signs of chronic liver disease.

- Jaundice
- Dupuytren's contracture
- Spider angiomata
- Palmar eythema
- Telangectasia
- Hyperpigmentation
- Loss of lunulae
- White nails
- Clubbing
- Excoriations
- Xanthelasma
- Xanthomata

13. Give 10 common causes for elevation of aminotransferases.

- Marked elevation (up to 20+ fold)
  - Acute hepatitis due to viruses, ischemia or drugs
- Moderate elevation (up to 8 fold)
  - Chronic hepatitis, cirrhosis, cholestatic diseases, and replacement disease
- Minimal elevation (up to 2+ fold)
  - Non-alcoholic liver disease, chronic viral hepatitis (C and B), alcoholism, obesity

14. Give 10 common causes for elevation of gamma glutamyltranspeptidase (GGT).

- Hepatobiliary disease
- Replacement disease
- Enzyme induction
- Miscellaneous causes

- Anorexia, hyperthyroidism
- Guillain-Barre, myotonic dystrophy
- PCT, obesity, diabetes mellitus

15. Give 6 causes of chronically elevated aminotransferase levels without cholestasis, and 6 causes with cholestasis.

➢ Without cholestasis
- Medication, herbal products, illicit drugs and substance abuse
- Infection – HBV, HCV
- Drugs/toxins, alcohol
- NAFLD, NASH
- Autoimmune liver disease
- Genetic – hereditary hemochromatosis
  - α, AT deficiency
  - Wilson's disease
- Celiac disease
- Striated muscle diseases
- Screening
  - Colon
  - Mammography
  - HCC
  - Pap smear
  - DRE-PSA
- Social support for addiction
- Liver transplant
  - BMI
  - Type/cross
  - Comorbidity
  - Infection
  - Vascular
  - Abnormal TIPS
  - Liver surgery

➢ With cholestasis
- Bile duct obstruction
- Idiopathic ductopenia
- Primary biliary cirrhosis
- Autoimmune cholangitis
- Primary sclerosing cholangitis
- Sacroidosis
- Granulomatous hepatitis
- Hepatic tumours (primary or metastic)
- Medications
- Diet

- Drugs
- Bllod products
- Infection
- Renal/ascites
- PSE
- Fluid and electrolyte balance
- Lung – O_2
- Heat – BP, CCF

16. Give 10 laboratory evaluations of conjugated hyperbilirubinemia in children.

- Total and direct serum bilirubin
- Alkaline phosphatase, aminotransferases, γ-glutamyl transpeptidase
- Prothrombin time or INR, serum albumin (factor V levels, if available)
- Complete blood cell count, differential
- Urine culture (blood/cerebrospinal fluid, if indicated)
- Serology for cytomegalovirus, rubella, herpes simplex, herpes type 6, toxoplasmosis, syphilis (adenovirus, Coxsackie virus, reovirus III, parvovirus B19, if available)
- Urine for reducing substances, serum galactose-1-phosphate uridyltransferase, serum/urine amino acids and organic acids
- Sweat chloride, genotyping for cystic fibrosis
- α_1-antitrypsin level and Pi phenotype
- Urine for bile acid metabolites
- Serum ferritin
- TSH
- T4, glucose, cortisol

Permission granted: Robertson, M. and Martin, SR. Approach to the Jaundiced Neonate. *First Principles of Gastroenterology* 2005. pg. 733

- Liver test
  - R value
    - ALT/AP
  - >5, hepatocellular disease
  - <2, cholestatic disease

  - ALT, AST in liver, muscle, kidney

- AST > ALT in ALD, fibrosis
  Alcohol – mitochondria produce AST↓

- AST, ALT > 1000
  - ischemia
  - drugs
  - viral hepatitis
  - autoimmune
  - B - Chiari
  - CBD stones
- Macro AST
  - isolated ↑ AST

Alcoholic liver disease (ALD)

17. Give 8 laboratory abnormalities commonly seen in persons with alcoholic hepatitis.

- Hematology
  - Macrocytic anemia (increased MCV)
  - ↑ WBC
  - ↓ platelets

- General chemistry
  - ↑ blood sugar
  - ↑ uric acid
  - ↑ triglycerides
  - Ketosis

- Tests of liver function and injury
  - ↓albumin
  - ↑ bilirubin
  - ↑ INR
  - ↑ AST/ALT (ratio of 1.5 to 2.5 and total increase <10-fold)
  - ↑ GGT
  - ↑ alkaline phosphatase (mild)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; MCV, mean corpuscular volume.

Printed with permission: Shah VH. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 331.

18. Compare and contrast viral hepatitis and alcoholic hepatitis based on histology and physical, laboratory tests and liver histology.

	Viral hepatitis	Alcoholic hepatitis
○ History	Risk factors	Significant alcoholic intake
○ Physical examination	Mild hepatomegaly, extrahepatic stigmata not prominent	Moderate to marked hepatomegaly, florid stigamata
○ Laboratory tests	AST variable - Mononuclear cells	AST <3 00 - Polymorphs
○ Liver histology	- Portal tract centered - Ground glass cells (HBV) - Special stains (HBV) - Fat, esp. HCV	- Pericentral, diffuse - Mallory's hyaline - Macrovesicular fat -

Useful background: Alcoholic hepatitis

- Several positive RCT's and meta-analyses support the utility of steroids in patients with alcoholic hepatitis and discriminant function (DF)>32, or in those with hepatic encephalopathy; one study has shown a benefit at one year, but patients with infection or GI bleeding should be excluded (Shah V. Alcoholic hepatitis: are we back to prednisone? *ACG Annual Scientific Meeting Symposia Sessions* 2009:64-66.)

- Pentoxifylline used in patients with alcoholic hepatitis decrease the risk of hepatorenal syndrome, and improve survival (Akriviadis E, Botla R, Briggs W et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis. A double blind, placebo-controlled trial. *Gastroenterology* 2000;119(6):1637-48).

- Characteristic ages of presentation of chronic liver diseases
  - Wilson's Disease (13-30)
  - Chronic Viral hepatitis (20-40)
  - PBC (30-60)
  - ALD (40-60)
  - Hemochromatosis 40s (men) to 50s (women)

19. Give the Peri-operative mortality rates (MR) in persons with cirrhosis.

Child's	Surgical MR (%)
A	5-10
B	30
C	70-80

- 30-day perioperative mortality, 30% (total):
  - Pneumonia 8%
  - Infection 8%
  - Bleeding 10%
  - Worsening Ascites 7%

Source: Sterling RK. Evaluation and management of the surgical patient with cirrhosis: when they have to go to the operating room. *ACG Annual Scientific Meeting Symposia Sessions* 2009; 71-77.

20. Give the use of the MELD score to predict perioperative complications.

- MELD score
  - 5-20
    - 1% increase in mortality with each 1 point increase
  - >20
    - 2% increase in MR for each MELD point increase

- Summary of findings: "MELD Plus"
  - MELD, ASA class, and age were most important
    - www.mayoclinic.org/meld/mayomodel9.html
    - C-statistic is 0.80 (30d) and 0.84 (90d)
  - Emergency surgery predicted duration of hospitalization ($p<0.001$) but not mortality
  - ASA class V best to predict 7d mortality
  - MELD is best beyond 7 days
  - If MELD < 11 (especially < 8), acceptable risks
  - If MELD > 20, elective surgery should be postponed
  - If MELD 12-20, complete OLT evaluation in case they deteriorate

Adapted from: Teh SH, Nagorney DM, Stevens SR et al. Risk factors for mortality after surgery in patients with Cirrhosis. *Gastroenterology* 2007;132:1261-9.

21. Give the mucosal changes in the stomach associated with portal hypertensive gastropathy*.

- Mosaic- like mucosal pattern
  - Small, polygonal areas surrounded by a whitish- yellow depressed border (snake skin appearance) can be categorized as mild (pink mucosa), and moderate (diffuse red mucosa)

- Red point lesions
  - Small (<1 mm), red, flat, point like marks

- Cherry red spots
  - Large (>2 mm), round, red coloured, protruding lesions

- Black-brown spots
  - Irregularly shaped black and brown flat spots that do not fade upon washing (these changes might represent intramucosal hemorrhage)

* These changes are characterized endoscopically by the presence of four main findings, as described by the New Italian Endoscopic Club (NIEC).

Printed with permission: Macmillan Publishers Ltd: Perini et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009; 6(3):150-8, Box 1, page 152.

Autoimmune hepatitis (AIH)

22. List 5 prescription medications, OTC preparations or herbs which may induce or unmask an AIH-like syndrome.

- Antibiotics
  - Minocycline
  - Nitrofurantoin
  - Rifampin
  - Interferon
  - INH

- Metabolic
  - Orlistat
  - Statins
  - Propyl thiouracil

- Antihypertensives
  - Alpha methyl dopa

- Herbs
  - St. John's Wort
  - Chapannal leaf
  - Black cohosh

- Immune
  - Anti-TNF therapy

Printed with permission: Heathcote EJ. *2007 AGA Institute Spring Postgraduate Course Syllabus*: 96.

23. Give 4 forms or types of AIH.

- I (f, 50) ANA+ ASM+ IgG↑
- II (children) ALKMI+
- III (M, 30) ASLA/LP+
- Overlap syndrome AMA-neg. PBC, PSC, AMA-

Adapted from: Czaja AJ. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease* 2006. pg. 1872-1875; and 2010, pg. 1467.

24. Give 5 clinical presentations of AIH.

- Acute hepatitis
- Fulminant hepatitis
- Asymptomatic chronic hepatitis +/- cirrhosis
- Symptomatic chronic hepatitis +/- cirrhosis
- "Burned out" decompensated cirrhosis +/-
- *De novo* or recurrent AIH after liver transplantation (alloimmune)
- AIH with overlapping PBC/PSC/AMA-neg PBC
- Suspected from liver disease associated with other conditions
- HCC

25. Give 15 immune diseases/disorders which are associated with AIH.

- Skin, eye
  - Iritis
  - Gingivitis
  - Dermatitis herpetiformis
  - Erythema nodosum
  - Lichen planus
  - Pyoderma gangrenosum
- CNS/PNS
  - Peripheral neuropathy
  - Myasthenia gravis
- Thyroid
  - Autoimmune thyroiditis
  - Graves' disease*
- Heart, lung
  - Pleuritis
  - Fibrosing alveolitis
  - Pericarditis
- Pancreas
  - Insulin-dependent diabetes
  - Autoimmune pancreatitis
- Gut, liver
  - Celiac disease
  - Ulcerative colitis*
  - Autoimmune sclerosing cholangitis
  - Pernicious anemia
  - Autoimmune cholangitis (PSC)
- Kidney
  - Glomerulonephritis (immune complex)
- Blood
  - Coomb's- positive hemolytic anemia
  - Cryoglobulinemia
  - Idiopathic thrombocytopenic purpura
  - Pernicious anemia ITP+ PA (Evan's syndrome)
  - Neutropenia
- MSK
  - Rheumatoid arthritis
  - Sjögren's syndrome
  - Synovitis
  - Systemic lupus erythematous
  - Focal myositis

Printed with permission: Czaja AJ. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 398.

26. Give the treatments of the variant syndromes of AIH.

Variant syndrome	Salient features	Empiric treatment strategies
➢ AIH and primary biliary cirrhosis (PBC)	○ AMA positivity ○ Cholestatic and hepatitic tests ○ Increased serum IgM and IgG levels	○ Corticosteroids if serum ALP is ≤ twice ULN ○ Add ursodeoxycholic acid (UDCA) if serum ALP is > twice ULN and/or florid duct lesions in liver tissue
➢ AIH and primary sclerosing cholangitis	○ Ulcerative colitis ○ Pruritus ○ Cholestatic and hepatic tests ○ ALP:AST>1.5	○ Corticosteroids and UDCA
➢ AIH and cholangitis (possibly AMA-negative primary biliary sclerosis)	○ Abnormal cholangiogram ○ Fatigue ○ Pruritus ○ Cholestatic and hepatitic tests ○ AMA negative ○ ANA and/or SMA positive ○ Normal cholangiogram	○ Prednisone, ursodeoxycholic acid, or both, depending on hepatic and cholestatic components

Abbreviations: ALP, Alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; AST, aspartate aminotransferase; SMA, smooth muscle antibodies; ULN, upper limit of normal.

Adapted from: Czaja AJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1874.

27. Give 10 preventative measures about which to advise patients with AIH treated with prednisone +/- azathioprine.

➢ General
- ○ Monitor for weight gain
- ○ Supplement with calcium, vitamin D, +/- bisphosphonates
- ○ Monitor blood sugar, lipids, fat soluble vitamins
- ○ Monitor CBC, ALT (if on Azathioprine)
- ○ Annual checks for BP, cataract, glaucoma, BMD, Pap' smear, esophageal varices
- ○ Check stools for ova/parasites after foreign travel

- "Stop" order on Rx
- Screening mammography, colonoscopy
- Access for depression
- Stress high doses of steroids, if necessary
- Wear medical alert bracelet.
- Avoid stopping steroids suddenly (Addisonian crisis, recurrence of AIH)
- Avoid unplanned pregnancy; consider avoiding pregnancy if portal hypertension is marked; contraception
- Drug interactions
- Immunizations (see below)

➢ Specific
- If cirrhotic: avoid sedation, NSAIDs, anesthesia, interferon
- If cirrhotic, screen for HCC
- Avoid vaccination with varicella, MMR, yellow fever
- Vaccination for H. influenza, HAV, HBV, pneumococcus (hyposplenism)
- Assess for esophageal varices for primary prevention with banding or beta blockers (avoid use in pregnancy – fetal hypoglycemia)
- Assess for Ascites (SBP)

Adapted from: Heathcote J. *Am J Gastroenterol* 2006;101:S630–S632.

Useful background: Definite and probable criteria for the diagnosis of AIH

Diagnostic criteria

Definite AIH	Probable AIH
➢ Exclude other causes of chronic liver disease ○ Normal AAT phenotype ○ Normal ceruloplasmin level ○ Normal iron and ferritin levels ○ No active hepatitis A, B, or C infection ○ Daily alcohol <25 g ○ No recent hepatotoxic drugs ○ Predominant serum aminotransferase abnormality	○ Partial AAT deficiency ○ Abnormal copper or ceruloplasmin level but Wilson's disease excluded ○ Nonspecific iron or ferritin abnormalities ○ No active hepatitis A, B, or C infection ○ Daily alcohol <50 g ○ No recent hepatotoxic drugs ○ Predominant serum aminotransferase abnormality

- Suggestive lab tests
  - Globulin, γ-globulin, or IgG level ≥1.5 times normal
  - ANA, SMA, or anti-LKM1 ≥1:80 in adults and ≥1:20 in children; no AMA
  - Hypergammaglobulinemia of any degree
  - ANA, SMA, or anti-LKM1≥1:40 in adults; other autoantibodies
- Liver biopsy
  - Interface hepatitis–moderate to severe
  - No biliary lesions, granulomas, or prominent changes suggestive of another liver disease
  - Interface hepatitis–moderate to severe
  - No biliary lesions, granulomas, or prominent changes suggestive of another disease

Printed with permission: Czaja AJ. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 392.

Useful background: The Mayo Clinic treatment schedules for adults with severe autoimmune hepatitis

Treatment duration (weeks)	Combination therapy		Prednisone monotherapy (mg daily)
	Prednisone (mg daily)	Azathioprine (mg daily)	
1	30	50	60
1	20	50	40
2	15	50	30
Maintenance until end point	10	50	20

Printed with permission: Loza AJM, and Czaja AJ. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(4): pg. 204.

Useful background: For patients with AIH, the first and second choice conventional and empiric treatments, as well as the third and fourth choice possible empiric treatments for suboptimal responses to firstline treatment

Clinical event	Conventional treatments		Possible empiric treatments	
	1st choice	2nd choice	3rd choice	4th choice
○ Treatment failure	Prednisone (30 mg daily) and Azathioprine (150 mg daily), or prednisone alone (60 mg daily)	Prednisone (30 mg daily) Plus Mercaptopurin (1.5 mg/kg body weight daily)	Ciclosporin (5-6 mg/kg body weight daily) or prednisone (30 mg daily) plus Mycophenoate mofetil (2 g daily)	Tacroli-mus (4 mg twice daily)
○ Drug toxicity	Azathioprine (2 mg/kg body weight daily) if prednisone intolerant	Prednisone (20 mg daily) if Azathioprine intolerant	Budesonide (3 mg twice daily)	UDCA (13-15 mg/kg body weight daily)
○ Incomplete response	Prednisone maintenance (≤ 10 mg daily) if serum AST level < three times normal value	Azathioprine maintenance (2 mg/kg body weight daily) if serum AST level <threetimes normal value)	Budesonide Maintenance (3 mg twice daily)	UDCA Mainten-ance (13-15 mg/kg body weight daily)
○ Relapse	Azathioprine maintenance (2 mg/kg body weight daily) if serum AST level <three times normal value	Prednisone Maintenance reduced to (≤ 10 mg daily) if serum AST level <three times normal value	Mycophel-ate mofetil maintenance (2 g daily)	Ciclo-sporin Mainten-ance (5-6 mg/kg body weight daily)

Abbreviations: AST, aspartate aminotransferase; UDCA, ursodeoxycholic aid

Printed with permission: Loza A, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(4): pg. 206.

Useful background: Revised original scoring system for the diagnosis of autoimmune hepatitis

Category	Variable	Score
➢ Gender	○ Female	+2
➢ AP/AST	○ >3	-2
	○ <1.5	+2
➢ Gamma globulin or lgG level above normal	○ >2.0	+3
	○ 1.5-2.0	+2
	○ 1.0-1.5	+1
	○ >1.0	0
➢ ANA, SMA, or anti-LKM1 titer	○ >1:80	+3
	○ 1:80	+2
	○ 1:40	+1
	○ <1:40	0
➢ AMA	○ Positive	-4
➢ Viral markers	○ Positive	-3
	○ Negative	+3
➢ Drug history	○ Yes	-4
	○ No	+1
➢ Alcohol	○ <25 g/day	+2
	○ >60 g/day	-2
➢ HLA	○ DR3 or DR4	+1
➢ Immune disease	○ Thyroiditis, ulcerative colitis, synovitis, others	+2
➢ Other liver define autoantibodies	○ Anti SLA, anti actin, anti LC1, Panca	+2
➢ Histologic features	○ Interface hepatitis	+3
	○ Plasmacytic infiltrate	+1
	○ Rosettes	+1
	○ None of above	-5
	○ Biliary changes	-3
	○ Other features	-3
➢ Treatment response	○ Complete	+2
	○ Relapse	+3

➢ Pre-treatment score
- ○ Definite diagnosis >15
- ○ Probable 10-15

diagnosis

- Post treatment score
  - Definite diagnosis >17
  - Probable diagnosis 12-17

Adapted from: Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group report: Review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; 31: 929-38.

Useful background: Simplified scoring system for diagnosis of autoimmune hepatitis

Category	Variable	Score
➢ Autoantibodies		
○ Antinuclear antibodies	- 1:40	+1
○ Smoth muscle antibodies	- >1:80	+2
○ Antibodies to liver kidney microsome type 1	- >1:40	+2
○ Antibodies to soluble liver antigen	- Positive	+2
➢ Immunoglobulin level		
○ Immunoglobulin G	- >Upper limit of normal	+1
	- >1.1 times upper limit of normal	+2
➢ Histologic findings		
○ Morphologic features	- Compatible with autoimmune hepatitis	+1
	- Typical of autoimmune hepatitis	+2
➢ Viral disease		
○ Absence of viral hepatities	- No viral markers	+2
➢ Pre-treatment aggregate score		
○ Definite diagnosis		>7
○ Probable diagnosis		6

Adapted from: Hennes EM, Zeniya M, Czaja AJ, et al. Simplified diagnostic criteria for autoimmune hepatitis. *Hepatology* 2008;48:169-76.

Primary biliary cirrhosis (PBC)

28. Give 12 examples of chronic benign biliary disorders involving the intrahepatic, extrahepatic, and combined intra- and extrahepatic ducts (big duct abnormalities), which may mimic PBC).

- Congenital
  - Alagille syndrome (and nonsyndromatic)
  - Cystic fibrosis
  - Duct plate abnormalities
  - Choledorhal cysts
- Infectious
  - Cytomegalovirus
  - Biliary sepsis
  - Parasites
  - HIV (intrahepatic), AIDS cholangiopathy (extrahepatic)
- Infiltrative
  - Cholangiocarcinoma
  - Histiocytosis X
  - Lymphoma
  - Mastocytosis
- Ischemic
  - Thrombosis of hepatic artery
  - Proxysmal nocturnal hemoglobulinuria (PNH)
  - Vasculitis
  - Henoch-Schōnlein
  - Ischemic strictures (post liver transplantation)
- Immune
  - PBC
  - PSC, secondary sclerosing cholangitis
  - Sarcoid autoimmune cholangiopathy
  - Graft vs host disease
  - Allograft rejection
- Drugs and toxins
  - Drugs
  - Floxuridine
  - TPN-associated cholestasis
- Idiopathic
  - Caroli's syndrome

Abbreviation: PNH, proxysmal nocturnal hemoglobulinuria

29. Compare and contrast PBC and AIH under the following headings.

Finding	PBC	AIH
○ Gender	F>M	F>M
○ Prominent symptoms	Pruritus	Fatigue
○ Laboratory	AMA+, ↑ IgM (if associated autoimmune syndromes)	AMA-, ↑ IgG, ASA+, Anti-DNA+
○ Pathology		
- Ducts	Florid duct damage	Minimal duct damage
- Hepatocytes	Intact lobules	Interface hepatitis (zone 1)
- Infiltration	Lymphoid aggregates	Lymphocytes and plasma cells

Abbreviation: ASA, anti-smooth muscle antibody

30. Give 6 hepatocyte and ileal enterocytes transporters responsible for the enterohepatic circulation of bile salts.

- Hepatocyte
  - Blood side (sinusoidal /BLM)
    - NTCP/SLCIOAI (sodium-taurocholate cotransporting polypeptide)
    - Na+/K+-ATPase
    - OATPs/SLCOI (organic anion transporting peptides)
  - Bile side
    - BSEP/ABCBII (bile salt export pump)
    - MRP_3/$ABCC_3$ and MRP_4/$ABCC_4$ (multidrug resistance-associated proteins 3 and 4)
    - OST2/B (organic solute transporter alpha-beta)

- Enterocyte
  - Lumen side (BBM)
    - $ASBT/SLCIOA_2$ (apical Na+- dependent bile salt transporter)
    - OST2/B (organic solute transporter alpha-beta)

Adapted from: Dawson PA. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1374.

31. Give 4 proteins involved in the hepatic transport, metabolism and signaling of secretion of bile; indicate the diseases associated with defects in these proteins, and the potential implications for therapy of ductopenia (VBDS, vanishing bile duct syndrome).

- FXR agonists (for cholestasis and NAFLD)
- Nuclear receptor (PXR CAR) stimulation to activate cytochromes
- Stimulate phospholipid export pumps (Madrs[Abcb4])
- Statins (↑PPARα)
- Replace toxic CDCA with KDCA (NOX3-rich cholaresis, but high doses cause bile infarcts and ↑ mortality) or modified KDCA (Norkoca), resistant to tamrine conjugation
- VCAM reduction by NARKDCA (silence the active phenotypes so there is less vascularisation – bile ducts both cause duct damage, and are themselves damaged)
- AKT, mTER, Rp56 stimulation

Adapted from: Francis GA, et al. *Annu Rev Physiol* 2003;65:261-311. Epub 2002 May 1.

32. Give the factors that increase the risk of bone disease in patients with chronic cholestatic liver disease.

- General
  - Reduced physical activity
  - Low body mass index
  - Increasing age
  - Smoking
  - Female sex
  - Reduced sunlight exposure
  - Family history
- ↓ Intake
- ↓ Absorption - Cholestasis
  - Vitamin D and K deficiency
  - Reduced calcium availability (steatorrhea)
  - Increased serum bilirubin
  - Genetically abnormal vitamin D receptor genotype
- ↑ Requirements
  - Menopause/hypogonadism

- Therapy
  - Steroids
  - Furosamide
  - Cholestyramine
- Associated proximal renal tubular disease (Type II)

Adapted from: Angulo P, and Lindor KD. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006; pg.1894.; and Glasova H, and Beuers U. *J Gastroenterol Hepatol* 2002; 17(9): 938-48.

Primary sclerosing cholangitis (PSC)

33. Give a classification of the secondary causes/ associations of secondary sclerosing cholangitis (SSC), and provide 15 examples.

- GI disease associations
  - Inflammatory bowel disease
    - Ulcerative Colitis
    - Crohn's colitis or ileocolitis
    - Cholangiocarcinoma

- Hepatobiliary/Pancreatic
  - Hepatic allograft rejection
  - Hepatic graft-versus-host disease (after bone marrow transplantation)
  - Choledocholithiasis
  - Stricture
  - Biliary parasites
  - Recurrent pyogenic cholangitis
  - Fungal infection
  - Cystic fibrosis
  - Chronic pancreatitis

- Systemic diseases with fibrosis
  - Retroperitoneal fibrosis
  - Riedel's thyroiditis
  - Mediastinal Fibrosis
  - Pseudotumour of the orbit
  - Inflammatory pseudotumour
  - Peyronie's disease
  - Chronic sclerosing sialadenitis

- Autoimmune or collagen vascular disorders

- Systemic lupus erythematosus
- Systemic sclerosis
- Type I diabetes mellitus
- Rheumatoid arthritis
- Sjörgen's syndrome
- Autoimmune hemolytic anemia
- IgG4-associated cholangitis (IAC), with or without IgG4-associated pancreatitis

- Kidney
  - Membranous nephropathy
  - Rapidly progressive glomerulonephritis

- Infections
  - Biliary TB

- Sarcoidosis
  - Hypereosinophilic syndrome
  - HIV

- Immunodeficiency diseases
  - Congenital immunodeficiency
  - Combined immunodeficiency
  - Dysgammaglobulinemia
    - X-linked agammaglobulinemia
  - Acquired immunodeficiency
    - Selective immunoglobulin A deficiency
    - Acquired immunodeficiency syndrome (HIV/AIDS)
    - Angioimmunoblastic lymphadenopathy

- Congenital abnormalities
  - Caroli's disease
  - Choledochal cyst

- Iatrogenic
  - Hepatic arterial infusion of chemotherapy, intraductal formaldehyde or hypertonic saline (used for echinococcal cyst removal)
  - Intra-arterial floxuridine (FUDR, causing ischemia and toxic vasculitis)

- Ischemic
  - Vascular injury from liver surgery
  - Hepatic allograft arterial occlusion
  - Paroxysmal nocturnal hemoglobinuria
  - Prolonged circulatory failure (shock)
  - Systemic vasculitis

- Infiltration
  - Benign
    - Mastocytosis
    - Histiocytosis X
    - Biliary papillomatosis
  - Malignant
    - Cholangiocarcinoma
    - Hepatocellular carcinoma (HCC)
    - Metastatic cancer
    - Lymphoma

Adapted from: Tung BY, and Kowdley KV. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease:Pathophysiology/Diagnosis/Management* 2006 pg. 1462.

"Whoever said that old age was "The Golden Years"
was already demented."

Grandad

Viral hepatitis

34. Compare viral hepatitis (A, B, C, D, E) under the headings - virus type, mode of transmission, incubation period, serological diagnosis, risk of fulminant hepatitis and risk of chronicity.

	Virus type	Trans-mission	Incuba-tion (days)	Serologic diagnosis	Fulminant hepatitis	Risk of chronicity
➢ Fecal/oral						
○ HAV	RNA		20-35	HAV-IgM	0.1-2.0%	No
○ HEV	RNA		10-50	Anti-HEV	1-2% 15-20% Pregnant	No
➢ Percutaneous						
○ HBV*	DNA	-IVDU	60-110	HBsAg	0.1-0.5%	Adults < 5% Preschoolers 25% Neonates >90%
○ HCV**	RNA	-Sexual (homo-sexual, prostitute services, promi-scuity)	35-70	Anti-HCV	<1%	> 80%
○ HDV	RNA	-IVDU (IV drug use) (even once), pre-1990 blood transfu-sions -Sexual promis-cuity	60-110	Anti-HDV		Usual in a superinfection with HBV; rare by itself

* Also perinatal
** Pre-1990 blood transfusion

Adapted from: Grover PT, and Ma M. *First Principles of Gastroenterology* 2005: pg. 552.

35. Give the screening, vaccination, and prophylaxis on exposure to HAV, HBV, and HCV.

- Prevention
  - Good sanitation and hygiene
  - Avoid high risk behavior
  - For HBV condoms advised for multiple sex partners, anal intercourse, and intercourse during menses
- Vaccination
  - HAV
  - HBV
  - HCV
    - No vaccine
- Treatment when exposed (post exposure prophylaxis)
  - HAV
    - Children ≥ 2 years of age in communities with high rates of Hep A
    - Chronic liver disease
    - All household and sexual contacts
    - Immune serum globulin 0.02 mL/kg IM if within 2 weeks of exposure
      - Vaccinate
    - No treatment for casual school or work contacts
  - HBV
    - When HBC reactivation (“flare”, decompensation) may occur – use of chemotherapy, prednisone, anti-TNF therapy
  - HCV
    - Needlestick injury:
    - Test for HCV-RNA, AST, bilirubin at baseline, then at 4 and 12 weeks—of positive, treat with PEG-IFN and Ribavirin
    - Perinatal: Rare transmission—more likely of mother is immunosuppressed
- Treatment when infected
  - Supportive care. Most cases resolve spontaneously. Hospitalization rarely needed. Prophylaxis and prevention of secondary spread is perhaps the most important aspect of treatment.
  - Activity—symptom guided return to work: no activity limitations.
  - Diet—fatty foods poorly tolerated,
    - exclude ETOH, no other dietary restrictions.
  - Drugs—no role of corticosteroids—may increase the risk of a chronic carrier state, avoid sedatives, tranquilizers.

Adapted from: Grover PT, and Ma M. *First Principles of Gastroenterology* 2005: pg. 547-552.

36. Give the METAVIR system for staging/grading chronic hepatitis.

	Piecemeal and lobular necrosis *(A)	Fibrosis (F)
0	None	None
1	Mild activity	Portal fibrosis without septa
2	Moderate activity	Portal fibrosis with septa
3	Severe activity	Numerous septa (bridging) without cirrhosis
4		Cirrhosis

Printed with permission: Grover PT, and Ma M. *First Principles of Gastroenterology* 2005. pg. 547-552.

37. Give the geographic site for the most common distribution of Hepatitis B genotypes A-H .

A. Northwestern Europe, North America, Central Africa

B,C. Southeast Asia, including China, Japan, and Taiwan (prevalence is increasing in North America)

D. Southern Europe, Middle East, India

E. West Africa

F. Central and South America, United States (Native Americans), Polynesia

G. United States, France

H. Central and South America

Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. 2010, Table 78-1.

38. Give a comparision of the histologic features of recurrent hepatitis C virus infection versus acute cellular rejection after liver transplantation.

Histological features	HCV Recurrence	Rejection
➢ Time of onset	○ Usually within the first year	○ Usually within the first 2 months
➢ Portal inflammation	○ Bland, uniform	○ Activated
➢ Lymphocytes	○ Common	○ Uncommon
➢ Lymphoid aggregates	○ 50% of cases	○ Rare
➢ Lymphoid follicles		
➢ Eosinophils	○ Inconspicuous	○ Common
➢ Steatosis	○ Common	○ Never
➢ Acidophilic bodies	○ Common	○ Uncommon
➢ Bile ductule damage	○ Common	○ Common
➢ Atypical features	○ Cholestasis, ballooning degeneration without significant inflammation,	○ Prominent periportal and lobular necroinflammatory activity without sub-endothelial venular inflammation

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 95.10, page 1609,

Hepatitis B (HBV)

39. List 5 markers of HBV infection, and what they signify.

- HBsAg – appears first and if persists for > 6 months, the patient is chronically infected (exposed, chronic infection)
- HBsAb – implies recovery or immunity to HBV, either naturally occurring or after vaccination
- HBcAb-IgM – past or present HBV infection (newer and more sensitive assays may also be positive during reactivation of chronic infections)
- HBeAg – indicates active infection/replication of HBV, but absence cannot be taken as absence of viral replication (i.e., precore mutant, e.g. eAg negative)

- Anti-HBe – presence indicates seroconversion but can also be found in active disease in patients with HBeAg negative chronic hepatitis. (not replicating – precore mutant)
- HBV-DNA – detectable in serum, it is a measure of the level of viral replication. (infected) (reflects risk of HCC)

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40. Define the following terms:

- Chronic active HBV (active HBsAg carrier)
  - HBsAg positive for more than 6 mon HBe Hg positive
  - HBV-DNA > 10^5 copies/mL (>20,000 Ik)
  - Persistent or intermittent ALT/AST elevation
  - Liver biopsy showing chronic hepatitis
  - Evidence of on-going replication (active carrier), active chronic HBV infection

- Chronic inactive HBV (inactive HBsAg carrier)
  - HBsAg positive for more than 6 mos
  - HBeAg negative, anti-HBe positive
  - HBV-DNA <10^5 copies/mL (<20,000 Ik, low risk of HCC)
  - Persistently normal ALT/AST (low risk of progression)
  - Liver biopsy showing no inflammation
  - No evidence of on-going replication (inactive chronic HBV infection)

- Resolved hepatitis B
  - Previous known history of acute or chronic hepatitis B
  - HBsAg negative
  - HBeAg negative
  - HBcAb positive/HBsAb positive
  - Undetectable HBV-DNA
  - Normal ALT

Adapted from: Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62. Epub 2006 Jul 14.

41. Give 10 extrahepatic manifestations of Hepatitis C (HCV) infections.

- Thyroid
  - Autoimmune thyroiditis
  - Thyroid cancer
- Lung
  - Idiopathic pulmonary fibrosis

- Skin
  - Lichen planus
  - Porphyria cutanea tarda
  - Vitiligo

- MSK
  - Chronic polyarthritis
  - Sicca syndrome

- Kidney
  - Non cryoglobulinemic nephropathies
  - Renal cell carcinoma

- Hematology
  - Mixed cryoglobulinemia
  - Monoclonal gammopathies
  - B cell non Hodgkin's lymphoma

- Endocrine
  - Diabetes mellitus

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management.* Ninth edition, 2010, Table 79.1, page 1320,

42. Group the oral anti-viral agents utilized for treatment of chronic active HBV by the site of their action.

Site 1	Site 2	Site 3
➢ Lamivudine ➢ Telbuvidine ➢ Emtricitabine ➢ Entecovir	Adefovir	Tenofovir

Printed with permission: Shiffman ML. *2008 AGA Annual Postgraduate Course Syllabus*: pg. 167.

43. Name 10 high-risk groups for whom hepatitis B virus (HBV) vaccination should be considered.

- Health care workers
- Hemodialysis patients
- Household contacts and sexual partners of HBV carriers or patients with acute hepatitis B
  Injection drug users
- Inmates of correctional facilities: International travellers to areas endemic for HBV who may have intimate contact with the local population or take part in medical activities
- Men who have sex with men
- Patients who are likely to require multiple transfusions with blood or blood products
- Patients with chronic liver disease (other than chronic hepatitis B)
  Potential organ transplant recipients
- Public safety workers with likelihood of exposure to blood
- Sexually active heterosexual men and women, if they have more than one partner
- Staff and clients of institutions for developmentally disabled

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 78.6, page 1308.

44. Give 8 reasons for failure of the usual expected antibody response to HBV vaccine.

- Age > 50 years
- Underlying disease (chronic renal failure, esp. hemodialyisis)
- Immunosuppressed, immunodeficient
- HIV positive
- HCV co-infection
- Genetics (HLA-B8)
- Buttock injection
- Frozen vaccine
- Wrong timing or dose of injections

- Smoker
- Obese
- (immunoglobulin, HBIG)

45. Give the immunoprophylaxis for HBV in adults accidentally exposed to possibly infectious blood (within the last 7 days), or sexual contacts (within the past 14 days).

- Check donor blood for HBsAg; check victim's blood for HBsAg and HBcAb

- Give at once 0.06 ml/kg HBIG plus first dose of hepatitis B vaccine

	HBsAg	HBcAb	Further action to victim
Victim	-ve	+ve	None: Immune
"Donor" (source)	+ve	-ve	Continue vaccine course
	-ve	-ve	None, or continue vaccine course if victim is at risk of further hepatitis B exposure

Adapted from: Sherlock S, and Dolley J. *Diseases of the Liver and Biliary System* (Eleventh Edition) 2002. pg. 285-303.

46. Give the general management strategy of the person with HBV.

- Prevention, vaccination, prophylaxis on exposure (see question 38)

- General management strategy
  - Baseline evaluation should include HBV genotype, particularly if peginterferon therapy considered
  - Preferred first line treatment options: adefovir, entecavir, peginterferon alfa-2a, and possibly telbivudine (Lamivudine not first-line choice secondary to high rate of resistance to Interferon alfa-2b
  - Revised normal ALT levels (30 IU/L for men, and 19 IU/L for women) should be used as criteria for treatment
  - Liver biopsy should be considered for patients with normal ALT levels, especially if age >35-40 years
  - Baseline laboratory assessment

- Assessment of risk (risk to develop fibrosis progression, cirrhosis and those at greatest risk for development of HCC)
  - Active HBV:

- eAg (+), HBV DNA >500,000 copies/mL (20,000 Iμ/ml), and elevated ALT > 2 X ULN
  - Active hepatitis with variable degrees of fibrosis on liver biopsy
  - Pre-core mutations of HBV:
    - Includes patients with all features above, except eAg(-)
  - Inactive HBV:
    - patients with inactive HBV, and HBV DNA < 500,000 copies/mL are NOT currently considered candidates for HBV therapy, unless they have evidence of cirrhosis on liver biopsy. These patients are at low risk to develop fibrosis progression or HCC.

- Assessment of factors predictive of VR
- Specific treatment algorithms
  - HBeAg+
  - HBeAg-
- Select optimal agent
- Reassess therapy
- Screen for HCC

Adapted from: Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62. Epub 2006 Jul 14.

47. Give 6 goals for the treatment of $HbEag^+$ and $HbEag^-$ HB.

E-antigen (+) HB E-antigen (-) (+)

- Loss of E-antigen
- Appearance of anti-E
- Conversion to inactive status
- Normalization in serum liver aminotransferase
- Loss of detectable HBV DNA
- Improvement in liver histology
- Reduce the risk of hepatocellular carcinoma
- Loss HBs Ag

Printed with permission: Shiffman ML. *2008 AGA Annual Postgraduate Course Syllabus*: pg. 166.

48. Give the comparisons of HBeAg positive and HBeAg negative HBV, under the headings epidemiology, natural history, treatment response, monitoring of treatment response.

Comparisons	HBeAg positive	HBeAg negative
➢ Epidemiology	○ Most common type in North America	- Higher incidence in Asia, Europe and other Mediterranean countries
➢ Natural History	○ Lower rate of progression to cirrhosis (10-20% /yr) (immune tolerance)	- Higher rate of progression to cirrhosis
➢ Treatment response	○ Higher sustained response rate to IFN-α therapy	- Lower sustained response rate to IFN-α therapy
➢ Monitoring of treatment response	○ HBeAg seroconversion to anti-HBV positive (also, possibly seroconversion to HBs Ag negative) ○ Normalization of liver enzymes and marked reduction in HBV DNA	- Normalization of liver enzymes and marked reduction in HBV DNA

Printed with permission: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005:547-552.

49. Give the recommendations for treatment strategy (treatment algorithm) of HBeAg-positive compensated patients, based on their HBV DNA and ALT.

HBV DNA	ALT	Treatment Strategy
○ <20,000 Iμ/ml	Normal	- No treatment - Monitor every 6-12 months - Consider therapy in patients with known significant histological disease even if low-level replication
○ ≥20,000 Iμ/ml	Normal	- Low rate of HBeAg seroconversion for all treatments - Monitor every 3-12 months

		- Younger patients often immune tolerant - Consider biopsy; particularly if older than age 35-40 years; treat if significant disease. In the absence of biopsy, observe for rise in ALT levels. - If treated, adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine preferred.
○ ≥20,000 Iμ/ml	Elevated	- Adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine are preferred - If "high" HBV DNA: adefovir, entecavir or telbivudine preferred over peginterferon alfa-2a.

b) Give the recommendations for treatment strategy of HBeAg-negative compensated patients, based on their HBV DNA and ALT.

HBV DNA	ALT	Treatment strategy
○ <2,000 Iμ/ml	Normal	- No treatment: majority inactive HBsAg carriers - Monitor every 6-12 months
○ ≥2,000 Iμ/ml	Normal	- Consider biopsy; treat long term if disease present. In the absence of biopsy, observe for rise in serum ALT levels (ALT often fluctuates). - If treated, adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine preferred.
○ ≥2,000 Iμ/ml	Elevated	- Adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine are preferred - Long term treatment required for oral agents

Printed with permission: Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62.

c) Give the recommendations for treatment of HBV-associated cirrhotic patients (HBeAg positive or negative).

HBV DNA	Cirrhosis	Treatment strategy
○ <2,000	Compensated	○ May choose to treat or observe ○ Adefovir or entecavir preferred[b]
○ ≥2,000	Compensated	○ Adefovir or entecavir are first-line options ○ Long-term treatment required, and combination therapy may be preferred[b]
○ <200 or ≥200	Decompensated	○ Combination with lamivudine, or possibly entecavir, plus adefovir preferred[c,d] ○ Long-term treatment required, and combination therapy may be preferred[c] ○ Wait list for liver transplantation

d) Give when HBV therapy should be reassessed or stopped.
- ○ HBeAg+: HBeAg seroconversion and – HBV DNA
- ○ HBeAg-: ? Long term therapy
- ○ Inadequate VR (<2,000 IU/mL) at week 24
- ○ Development of antiviral drug resistance

Abbreviation: VR, viral response

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50. Give 8 pros and cons of Lamivudine versus interferon (IFN) for the treatment of HBV.

<u>Favoring lamivudine</u>
- ➢ Needle phobia
- ➢ HIV co-infection
- ➢ Other immunosuppresion
- ➢ (e.g. transplantation)
- ➢ Patients with depression
- ➢ Low WBC count
- ➢ Low platelet count
- ➢ Autoimmune disease
- ➢ Decompensated cirrhosis

<u>Favoring IFN</u>
- ○ Young Asian
- ○ Genotype A
- ○ Recent infection
- ○ AST > 100
- ○ Low serum HBV-DNA
- ○ Active liver biopsy
- ○ eAg+
- ○ Possibility of seroconversion (eAg+→eAb+)

Favouring lamivudine

- Vertical transmission
- Cost concerns
- Pregnancy, may be used
- Has 70% resistance rate at 5 years. It acts as an immunomodulatory agent resulting in loss of circulating HBeAg and HBV DNA in 30-40% of cases, and to a lesser extent as an antiviral agent resulting in loss of HBsAg in less than 5% of cases.
- Cross reistance with tenofovir

Favouring IFN

- Marginal benefit to baby
- Ontraindicated with depression, renal failure

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005:547-552.

51. Give the advantages and disadvantages of current therapies for chronic HBV hepatitis.

Agent	Advantages	Disadvantages
○ Interferon	- HBsAg loss - Short treatment duration - No drug resistance	- Parenteral administration - Frequent side effects
○ Peg-IFN	- HBsAg loss - Fixed duration of treatment - No drug resistance	- Parenteral administration - Frequent side effects but less than interferon
○ Lamivudine	- Oral administration - Excellent tolerance - Use in ESLD - Use in adefovir failures	- Drug resistance: common (~20%/year, and up to 70% with 4-5 years of therapy)
○ Adefovir	- Oral administration - Excellent tolerance - Use in ESLD - Use in lamivudine failures	- Less potent, with suboptimal responses not uncommon - Drug resistance: delayed and less common (0% at year 1, 2% at year 2, 7% at year 3, 15% at year 4, and 29% at year 5 of therapy)

○ Entecavir	- Oral administration - Excellent tolerance - High potency in lowering HBV DNA levels - Use in adefovir failures	- Drug resistance: rare in nucleoside naïve patients (0.1% at year 1, 0.4% at year 2 and 1.1% at year 3), but common in patients with lamivudine resistance (6% at year 1, 14% at year 2, and 32% at year 3)
○ Telbivudine	- Oral administration - Excellent tolerance - High potency in lowering HBV DNA levels	- Drug resistance: intermediate rates (5% at year 1, and 21.6% at year 2 in HBeAg-positive patients, and 8.6% in HBeAg-negative patients)

Abbreviation: ESLD, end-stage liver disease
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Useful background: Overview of response rates in HBeAg positive and HBeAg negative patients with currently available antiviral drugs.

Antiviral therapy	HBeAg positive HBeAg seroconversion		HBeAg negative Undetectable HBV DNA	
	End of therapy	Post treatment	End of therapy	Post treatment
➢ Alpha interferon	35%	30%	60%	35%
➢ Peginterferon	40%	35%	63%	19%
➢ Lamivudine	19%	12%	65%	10%
➢ Adefovir	12%	NA	51%	NA
➢ Adefovir in lamivudine resistance	20%	NA	19%	NA
➢ Entecavir	21%	NA	90%	NA
➢ Entecavir in lamivudine resistance	8%	NA	26%	NA
➢ Telbivudine	22%	NA	88%	NA
➢ Tenofovir	21%	NA	92%	NA

Abbreviation: NA, not applicable
Printed with permission: Buster, et al. *Best Practise Res Clin Gastroenterol* 2008;22:1093-1108.

52. Give the potential management strategies for HBV by on-treatment virologic response categories.

Category	Strategy*
○ Primary treatment failure at week 12	- If noncompliant, counsel patient on importance of adherence to prescribed drug regimen - If compliant, change therapy to more potent drug or possibly a drug combination
○ Complete virologic response at week 24	- Continue therapy with same drug; monitoring may be extended to 6-month intervals
○ Partial virologic response at week 24	- If drug has a low genetic barrier to resistance, add a second drug that is not cross-resistant - If drug has a high genetic barrier to resistance, repeat monitoring at 3-month intervals and continue beyond 48 weeks - If drug has a delayed antiviral effect e.g. adefovir, repeat monitoring at 3-month intervals and if response becomes complete at 48 weeks, continue therapy; but if response remains partial or becomes inadequate at 48 weeks, add a more potent drug
○ Inadequate virologic response at week 24	- Add another drug (preferably one that is more efficacious, or if such a drug is not available, then add one that is not cross-resistant) - Repeat monitoring at 3-month intervals - Monitoring after 48 weeks may be extended from 3 to 6 months if response becomes complete

*patients with advanced disease should be monitored at 3-month intervals while on treatment, regardless of virologic response

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53. Give the management options of rescue therapy for HBV when there is resistance to lamivudine, adefovir, entecavir or telbivudine.

Resistant drug	Rescue therapy
○ Lamivudine	-Continue lamivudine and add adefovir or tenofovir -Switch to emtricitabine/tenofovir
○ Adefovir	-Continue Adefovir and add lamivudine -Switch to or add entecavir (if no prior LAM-R) -Switch to emtricitabine/tenofovir
○ Entecavir	-Switch to or add adefovir or tenofovir
○ Telbivudine	-Continue telbivudine and add adefovir or tenofovir -Switch to emtricitabine/tenofovir

Abbreviation: LAM-R, resitance to LAM
Printed with permission: Keeffe EB, et al. A *Clin Gastroenterol Hepatol* 2008;6(12):1315-41; quiz 1286. Epub 2008 Aug 23.

54. Give 5 causes of "flares" of acute hepatitis (reactivation, decompensation) in persons with chronic HBV.

Cause of flares	Comment
○ Spontaneous	- Seroconversion HBeAg+ →HBeAg- - Reappearance of IgM anti-HBC
○ Drugs – Immunosuppressive therapy – Steroids Interferon (systemic (interferon), common; oral agents, rare – Antiviral therapy – Lamivudine	- Flares are often observed during withdrawal of immunosuppressants; requires preemptive antiviral therapy - Flares are often observed during the second to third month: may herald virologic response
○ During treatment	- Flares are no more common than with placebo
○ YMDD mutant	- Can have severe consequences in patients with advanced liver disease
○ Adefovir, entecavir	- On withdrawal, flares are caused by rapid reemergence of wild-type HBV; can have severe consequences in patients with advanced liver disease

Cause of flares	Comment
○ HIV treatment	- Flares also can occur with immune reconstitution or secondary to antiretroviral drug hepatotoxictity
○ Genotypic variation – Precore and core promoter mutants	- Fluctuations in serum ALT levels are common with precore and core promoter mutants
○ Superimposed infection with	
	- HAV, HCV, HDV may be associated with suppression of
○ Other hepatitis viruses	HBV replication
○ Alcohol use	

Adapted from: Poterucha JJ. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg.298.

55. Give 5 characteristics of healthy HBV carriers (no cirrhosis) who are candidates for HCC screening.

- African males/ females > 20 years
- Asian male >40 years
- Asian female >50 years
- Caucasian inactive or active disease with cirrhosis*
- Family history of HCC
- Co-infection with HCV, HIV

*Caucasians with inactive disease and no cirrhosis have a low risk of HCC development, and HCC screening is generally not recommended, but may be considered if there is a family history of HCC, or co-infection with HCV.

Adapted from: Sherman M. *Best Practice & Research Clinical Gastroenterology* 2005;19(1): pg 105.

56. Give the potential management of HBV antiviral drug resistance.

➢ Lamuvidine resistance	○ Continue lamivudine and add adefovir (preferred over switch to adefovir) or tenofovir ○ Switch to emtricitabine/tenofovir
➢ Adefovir resistance	○ Continue adefovir and add lamuvidine (preferred over switch to lamuvidine) ○ Switch to or add entecavir (if no prior lamivudine resistance) ○ Switch to emtricitabine/tenofovir[1]
➢ Entecavir resistance	○ Switch to or add adefovir or tenofovir
➢ Telbivudine resistance	○ Continue telbivudine and add adefovir or tenofovir ○ Switch to emtricitabine/ tenofovir

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57. Give the laboratory assessment prior to therapy of HBV, and explain why.

- HBsAg – if positive, measure
- HBeAg and anti-HBe
- Measure HBV DNA if ALT elevated
- ALT, ALP, bilirubin, albumin, PT INR, CBC, HIV, anti-HCV

Printed with permission: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005:547-556.

Useful background: Hepatitis B (HBV)

- The CDC now recommends HBV diagnostic testing in all persons going on immunosuppressants or undergoing cancer chemotherapy

- Natural clearance of HBV occurs in 5% of neonates and 95% of adults infected with HBV

- Baseline HBV DNA levels in patients aged 30-65 years are directly related to the likelihood of developing HCC 10 years later

a) Clinical characteristics of the different phases of chronic hepatitis B infection

Features	Immune tolerant	Immune reactive	Low replicative stage	e- Ag negative reactivation
➢ ALT	○ Normal	○ Elevated	○ Normal	○ Fluctu-ates (fluctu-ating viremia)
➢ HBV-DNA by PCR	○ >20,000 IU/ml	○ >20,000 IU/ml	○ <2,000 IU/ml	○ >2,000 IU/ml
➢ e-antigen	○ (+)	○ (+)	○ (-)	○ (-)
➢ e-antibody	○ (-)	○ (-)	○ (+)	○ (+)
➢ Liver biopsy	○ Inactive	○ Active/+fibro sis	○ Inactive	○ Active/+ fibrosis
➢ Treatment	○ Not recomm-ended	○ Recomm-ended	○ Not recom mended	○ Recomme nded
➢ Liver biopsy recomm-ended	○ No progression of disease for about 3-6 months	○ HBeAg seroconversi on with treatement		○ 8-10% develops cirrhosis each year, compared with 2-6% of HBeAg positive patients

Adapted from: Herrera JL. *2009 ACG Annual Postgraduate Course:*161-166.

- Treatment does not completely eliminate HBV infection, since the HBV (a DNA virus) becomes integrated within the hepatocyte genome as CCC DNA, covalently closed circular DNA

- The goals of therapy in HBV infection (Herrera 09):
  - Reduce viral load as much as possible to control the disease
  - Normalize liver enzyme levels
  - Advine resolution of hepatic necroinflammation
  - Achieve e-Ag seroconversion (note that e-Ag seroconversion is not possible if the patient is infected with the e-Ag mutant of the HB virus)

- HBsAg seroconversion (occurs in < 10%, and is often not seen for 4-5 years after therapy has been completed and e-Ag has occurred

- Lamuvidine has high resistance rates; because telbivudine develops resistance mutations at the same site as for lamivudine, telbivudine is not effective in persons who have lamivudine resistance

- Entecavir has low rates of resistance (1.2% after 5 years), and 20% rate of eAg seroconversion after 48 weeks

- The diagnosis of chronic HBV infection in an HIV patient is an indication to start tenofovir-based HAAR therapy

- Tenofovir is a patent selective inhibitor of HBV-DNA polymerase, and is active in HBV

- A roadmap to treatment of HBV has been updated (166-8). HBe-Ag positive and negative persons. After 48 weeks of therapy, HBV-DNA becomes negative in 76% of HBeAg positive and 91% of HBeAg-negative persons

Abbreviation: HBV, Hepatitis B

58. Give 5 factors that are predictive of a viral response (VR) to treatment of HBV infection.

- Patient
  - Immunocompetent

- HBV
  - Adult-acquired infection
  - Low HBV-DNA level
  - Absence of HDV or HIV co-infection
  - HBeAg +ve

- Biopsy
  - Active liver disease—ALT > 5x upper limit of normal (ULN), active hepatitis on biopsy

Useful background: Comparisons among current nucleos (t)ide analogues in treatment-naïve patients with chronic hepatitis B , in terms of (by reduction and undetectable) HBV-DNA (PCR) and HBeAg seroconversion and drug resistance

	Lamivudine		Adefovir		Entetavir		Telbivudine		Tenotovir	
HBV-DNA (PCR)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)
Log reduction:										
Year 1	5.4	4.5	3.6	3.7	6.9	5.0	5.7	4.4	6.5	4.5
Undetectable:										
Year 1	40%	7.3%	21%	61%	6.7%	9%	60%	88%	76%	93%
Year 2	39%	52%	NA	71%	74%	NA	5.6%	82%	78%	99%
Year 3	20%	40%	NA	77%	NA	NA	NA	NA	NA	NA
Year 4	NA	34%	NA	73%	NA	NA	NA	NA	NA	NA
HBeAg Serocon-version	20%	NP	13%[a]	NP	21%	NP	23%	NP	23%	NP
Year 1	26%	NP	29%[a]	NP	31%	NP	30%	NP	26%	NP
Year 2	40%	NP	37%[a]	NP	NA	NP	NA	NP	NA	NP
Year 3	47%	NP	35%[a]	NP	47%	NP	NA	NP	NA	NP
Year 4										
Drug resistance										
Year 1	11-	6-	0%	0%	0%	0%	5%	2%	0%	0%
Year 2	14%	27%	NA	3%	0%	NP	25%	11%	0%	0%
Year 3	40%	26-	NA	11%	1.2%	NP	NA	NA	NA	NA
Year 4	56%	54%	20%	29%	1.2%	NP	NA	NA	NA	NA

Abbreviations: HBV, hepatitis B virus; PCR, polmerare chain reaction; E, hepatitis B e antigen; NA, not available; NP, not applicable
[a]Cumulative incidence

Printed with permission: Chien RN and Liaw YF. *Best Practise Res Clin Gastroenterol* 2008;22:1081-1092.

- HBV pregression
  AC HBV → chronic HBV:
  - Neonate 90 asymptomatic enteric disease
  - Children 50
  - Adults 10 symptoms

Source: *Clin Liver Disease* 10; 14: 75-91; *Hepatology* 07; 45:1056-75

- HBV disease "acute" > 20,000 HBV DNA IU/ml
  "inactive" < 20,000 HBV DNA IU/ml

HBV Lam < adefovir (Ade) < enterocovir < telbivudine (Tel) < tenofovir (Ten) viral suppression

- When immune tolerant, then no liver damage and no Rx needed

In HBV, "Be patient and wait" – 50% become acute over 5 years, and should then be treated

- When HBV DNA > 10^5, then risk of HCC↑

"AT", aminotransferases AP, alkaline phosphatase

Peginterferon 180 µg/wk - 35% $E^+ \rightarrow E^-$ seroconversion
Genotype A 50%
B, C, D 30%

TEN > THE > ENT >ADE

- Rate of resistance
  - LAM 69% / 5 yrs
  - ADE 30% / 4 yrs
  - TEN rare

  ] don't use

- HBV
  - Anti-core$^+$ can reactivate with Pred, AZA, TNFB

Hepatitis C (HCV)

59. Give six groups of persons at risk of hepatitis C virus (HCV) infection. Give the estimated prevalence of these persons who are infected with HCV in industrialised countries.

Groups at risk	Estimated prevalence (range %)
➢ Injection drug users	○ 35-90
➢ Hemophilianc treated before 1990	○ 50-90
➢ Thalassemics	○ 42-83
➢ Hemodialysis patients	○ 10-45
➢ People who received a blood transfusion before 1991	○ 5-10
➢ Children born from HCV positive mothers	○ 3-10

➢ Incarcerated persons	○ 30-80
➢ Migrants coming from endemic regions	○ Related to country of origin
➢ Health care workers	○ Related to country of origin
➢ HIV infected persons	○ 25-35
➢ Persons with unexplained persistently elevated ALT	○ 15

Abbreviation: ALT, alanine aminotransferase

Printed with permission: Van Herck, et al. *Best Practice Res Clin Gastroenterol* 2008;22:6:1009-1029.

60. Give the pros and cons of performing a percutaneous liver biopsy in a patient with HBC.

Issues	Argument in favor of biopsy with acceptable risk	Reasons for not performing a biopsy.
○ Decision to treat	Consider biopsy if minimal elevation or fluctuating ALT; consider treatment if at least moderate inflammation	Hepatitis B serologies, HBV DNA levels, and ALT generally determine decision to treat
○ Identify cirrhosis	Prompts screening for varices and HCC	HCC surveillance recommended whether cirrhosis is present or not

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<u>Thoughtful reflections</u>

Discuss the ethical considerations relating to a serological screening program for celiac disease

61. In the patient with HCV, define the terms RVR, EVR, ETR and SVR, as well as the definition and clinical implication of each of the 4 types of responses.

Response	Definition	Implication
➢ Rapid viral response (RVR)	HCV RNA undetectable by PCR or TMA at 4 weeks of treatment	Higher chance of SVR; may respond as well with only 24 weeks of treatment
➢ Early virologic response (EVR)	HCV RNA decreased by $\geq$ 2 logs from baseline or HCV RNA undetectable at 12 weeks after healmark slated	Failure to achieve EVR associated with almost no chance of SVR and treatment can usually be stopped
➢ End-of-treatment response (ETR)	HCV RNA undetectable by PCR or TMA at end of treatment wk 48 – 1 genotype, wk 24 – 2,3	On treatment response. Observe for SVR.
➢ Sustained virologic response (SVR)	HCV RNA undetectable by PCR or TMA, 24 weeks after treatment slated	Eradication of virus

Printed with permission: Davis GL. *AGA Institute 2007 Spring Postgraduate Course Syllabus*: 56.

62. Give the HCV-RNA levels at week 4,12 and 24 in persons with rapid virologic response (RVR), early virologic response (EVR), slow virologic response (SVR) and no virologic response (NVR).

	HCV-RNA		
	Week 4	Week 12	Week 24
➢ Rapid virologic response (RVR)	○ Undetectable (<50 IU/ml) [a]	○ Undetectable	○ Undetectable
➢ Early virologic response (EVR)	○ >50 IU/ml	○ Undetectable	○ Undetectable
➢ Slow virologic response (SVR)	○ >50 IU/ml	○ >50 IU/ml, but >log 2 drop	○ Undetectable

Week 4	Week 12	Week 24	Week 4
➢ No virologic response (NVR)	○ >50 IU/ml	○ >50 IU/ml, but ○ < log 2 drop	○Detectable

[a] Level of detection (LOD) chnges ith more sensitive test. The currently available new tests have a LOD <15 IU/ml , no prospective studies using these tests have been performed.

Abbreviations: EVR, early virologic response; NVR, no virologic response; RVR, rapid virologic response; SVR, slow virologic response

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63. Give 10 types of persons who should be screened for HCV.

- IV drug users
- Those with unexplained elevated ALT
- Hemodialysis patients
- Transplanted patients
- immunosuppressed patients
- Those with > 50 lifetime sexual partners
- Those with a history of STD
- Needle stick injury
- Hemophylics
- Inmates
- Immigrants
- STDs
- Blood transfusion before approximately 1990 (depends on country)
- HIV-positive patients
- Men who have sex with men (MSM)
- Sex trade workers (STWs)

64. Give the management of persons with HCV.

- Prevention, screening, vaccination (none), prophylaxis on exposure
- General management strategy
- Assessment of factors predictive of viral response (see question 56)
- Specific treatments
- Select optimal agent
- Reassess therapy
- Screen for HCC

Adapted from: Berenguer M, and Wright TL. Hepatitis C. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006. pg. 1681-1712.

65. Give 10 extrahepatic manifestations of Hepatitis C (HCV) infections.

- Skin
  - Vitiligo
  - Lichen planus
  - Porphyria cutanea tarda
- Thyroid
  - Autoimmune thyroiditis
  - Thyroid cancer
- Lung
  - Idiopathic pulmonary fibrosis
- Endocrine
  - Diabetes mellitus
- MSK
  - Chronic polyarthritis
  - Sicca syndrome
- Kidney
  - Non cryoglobulinemic nephropathies
  - Renal cell carcinoma
- Hematology
  - B cell non Hodgkin's lymphoma

- Mixed cryoglobulinemia
- Monoclonal gammopathies

Adapted from: *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* Table 79-1, page. 2010

66. Give 6 key factors which predict the likelihood of achieving SVR and thereby influence the decision to begin treatment for HCV.

- Risk of liver complications in the absence of treatment
  - Stage of fibrosis
  - Severity of necroinflammatory activity

- Presence of relative or absolute contraindications to treatment
  - Pregnancy or attempting conception
  - Active autoimmune diseases
  - Significant cardiopulmonary disease
  - Uncontrolled psychiatric disease
  - Uncontrolled seizures
  - Severe cytopenias, including transfusion-dependent anemia

- Motivation of patient to undertake treatment

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67. Give the laboratory assessment prior to therapy of HCV, and explain why.

- Anti-HCV
- HCV RNA (qualitative +/- quantitative)
- HCV genotyping
- ALT, ALP, bilirubin, albumin, PT INR, HBsAg, HIV
- CBC, glucose, TSH, ANA, smooth muscle antibody (SMA), quantitative immunoglobulins, creatinine, B-HCG
- Abdominal Ultrasound, ECG (if age >50, cardiac disease history)
- Liver biopsy recommended but not mandatory

Printed with permission: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005:547-556.

68. Give 8 pretreatment factors which are predictors of poor treatment response in HCV.

Host	Viral	Disease-specific
➢ African race	Genotype I	Advanced fibrosis score
➢ Latino ethnicity	High HCV RNA	Steatosis
➢ Older age	HIV coinfection	
➢ Male sex		
➢ Insulin resistance		
➢ High BMI		

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69. Give 10 pretreatment factors which are predictors of good treatment response in HCV.

- Non-I
- Viral genotype: Genotype 1&4 (42-46%), Genotype 2, 3 (76-82%)
- Lower viral levels: >2 x 10^6 (42-53%), <2 x 10^6 (62–78%)
- Liver histology: No or minimal fibrosis (57%)
- Age: Younger patients (<40) more likely to respond (odds ratio 2.60)
- Weight: lighter patients (<75kg) more likely to respond (odds ratio 1.91) (fixed dose)
- Women
- Caucasian race (non-african american)
- No HBV, HIV, no alcohol
- No comorbidity to prevent full drug dose (anemia, thrombocytopenia)
- Compliant
- Incarcerated (they get their Rx)
- Good social support
- No immunosuppression
- Normal renal function (ribavirin contraindicated with ↑ GFR)
- No psychiatric comorbidity
- Early virologic response: negative EVR (defined as 2-log decrease in HCV RNA in first 12 weeks of treatment) is predictive negative SVR (97%)
- Overall sustained virologic response (SVR) (undetectable HCV RNA 24

weeks after cessation of therapy) to inferon monotherapy: 5-15%, to combined interferon and ribavirin: 30-40%, to combined pegylated interferon and ribavirin: 54-56%.

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005: 547-552.

70. Give 10 established or likely factors that are associated with progression of HCV.

- Established
  - Age at infection (>40 yrs)
  - Gender (Male)
  - Race (Caucasian)
  - Immunosuppression (HIV coinfection, agammaglobulinemia, organ transplantation)
  - Genotype, no association
  - Level of viremia, no association
  - Alcohol (>50 g/day)

- Likely
  - HBV coinfection
  - NASH/obesity/diabetes (hepatic steatosis)
  - Schistosomiasis
  - Smoking
  - Iron overload
  - Elevated serum ALT levels (elevated)
  - Histology - Moderate to marked necroinflammation

Adapted from: Berenguer M, and Wright TL. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1696.; and 2010: pg. 1325.

71. Give the early and late adverse effects of interferon.

- Early
  - Flu-like illness; headaches, nausea
  - Tenderness at site of infection

- Late
  - Fatigue
  - Muscle aches
  - ↑retinopathy m'DM
  - Irritability Anxiety and depression
  - Weight loss

- Diarrhea
- Alopecia
- Bone-marrow suppression
- Bacterial Infections
- Autoimmune autoantibodies
- Optic tract neuropathy
- Anorexia
- Worsening thyroid disease
- CNS (neuropsychiatric)
- Bone marrow
- HCV?
- Child pregnancy
- Eyes
- Head/neck
- Lichen planus worsens
- IBD worsens
- Autoimmune diseases worsen
- Class C for pregnancy

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005: 547-563.

72. What are the contraindications to the use of Ribavirin?

- Pregnancy
- Inadequate contraception
- End-stage renal disease
- Anemia
- Angina pectoris (possible)
- Old age (possible)
- Known allergy to ribavirin

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005: 547- 562.

73. Give the common adverse effects (AEs)of Ribavirin (RIB) in the treatment of HCV, and give the management of these AEs.

- Common AEs: “flu-like symptoms”, fatigue, anorexia, nausea, nasal congestion, irritability, cognitive impairment, insomnia
- Overall dose reduction in19% of Ribavirin treated persons, with discontinuation in 10%
- Major AEs of Ribavirin
  - RBC, WBC, platelets
  - Management of major AEs

	Level	Other clinical considerations
➢ Hemoglobin	10 gm/dL - Reduce ribavirin by 200 mg/day	- Consider starting erythropoietin; if Hgb responds poorly to dose reduction, check iron studies and consider reducing peginterferon
	8.5 gm/dL - Stop ribavirin	- Hold ribavarin and consider stopping; transfuse as necessary
➢ White blood cells	1500/µL - Reduce peginterferon by 50%	- Monitor more closely
	1000/µL - Stop treatment	- Monitor more closely; consider G-CSF
➢ Absolute neutrophils	750/µL - Reduce pegIFN by 50%	- Monitor more closely
	500/µL - Stop pegIFN	- Monitor more closely
➢ Platelets	50,000/µL - Reduce pIFN by 50%	- Individualize dose adjustment
	25,000/µL - Stop IFN	- Consider platelet transfusion or platelet stimulating factor

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74. Give the standard therapy for chronic HCV according to viral genotype.

Genotype	Interferon dose (per week)	Ribavarin dose (mg/day)	Duration (weeks)	SVR
1	180 µg PEG alfa-2a or 1.5 µg/kg PEG alfa-2b	800-1400 mg/day weight-based	48	41-42%
2	180 µg PEG alfa-2a or 1.5 µg/kg PEG alfa-2b	800 mg/day	24	66-75%
3	180 µg PEG alfa-2a or 1.5 µg/kg PEG alfa-2b	800 mg/day	24	66-75%
4	180 µg PEG alfa-2a or 1.5 µg/kg PEG alfa-2b	1000-1200 mg/day	48	55%
5	180 µg PEG alfa-2a or 1.5 µg/kg PEG alfa-2b	1000-1200 mg/day	48	64%
6	180 µg PEG alfa-2a or 1.5 µg/kg PEG alfa-2b	1000-1200 mg/day	48	63%

Abbreviation: SVR, sustained viral response

Printed with permission: Davis GL. *2007 AGA Institute Postgraduate Course*: pg. 56.

75. Give the definitions of four of the treatment responses (RVR, EVR, ETR, SVR)of HCV*).

Response	Time to assess	Implication
➢ Rapid viral response (RVR)	○ No HCV RNA at 4 weeks of treatment	- Higher chance of SVR; may respond as well with only 24 weeks of treatment
➢ Early virologic response (EVR)[complete]	○ HCV RNA decreased by ≥ 2 logs from baseline at 12 weeks	- Almost no chance of SVR, and treatment can usually be stopped
➢ End-of-treatment response (ETR)	○ No HCV at end of treatment	- On treatment response. Observe for SVR
➢ Sustained virologic response (SVR)	○ No HCV at 24 weeks of treatment	- Eradication of virus

*these treatments are for genotype ¼; for genotype 2/3; and for details of partial EVR on non-EVR, see the following Useful background.

Printed with permission: Davis GL. *2007 AGA Institute Postgraduate Course*: pg. 56.

76. Give the pros and cons of performing a percutaneous liver biopsy in a patient with HCV.

Issues	Argument in favor of biopsy with acceptable risk	Reasons for not performing a biopsy.
➢ Prognosis	○ Extent of fibrosis and inflammation are best predictors of disease progression	- Non-invasive markers may accurately stage and grade disease
➢ Decision to treat	○ Genotype 1: Identify those most in need of therapy (therapy longer in duration and less likely to succeed)	- Genotypes 2 and 3: Patients motivated for therapy may forgo biopsy (therapy shorter in duration and more likely to succeed)

Issues	Argument in favor of biopsy with acceptable risk	Reasons for not performing a biopsy.
➢ Treatment-related side effects	○ Severity of liver disease helps in deciding of whether to endure or stop therapy	- Commitment to therapy should be independent of disease severity
➢ Previously treated	○ Lower success with retreatment. Identify those most in need of therapy (advanced fibrosis)	- Motivated patients who are genotype 2 or 3, were previously treated with interferon monotherapy, are candidates for re-treatment regardless of disease severity

Printed with permission: Reddy K R. *2006 AGA Institute Postgraduate Course Syllabus:* pg. 81.

Useful background: The week of assessment, interpretation in genotype1/4 HCV and genotype 2/3 HCV patients, for week of assessment

Assessment	Week of assessment	Interpretation	Management implications
➢ Genotype 1, 4	4	HCV RNA <50 IU/ml predicts 90% SVR	Duration of treatment of 24 weeks can be considered
➢ RVR	12	HCV RNA <50 IU/ml predicts SVR in 70%	Duration of treatment can be 48 weeks
➢ Complete EVR	12	HCV-RNA decline of >2-log but >50 IU/ml is associated with higher relapse (30%) than complete EVR (15%)	Duration of treatment should be extended to 72 weeks to reduce relapse and increase SVR
➢ Partial EVR	12	HCV-RNA decline <2 log is associated with SVR in 2% with 48 weeks treatment	Treatment should be stopped
➢ Non-EVR	24	HCV RNA >50 IU/ml (detectable) is associated	Treatment should be stopped

		with non-SVR	
➢ 24-week Response			
➢ Genotype 2/3	4	HCV RNA <50IU/ml predicts 90% SVR	Duration of treatment of 12-16 weeks can be considered
➢ RVR	4	HCV RNA >50 IU/ml predicts SVR < 50%	Consideration of treatment for duration longer than 24 weeks
➢ Non-EVR			

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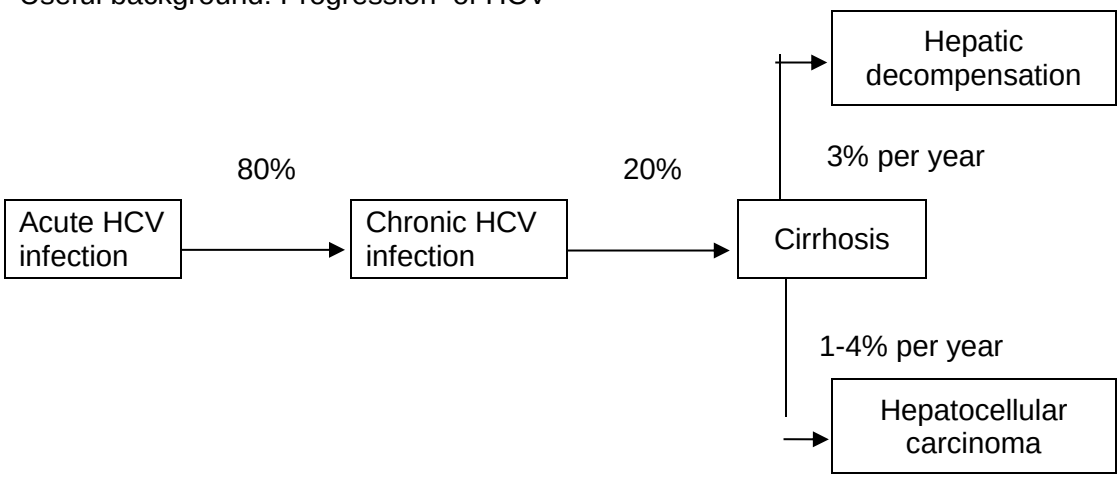
Useful background: Progression of HCV



77. Give 5 reasons for biopsying the liver of persons with HCV, genotype 1, without obvious cirrhosis.

- There is no correlation between ALT or viral load, and stage of fibrosis.
- Surrogates for the presence of advanced fibrosis such as reversal of ALT/AST ratio, platelet count, pro time-INR are not sensitive.
- Markers of fibrosis such as hydroxyl proline are not sufficiently specific.
- Given the variable natural history and the complexity and cost of treatment, informed decision can only be made based on histology.
- Patients who do not respond need further advice on what is next and histology may be essential in these persons.
- Liver biopsy may be safer than treatment when you consider alternatives such as treating everyone.

- Post-liver transplantation (to distinguish between acute cellular rejection or HCV recurrence; see question 65).

78. Give the interpretation of anti HCV results obtained by ELISA and by RIBA.

Anti HCV by ELISA	Anti HCV by RIBA	Interpretation
➢ Positive	➢ Negative	○ False positive ELISA; patient does not have true antibody
➢ Positive	➢ Positive	○ Patient has antibody[a]
➢ Positive	➢ Indeterminate	○ Uncertain antibody status

Abbreviations: ELISA, enzyme linked immunosorbent assay; HCV, hepatitis C virus; RIBA, recombinant immunoblot assay
[a]Anti- HCV does not necessarily indicate current hepatitis C infection

- Ribavirin (RBR)
  - Skin drug reaction with eosinophilia – stop TVR/Boc
  - RBR dose ↓ for anemia does not affect all with TVR/Boc
  - Contraception with RBV: no conception for 6 months after RBV stopped
  - Nucleoside polymerase inhibitor plus protease inhibitor

<u>Iron overload conditions</u>

79. Classify inherited iron overload.

- HFE-related hereditary hemochromatosis
  - C282Y/C282Y
  - C282Y/H63D
  - Other HFE mutations

- Non-HFE related mutations
  - Neonatal hemochromatosis
  - Juvenile hemochromatosis
  - Hemojuvelin (HJV)
  - Transferrin receptor-2 (TfR-2)
  - Atransferrinemia
  - Ferroportin (SLC40A1)
  - Hepcidin (HAMP)

80. Give a classification of the acquired iron overload syndromes.

- Hematological disorders
  - Iron-loading anemias
  - thalassemia major
  - sideroblastic anemia
  - chronic hemolytic anemia
  - ineffective erytheroporesis
- Chronic liver disease (end stage, cirrhosis)
  - HCV, HBV
  - PCT (porphyria cutanea tarda)
  - Alcoholic liver disease
  - NAFLD/NASH
  - Porta-caval shunt
- Increased iron intake
- Dietary iron overload (African iron syndrome)
- Parenteral iron overload
- Longterm hemodialysis
- Mulitple blood transfusions (for example, for chronic hemolytic anemia)
- Acerloplasminemia

Adapted from: Nairz M, and Weiss G. *Wien Klin Wochenschr* 2006;118(15-16):442-62.

81. A 30-year-old man's biological father died of cryptogenic cirrhosis, and the young man requests genetic testing for hemochromatosis. He is found to be a C282Y homozygote (C282Y +/+). What are the next steps for him and his family?*

  - Normal iron studies - repeat iron studies every 5 years.
  - Abnormal iron studies - liver biopsy and liver iron index, needed if >40years, ferritin >1000, ↑ AST; exclude HCV, alcohol, NAFLD/NASH
  - Assess liver enzymes and function – blood, ultrasound
  - Education

- Assess and treat
  - Extraintestinal manifestations (diabetes, heart, arthritis)
  - Avoid liver toxins, including alcohol
  - Screen for HCV, HCC
  - Preventative care: vaccinate against HAV, HBV
  - Phlebotomy if ↑ liver iron index

- Screen
  - Siblings – screen
  - Spouse - screen to determine if their children should be screened
  - Avoid high intake of Fe, vitamin C

*Remember, there is non-expression of the phenotypic abnormality in 50% of the hereditary hemochromatosis genotype

82. Give the interpretation of the following genetic test results in persons suspected as having hemochromatosis.

- C282Y homozygote
  - Seen in >90% of genetic Hemochromatosis. Wide range of clinical iron overload from no disease to total body iron overload and organ failure. Siblings of a homozygote should be screened with genetic tests, transferring saturation and serum ferritin, since they have a 1 in 4 chance of also being homozygous. Children of a homozygote are obligate heterozygotes but will only be homozygous if the other parent is at least a heterozygote. Testing of the second parent can identify the risk to the children with further testing of the children only recommended if the second parent is at least heterozygous for C282Y mutation.
  - False genetic results may occur but are rare.
  - Approximately 50% of homozygotes do not have clinical iron overload (normal serum ferritin and transferring saturation). Such individuals are considered to be non-expressing homozygotes and may never develop disease. They should probably be followed with repeat serum ferritin and transferring saturation every 5 years.

- C282Y/H63D compound heterozygote
  - Patients can carry one major mutation and one minor mutation. Typically iron studies are normal, although mild to moderate iron overload may occur. Severe iron overload is typically only seen in the setting of other causes of liver disease.

- C282Y heterozygote
  - Occurs in approximately 10 per cent of the Caucasian population in which individuals carry one copy of a major mutation. Typically associated with normal iron studies. In rare circumstances that biochemical iron studies suggest significant iron overload (e.g. serum ferritin >1000µg/l) liver biopsy for hepatic iron index may be helpful in distinguishing between the genetic disorder and other causes of liver disease. It is recommended that siblings of a C282Y heterozygote be tested for this mutation.

- H63D homozygote
  - Patients carry two copies of a minor mutation. Iron studies are typically normal, although mild to moderate iron overload is occasionally seen. In patients with biochemical evidence of iron overload, liver biopsy may be helpful to quantitate hepatic iron and determine need for treatment with phlebotomy.

- H63D heterozygote
  - Occurs in approximately 20 per cent of the Caucasian population in which individuals carry one copy of a minor mutation. If biochemical iron studies are abnormal, these changes are more likely due to other non-genetic causes of iron overload.

- No HFE mutations
  - If iron overload is present without any HFE mutations, non-genetic causes of iron overload are likely. Rarely patients may have mutations of other iron-related proteins such as transferring receptor-2, but these variants cannot be readily detected by genetic tests.

Printed with permission: Wright TL. *2007 AGA Institute Postgraduate Course*. pg. 47.

Useful background: Hereditary hemochromatosis (HH)

- Persons with HH are homozygous for C282Y, or heterozygous for C284Y plus H63D, but phenotypic expression requires a trigger such as HCV, alcohol, or down-regulation of a modifier gene

- 24-58% of C284Y homozygotes have a normal serum ferritin concentration

- Liver biopsy in the person with HH is not necessary of they are young (< 40 years), liver enzymes are normal, and if serum ferritin concentration is < 1000 mg/ml. Otherwise, fibrosis or cirrhosis might be suspected, and liver biopsy would be indicated

- Perl's Prussian blue stain shows excess iron in the hepatocytes in HH, with fibrosis around the portal area, especiallu when the hepatic vein concentration is > 16, 000 µg/g liver dry weight

- Phlebotomy of one unit of blood removes about 250 mg of iron, and phlebotomy is performed weekly until the serum ferritin is< 50 mg/ml (removal of 1 unit of blood lowers serum ferritin concentration by about 30 mg/ml) and trasnferrin saturation is < 50%

- Serum iron studies but not hepatic iron levels may be abnormal in PCT (porphyria cutanea tarda), NASH, chronic HCV, and alcoholic liver disease. About 40% of PCT patients have a mutation in C282Y, and NASH patients have a higher prevalence of C282Y mutations. The prevalence of HFE mutations is not increased in chronic HCV, but 22-62% of these persons have elevated serum ferritin concentrations, and 18-32% have elevated transferring saturation levels. There is no enrichment of HFE mutations in persons with alcoholic liver disease and elevated iron studies (Bacon 09).

Drug- induced liver injury

83. Give 5 drugs that have been reported to have an increased risk of hepatotoxicity in patients with chronic liver disease.

Drug	Underlying liver disease as a risk factor
➢ Methotrexate	○ Alcoholic liver disease, NAFLD
➢ Vitamin A (high doses)	○ Alcoholic liver disease
➢ Rifampin	○ Primary biliary cirrhosis
➢ Methimazole	○ Chronic hepatitis B
➢ Ibuprofen (NSAIDs)	○ Hepatitis C
➢ Antiretrovirals (e.g. zalcitabine, saquinavir)	○ Hepatitis B, C
➢ Antiandrogens	○ Chronic viral hepatitis B, C
➢ Oral contraceptives	○ Women with liver tumours, or history of jaundice of pregnancy

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.

84. Give 6 risk factors for methotrexate induced hepatic fibrosis, their clinical importance, and their implications for prevention.

Risk factors	Importance	Implications for Prevention
➢ Age	○ Increased risk >60 yr, possibly related to renal clearance and/or biological effect on fibrogenesis	- Care in use of methotrexate in older persons

➢ Dose	○ Incremental dose ○ Dose frequency ○ Duration of therapy ○ Cumulative (total) dose	- 5-15 mg/wk is safe - Weekly bolus (pulse) safer than daily schedules - Consider liver biopsy every 2 years - Consider liver biopsy after each 2 g methotrexate
➢ Alcohol consumption	○ Increased risk with daily levels > 15 g (1-2 drinks)	- Avoid methotrexate use if alcohol intake not curbed. Consider pre-treatment liver biopsy with relevant history of alcohol use.
➢ Obesity	○ Increased risk	- Consider pre-treatment and interval liver biopsies
➢ Diabetes mellitus	○ Increased risk in obese persons (type 2 diabetes mellitus)	- Consider pre-treatment and interval liver biopsies

Risk factors	Importance	Implications for Prevention
➢ Pre-existing liver disease	○ Greatly increased risk, particularly related to alcohol, obesity, and diabetes (NASH)	- Pretreatment liver biopsy mandatory - Avoid methotrexate, or used scheduled interval biopsies according to severity of hepatic fibrosis, total dose, and duration of methotrexate therapy

➢ Systemic disease	○ Possibly risk greater with psoriasis than rheumatoid arthritis (may depend on preexisting liver disease, alcohol intake)	- None
➢ Impaired renal function	○ Increased risk because of reduced clearance of methotrexate	- Reduced dose, greater caution with use
➢ Other drugs	○ NSAIDS, vitamin A and arsenic may increase risk	- Greater caution with use - Monitor liver biochemical tests

Abbreviations: Nash, non-alcoholic steatohepatitis; NSAIDS, nonsteroidal anti-inflammatory drugs

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 86.7, pg 1443.

85. List 10 drugs which are relatively contraindicated and must be used cautiously in persons with liver disease.

- Clonazepam
- Conjugated estrogen/medroxyprogesterone
- Dantrolene
- Felbarnate
- Gemfibrozil
- Lovastatin and other HMG-CoA reductase inhibitors (statins)
- Metformin
- Methotrexate
- Naltrexone
- Niacin
- Pemoline
- Phenelzine
- Tacrine (in persons with prior jaundice)
- Ticlopidine
- Tolcapone
- Valproic acid
- Zalcitabine

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.

86. Give 10 drugs for which lower doses are recommended in patients with cirrhosis ("hepatic dosing").

- Acetominphine
- Benzodiazepines
- Beta blockers
- Cetirazine
- Fluoxetine
- Indinavir
- Lamotrigine
- Losartan
- Moricizine
- Narcotics
- PPIs
- Repaglinide
- Risperidone
- Sertraline
- Topiramate
- Tramadol
- Valproic acid
- Venlafazine
- Verapamil

Adapted from: Gupta NK, and Lewis JH. *Aliment Pharmacol Ther* 2008; 28(9): 1021-41.

87. Give 7 hepatobiliary complications of the use of oral contraceptive agents (OCAs).

- Gallstones
- Cholestasis
- Unmasking PBC, and other cholestatic diseases
- Unmasking porphyria
- Tumours
    - Adenomas
    - ↑ size of FNH (focal nodular hyperplasia)
    - Hepatocellular carcinoma (rare)

- Increased risk of NASH
- Vascular
    - Budd-Chiari syndrome
    - Peliosis hepatic (sinusoidal dilation)

Adapted from: Simon JB. *First Principles of Gastroenterology* 2005: pg. 583.

Vascular diseases

88. Classify, and give 6 examples of the vascular diseases of the liver.

- Disorders of portal venous inflow
    - Acute mesenteric/portal venous thrombosis
    - Chronic mesenteric/portal venous thrombosis

- Disorders of hepatic arterial inflow
    - Hepatic artery thrombosis
    - Hepatic arteriovenous fistula
    - Ischemic hepatitis

- Disorders of hepatic venous outflow
    - Veno-occlusive disease
    - Budd-Chiari syndrome

Printed with permission: Kamath PS. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 337.

89. Give the presentation, etiology, diagnostic imaging and histological changes, as well as management of hepatic vein occlusion (Budd-Chiari syndrome).

- Presentation
    - Abdominal pain
    - Hepatomegaly
    - Ascites
    - Hepatic failure (if acute)

- Etiology
    - Hypercoagulable states
        - Inherited
            - Factor V Leiden mutation
            - Prothrombin mutation
            - Antithrombin deficiency
            - Protein C deficiency

        - Protein S deficiency
        - Antiphospholipid syndro
    - Acquired
        - Myeloproliferative disorders
        - Cancer
        - Pregnancy
        - Oral contraceptive use
        - Paroxysmal nocturnal hemoglobinuria (PNH)
        - Polycythemia rubra vera (PRV)

- Tumour invasion
    - Hepatocellular carcinoma
    - Renal cell carcinoma
    - Adrenal carcinoma

- Miscellaneous
    - Aspergillosis
    - Behçet's syndrome
    - Inferior vena cava webs
    - Trauma
    - Inflammatory bowel disease
    - Dacarbazine therapy
- Idiopathic

- Diagnostic imaging/histology
    - Doppler ultrasound
    - MRI (contrast enhanced); multiphasic CT
    - Liver biospy (zone 3 congestion)

- Management
    - Cause
        - Treat any esophageal
        - Anticoagulants, thrombolysis, venesection
        - Cytotoxic drugs
    - Surgical
        - Porta-caval shunt
        - TIPS (if incomplete obstruction)
        - Embolectomy (selected cases)
        - Liver transplantation

Adapted from: Stevens WE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1756.; and Printed with permission: Kamath PS. *Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 343; and 2010, pg. 1372.

90. Classify and give 10 causes of portal vein thrombosis.

- Hypercoagulable states
  - Antiphospholipid syndrome
  - Antithrombin deficiency
  - Factor V Leiden mutation
  - Methylenetetrahydrofolate reductase mutation TT677
  - Myeloproliferative disorders
  - Nephrotic syndrome
  - Oral contraceptives
  - Paroxysmal nocturnal hemoglobinuria
  - Polycythemia rubra vera
  - Pregnancy
  - Prothrombin mutation G20210A
  - Protein C deficiency
  - Protein S deficiency
  - Sickle cell disease

- Impaired portal vein flow
  - Budd-Chiari syndrome
  - Cirrhosis
  - Nodular regenerative hyperplasia
  - Sinusoidal obstruction syndrome

- Inflammatory diseases
  - Behçet's syndrome
  - Inflammatory bowel disease
  - Pancreatitis

- Infections
  - Appendicitis
  - Cholangitis
  - Cholecystitis
  - Diverticulitis
  - Liver abscess

- Cancer
  - Pancreas
  - Cholangiocarcinoma
  - HCC
  - Bladder cancer

- Intra-abdominal procedures
  - Alcohol injection

- Colectomy
- Endoscopic sclerotherapy
- Fundoplication
- Gastric banding
- Hepatic chemoembolization
- Hepatobiliary surgery
- Islet cell injection
- Liver transplantation
- Peritoneal dialysis
- Radiofrequency ablation of hepatic tumour (s)
- Splenectomy
- TIPS procedure
- Umbilical vein catheterization

Adapted from: Stevens WE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1762; and 2010, pg. 1378.

91. Give the diagnostic tools in the assessment of systolic and diastolic dysfunction in persons suspected of having cirrhotic cardiomyopathy.

- Systolic function
  - Echocardiography/MRI:
    - Volumes
    - Fractional shortening
    - Velocity of fractional shortening
    - Ejection fraction (planimetry)
    - Response to stress (dobutamine)
    - Wall motion
  - Exercise ECG
    - Exercise capacity
    - Oxygen consumption*
    - Pressure x heart rate product
  - Radionuclide angiography (MUGA)
    - Ejection fraction
    - Cardiac volumes
    - Pattern of contractibility
  - Myocardial perfusion imaging with gating
    - Regional myocardial perfusion
    - Cardiac volumes
    - Ejection fraction
    - Wall motion and wall thickening

- Diastolic function
  - Echocardiography/MRI/MUGA
    - E/A ratio

- Deceleration time
- A and E waves
- Relaxation times

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Thoughtful reflections

Discuss the ethical considerations relating to screening for HBV and HCV in applicants to medical school, and to a fellowship training program in gastroenterology.

92. Give 4 clinical uses of Doppler ultrasound in patients with suspected liver disease.

- Portal vein
  - Patency
  - Anatomical abnormalities (useful pretransplant)
  - Acute flow changes
  - Direction of flow

- Hepatic artery
  - Patency
  - Anatomical abnormalities

- Hepatic veins
  - Patency (Budd-Chiari syndrome)

Adapted from: Robinson KA, et al. *Ultrasound Q* 2009;25(1):3-13.

93. Define cirrhotic cardiomyopathy, and give the criteria that help to make or support the diagnosis.

- A working definition of cirrhotic cardiomyopathy
  - A cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other know cardiac disease.

- Diagnostic criteria
  - Systolic dysfunction
    - Blunted increase in cardiac output on exercise, volume challenge or pharmacological stimuli

- Resting ejection fraction <55%
  - Diastolic dysfunction
    - E/A ratio <1.0 (age-corrected)
    - Prolonged deceleration time (>200 ms)
    - Prolonged isovolumetric relaxation time (>80 ms)

- Supportive criteria
  - Electrophysiological abnormalities
  - Abnormal chronotropic response
  - Electromechanical uncoupling/dys-synchrony
  - Prolonged Q-T_c interval
  - Enlarged left atrium
  - Increased myocardial mass
  - Increased BNP and pro-BNP
  - Increased troponin I

Abbreviations: BNP, brain natriuretic peptide; E/A ratio, ratio of early to late (arterial) phases of ventricular filling

Printed with permission: Møller S, and Henriksen JH. *GUT* 2008; 58: pg. 274.

Useful background: Cirrhotic cardiomyopathy

- Definition: chronic cardiac dysfunction in the patient with cirrhosis, with reduced contractile response to stress and/ or diastolic dysfunction in the absence of other known cardiac disorders

- The prolonged QT interval seen in 60% of persons with cirrhosis correlate with the severity of the liver disease, and predisposes the person to ventricular arrhythmias

- Hyperdynamic circulation from anterior vasodilation increases heart rate and cardiac output, and reduce systemic vascular resistance and arterial blood pressure, with increased peripheral but not central intravascular volume

- Left heart failure is rare because of the reduced systemic vascular resistance; preload reduction (O_2 diuretics, sodium redirection) is needed, other than afterload reduction

94. Compare and contrast portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE).

	PHG	GAVE
➢ Distribution	Proximal stomach	Distal stomach
➢ Mosaic pattern	Present	Absent
➢ Red signs	Present	Present
➢ Biopsy		
○ Thrombi	-	+++
○ Spindle cell proliferation	+	++
○ Fibrohyalinosis	+	+++
➢ Definitive treatment	Beta-blockers TIPS	Argon laser Banding Cryotherapy Antrectomy

Printed with permission: Garcia-Tsao G., and Kamath PS. *2007 AGA Institute Psotgraduate Course*: pg. 619.

95. Give the clinical features and treatment of hepatic artery stenosis and thrombosis, as well as portal vein stenosis or thrombosis.

Time of occurrence	Leading symptoms	Treatment
➢ Hepatic artery thrombosis		
○ Early	Fulminant increase in LFTs Acute liver failure Hemodynamic instability	Urgent acute thrombectomy or urgent retransplantation
○ Late	Biliary complications Strictures, intrahepatic abscesses Cholangitis and sepsis	Management of biliary complications using ERC, PTC Rt-PA lysis therapy Elective retransplantation
➢ Hepatic artery stenosis	Slight increase in LFTs Mild or late biliary complications	Reoperation with resection of the anastomosis and end-to-end reconstruction
○ Early	Acute liver failure, fulminant increase in LFTs, hemodynamic instability Ascites, variceal bleeding	Urgent thrombectomy Urgent retransplantation

Time of occurrence	Leading symptoms	Treatment
○ Late	Slight increase in LFTs Portal hypertension, Ascites, variceal bleeding	Endoscopic treatment Rt-PA lysis therapy Elective retransplantation
➢ Portal vein stenosis		
	Slight increase in LFTs, Portal hypertension, Ascites	Resection and end-to-end reconstruction

Printed with permission: Mueller AR, Platz KP, and Kremer B. *Best Practice & Research Clinical Gastroenterology* 2004;18(5): pg. 884.

Useful background. The vasodilating and vasoconstricting forces involved in the disturbed hemodynamics in cirrhosis (alphabetic order)

- Vasodilator systems
  - Adenosine
  - *Adrenomedullin*
  - Arterial natriuretic peptide (ANP)
  - Bradykinin
  - *Brain natriuretic peptide (BNP)*
  - *Calcitonin gene-related peptide (CGRP)*
  - *Carbon monoxide (CO)*
  - *Endocannabinoids*
  - Endothelin-3 (ET-3)
  - Endotoxin
  - Enkephalins
  - Glucagon
  - Histamine
  - *Hydrogen sulphide*
  - Interleukins
  - Natriuretic peptide of type C (CNP)
  - *Nitric oxide (NO)*
  - Prostacyclin (PGI_2)
  - Substance P
  - Tumour necrosis factor-α (TNF-α)
  - Vasoactive intestinal polypeptide (VIP)

- Vasoconstrictor systems
  - *Angiotensin II*
  - *Adrenaline and noradrenaline*
  - *Sympathetic nervous system (SNS)*

- *Endothelin-1 (ET-1)*
- *Neuropeptide Y*
- *Renin-angiotensin-aldosterone system (RAAS)/*
- *Vasopressin (ADH)*

Printed with permission: Møller S, and Henriksen JH. *GUT* 2008; 58: pg. 271.

Useful background: The circulatory changes in specific vascular beds in cirrhosis

- Systemic circulation
  - Plasma volume ↑
  - Total blood volume ↑
  - Non-central blood volume ↑
  - Central and arterial blood volume ↓ (→)
  - Arterial blood pressure ↓ (→)
  - Systemic vascular resistance ↓

- Cutaneous and skeletal muscle circulation
  - Skeletal muscular blood flow* ↑ → ↓
  - Cutaneous blood flow* ↑ → ↓

- Heart
  - Heart rate ↑
  - Cardiac output ↑
  - Left atrial volume ↑
  - Left ventricular volume → (↑)
  - Right atrial volume → ↑ ↓
  - Right atrial pressure → ↑
  - Right ventricular end-diastolic pressure →
  - Pulmonary artery pressure → ↑
  - Pulmonary capillary wedge pressure →
  - Left ventricular end-diastolic pressure →
  - Total vascular compliance ↑
  - Arterial compliance ↑

- Hepatic and splanchnic circulation
  - Hepatic blood flow† ↓ → (↑)
  - Hepatic venous pressure gradient ↑
  - Postsinusoidal resistance ↑

- Renal circulation
  - Renal blood flow ↓

- Glomerular filtration rate (↑) ↓ →

- Cerebral circulation
  - Cerebral blood flow ↓ →

- Pulmonary circulation
  - Pulmonary blood flow ↑
  - Pulmonary vascular resistance ↓ (↑‡)
  - Pulmonary blood volume ↓
  - Pulmonary transit time ↓

↑→↓ denote: increased, unchanged and decreased, respectively. Arrows in parentheses describe early/less typical changes.

*Available data are highly dependent on the applied technique
†Changes in intrahepatic blood flow due to variable co-determination of portosystemic shunts
‡Increased in portopulmonary hypertension

Printed with permission: Møller S, and Henriksen JH. *GUT* 2008; 58: pg. 269.

Useful background: The treatment options and indications for the use of 4 different modalities in the patient with Budd-Chiari Syndrome (BCS), and give their advantages and disadvantages

Treatment	Indication	Advantages	Disadvantages
○ Thrombolytic therapy	Acute thrombosis	Reverses hepatic necrosis	Risk of bleeding Limited success
○ Angioplasty with and without stenting	IVC webs IVC stenosis Focal hepatic vein stenosis	No long-term sequelae Averts need for surgery	High rate of restenosis or shunt occlusion
○ TIPS	Possible bridge to transplantation in fulminant BCS Acute BCS	Low mortality Useful even with compression of IVC by caudate lobe	High rate of shunt stenosis Extended stents may interfere with liver transplantation
○ Surgical shunt	Subacute BCS if portacaval pressure gradient <10 mm Hg or occluded IVC	Definitive procedure for many patients	Risk of procedure-related death Limited applicability

			Low rate of shunt dysfunction with portacaval shunt	
○	Liver transplantation	Subacute BCS Portacaval pressure gradient >10 mm Hg Fulminant BCS Presence of cirrhosis Failure of portosystemic shunt	Reverses liver disease May reverse underlying thrombophilia	Risk of procedure-related death Need for long-term immunosuppression

Abbreviations: IVC, inferior vena cava; TIPS, transjugular intrahepatic portasystemic shunt

Printed with permission: Kamath PS. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 344.

Pregnancy

96. Complete the table describing various liver conditions which occur in pregnancy.

	Viral Hepatitis (flaring in pregnancy)	Gallstones
Time of onset in pregnancy	Variable	Variable
Nausea/vomiting	Yes	Variable
Abdominal pain	Variable	Variable
Pre-eclampsia	No	No
Cholestasis	Mild to marked	Marked
AST/ALT elevation	High	Low
Coagulopathy	Rare and late (acute fulminant)	No
Hepatic failure	Rare	No
U/S	Nonspecific	Dilated bile ducts, stones
Liver biopsy	Inflammatory infiltrate, spotty hepatocyte necrosis	Cholestasis, variable inflammation
Management of mother and child	Support HBV – Lamivudine for	Support, avoid cholecystectomy if possible

	mother, mT_3 HBIG at birth for child; immunize child
	HCV – none; check child at 18 weeks

Abbreviation: HELLP - hemolysis, elevated serum liver enzymes, low platelets

B, C – rarely transmitted to fetus
E – often fatal in Africa and Asia
Underlying chronic liver disease. Rare to become pregnant, prognosis variable, stillbirths increased, high bilirubin - kernicterus

Adapted from: Myers RP, and Shaffer EA. *First Principles of Gastroenterology* 2005. pg. 652.

	Intrahepatic cholestasis of pregnancy	Acute fatty liver of pregnancy(AFLP)	HELLP syndrome (severe form of preclampsia)
Time of onset in pregnancy	– T3	– Second half of pregnancy, or postpartum	– Second half of pregnancy, or postpartum
Nausea/ vomiting	– rare	– Yes (80%)	– yes
Abdominal pain	– Rare	– Yes (60%)	– Yes (100%)
Pre-eclampsia	– No	– Often (25%)	– 100%
Cholestasis	– Marked	– Modest and late	– Mild or absent
AST/ALT elevation	– Low	– Modest (5-10X↑)	– Modest to high
Coagulopathy	– No	– In severe cases, late	– Early: thrombocyto penia – Late: DIC
Hepatic failure	– No	– Yes (70% when severe)	– Rare

U/S	– Normal	– No change or fatty liver	– Areas of necrosis, infarction , or hematoma
Liver biopsy	– Cholestasis	– Microvesicular fatty infiltration	– Periportal patchy, hemorrhagic necrosis, – Fibrin deposition – Perisinusoidal mild microvesicular fat
Management of mother and child	– UDCA, vitamin K	– Early delivery (cesarian section) increased risk of AFLP in next pregnancy, check LCHAD in fetus(unknown risk of recurrence of AFLD)	– Early delivery (cesarian section) for severe uncontrolled pre-eclampsia (hemolysis, seizures)

Adapted from: Myers RP, and Shaffer EA. *First Principles of Gastroenterology* 2005. pg. 652.

97. For 8 liver enzymes/ tests of liver function, indicate which increase, decrease, or remain unchanged in normal pregnancy.

- Unchanged
  - AST, ALT
  - INR
  - Bilirubin
  - GGT

- Increased
  - Alkaline phosphatase (↑ 2-400%)
  - Fibrinogen (↑ 50%)

- α- and ß- globulins
- Alpha-fetoprotein*
- Leukocytes
- Ceruloplasmin
- Cholesterol
- Triglycerides

➢ Decreased
- γ- globulin
- Platelets (>50,000)
- Hemoglobin
- Albumen

* Moderate increase, especially with twins

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Adapted from Hay E. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 419.

98. Give the trimester of onset and treatment of 4 liver diseases unique to pregnancy.

Liver disease	Onset	Treatment
➢ Hyperemesis gravidarum	T1	-Supportive care, rehydration
➢ Intrahepatic cholestasis of pregnancy (ICP)	T2-3	-Ursodeoxycholic acid (UDCA)or cholestyramine -Preterm delivery if fetal compromised
➢ Pre-eclampsia and eclampsia	T2-3	-Antihypertensive drugs, magnesium sulfate
➢ HELLP syndrome	T3	-Induction of delivery
➢ Acute fatty liver of pregnancy	T3	-Consider early induction of delivery

HELLP, a syndrome characterized by hemolysis, elevated liver enzymes and a low platelet count; T, trimester

Printed with permission: Keller Jutta, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008: 5(8): pg. 437.

99. Give the cautions to be considered when treating the following liver conditions during pregnancy.

- Viral hepatitis
  - Hepatitis A and B vaccines are low risk in pregnancy
  - Lamivudine is low risk in pregnancy
  - Adefovir and entecavir have no data in human pregnancy
  - Interferon and ribavarin are <u>contraindicated</u> in pregnancy (use lamivudine, tenofovir)
  - Vaccinate child and give HBIG
  - HCV – don't treat in pregnancy

- Wilson's disease
  - Penicillamine should be avoided, or dose adjusted
  - If necessary, switch to oral zinc

- PBC/PSC/ICP
  - UDCA low risk after first trimester and effective for cholestasis of pregnancy

- Portal hypertension
  - Propranolol -avoid after first trimester (fetal cardiotoxicity)
  - Nadolol has a long half life- should be avoided

- Liver transplantation
  - Cyclosporine, tacrolimus- low risk
  - Sirolimus-limited data suggest low risk
- Mycophenalote mofetil-associated with increased malformations

Abbreviation: ICP, intrahepatic cholestasis of pregnancy

Printed with permission: Mahadevan U. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 867.

100. Give the clinical presentation and outcomes from intrahepatic cholestasis of pregnancy (ICP).

Clinical presentation	Maternal outcome	Fetal outcome
○ Second or third trimester (T_2, T_3) ○ Generalised pruritus with no rash	-Pruritus and abnormal laboratory tests resolve with delivery -Recurs 40-60%)with subsequent gestations	Increase risk for prematurity, still birth, spontaneous preterm labour and delivery, fetal compromise, fetal cardiac

○ Marked increases in serum alkaline phosphatase, bilirubin, and serum bile acid levels ○ Normal or slight increases in GGT levels ○ Mild increases in serum aminotransferase levels	-Increased risk for cesarean delivery due to fetal compromise -Can recur with subsequent use of oral contraceptives (OCAs) and hormonal fluctuations	dysrhythmias, meconium stained amniotic fluid, and intrauterine fetal death

Printed with permission: Schutt VA, and Minuk GY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 778.

Useful background: Intrahepatic cholestasis of pregnancy (ICP)

- Present in 2% of pregnancies in America, 6% in Chile and Scandinavia
- Due to the usual cholestatic effects of estrogen in pregnancy, plus a genentic predisposition (imitations in canadlucular transporters for bile acids, phospholipids and cholesterol [amino phospholipid flippase], as well as FXR, the nuclear regulator of bile acid synthesis)
- 10-15% of first degree relatives of women with ICP also develop ICP
- Usual presentation is painless jaundice and pruritus, possibly due to elevated serum bile acid concentrations
- Liver biopsy is not necessary, but would show intrahepatic cholestasis, centralobular, with bile plugs in cannaliculi and hepatocytes
- Fetal complications usually occur after 32 weeks and include intrauterine growth retardation, fetal disease and premature labour. Fetal death rates in ICP are two-fold increased, usually occur between 37-40 weeks, are associated with much higher concentrations of serum bile acids, and may be sudden and intrauterine; for this reason the fetus should be delivered early (36-37 weeks of pregnancy)

Abbreviation: ICP, intrahepatic cholestasis of pregnancy

101. Give the FDA class and risk of liver disease-treating drugs during pregnancy and lactation.

Drug	FDA class	Risk in pregnancy	Risk with nursing
○ Adefovir	C	Low risk	+
○ Interferon	C	Not recommended	+
○ Lamuvidine	C	Low risk	-
○ B blockers	C 1st trimester, D others	IUGR, fetal brachycardia	-
○ Penicillamine	D	Significant embryopathy	-
○ Ribavirin	X	Contraindicated	+
○ Trientine	C	Alternative to pen.	-
○ Ursodiol (UDCA)	B	Low risk	+
○ Methotrexate	X	Contraindicated	

Printed with permission: Katz PO. *2008 ACG What's New in Pharmacology Course:* pg. 50.

102. Give the FDA class and risk of liver transplantation-treating drugs during pregnancy and lactation.

Drug	FDA class	Risk in pregnancy	Risk with nursing
○ Antithymocyte globulin	C	Low risk	?
○ Mycophenolate	C	Not recommended	+
○ OKT3	C	Probably low risk	-
○ Sirolimus	C	Not recommended	-
○ Tacrolimus	C	Use if mandated	-

Printed with permission: Katz PO. *2008 ACG What's New in Pharmacology Course:* pg. 50.

Thoughtful reflections

Discuss the ethical considerations relating to a screening and surveillance program for colorectal cancer for "average risk" persons.

Useful background: Pregnancy and liver disease

- Signs
  - Palmar erythema and spider angiomas occur in two thirds of women with normal pregnancies

- Physiology
  - Increased maternal nitric oxide (NO) release during pregnancy causes maternal vasodilation, ↓ systemic vascular resistance, mean arterial blood pressure, reduced responsiveness to vasoconstrictors, resulting in maternal cardiac output rising 30-50%, sixth activation of the rennin-angiotensin system, and increased GFR as well as renal blood flow (Van Dyke 09)

- Gallstones
  - The increased risk of biliary sludge (10-30%) and cholelithiasis (2-3% of all pregnant women) during pregnancy is due to estrogen-associated with increased transport of cholesterol into bile from the liver, and reduced solubalization of this cholesterol as the result of reduced hepatobiliary transport of bile acids and phosphoplipids. In addition, the slowing of gallbladder emptying contributes to the formation of stones.
  - The pregnancy-associated increase in estorgens increases the risk of biliary pain in 28% of pregnant women who had pre-existing gallstones

- Hepatitis
  - HEV hepatitis in pregnant women is associated with a high rate of fulminant hepatic failure, and maternal as well as fetal death. Transmittion of HEV is vertical, and the HEV vaccine will soon be available.
  - Vertical transmission from mother to child is the commonest route for HBV infection, and depending upon the viral load, may be 80-90%. HDV may be transmitted at the same time as HBV. In contrast, only 5-8% of HCV infections are the result of vertical transmission, but rises to 30% if the mother is both HCV and HIV positive.
  - Babies born to HBV positive mothers should receive HB16 and HB vaccine at birth, and further vaccine at one and six months of age. at 18 months of age, the child born to the HCV positive mother should have HCV RNA testing.
  - The risk of herpes simplex hepatitis is increased during pregnancy, and may present with markedly elevated transaminases or with fulminant hepatic failure.
  - Maintenance medications for autoimmune hepatitis (AIH) should not be stopped during pregnancy, and even with these being continued,

there is an increased risk of spontaneous abortion (12%) and perinatal deaths (7%)

- Wilson's disease
  - Maintenance medications for Wilson's disease must be continued during pregnancy. The rate of infant congenital defects is 1.3% when the pregnant mother continues d-penicillamine

- Complications of cirrhosis
  - In the pregnant woman with cirrhosis, the maternal mortality rate is 10%, and there is a 3-25% risk of abortion, premature birth and perinatal death (Van Dyke 09)
  - In the pregnant woman with portal hypertension, 18-50% will bleed during pregnancy from esophageal varices

Abbreviation: AIH, autoimmune hepatitis

Useful background: Pre-eclampsia and HELLP syndrome

- Pre-eclampsia occurs in 5-10% of pregnancies, and accounts for 20% of maternal deaths (Van Dyke 09)

- Pathophysiology relates to the fetal and maternal sides of the placenta
  - On the fetal side, the high capacity low resistance placental vessels do not develop, which leads to fetal ischemia and intrauterine growth retardation

- On the maternal side, there is increased release of anti-angiogenic and decreased release of pro-angiogenic factors, leading to maternal vessel vasoconstriction, increased sensitivity to vasoconstrictors, damage to the endothelium of the maternal blood vessels and deposition of fibrin. This in turn leads to ischemic infarcts, including acute hepatic necrosis in 10-20% of pre-eclamptic women.

- Pre-eclampsia and the HELLP syndrome usually occur in the 3rd trimester, but in 28% HELLP occurs in the early post-partum period.

- In HELLP, there are the usual laboratory findings of hemalysis (H). The elevated liver tests (EL) include a wide range of changes in ALT/ AST, further increased in alkaline phosphatase, and jaundice in 5-40% depending on the extent of patchy ischemic necrosis and fibrin deposition, and hemolysis. The thrombocytopenia (LP) may be associated with low fibrinogen, increased fibrin degradation products and renal dysfunction.

- Fetal hypoxia may develop quickly, with sudden intrauterine death,so early delivery of the fetus is recommended. Fetal mortality is 3-23%, and maternal mortality is up to 3.5%

- The usual patchy hepatic necrosis may lead to confluent necrosis, hepatic hematoma, and even hepatic rupture requiring surgical intervention or hepatic artery embolization. Maternal and fetal mortality from a free rupture is 50-100%
- There is an increased risk of recurrence of HELLP in women with severe hypertension, chronic renal disease, lupus anticoagulant, or women with a liver transplantation (or other organ transplantation)

Abbreviations: H, hemalysis; LP, thrombocytopenia

Useful background: Acute fatty liver of pregnancy (AFLP)

- Seen in 1/1000 pregnancies

- AFLP accounts for 16-70% of severe liver disease as well as maternal nad fetal deaths during pregnancy

- Associated with pre-eclampsia in 30%, genetic abnormality in LCHAD (long chain 3-hydroxyacyl-CoA-dehydrogenase) in 20%, possibly other as yet unkown genetic mutations, and the use of drugs such as ASA/ NSAIDs

- When mother is LCHAD heterozygote but fetus is homozygote, the risk of AFLP is 43%; when the fetus is a heterozygote or normal, the risk of AFLP is 2.7%

- Pathophysiology: impaired mitochondrial beta-oxidation or oxidative phosphorylation of fatty acids, resulting in mitochondrial damage, reduced ATP production, and destructive of hepatocytes

- The presentation os that of acute liver failure, including hepatic encephalopathy, coagulopathy, jaundice, ascites, hypoglycemia, renal impairment and pancreatitis

- The level of the altered serum transaminases do not reflect the severity of the liver damage and failure. In addition to an elevated INR, anti-thrombin III levels are often increased as well

- Intrauterine fetal mortality may be as high as 32%, and maternal mortality rates of 5-26%

- Urgent delivery is required; test the mother and infant for LCHAD mutations

Abbreviations: AFLP, acute fatty liver of pregnancy; LCHAD, long chain 3-hydroxyacyl-CoA-dehydrogenase

Jaundice

103. Give 10 major intrahepatic and extrahepatic causes of cholestasis leading to jaundice.

- Intrahepatic
  - Drugs
  - Alcoholic hepatitis ± cirrhosis
  - PBC
  - Viral hepatitis
  - Chronic hepatitis ± cirrhosis
  - Cholestasis of pregnancy
  - Sepsis
  - TPN

- Extrahepatic
  - Common bile duct stone(s)
  - Pancreatic/periampullary cancer
  - Benign biliary stricture
  - PSC, SSC (secondary sclerosing cholangitis)
  - Bile duct carcinoma
  - Benign pancreatic disease
  - Extrinsic duct compression

Adapted from: Heathcote J. *First Principles of Gastroenterology* 2005: pg. 590.

104. Give the mechanisms of action of 8 different types of drugs used for the treatment of pruritus in patients with cholestatic liver disease.

- Decrease degree of cholestasis: UDCA
- Non-absorbable anion exchange resins: cholestyramine
- Changes in opioidergic neurotransmission : naloxone, natrexone
- Hepatic enzyme (cP452) inducers: rifampicin, metronidazole, phenobarbitol
- Cannabinoid agonist
- Serotonin antagonists: ondansetron

- Changes in threshold to experience nociception: dronabinol
- Antidepressants (SSRIs)
- Sedation (antihistamines)
- Invasive procedures: plasmapheresis, MARS (extracorporeal albumin dialysis), biliary drainage
- IV propofol
- Gabaergic changes: gabapentin
- UV light
- Liver transplantation – removes cause of cholestasis

Adapted from: Kremer AE, et al. *Drugs* 2008;68(15):2163-82.

105. Give 10 causes of post-operative jaundice, associated first with hepatocellular Injury (predominant serum ALT elevation with or without hyperbilirubinemia), and secondly with cholestastic jaundice (elevated serum alkaline phophatase [AP], GGT, direct hyperbilirubinemia).

- Hepatocellular Injury (predominant serum ALT elevation with or without hyperbilirubinemia)
  - Inhalational anesthetics-halothane, others
  - Ischemic hepatitis (shock liver)
  - Hepatic artery thrombosis
  - Other drugs-antihypertensives (eg: labetalol), heparin
  - Acute post-transfusion hepatitis
  - Unrecognized previous chronic liver disease-NASH, HCV etc
  - Hepatic allograft rejection

- Cholestastic Jaundice (elevated serum alkaline phophatase, GGT, direct hyperbilirubinemia)
  - Benign postoperative cholestasis
  - Cardiac bypass of prolonged duration
  - Sepsis
  - Acalculous cholecystitis
  - Common bile duct obstruction-gallstones, pancreatitis
  - Cholangitis
  - Bile duct injury-post-cholecystectomy, post-liver transplantation
  - Microlithiasis (biliary sludge)
  - Prolonged total parenteral nutrition
  - Hemobilia
  - Drugs-amoxicillin-clavulanate. chlorpromazine, erythromycin, telethromycin, trimethoprim-sulfamethoxazole, warfarin, others

- Indirect hyperbilirubinemia (serum alkaline phosphatase and ALT often normal)
  - Multiple blood transfustions
  - Resorbing hematoma
  - Hemolytic anemia

Adapted from: Stevens WE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1856.

106. Give 15 causes of postoperative jaundice .

- Increased bilirubin production (indirect hyperbilirubinemia; AP/ALT often normal)
  - Destruction of transfused erythrocytes
  - Hemolysis secondary to pre-existing hemolytic conditions (eg: G6PD deficiency, hemoglobinopathies)
  - Hemolysis secondary to mechanical heart valve prostheses
  - Reabsorption of hematomas
  - Multiple blood transfusions

- Hepatocellular Injury
  - Ischemic hepatitis ("shock liver")
  - Hepatic artery thrombosis
  - Hepatic allograft rejection
  - Drug- or anesthetic-induced hepatotoxicity
  - Viral hepatitis

- Intrahepatic cholestasis (↑ AP; GGT; direct hyperbilirubinemia)
  - Sepsis, bacterial abscess
  - Drug-induced cholestasis
  - Total parenteral nutrition
  - Benign postoperative cholestasis
  - Prolonged cardiac bypass

Adapted from: Faust TW, and Reddy KR. *Clin Liver Dis* 2004;8(1):151-66.

107. Give 5 factors contributing to physiological jaundice in the neonate.

- Absence of placental bilirubin metabolism
- Reduced hepatic blood flow via ductus venosus shunting
- Decreased red blood cell survival
- Proportionally increased red blood cell mass

- Reduced enteric bacterial flora
- Presence of intestinal β-glucoronidase
- Immature liver function
- Delayed oral feeding

Printed with permission: Machida H. *First Principles of Gastroenterology* 2005: pg. 725.

108. Give 10 causes of <u>unconjugated</u> hyperbilirubinemia in the neonate.

- Increased bilirubin production (Hemolytic disease)
  - Blood group incompatibility (Rh, ABO, minor groups)
  - Membrane defects (spherocytosis, elliptocytosis, infantile pyknocytosis)
  - Enzyme deficits (G6-PD, hexokinase, pyruvate kinase)
  - Drugs (oxytocin, vitamin K)

- Increased RBC breakdown
  - Infection

- Hematoma, Extrahepatic biliary obstruction
  - Bile duct ligation/injury
  - Choledocholithiasis
  - Acaluclons cholecystitis
  - Post cholecystectomy, post liver transplantation
  - Microlithias (biliary sludge)
  - Postoperative pancreatitis
  - Extrinsic compression of common bile duct or common hepatic duct
  - Hemobilia

- Pre-existing Abnormalities in Bilirubin Metabolism/Excretion
  - Chronic liver disease
  - Gilbert's syndrome
  - Swallowed maternal blood

- Increased RBC mass
  - Polycythemia (maternal diabetes, delayed cord clamping, small for gestational age, high altitude)

- Decreased bilirubin metabolism
  - Reduced uptake
    - Portacaval shunt, hypoxia, sepsis, acidosis, congenital heart disease
  - Decreased conjugation (unconjugated)

- Crigler-Najjar type I, II
- Gilbert's syndrome
- Lucey-Driscoll syndrome
- Hypothyroidism
- Panhypopituitarism

- Altered enterohepatic circulation
  - Breastfeeding
    - Free fatty acids, steroids, breast milk β-glucuronidase
  - Intestinal hypomotility
    - Retained meconium
  - Reduced intestinal flora
    - Newborn antibiotic use

Printed with permission: Robertson M, and Martin SR. *First Principles of Gastroenterology* 2005: pg. 727.

Useful background: A comparison of four congenital syndromes of conjugated hyperbilirubinemia (Gilbert's, Crigler-Najjar types 1 & 2 [CN-T_1, CN-T_2], Dubin-Johnson (DJ), and Rotor's syndrome) in terms of their prevalence, autosomal inheritance, serum bilirubin concentration, diagnostic features, prognosis and treatment.

	Gilbert's	CN-T1	CN-T2
○ Prevelence	7% of population	Very rare	Uncommon
○ Inheritance (all autosomal)	Dominant	Recessive	Dominant
○ Serum bilirubin concentration (µmol/L)	<100 (all conjugated)	>400 (all conjugated)	<100 (about half conjugated)
○ Diagnostic features	Bilirubin conc' ↑with fasting ↓ with phenobarbital	Bilirubin conc'- no response to phenobarbital	Bilirubin conc' ↓ with phenobarbital
○ Prognosis	Normal	Early death from kernicterus	Usually normal
○ Treatment	None needed	Liver graft	Phenobarbital

	D-J	Rotor's
○ Prevelence	Uncommon	Rare
○ Inheritance (all autosomal)	Recessive	Recessive
○ Serum bilirubin concentration (µmol/L)	<100 (about half conjugated)	<100 (about half conjugated)
○ Diagnostic features	Coproporphyrin excretion (>80% isomer !) Pigment in centrolubular hepatocytes	Normal gallbladder visualization at oral cholecystography
○ Prognosis	Normal	Normal
○ Treatment	Avoid estrogen	None available

Printed with permission: Paré P. *First Principles of Gastroenterology* 2005. pg. 528

109. Give 5 causes of <u>conjugated</u> hyperbilirubinemia in the neonate, and give 5 examples of each.

- Infection
  - Bacterial urinary tract infection/sepsis
  - Cytomegalovirus
  - Rubella
  - HSV, type 6
  - Toxoplasmosis
  - Syphilis
  - Other viruses: adenovirus, Coxsackie virus, echovirus, parvovirus B19

- Metabolic
  - Galactosemia
  - Fructosemia
  - Tyrosemia
  - Peroxisomal disorders
  - Bile acid synthesis disorders
  - α_1-antitrypsin deficiency
  - Cystic fibrosis
  - Niemann-Pick disease

- Endocrine disorders: hypopituitarism, hypothyroidism
- Neonatal hemochromatosis
- Progressive familial intrahepatic cholestasis

- Bile duct disorders
  - Extrahepatic
    - Biliary atresia
    - Bile duct perforation, stenosis
    - Neonatal sclerosing cholangitis
    - Choledochal cyst
    - Cholelithiasis
    - Intra/extrahepatic masses
    - Inspissated bile/bile plug
  - Intrahepatic
  - Alagille's syndrome
    - Byler's disease (familial progressive disorder)
    - Nonsyndromic bile duct paucity

- Miscellaneous
  - Parenteral nutrition
  - Intestinal obstruction
  - Shock
  - Trisomy 21

Printed with permission: Robertson M, and Martin SR. *Principles of Gastroenterology* 2005: pg. 728.

110. Give 10 causes of jaundice in patients with lymphoma.

- Related to lymphoma
  - Hepatic infiltration
  - Jaundice without infiltration
  - Intrahepatic cholestasis
    - Rare
    - Hodgkin's disease
    - (Stauffer's syndrome-like [renal cell Ca])
  - Extrahepatic obstruction
    - Usually hilar
    - Usually non-Hodgkin's lymphoma
  - Autoimmune hemolytic anemia, DIC
  - Hepatic artery clots

- Related to therapy
  - Chemotherapy (can cause acute liver failure)
  - Hepatic irradiation
  - Infection

- Post-transfusion HCV
- HBV reactivation
- Opportunistic infections

Adapted from: Sherlock S, and Dolley J. *Diseases of the Liver and Biliary System* (Eleventh Edition) 2002: pg. 60.

Useful background: Gallbladder

- Gallbladder (GB) may be often enlarged without a palpable liver; you can feel the GB better with the patient on her/his left side.
- Obstructive jaundice plus palpable GB-unlikely to be due to stones (unless stones in cystic duct or Hartmann's pouch).
  - 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 tumours rarely
  - Ovarian tumours may be palpated in the midline, including at the umbilicus
  - Distended bladder is symmetrical, unless a diverticulum is present

Acute liver failure (ALF)

111. Give a classification of the causes of acute hepatic failure (ALF), and give 15 examples.

- Viral
  - Hepatitis A-E
  - Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes simplex (HSV)
  - Parvovirus B19, adenovirus
  - Viral hemorrhagic fever
  - Rarely Herpes zoster, Human herpes virus-6, West Nile virus, coxsackie B virus

- Drugs
  - Acetominophen, isoniazid, NSAIDs, sulfonamides
  - Tetracycline, rifampin, valproic acid, phenytoin, halothane
  - Telithromycin, orlistat, amiodarone

- Metabolic causes
  - Wilson's disease, alpha-1 antitrypsin deficiency, galactosemia
  - Tyrosinemia, Reye's syndrome, hereditary fructose intolerance
  - Neonatal iron storage disease
  - Lecithin-cholesterol acyltransferase deficiency

- Vascular causes
  - Left heart failure
  - Shock
  - Venocclusive disease
  - Budd-Chiari syndrome
  - Heat stroke

- Hematologic/Oncologic causes
  - Leukemia, lymphoma, metastatic carcinoma

- Miscellaneous
  - Acute fatty liver of pregnancy (AFLP), HELLP syndrome (rare)
  - Syncythial giant cell hepatitis
  - Primary graft non-function post-liver transplantation

Adapted from: Khashab M, Tector AJ, and Kwo PY. *Curr Gastroenterol Rep* 2007;9(1):66-73.

112. Give the King's College risk stratification criteria for liver transplantation in ALF.

- Acetaminophen
  - INR > 6.5 (PT > 100 sec), serum creatinine > 3.4 mg/dl, stage 3 or 4 encephalopathy
  - Arterial lactate > 3.5 4 hours after resuscitation
  - pH < 7.30 or arterial lactate > 3.0 12 hours after resuscitation; or

- Non-acetaminophen
  - INR > 6.5 (PT > 100 sec); or
  - Any 3 of the following:
  - INR > 3.5 (PT > 50 sec)
  - Age < 10 or > 40 years
  - Bilirubin > 17.5 mg/dl
  - Duration of jaundice > 7 days
  - Etiology: drug reaction

Printed with permission: Fontana RJ, and Chung RT. *AGA Institute 2007 Spring Postgraduate Course Syllabus*: 636.

113. Outline the management of the patient with acetaminophen (ACM) overdose.

- Initial measures
  - ABC`s

- Rule out other co-ingestions
- Contact liver centre
- Serum ACM level, urine toxicology screen, LFT's, INR, arterial lactate
- Determine likelihood of hepatotoxicity from nomogram (except in non-intentional cases)
- Lavage stomach if presenting within 12 hours of ingestion or narcotic/anticholinergic ingestion
- 60 grams of activated charcoal if within 12 hours of ingestion

- Oral N-Acetylcysteine (NAC)
  - Loading dose: 140 mg/kg po/NG x 1
  - 70 mg/kg q 4 hours x 17 doses
  - Compazine/raglan for nausea prn
  - Cimetidine (P450 inducer)

- IV N-Acetylcysteine (NAC)
  - Dose 1. Loading dose: 140 mg/kg NAC in 200 ml D5W over 1 hour
  - Dose 2. 50 mg/kg NAC in 500 ml D5W over 4 hours.
  - Dose 3. 125 mg/kg NAC in 1000 ml D5W over 19 hours.
  - Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 hours.
  - Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 hours.

- Caution:
  - Do not administer NAC to patients with known sulfa allergy
  - Administer IV formulation of oral NAC through a leukopore filter in a monitored setting after consent obtained from patient/family.
  - IV infusion of NAC leads to anaphylactoid/hypersensitivity reactions in 3 to 5% most commonly during loading dose.
  - Hold and reduce infusion rate by 50% if rash/nausea occurs. Administer fluids, IV benadryl, IV steroids as needed.

- Psychological assessment

- Treat complications if ALF present

Adapted from: Chun LJ, et al. *J Clin Gastroenterol* 2009;43(4):342-9.

114. Give an outline of the investigations performed on the patient with ALF, being assessed for possible liver transplantation.

- Treat cause of ALF

- Medical/Surgical Candidacy
  - Transplant hepatology evaluation

- Transplant surgery evaluation
- Transplant social work/psychosocial/nutritional evaluation
- Dental examination
- Risk stratification (MELD or modified MELD)

- Blood work
  - AFP
  - ALT, AST, AP, GGT
  - Albumin, INR, bilirubin
  - 1° /2° electrolytes
  - Type and screen
  - Factor V, lactate
  - Serum copper, ceruloplasmin, 24 hour copper
  - Ferritin, iron, % saturation
  - Alcohol, drug screen
  - Autoimmune markers

- Cultures/Microbiology
  - Blood, urine, and peritoneal fluid
  - PPD and Candida

- Serologies
  - HIV
  - HAV – IgM
  - HBV - sAg, sAb, IgM anticore
  - HDV (if HBV positive), HEV (if pregnant)
  - HCV
  - CMV/HSV/EBV/Toxo' titers

- Imaging
  - Liver US with Doppler
  - Chest x-ray

- Cardiopulmonary evaluation
  - ECG
  - 2-D surface echo with Doppler
  - Pulmonary function tests

- Cancer Surveillance
  - Pelvic, prostate, breast, colon and HCC, as indicated

Adapted from: Gill RQ, and Sterling RK. *J Clin Gastroenterol* 2001;33(3):191-8.

Useful background: Acute liver failure (ALF)

- Definition: A sudden (usually < 24 weeks length of illness) loss of hepatic function in a patient without preexisting liver disease, with the development of coagulopathy) INR > 1.5) and hepatic encephalopathy (Ritt DJ, et al. *Medicine (Baltimore)* 1969:151-72.)

- The causes of ALF in America are as follows:
  - Acetominophen overdose (46%)
  - Indeterminate 14%
  - Drug-related 11%
  - HBV 7%
  - Other causes 7%
  - Autoimmune 5%
  - Ischemic 4%
  - HDV 3%
  - Wilson's disease 2%
  - (156-8)

- The spontaneous recovery rate is 58-64% for acetominophen, ischemia and HDV, and 20-25% for all other causes of ALF (Lee WM, et al. *Hepatology* 2008;47:1401-15.)

- Specific treatments for causes of ALF (McCashland 09)
  - Acetominophen-n-acetylcysteine, NAC
  - AFLP (acute fatty liver of pregnancy), pre-eclampsia – delivery of fetus
  - Amanitia toxicity
  - Herpes – acyclovir
  - Autoimmune – steroids
  - HBV – nucleoside or nucleotide analogues

- CT of the head in ALF is neither sensitive nor specific to detect intracerebral hypertension, but can identify the advanced stages of ontracerebral hypertension and brainstem herniation (Larsen FS, Wendon J. *Liver Transpl* 2008;14:S90-6.)

- NAC may offer benefit to persons with early coma stages (i-II) of non-acetominphen ALF (Lee WM, et al. *Hepatology* 2007;46:A79.)

- Management for coma stages III-IV in ALF includes intubation, epidural monitoring of intracerebral pressure (ICP) of < 25 mmHg, and cerebral perfusion pressure of 50-80 mmHg, 30˚ elevation of the head of the bed, factor VII or FFP to get INR < 1.8, mannitol, hypothermia, or indomethacin, cultures, antifungal coverage, vasopressors

(norepinephrin) to maintain cerebral perfusion pressure > 50 mmHg, enteral nutrition (McCashland 09)

Abbreviations: ALF, acute liver failure; ICP, intracerebral pressure

115. Give the pathogenesis of 6 major complications of acute liver failure

Complication	Pathogenesis
➢ Hypoglycemia	○ ↓ hepatic glucose synthesis
➢ Encephalopathy	○ Cerebral edema
➢ Infections	○ Reduced immune function ○ Invasive procedures
➢ Gastrointestinal hemorrhage	○ Stress ulceration ○ Esophageal varices (PHT)
➢ Coagulopathy	○ ↓ clotting factor synthesis ○ Thrombocytopenia ○ Fibrinolysis
➢ Hypotension	○ Hypovolemia ○ Decreased vascular resistance
➢ Respiratory failure	○ ARDS (DAD)
➢ Pancreatitis	○ Unknown
➢ Renal failure	○ Hypovolemia ○ Hepatorenal syndrome ○ Acute tubular necrosis ○ NSAID damage

Abbreviations: ARDS, Acute respiratory distress syndrome; CT, computed tomography; DAD, diffuse alveolar damage; ICP, intracranial pressure; NSAIDs, nonsteroidal anti inflammatory drugs; PHT, portal hypertension.

Adapted form: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 93-4: pg. 1561.

Cirrhosis and portal hypertension

116. Give 8 pathophysiological factors responsible for the development of hepatic fibrosis.

- Extracellular matrix proteins (EMP)
- Hepatic stellate cells (HSC)
- Activation of HSC to form myofibroblasts
- Other mesenchymal cell populations and bone marrow-derived cells
- Hepatocyte growth factor (HGF)
- TGF B
- Renin-angiotensin system (RAS)
- Angiotensin-converting enzyme (ACE)
- Angiotensin I and II receptors
- Endotoxin, lipopolysaccharide (LPS)
- Toll-like receptor (TLR4)
- Angiogenesis
  - Vascular endothelial growth factor (VEGF)
  - Angioporetin 1, 2

Adapted from: Jiao J, et al. *Curr Opin Gastroenterol* 2009;25(3):223-9.

117. Classify and give 8 causes of cirrhosis.

- Viral hepatitis
  - HBV, HCV, HDV

- Metabolic
  - NASH
  - Hemochromatosis
  - Wilson's disease
  - 1-antitrypsin deficiency
  - Galactosemia
  - Tyrosinemia
  - Autoimmune
  - Sclerosing cholangitis
  - Primary biliary cirrhosis
  - Autoimmune Hepatitis

- Drugs/toxins
  - Alcohol

- Conjestive
  - Cardiac failure
  - Budd-Chiari

- Cystic fibrosis

Adapted from: Heathcote J. *First Principles of Gastroenterology* 2005: pg. 598.

118. Give 10 points in the preventive care of the patient with cirrhosis.

- Prevention of first variceal hemorrhage: EGD q3 years, with banding or beta blockers (primary prophylaxis)

- Prevention of recurrent variceal hemorrhage (secondary prophylaxis)
  - Beta-blockers
  - Banding
  - Sclerotherapy
  - Shunts (TIPS)

- Prevention of bacterial infections after GI bleeding (antibiotic prophylaxis)
- Prevention of SBP (antibiotics for previous SBP)
- Assess for minimal (subclinical) HE (grade 0), and treat appropriately; testing for driving competence
- Vaccination – Influenza, Pneumococcus, HAV, HBV
- Nutrition assessment and treatment
- Avoid alcohol, Viagra, vasodilators, NSAIDs, hepatotoxic herbs, benzodiazepines
- Education, family counseling
- Screening for CEA, DM, HBP, HCC, osteoporosis, diabetes, hypertension; usual screening for breast, prostate, cervix, colon
- Medialert bracelet
- Ongoing evaluation for possible liver transplantation

119. Give 6 hepatic/extrahepatic signs of cirrhosis on hepatic imaging CT and/or MR.

- Hepatic
  - Nodularity
  - ↑ periportal space
  - Posterior notch
  - ↑ caudate and lateral segment
  - ↑ candate-to-right lobe size
  - Enlarged gallbladder

- Extrahepatic
  - Splenomegaly
  - Varices
  - Ascites
  - Gamma-gandy bodies

Adapted from: Ito K, et al. *Magn Reson Imaging Clin N Am* 2002;10(1):75-92, vi.

120. Give the pathophysiological components producing the hyperdynamic circulation and cardiovascular dysfunction in persons with cirrhosis.

- Peripheral and splanchnic arterial vasodilatation
  - Baroreceptor-induced increase in heart rate

- Autonomic dysfunction
  - Increased sympathetic nervous activity
  - Vagal impairment

- Alterations in cardiac preload
  - Increased portosystemic shunting
  - Increased blood volume
  - Effects of posture
  - Decreased blood viscosity

- Alterations in oxygen exchange
  - Anemia
  - Hypoxemia
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension

Printed with permission: Møller S, and Henriksen JH. *GUT* 2008; 58: pg. 271.

Cirrhosis and endocrinology

121. a) Give examples of endocrine complications affecting patients with PBC, alcohol – or hemochromatosis – associated cirrhosis disease.

- Alcoholic cirrhosis
  - Gonadal insufficiency
  - Hypothalamic dysfunction
  - Gynecomastia

- Hemochromatosis
  - Gonadal insufficiency
  - Hypothalamic dysfunction
  - Diabetes mellitus

- Primary biliary cirrhosis
  - Autoimmune thyroid disease
  - Metabolic bone disease

Adapted from: Fitz JG. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1982.

b) Give 2 examples of the effect of cirrhosis on the assessment of endocrine function.

- Hypothyroidism
  - ↓ T3
  - N/↑ thyroxine binding globulin level
  - ↑ ALT/AST (also seen with hyperthyroidism)

- Diabetes mellitus (or insulin resistance)
  - Elevated fasting blood glucose level

- Feminization and hypogonadism
  - ↑ estrogen level
  - ↑ sex hormone-binding globulin level
  - ↓ total and free testosterone levels
  - Loss of diurnal variation
  - Hypothalamic dysfunction
  - Testicular atrophy

Adapted from: Fitz JG. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006; pg. 1982

Hepatocellular cancer and other liver tumours

122. Give the causes of hepatic masses seen on abdominal ultrasound.

- Tumours
  - Primary and secondary metastases

- Benign lesions that usually require no further treatment
  - Cavernous hemangioma
  - Focal nodular hyperplasia (reaction to an arterial malformation; the telangiectatic subtype of FNH is associated with estrogen use; 10% multiple, 20% associated with cavernous hemangioma)
  - Simple liver cysts
  - Focal fatty liver areas

- Benign lesions that require further follow-up and management
  - Hepatic adenoma (associated with the use of OCA)

- Malignant lesions that require appropriate therapy
  - Liver metastases
  - Primary hepatocellular carcinoma
  - Cholangiocarcinoma (CA 19.9)
  - Mixed hepatocellular-cholangiocarcinoma
  - Cystadenocarcinoma
  - Hemangioendotheliomatosis
  - Epithelioid angiomyolipoma
  - Mixed epithelial and stromal tumours
  - Sarcomas
  - Lymphomas

- Abscesses
  - Pyogenic liver abscess
  - Nodular regenerative hyperplasia
  - Biliary cystadenoma
  - Inflammatory pseudotumour
  - Granulomatous abscesses
  - Amebic liver abscess
  - Echinococcal cysts

Adapted from: Roberts LR. *2008 AGA Annual Postgraduate Course Syllabus*: pg 245.

123. Compare and contrast focal nodular hyperplasia (FNH) and hepatic adenoma (HA).

Characteristic	FNH	Adenoma
➢ Gender	Female	Female
➢ Hormone therapy	0	+++
➢ Symptoms	Rare	Occasional
➢ Multiple	About 30%	12-30%
➢ Pathological associations	Hemangiomas	Glycogenoses, androgens, peliosis
➢ Central arterial scar	Yes	No
➢ Growth Static*	If stimulated (estrogens, OCA)	
○ Treatment	Conservative	Resection if symptomatic
○Malignant potential	-	+

*the telangiectatic subtype of FNA is associated with estrogen use

124. Give 3 precursor lesions of HCC (hepatocellular cancer) in the patient with hereditary hemochromatosis.

- ➢ Males with iron overload and advanced fibrosis
- ➢ Dysplastic lesions
- ➢ Proliferative lesions
- ➢ Increased number of iron free foci (IFF, >50% at risk to develop HCC)

Adapted from: Hytiroglou P, et al. *Gastroenterol Clin North Am* 2007;36(4):867-87, vii.

125. Give the diagnostic imaging characteristics on CT/MRI/PET scan/nuclear medicine of hemangioma, focal nodular hyperplasia (FNH), adenoma, HCC, and metastases.

- Hemangioma – nodular, no washout at periphery; RBC scan, triphasic CT scan (arterial phase); MRI
- Focular nodular hyperplasia (central vessel, stellate central scan), central scar, homogenous
- Adenoma - heterogeneous, hemorrhage, fat, necrosis, impaired arteriole (no bile duct) "feeding" lesion
- HCC (tumour thrombus in vessel, fat, cirrhosis, capsule heterogeneous, bile production, extrahepatic involvement)
- Metastases (washout at periphery, ring enhancing; fat, blood, calcification; new or increasing size – may be hyper/hypo-vascular); renal, thyroid, sarcomas, melanomas, neuroendocrine (islet, carcinoid, pheochromocytoma)

Adapted from: Hussain SM, and Semelka RC. *Magn Reson Imaging Clin N Am* 2005;13(2):255-75.

126. Give 4 non-histological diagnostic criteria for HCC (hepatocellular cancer).

- Hepatic mass on ultrasound in cirrhotic
- Focal lesion > 2 cm with evidence of cirrhosis (if <2 cm, on 2 imaging modalities – CT angiogram Arterial hypervascularization and venous washout MRI (contrast enhanced ultrasound; MRI – triphasic (hyper T_2, 150-T_1)
- AFP > 200 ng/ml (normal AFP does not R/o HCC)
- Sulphur colloid scan – old (Kupfer cells positive in FNH)
- Non-cirrhotic HBV, HCV (Japan), hemochromatosis, αAT deficiency

Adapted from: Talwalkar JA, and Gores GJ. *Gastroenterology* 2004;127(5 Suppl 1):S126-32.

127. Give 15 risk factors for developing HCC.

- Patient
  - Africans > 20 years (HBV^+)
  - Asian males> 40 years (HBV^+)
  - Asian females >50 years (HBV^+)
  - FH of HCC
  - Dietary afla toxin exposure
  - Obesity
  - Tobacco, marijuana smoking
  - Oral contraceptives

- Without cirrhosis
  - Chronic HBV infection (even without cirrhosis)
  - Chronic HCV infection (Japan; all others, HCV cirrhosis)
  - Hepatic adenoma
  - Hemochromatosis
  - Aflatoxin BI
  - Congenital/familial
  - Previously resected HCC

- Cirrhosis
  - HCV
  - HCV +ALD + obesity (accelerated)
  - ETOH
  - Hemochromatosis- dietary Fe overload in persons of African ancestry; hereditary hemochromatosis
  - PBC
  - alpha-1-antitrypsin deficiency
  - NASH
  - autoimmune hepatitis
  - Wilson's disease
  - Type 1 hereditary tyrosinemia
  - Type 1 and type 2 glycogen storage disease
  - Hypercitrulinemia
  - Ataxia-telangiectasia

Abbreviations: ALD, alcoholic liver disease; FH, family history; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis

Adapted from: Gores GJ. *AGA Institute Postgraduate Course Book* 2006: pg. 257.; and Kew MC. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg.2014; and 2010: pg. 1575.

128. Give 4 risk factors for the development of HCC associated with HCV.

- Male
- Cirrhosis
- Long duration of HCV
- Older age
- Hepatitis B co-infection with HBV, HIV
- Heavy alcohol intake
- Obesity +/- NASH

Adapted from: Gores GJ. *AGA Institute Post Graduate course book* 2006: pg. 251-2.

129. Give 10 paraneoplastic syndromes associated with hepatocellular carcinoma.

- CNS
  - Neuropathy
- Endocrine
  - Sexual changes- isosexual precocity, gynecomastia, feminization
- MSK
  - Carcinoid syndrome
  - Hypercalcemia
  - Hypertrophic osteoarthropathy
  - Hypoglycemia
  - Osteoporosis
  - Polymyositis
  - Thyrotoxicosis
  - Thrombophlebitis migrans
- CVS
  - Systemic arterial hypertension
- Skin
  - Porphyria
- GI
  - Watery diarrhea syndrome
- Hematology
  - Polycythemia (erythrocytosis)

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 94.2: page 1571.

130. Give 6 treatment options for the patient with HCC.

- Staging, MRI – Barcellona criteria, Child's stage
- Surgical resection
  - Partial hepatectomy (HBV) satisfying Milan criteria:
    - 1 tumour, < 5 cm
    - 3 tumours, each < 3 cm
    - Edmonton volume criteria <115 mm^3
    - no distant metastasis
    - no portal vein distension
- Liver transplantation
- Chemotherapy: po, iv, transarterial (TA) chemoembolization (TACE), TA chemotherapy infusion; drug eluting beads
- Percutaneous hepatic injection: ethanol or acetic acid injection
- Energy-mediated ablation: cryoablation, microwave or radiofrequency ablation (RFA), for < 2 cms potentially curative
- Radiotherapy: internal, external
- Palliative care
- Investigational: somastostatin, immune modulation, gene therapy, PDT
- Mixed tyrosine kinase inhibitors (sorafanib)

Adapted from: Nguyen MH, and Keeffe EB. *Best Practice & Research Clinical Gastroenterology* 2005;19(1): pg 164.; and Tranberg KG. *Best Practice & Research Clinical Gastroenterology* 2004;18(1): pg.127.

131. Compare and contrast the prevention and treatment of HCC in persons with HBV and HCV infection.

	HBV	HCV
➢ New infection	○ Neonate vaccination	○ general infection control
➢ Existing infection	○ Antiviral therapy (suppression) ○ Nucleos (t) ide analogues	○ Antiviral therapy (eradication) ○ Interferon plus ribavirin
➢ Treatment	○ Early diagnosis and curative treatment	
➢ Prevent	○ Transplantation	

recurrence	○ Antiviral therapy (?) ○ Molecular targeting drug		

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

Printed with permission: Masuzaki, et al. *Best Prac Res Clin Gastroenterol* 2008:1137-1151.

132. Give the management strategy of HCC based on CTP class, size and performance status.

➢ CTP A, PS-O	○ Single HCC <2cm	○ HVPG <10mm Hg and bilirubin < 1.5 mg/dl ○ Varices/collaterals or HVPG ○ >10 mm Hg or bilirubin >1.5mg/dl	○ Surgical resection ○ Live transplant evaluation ○ RFA/PEI
➢ CTP A-B, PS, 0-2	○ Single HCC 2-5 cm	○ HVPG <10mm Hg and bilirubin <1.5 mg/dl ○ Varices/collaterals or HVPG ○ >10 mm Hg or bilirubin >1.5mg/dl	○ Surgical resection ○ Liver transplant evaluation ○ RFA/PEI
	○ 2 or 3 HCC masses <3 cm (the largest) ○ Intermediate stage (multinodular, PS,O) ○ Advanced stage (portal invasion, metastases)		○ Liver transplant evaluation ○ Radiofrequency ablation ○ Transarterial chemoembolization ○ Sorafenib
➢ CTP C,	○ Terminal		○ Symptomatic

PS>2	stage	treatment, palliative care

Abbreviations: CTP, Child Turcotte Pugh; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; PEI, percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation.

Printed with permission: Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104:1824.

133. Give the diagnostic workup of a liver mass in a patient with chronic liver disease.

➢ Mass <1 cm	○ Diagnosis ○ Follow up	○ Low likelihood of being HCC, therefore no specific diagnostic tests ○ Repeat imaging study every 3 months ○ If no growth in 1-2 years, no HCC; continue screening every 6 months ○ If growth, treat as HCC		
➢ Mass 1-2 cm	○ Diagnosis ○ Follow up after biopsy	○ Two dynamic imaging studies (US, CT scan, or MRI) ○ Biopsy confirms HCC ○ Non diagnostic biopsy	○ Both with typical vascular pattern ○ One typical and the other atypical ○ Both atypical ○ Treat as HCC ○ Repeat imaging study every 3 months: ○ If no growth in 1-2 years- no HCC ○ If growth, treat as HCC	○ Treat as HCC ○ Consider biopsy of mass ○ Consider biopsy of mass vs. close follow up
➢ Mass >2 cm	○ Diagnosis	○ One dynamic	○ Typical vascular	○ Treat as HCC

	imaging study (US, CT scan, or MRI)	pattern	
	○ Biopsy confirms HCC	○ Atypical vascular pattern	○ Biopsy of mass
○ Follow up after biopsy		○ Treat as HCC	
	○ Non diagnostic biopsy	○ Repeat imaging study every 3 months: ○ If no growth in 1-2 years- no HCC ○ If growth, treat as HCC	

Abbreviations: CT, computerized tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound

Printed with permission: Garcia Tsao, et al. The *American Journal of Gastroenterology* 2009; 104:1822.

Useful background: The Okuda staging system of HCC.

Criterion	Cut-off
○ Tumour size	>50% (largest cross-sectional area of tumour to largest cross-sectional area of liver) = positive <50% = negative
○ Ascites	Clinically detectable = positive Undetectable = negative
○ Serum albumin	<3g/dL = positive >3g/dL = negative
○ Serum bilirubin	<3g/dL = positive >3g/dL = negative
○ Stage	
○ I	No positive criterion
○ II	1-2 positive criteria
○ III	Three positive criteria

Printed with permission: Nguyen MH, and Keeffe EB. *Best Practice & Research Clinical Gastroenterology* 2005;19(1):pg 164.

Useful background: Key learning points on HCC

- Hepatocellular carcinoma (HCC) is one of the most common malignant tumours worldwide and its incidence is increased in industrialized countries
- Accurate staging at the time of diagnosis, based on the Barcelona Clinic Liver Cancer classification, is central to the choice of the appropriate therapeutic strategy
- Therapeutic options for advanced HCC have improved considerably during the past few years and now include targeted therapy with sorafenib, an inhibitor of multiple tyrosine kinases
- Novel therapeutic strategies are needed that will further improve survival of patients with HCC, especially for those who present with advanced disease at the time of diagnosis
- Clinical trails should follow guidelines that define meaningful primary and secondary end points and should be coordinated by centers with expertise in the care of patients with HCC

Abbreviation: HCC, hepatocellular carcinoma

Printed with permission: Spangenberg, et al. *Gastroenterol Hepatol* 2009;6: 423-432.

Useful background:

- Hepatocellular carcinoma (HCC) is one of the most common malignant tumours worldwide and its incidence is increased in industrialized countries
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Useful background: Hepatocellular cancer (HCC)

- Usually seen in the patient with cirrhosis, it with HBV, HCV in Japan, or the person with hemochromatosis
- In the presence of a liver mass in a person with cirrhosis and an AFP > 500, HCC is likely
- Sorafanib, a mixed kinase inhibitor, prolongs survival in persons with metastatic HCC

Abbreviation: HCC, hepatocellular cancer

What's new: Hepatocellular cancer (HCC)

- The most sensitive and specific imaging technique for the diagnosis of HCC is Gad-MR (gadolinium magnetic resonance). Other methods include contrast-enhanced ultrasonography, helical-computed tomography, and superparamagnetic iron oxide magnetic resonance (Lesni et al., AJC 2010; 105: 599-609).
- Hepatic nodules smaller than 2 cm in diameter may still contain a focus of HCC.
- Imaging techniques may show hypervascularization in the arterial phase, followed by washout in the venous phase, suggestive of malignancy.
- Non-invasive criteria have been established by American and European groups (AASLD and EASL), and provide a similar sensitivity of about 80% in making a diagnosis of what turns out to be HCC.
- Hepatic regenerative activity ↑AFD
- Risk of seeding from tumour biopsy ~ 3%
- 4 phase hepatic tumour protocol for HCC

- CT
  - ↓ HA, PV supply
  - Arterial neovascularization
  - Venous washout

- MRI
  - T2 hyperintensity

- MRI super-paramagnetic MRI
  - Iron oxide taken up by Kupffer cells, which are missing in HCC

- Slows up as dark HCC on this test
- Art phase gives sensitivity
- Venous phase gives specificity

- Fibrosis progression in HCC directly plus HBV related to viral load

Useful background: Nodular regenerative hyperplasia (NRH)

- Injury to the hepatic vasculature from autoimmune disorders, myeloproliferative syndromes and from antineoplastic medications results in remodeling of surrounding liver tissue into a nodule which contains liver tissue and no fibrosis
- The nodules of regenerative liver tissue may compress adjacent hepatic vasculature, leading to non-cirrhotic portal hypertension, and compress bile ducts, leading to jaundice
- MRI is the best diagnostic imaging test to distinguish HCC from a large cirrhotic nodule

Abbreviation: NRH, nodular regenerative hyperplasia

134. Cholangiocarcinoma is the second most common hepatic tumour. Give the causes, locations and imaging characteristics of cholangiocarcinoma.

- Etiologies
  - PSC
  - Caroli's
  - Choledochaul cyst
  - Thoratrast

- Locations
  - Hepatic bifurcation (Klatskin tumour)
  - Distal CBD
  - Intrahepatic (5-15%)

- Imaging
  - Variable fibrosis and necrosis
  - Atrophy
  - Capsular retraction
  - Biliary duct dilation
  - Hypovascular (progressive, delayed hyperenhancement)

Pulmonary complications of chronic liver disease

135. List 6 potential causes of increasing dyspnea in a patient with chronic liver disease.

- Cardiac failure (including cirrhotic cardiomyotomy)
- Pulmonary hypertension (portopulmonary syndrome)
- Pleural/pericardial effusions
- Atelectasis secondary to ascites
- Pulmonary embolus
- Pulmonary infection
- Pulmonary fibrosis (methotrexate)
- Interstitial lung disease
- Acidosis
- Severe anemia
- Hepatopulmonary syndrome
- Liver disease caused by cystic fibrosis, α_1 – antitrypin deficience, autoimmune hepatitis, pulmonary fibrosis from use of methotrexate

Adapted from: Kim YK, et al. *Radiographics* 2009;29(3):825-37.

136. Give the diagnostic criteria for hepatopulmonary syndrome

- There are three diagnostic criteria for hepatopulmonary syndrome:
  Chronic liver disease and portal hypertension;
  - An AaPO2 of $\geq$15 mm Hg $\geq$ 20 mm Hg or greater than or equal to the age-adjusted value and/or $PaO_2 \leq 80$ mm Hg[4] or $\leq$70 mm Hg;
  - Pulmonary vascular dilation at contrast-enhanced echocardiography or ^{99m}Tc-MAA

Abbreviations: $AaPO_2$, alveolar-arterial pressure gradient for oxygen; PaO_2, partial pressure gradient for oxygen; ^{99m}Tc-MAA, perfusion body scan with ^{99m} Technetium-labeled macroaggregated albumin

Printed with permission: Pastor CM, and Schiffer E. Nature *Clinical Practice Gastroenterology & Hepatology* November 2007;4(11): pg 615.

137. Give the different ways to distinguish between hepatopulmonary syndrome and portopulmonary hypertension.

Clinical feature	Hepatopulmonary syndrome (AV shunts)	Portopulmonary hypertension (constriction of pulmonary vessels)
➢Symptomatology	○ Progressive dyspnea ○ SOB on sitting up	- Chest pain - SOB on lying down
➢ Clinical examination	○ (Platypnea) ○ Cyanosis ○ Finger clubbing	- No cyanosis - RV heave - Pronounced P2 component
➢ ECG findings	○ Spider angiomas ○ None	- RBBB, rightward axis - RV hypertrophy - No/mild hypoxaemia
➢ Arterial blood gas levels	○ Moderate-to-severe hypoxemia	
➢ Chest radiography	○ Normal	- Cardiomegaly - Hilar enlargement

Clinical feature	Hepatopulmonary syndrome (AV shunts)	Portopulmonary hypertension (constriction of pulmonary vessels)
➢CEE	○ Tri-regurg; Always positive; left atria opacification for >3-6 cardiac cycles after ○ right atrial opacification	- Usually negative. Positive for <3 cardiac cycles; if arterial septal defect or patent foramen ovale
➢ ^{99m}TcMAA shunting index (“bubble study”)	○ >6% ○ Normal/low PVR	- <6% roatrial opacification - Elevated PVR - Normal mPAOP - Large pulmonary arteries
➢ Pulmonary hemodynamics	○ Normal/’spongy’ appearance (type I)	- Distal arterial pruning

Clinical feature	Hepatopulmonary syndrome (AV shunts)	Portopulmonary hypertension (constriction of pulmonary vessels)
➢ Pulmonary angiography	○ Discrete arteriovenous communications (type II) (usually lower lobe)	- Only indicated in mild-to-moderate stages
➢ OLT	○ Always indicated in severe stages	- Late contraindication

Abbreviations: ^{99m}TcMAA, technetium-99 m-labelled macroaggregated albumin; CEE, contrast enhanced echocardiography; ECG, electrocardiogram; mPAOP, mean pulmonary artery occlusion pressure; OLT, orthotopic liver transplantation; PVR, pulmonary vascular resistance; RBBB, right bundle branch block; RV, right ventricular

Printed with permission: Herve P, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 142.

138. Give the therapies for hepatopulmonary syndrome that have been tested in small and uncontrolled trials.

- Oxygen therapy
  - Oxygen therapy (0.5 l/min at rest and 2 l/min during exercise) prevents the deleterious consequences of hypoxemia, but few data exist on its efficacy and on patient compliance. Fukushima et al have shown that treatment for 1 year had a beneficial effect on liver function in two patients (their Child-Pugh score markedly improved).

- Transjugular intrahepatic portosystemic shunt
  - The placement of a transjugular intrahepatic portosystemic shunt (TIPS) to relieve portal hypertension that might participate in the pathophysiology of HPS has failed to improve patient outcome.

- Cavoplasty and coil emboli
  - In some patients with Budd-Chiari syndrome, cavoplasty reversed HPS. The injection of coil emboli that preferentially distribute to dilated vessels might also decrease hypoxemia by obstructing flow to these areas.

- Pentoxifylline
  - Pentoxifylline inhibits tumour necrosis factor-α overproduction and is effective in attenuating HPS in rats with ligated common bile ducts. The drug has not been tested in patients with HPS.

- Nitric oxide inhibition
  - As excess production of nitric oxide (NO) is central to pulmonary vascular dilatation, therapies that reduce pulmonary NO levels or control its effects have been tested. By blocking the NO-induced activation of guanylate cyclase in smooth muscle cells, methylene blue has been shown to improve pulmonary vascular dilatation and hypoxemia. Inhalation of the NO synthase inhibitor N^G-nitro-arginine methyl ester, by reducing intrapulmonary vascular dilatation, also improved by the PaO_2 and decreased the associated dyspnea in some patients, although such findings have not been replicated in other patients. Almeida *et al* have disputed whether there is any benefit from inhibiting the NO-cyclic guanosine monophosphate pathway.

Printed with permission: Pastor CM, and Schiffer E. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(11): pg. 615.

Useful background: Portopulmonary hypertension (PPH)

- Definition: Precapillary pulmonary hypertension in the setting of cirrhosis and for portal hypertension, in the absence of cirrhosis (e.g., portal vein obstruction, idiopathic portal fibrosis), with mean pulmonary capillary wedge pressure and an increased pulmonary vascular resistance > 240 dynes/see/cm^{-5} (Zetterman 09)

- Pathogenesis
  - Pulmonary artery (PA) pressure rise occurs as a result of volume overload and increased cardiac output (from reduced systemic vascular resistance and hyperdynamic circulation)
  - ↓ NO plus ↑ endothelin-1 lead to PA vasoconstriction
  - Obliteration of pulmonary arterioles may occur from intimal proliferation, adventitial fibrosis, and thrombosis of pulmonary vasculature
  - Occurs in 0.25-4.0% of persons with end-stage liver disease, and usually within 4-7 years of the diagnosis of portal hypertension (PHT) (even though there is not a direct correlation between the development of PPH and PHT
  - PPH is more common in persons with cirrhosis and refractory ascites, and in 12% of persons evaluated for liver transplantation

- Symptoms
  - Fatigue, SOBOE, orthopnea, hemoptysis, palpitations; hypoxemia and cyanosis are absent

- Prognosis
  - Median survival for persons with PPH only 2 years, but 91% 1 year survival from liver transplantation

- Treatment
  - Bosentan (anti-endothelin activity) plus sildenafil (a phosphodiesterase – inhibitor) and prostacyclin reduce PA pressure; anticoagulation plus long-term O_2 therapy; liver transplantation

Abbreviations: PA, pulmonary artery; PHT, portal hypertension; PPH, portopulmonary hypertension

139. Give 6 characteristics of pleural fluid in hepatic hydrothorax.

- Cell count <250 polymorphonuclear cells mm^3 (uncomplicated)
- Protein <2.5 g/dL
- Pleural fluid/serum total protein ratio <0.5
- Pleural fluid/serum lactate dehydrogenase ratio >0.6
- Pleural fluid/serum albumin gradient >1.1
- Pleural fluid/serum bilirubin ration <0.6
- pH >7.4
- Glucose level similar to that of serum

Printed with permission: Cárdenas A, and Arroyo V. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 69.

Useful background:Hepatopulmonary syndrome (HPS)

- Definition: Intra-pulmonary vasodilation and shunting occurring in the presence of chronic liver disease or pulmonary hypertension, resulting in acute or alveolar-arterial O_2 gradient > 15 mmHg (> 20 mmHg for persons > 64 years)
- Seen in 4-24% pf persons being evaluated for liver transplantation
- Hypoxemia (PaO2 < 70 mmHg) is usually persent, together with cyanosis and clubbing
- SOBOE, dyspnea worse when sitting up (platypnea from orthodeoxia) and better when lying down (the result of reduction of intra-pulmonary shunting when lying down, with improved oxygenation due to blood going to both lower and upper parts of the lungs)
- Orthodeoxia (worsening of hpoxemia when person sits up or stands) is due to more blood going to the lower lungs when standing, more intra-

pulmonary shunting, and a drop in blood gas arteria PaO_2 decreasing by more than 4 mmHg

- Orthodeoxia occurs in HPS, ASD and recurrent pulmonary emboli; oxygen deactivation during sleep may occur with orthodeoxia
- Chronic liver disease patients with numerous spider angiomas are more likely to have HPS
- Suspect HPS if alveolar-arterial PaO_2 gradient on room air is > 15 mmHg, and if PaO_2 is < 70 mmHg, or if arterial blood gas PaO_2 falls by more than 4 mmHg on standing
- Diagnosis
  - ↓ diffusion capacity on pulmonary function testing (PFT)
  - Pulmonary vasodilation on chest CT
  - Positive contrast echocardiogram
  - Tests of pulmonary shunting; using technetium macro-albumin aggregates
- Treatment
  - O_2, TIPS, liver transplantation
  - Prolonged post-operative mechanical ventilation may be needed, and mortality rate lower transplantation is high

Abbreviation: PFT, pulmonary function testing

Useful background: Risk of cirrhosis, hepatocellular carcinoma (HCC) and mortality in hepatitis B and hepatitis C virus (HBV/HCV) monoinfected and coinfected patients

	Cirrhosis	HCC	Mortality
Study	Zarski et al, 1998 33	Shi et al, 2005 Donato et al, 1998	Amin et al, 2006 Di Marco et al, 1999
HBV monoinfection	22%	OR 16-23	SMR 1.4-5.3
HCV monoinfection	30%	OR 8-17	SMR 2.4-3.1
HBV/HCV coinfection	50%	OR 36-165	SMR 5.6-49

Abbreviations: HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; OR, odds ratio; SMR, standard mortality ratio

Printed with permission: Wursthorn, et al. *Best Practice Res Clin Gastroenterol* 2008;22:1063-1079.

Useful background: Evaluation of hepatic mass

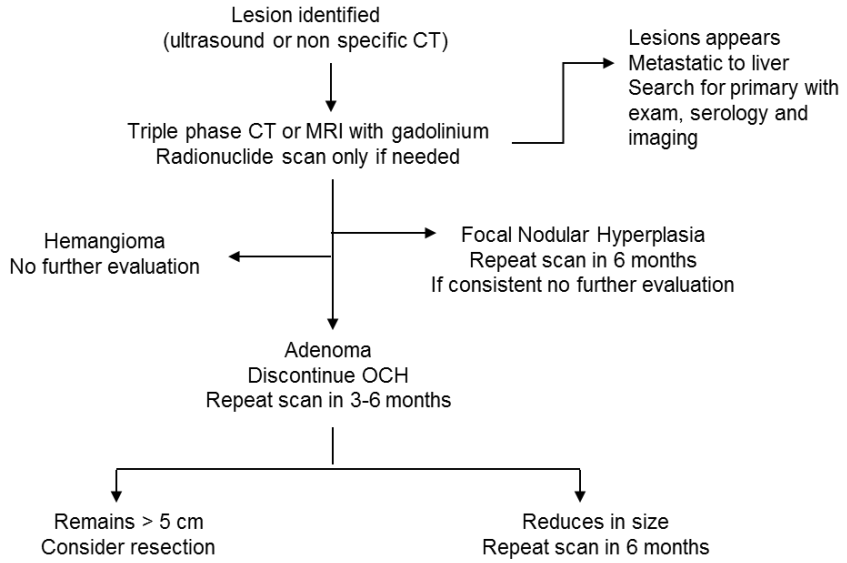
a) Imaging features of common benign liver mass lesions

	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 - 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 - T2: Heterogenous enhancement

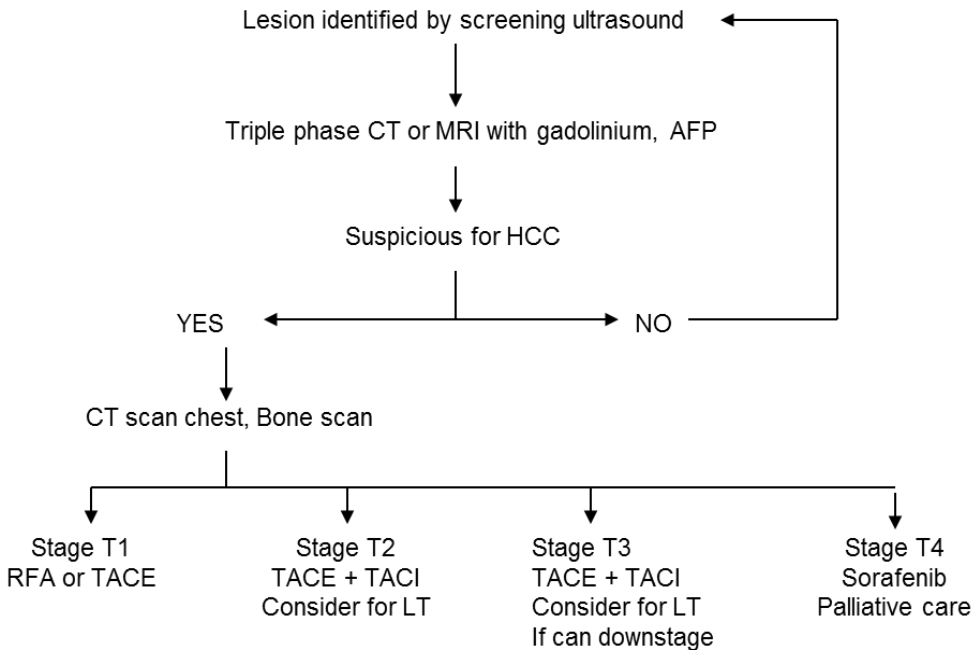
	Hemangioma	Focal nodular hyperplasia	Adenoma
➢ Gadolinium enhanced MRI	○ Progressive enhancement ○ Delayed washout on venous phase	- Homogenous arterial enhancement - Hypodense central scar - Contrast accumulates in scar on delayed T1	- Irregular enhancement with delayed washout
➢ Radionuclide scan (tagged RBC)	○ ↑ uptake during venous phase ○ Delayed emptying	- Equal or ↑ uptake compared to surrounding liver	- ↓ uptake compared to surrounding liver

Source: Shiffman ML. *2009 ACG Annual Postgraduate Course*:167-171.

b) Evaluation of hepatic mass in a patient without chronic liver disease



c) Evaluation of hepatic mass in a patient cirrhosis



Source: Shiffman ML. *2009 ACG Annual Postgraduate Course*:167-171.

- When a mass is identified in the liver of a person with or without chronic liver disease, a triple phase CT or MRI with gadolinium is performed

- Nuclear scintigraphy with sulphur calloid is taken up by the Kupffer cells; uptake is increased with metastatic lesions (thyroid, breast, lung, pancreas, colon), hemangioma or cysts, and is reduced with hepatic adenomas and HCC

- Radionucelotide scanning with RBC identifies an hepatic mass as an hemangioma

- Hepatic hemangioma
  - Common congenital malformation of the liver vasculature, with ectactic blood vessels with no malignant potential and not affected by oral contraceptive hormones. Because of tortuous vessels and stasis, thrombosis and pain may occur

- Focal nodular hyperplasia (FNH)
  - Common congenital malformation of the liver vasculature, with hyperplasia of hepatocytes around the vascular abnormality, leading to a central scan

- Hepatic adenomas
  - Usually seen in 1/ 10^6 women in their childbearing years, and especially if they are on OCA (3 x increased risk)
  - Premalignant, with risk of malignancy increasing with size
  - Features on triphasic CT or gadolinium enhanced MRI may be difficult to distinguish from HCC, so a technicium sulfur colloid scan may be needed to show the typical cold lesions (no sulfur colloid uptake); AFP may become positive when hepatic adenomas becomes malignant

Abbreviation: FNH, focal nodular hyperplasia

Useful background: Major HCC etiologies

- Chronic hepatitis B, C or D
- Toxins (e.g. alcohol, tobacco, aflatoxins)
- Hereditary metabolic liver diseases (e.g. hemochromatosis, a1-antitrypsin deficiency)
- Autoimmune hepatitis
- Obesity (males)
- Diabetes mellitus
- Nonalcoholic steatohepatitis
- Nonalcoholic fatty liver disease

Printed with permission: Macmillan Publishers Ltd: Spangenberg et al, Nat.Rev. *Gastroenterol Hepatol* 2009;6: 423-432.

140. Give the laboratory/radiological tests for the investigation of the pulmonary complications of cirrhosis.

- CVS
  - ECG
  - Echo cardiogram with Doppler
  - Right heart angiogram
- Lung
  - CXR (normal)
  - CT chest
  - ABG in erect and supine positions, for A-a O2 gradient
  - Hemoglobin concentration, electrolytes
  - PFT's
  - Echo bubble (shunting)

- Ascites
  - Radiolabeled ascites scan (technetium – labeled scan)
  - Methylene blue injection of ascites with pulmonary tap

Adapted from: Kew Michael C. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 2009.

Useful background: Hepatocellular cancer (HCC)

- Risk factors
  - 70-90% of HCC occur against the background of hepatic fibrosis grades 3 to 4, or cirrhosis, 1-4% per year (El-Serag HB, Rudolph KL. *Gastroenterology* 2007:2557-2576); the remainder are associated with HBV and hemochromatosis (HCV in Japan)
  - M:F 2:1-4:1; increased BMI, androgenic hormones

a) Risk factors for HCC in HBV

- Patient
  - Presence of cirrhosis
  - Young age of acquisition
  - Asian or African race
  - Male gender
  - Oler age
  - Family history of HCC
  - Exposure to aflatoxin, alcohol, and tobacco

- Infection
  - Co-infection with HCV, HDV, and possibly HIV
  - Active replication of HBV
  - Genotype C

b) Risk factor for HCC in HCV

- Patient
  - Alcohol drinking (heavy > 50 gm/d)
  - Male gender
  - Larger BMI

- Liver
  - Degree of hepatic fibrosis

- Infection
  - HBV coinfection
  - Older age of HCV onset and diagnosis
  - HIV co infection
  - Absence of previous HCV treatment
  - Long duration of active disease

c) Screening for HCC

- Hepatitis B carriers
  - Asian males >40
  - Asian females >50
  - Family history of HCC
  - African >20 years
  - All cirrhosis
- Non hepatitis B cirrhosis
  - Hepatitis C
  - Alcoholic cirrhosis
  - Hereditary hemochromatosis
  - Primary biliary cirrhosis
  - Possibly: alpha 1 antitrypsin, NASH, autoimmune

Adapted from: El-serag H.B. *2009 ACG Annual Postgraduate Course*: 39-43.

- Screening
  - Risk stratification, including HBV and HCV
  - 96 months AFP (alpha-fetoprotein) and abdominal ultrasound over 5 years improves survival from HCC in HBV-positive patients in China (42-5). Most of the detected HCC in the screened group were detected at an early stage; with 3 year survival rates after HCC resection of 53% in the screened group versus none in the non-screened group
  - Improved survival from HCC screening depends of course on the availability of effective therapy for the early detected lesions
  - HCC screening in persons awaiting liver transplantation is cost-effective

Abbreviation: AFP, alpha-fetoprotein; HCC, hepatocellular cancer

Useful background: HCC screening and diagnosis

- Abdominal ultrasound (US) sensitivity, > 60%, specificity, > 90% (Bolondi L, et al. *Gut* 2001251-259.; Singal A, et al. *Aliment Pharmacol Ther* 2009.)

- Only 1/3 of HCC patients have AFP > 100 mg/ml, but values > 200 mg/ml are highly specific for HCC, 10.9 mg/ml, sensitivity 66% (Marrero JA, et al. *Gastroenterology* 2009.)

- AFP

- Performance depends on cutoff value: 20 mg/ml, sensitivity 25-65%
- AFP in a person with a high rate of hepatocyte regeneration (e.g., HCV) can be eluded without presence of HCC (El-Serag 09)

➢ CT
- Arterial enhancement (hypervascular, supplied by hepatic artery) and washout, for HCC, sensitivity is 90% and specificityis 95%

➢ MRI
- Similar performance characteristics as CT, but size of HCC is a factor, with accuracy of > 90% for > 20 mm lesion seen on MRI, but 30% for lesion < 20 mm
- Biopsy under radiological guidance

	Sensitivity	Specificity
US	90%	91%
CT	92%	98%

- For hyper-enhanced nodule > 1 cm, suspect HCC

a) Imaging criteria applied for confirming HCC in patients with cirrhosis and a nodule detected by ultrasound.

➢ Lesion has nodular configuration

➢ Lesion is at least 1 cm in longest diameter*

➢ Lesion shows arterial hypervascularization:
- Hyper enhanced nodule in the arterial phase by two imaging techniques**
- Hyper enhanced nodule in the arterial phase and as hypo enhanced nodule in the portal venous or delayed phase by one imaging technique**

*apply to lesions emerged during Us surveillance. For lesions detected at first imaging examination, lesion diameter should be at least 2 cm to allow non-invasive diagnosis of HCC.

**imaging techniques include: contrast-enhanced US, contrast-enhanced spiral CT, and gadolinium enhanced MRI.

Source: El-serag H.B. *2009 ACG Annual Postgraduate Course*: 39-43.

141. Cholangiocarcinoma is the second most common hepatic tumour. Give the causes, locations and imaging characteristics of cholangiocarcinoma.

- Etiologies
  - PSC
  - Caroli's
  - Choledochal cyst
  - Thoratrast

- Locations
  - Hepatic bifurcation (Klatskin tumour)
  - Distal CBD
  - Intrahepatic (5-15%)

- Imaging
  - Variable fibrosis and necrosis
  - Atrophy
  - Capsular retraction
  - Biliary duct dilation
  - Hypovascular (progressive, delayed hyperenhancement)

Useful background: Diagnostic workup of a liver mass in a patient with chronic liver disease

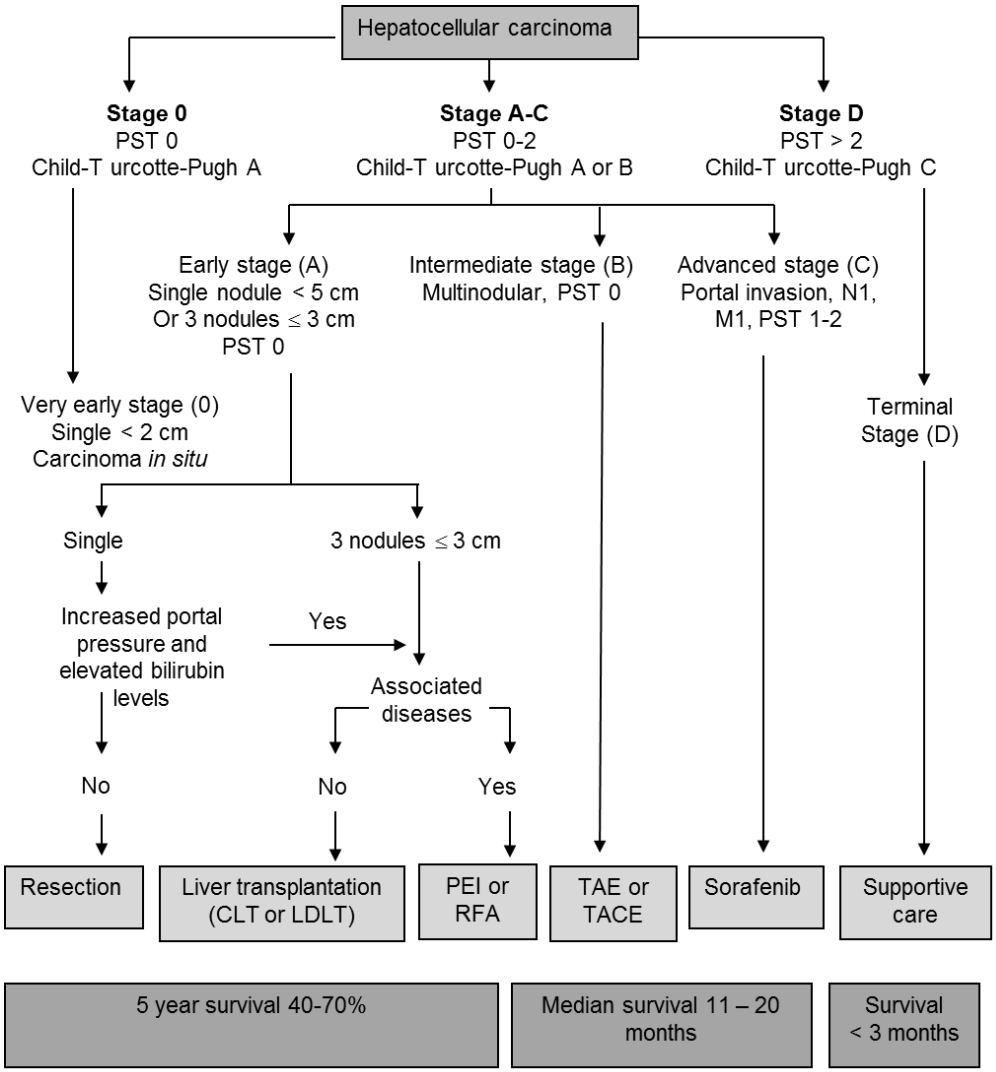
Size of mass				
Mass <1 cm	Diagnosis	Low likelihood of being HCC		- no specific diagnostic tests
	Follow up	Repeat imaging study every 3 months If no growth in 1-2 years If growth		- no HCC, continue screening every 6 months - treat as HCC
Mass 1-2 cm	Diagnosis	Two dynamic imaging studies (US, CAT scan, or MRI) showing arterial phase enhancement and venous washout	Both with typical vascular pattern	- Treat as HCC - Consider biopsy of mass
			One typical and the other atypical	- Treat as HCC

			Both atypical	
	○ Follow up after biopsy	○ Biopsy confirms HCC	Repeat imaging study every 3 months:	- Treat as HCC
		○ Non diagnostic		- no HCC
			If no growth in 1-2 years	- treat as HCC
			If growth	
➢ Mass >2 cm	○ Diagnosis	○ One dynamic imaging study (US, CAT scan, or MRI) with typical vascular pattern	Typical vascular pattern	- Treat as HCC
			Atypical vascular pattern	- Treat as HCC
	○ Follow up after biopsy	○ Biopsy confirms HCC	Repeat imaging study every 3 months:	- Biopsy mass
		○ Non diagnostic		- no HCC
			If no growth in 1-2 years	- treat as HCC
			If growth	

The contrast enhanced imaging studies of computed tomography (CT) and magnetic resonance imaging (MRI) can use the unique dynamic radiological behaviour of hepatocellular carcinoma (hypervascular on the arterial phase and washout on the delayed venous phase). The sequence of events needed to make the radiological diagnosis depends on the size.
Abbreviations: CAT, computerized axial tomography; HCC,hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound

Printed with permission: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829, Table 11, page 1822.

142. Algorithm for staging and treating patients diagnosed as having hepatocellular carcinoma. This algorithm is based on the Barcelona Clinic Liver Cancer guidelines.



Abbreviations: CLT, cadaveric liver transplantation; LDLT, live donor liver transplantation; PEI, percutaneous ethanol injection; PST, performance status test; RFA, radiofrequency ablation; TACE; transarterial chemoembolization; TAE, transarterial embolization.

Printed by permission: Cabibbo et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;6(3): 159-169, Figure 1, page 160.

Useful background: Management strategy of HCC based on CTP class, size and performance status

➢ CTP A, PS-O	Single HCC <2cm	HVPG <10mm Hg and bilirubin < 1.5 mg/dl Varices/collaterals or HVPG >10 mm Hg or bilirubin >1.5mg/dl	Surgical resection Live transplant evaluation RFA/PEI
➢ CTP A-B, PS, 0-2	Single HCC 2-5 cm	HVPG <10mm Hg and bilirubin <1.5 mg/dl Varices/collaterals or HVPG >10 mm Hg or bilirubin >1.5mg/dl	Surgical resection Liver transplant evaluation RFA/PEI
➢	2 or 3 HCC masses <3 cm (the largest) Intermediate stage (multinodular, PS,O) Advanced stage (portal invasion, metastases)		Liver transplant evaluation Radiofrequency ablation Transarterial chemoembolization Sorafenib
➢ CTP C, PS>2	Terminal stage		Symptomatic treatment

Abbreviations: CTP, Child-Turcotte- Pugh; HCC,hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; PEI,percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation.

Printed with permission: Macmillan Publishers Ltd: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829, Table 12, page 1824.

Useful background: Prognostic factors in HCC

- Patient
  - ECOG classification
  - Presence of symptoms

- Liver function
  - Child-Pugh class
  - Serum bilirubin
  - Albumin levels
  - Presence/absence of portal hypertension

- Tumour status
  - Number and size of nodules
  - Presence/absence of macrovascular invasion
  - Presence/absence of extraheaptic spread

Abbreviation:ECOG, Eastern Cooperative Oncology Group.

Ascites, renal dysfunction and SBP

143. Give the indications for treatment of spontaneous bacterial peritonitis(SBP), including recurrent SBP.

- Indications
  - Prior history of SBP
  - GI bleeding, with ascites (even without SBA [PMN > 250; WBC > 500))
  - Low ascitic fluid protein concentration
- Diagnosis
  - Consider SBP and perform diagnostic paracentesis if:
    - Symptoms/signs (abdominal pain, fever, chills)
    - Patient is in emergency room or admitted
    - Worsening renal function or encephalopathy
  - SBP is present if ascites PMN count >250 cells/ul (if fluid bloody, subtract 1PMN per 250 RBC/ul)
- General management
  - Avoid therapeutic paracenteses during active infection
  - Intravenous albumin (1g/kg of body weight) if BUN>30mg/dl, creatinine >1mg/dl, bilirubin >4 mg/dl, and repeat at day 3 if renal dysfunction persists
  - Avoid aminoglycosides

- Specific management
  - Cefotaxine (2 g IV every 12h) or
  - Ceftriaxone (2g IV every 24h) or
  - Ampicillin/clavulaiate (2g/1g i.v every 6h)
- Follow up
  - Continue therapy for 7 days
  - Repeat diagnostic paracentesis at day 2
  - If ascites PMN count decreases by at least 25% at day 2, intravenous therapy can be switched to oral therapy (quinolone such as ciprofloxacin or levofloxacin 250 mg p.o b.i.d) to complete 7 days of therapy
- Recommended therapy
  - Oral norfloxacin 400 mg p.o q.d (preferred) or
  - Oral ciprofloxacin 250-500 mg q.d* or
  - Oral levofloxacin 250 mg q.d*
- Alternative therapy
  - TMP-SMX 1 double strength tablet p.o q.d
  - (Patients who develop quinolone resistant organisms may also have resistance to TMP-SMX)
- Duration
  - Prophylaxis should be continued until the disappearance of ascites or until liver transplantation

* Empirical doses

Abbreviations: BUN, blood urea nitrogen; PMN, Polymorphonuclear (neutrophil) cell count; PO, orally; QD, once daily; RBC, Red blood cell count; SBP, spontaneous bacterial peritonitis; TMP-SMX, trimethoprim sulfamethoxazole
Printed with permission: Garcia-Tsao G, et al. Management and treatment of patients with cirrhosis and portal hypertension. *The American Journal of Gastroenterology:* page 1811.; and adapted from: Rimola A, et al. *J Hepatol* 2000;32(1):142-53.

144. Give a management strategy for refractory ascites.

- Definitions
  - Ascites that is not eliminated even with maximum and optimal diuretic therapy, or
  - Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic induced complications (renal failure)
- Recommended therapy
  - Total paracentesis +I.V. albumin (6-8 g of albumin per liter of ascites removed)

	○ If <5 L of ascites is removed, a synthetic plasma volume expander may be used instead of albumin ○ Continue with salt restriction and diuretic therapy, as tolerated
➢ Alternative therapy	○ TIPS for patients who require frequent paracenteses (every 1-2 weeks) and whose CHLD score is <11 ○ Peritoneovenous shunt for patients who are not TIPS or transplant candidates ○ Consider liver transplantation

Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt

Printed with permission: Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104:1816.

Useful background: Ascites and spontaneous bacterial peritonitis (SBP)

- Large volume paracentesis (> 5 L) is safe as long as 6-8 g albumin are given per liter fluid removed
- Lasix blocks active CL^- reabsorption from the loop of Henle, aldactone blocks active Na^+ reabsorption in the distal renal tubule
- Too aggressive diuretic therapy may be complicated by renal failure, hepatic encephalopathy, and electrolyte disturbances ($\uparrow Na^+$, $\uparrow$ or $\downarrow K^+$)
- Transjugular intrahepatic portosystemic shunt (TIPS) decreases sinusoidal portal pressure, and decreases Na^+ reabsorption in the proximal renal tubules, producing a diereses
- TIPS will modulize ascites in 70% of persons with diuretic-resistant ascites, but there is a 50% risk of the TIPS precipitating hepatic encephalopathy, and the shunt may become stenotic, requiring angiography and dilation of the shunt
- TIPS should not be performed for ascites mobilization in the patient who already has hepatic encephalopathy, whose MELD score is greater than 20 points
- SBP is present in at least 20% of cirrhotics at the time they are admitted to the hospital
- SBP worsens vasodilation, and thereby contributes to early variceal rebleeding and to the development of renal failure
- Persons at risk of developing SBP include those with a previous episode of SBP, SBP occurring with variceal hemorrhage, or low protein ascites

- Once SBP has occurred, the one year mortality rate is 50-70%

There are 4 types of SBP:

	>250 neutrophils	Ascitic culture
➢ Classical SBP	+	+
➢ Neutrocytic culture-negative ascites	+	-
➢ Nonneutrocytic monomicrobial	-	+
➢ Nonneutrocytic* polymicrobial	-	+

*Usually from needle perforation of the gut, is associated with severe symptoms and signs, low ascetic glucose (< 50 mg/dl), high LDH, and polymicrobial anaerobic infection

Abbreviations: SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt

145. Give the definition and diagnostic criteria for diuretic-resistant, and diuretic-intractable refractory ascites in patients with cirrhosis.

- Diuretic resistant ascites
  - Ascites that is difficult to mobilize, as defined by a failure to lose at least 1.5 kg/week of fluid weight, despite maximal diuretic therapy with spironolactone (400 mg/day) and furosemide (160 mg/day) or an equivalent dose of a distal-acting and loop-acting diuretic respectively.

- Diuretic intractable ascites
  - Ascites that is difficult to mobilize, as defined above, due to the inability to effectively dose diuretics because of diuretic-induced adverse effects e.g. azotemia, hyponatremia, etc.

- Requisites
  - Treatment duration: patients must be on intensive diuretic therapy (spironolactone 400 mg/day and Furosemide 160 mg/day) for at least 1 week and on a salt-restricted diet of less than 80 mmol/day
  - Lack of response: mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake
  - Early ascites recurrence: reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization
  - Diuretic-induced complications:
    - Diuretic-induced hepatic encephalopathy is the development of

encephalopathy in the absence of any precipitating factor
- Diuretic-induced renal impairment is an increase of serum Creatinine by >100% to a value >2 mg/dL in patients with ascites responding to treatment
- Diuretic-induced hypo- or hyperkalaemia is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures

Adapted from: Cárdenas A, and Arroyo V. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 66.

146. Give the diagnostic criteria for hepatorenal syndrome.

- Cirrhosis with ascites
- Serum creatinine level > 1.5 mg/dL (133 umol/L)
- No or insufficient improvement in serum creatinine level (remains > 1.5 mg/dL)
- 48 hr after diuretic withdrawal and adequate volume expansion with intravenous albumin
- Absence of shock
- No evidence of recent use of nephrotoxic agents
- Absence of intrinsic renal disease

Source: *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management 2010;* Table 92.3: pg 1547.

147. Give the major and minor criteria for the diagnosis of the hepatorenal syndrome, and distinguish this from acute tubular necrosis (ATN).

- Major criteria
  - Presence of cirrhosis
    - Renal failure (creatinine >1.5mg/dl); if no previous renal impairment, or a serum a ↑ by 50% over baseline
  - Lack of improvement in serum creatinine after ≥48 hrs of diuretic withdrawal and volume expansion with 1.5 L of normal saline
  - Absence of: shock, use of nephrotoxic drugs (eg: aminoglycosides), parenchymal renal diseasea (urine protein > 500 mg/day, granular or red cell casts, hematuria, urinary obstruction by sonography)

- Minor criteria (suggests HRS, or prerenal failure)

Parameter	Osmolarity mOsm/Kg	Urine (Na) mmol/l	Sediment	Protein mg/day
• Prerenal				
○ Hypovolemia	>500	<20	Normal	<500
○ Hepatorenal	>500	<10	Normal	<500
• Renal				
○ Acute tubular	<350	>40	Granular casts	500-1500
○ Interstitial	<350	>40	WBC eosinophils	500-1500

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1979.

148. Give the management strategy of hepatorenal syndrome (HRS).

- Diagnosis
  - Consider HRS in a patient with cirrhosis and ascites, as well as a serum creatinine level of >1.5 mg/dl
  - HRS is a diagnosis of exclusion. Before making the diagnosisof HRS, rule out and treat:
    - Sepsis
    - Volume depletion (hemorrhage, diarrhea, overdiuresis)
    - Vasodilators, NSAIDs
    - Organic renal failure (urine sediment, kidney ultrasound)

- Diuretics should be discontinued and intravascular volume expanded with i.v albumin
- If renal dysfunction persists despite above, diagnose HRS

- Recommended therapy
  - Liver transplant (priority dependent on MELD score)
  - If patient is on transplant list, MELD score should be updated daily and communicated to transplant center, if patient is not on transplant list, then should be prepared urgently

➢ Alternative (bridging therapy)	○ Vasoconstrictors <u>Plus</u> ○ Intravenous albumin (both for at least 7 days)	○ Octreotide ○ plus Midodrine or Terlipressin	○ 100-200 mcg s.c t.i.d ○ 5-15 mg p.o t.i.d ○ 0.5 – 2.0 mg i.v every 4-6 h ○ 50-100 g i.v q.d

Abbreviations: HRS, Hepatorenal syndrome; PO, Orally; QD, once daily; SC, subcutaneously; TID, thrice a day.

Printed with permission: Garcia-Tsao, et al. *The American Journal of Gastroenterology* 2009;104: 818.

Useful background: Hepatorenal syndrome (HRS)

- Definition: functional renal failure in the person with cirrhosis and ascites

- Type I, rapidly progressive; type II, slowly progressive

- SBP may precipitate type I HRS, and this risk can be reduced by using albumin with the initial antibiotic therapy for SBP

- Pentoxyfilline may reduce the risk of developing HRS in persons with alcoholic hepatitis

- Hypnotremin may preceed the development of HRS

- Most cirrhotics with renal dysfunction have hypodemia or acute tubular necrosis (ATN); only 15-20% have HRS

- Exclude hyporolemia from exces use of diuretics, diarrhea from the use of lactulose, and sepsis

- Type I HRS is associated with intense vasoconstriction, which may cause the HRS to preogress to ATN

- 35-50% of type I HRS responds to vasoconstrictors (midodrine, terlipressin, norepinephrine)

- Liver transplantation is the definitive treatment for type I HRS

- Renal dialysis for type I HRS may be a necessary bridge to liver transplantation

- The risk factors for developing HCC in HCV are:
  - Concurrent
    - Alcoholism
    - Hemochromatosis
    - HBV infection
    - Failure of HCV to respond to IFN
    - Males
    - Disease duration > 25 years

Abbreviation: ATN, acute tubular necrosis; HRS, hepatorenal syndrome

149. Give 8 complications of the TIPS (transjugular intrahepatic portosystemic shunt) procedure.

- Technical complications
  - Neck puncture
  - Access to hepatic vein
  - Creation of parenchymal tract to portal vein
  - May make liver transplantation technically more difficult

- Deployment of stent across parenchymal tract
- Stent-related complications – thrombosis, stenosis
- Unique complications of TIPS – hemolytic anemia, infectious endotipsitis
- Hepatic encephalopathy (HE) (new, or worse, or chronic)
- Pulmonary hypertension and right heart failure
- Intraperitoneal bleeding
- Hepatic infarction
- Hepatic rupture

- Sepsis
- Multiple organ failure syndrome
- Stent migration into portal vein or inferior vena cava (IVC)
- Fulminant hepatic failure (acute hepatic failure [AHF])
- Puncture of pulmonary artery (PA), pulmonary vein (PV), liver capsule
- Longterm presence of forein body
- Ischemia (hepatic artery thrombosis)

Adapted from: Sanyal AJ. *2006 AGA Institute Postgraduate Course:* pg. 195.

150. Give 5 types of ascitic fluid infection in SBP.

Types	Neutrophils	Cultures
○ Spontaneous bacterial peritonitis (SBP)	>250	+
○ Monomicrobial non-neutrocytic ascites	N	+
○ Culture-negative neutrocyte ascites	>250	(monomicrobial)
○ Secondary bacterial peritonitis		
○ Polymicrobial bacterial ascites (needle perforation of the bowel)		0

- ○ Usually from needle perforation of the gut, is associated with severe symptoms and signs, low ascetic glucose (< 50 mg/dl), high LDH, and polymicrobial anaerobic infection

Source: Runyon, Bruce A. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1946.

151. Give 4 causes of malignancy-related ascites.
- Peritoneal carcinoma (1°, 2°)
- Massive liver metastases
- Peritoneal carcinomatosis with massive liver metastases
- Hepatocellular carcinoma
- Malignant lymph node obstruction
- Malignant Budd-Chiari syndrome (tumour emboli in hepatic veins)

Source: Runyon, Bruce A. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1946.

Useful background: Variants of spontaneous bacterial peritonitis

Condition	Ascitic Fluid Polymorpho-nuclear cells/mL	Ascitic Fluid Culture results	Management
➢ Spontaneous bacterial peritonitis	○ >250	○ Positive	○ Antibiotics
➢ Culture-negative neutrocytic ascites	○ >250	○ Negative	○ Antibiotics
➢ Bacterascites	○ <250	○ Positive	○ Treat if symptoms of infection are present; otherwise repeat paracentesis for cell count and cultures

Useful background: Use of the serum ascites albumin gradient (SAAG) and ascites protein to determine the cause of ascites

SAAG, g/dL	Ascites Protein <2.5 g/dL	Ascites Protein >2.5 g/dL
>1.1	Portal hypertension due to cirrhosis	Portal hypertension due to hepatic venous outflow obstruction (including right heart failure)
<1.1	Nephrotic syndrome	Malignancy, tuberculosis

Abbreviation: SAAG, serum ascites albumin gradient

Useful background: Differential diagnosis for hepatorenal syndrome

Variable	Prerenal azotemia	Hepatorenal syndrome	Acute renal failure
➢ Urinary sodium concentration, MEq/L	○ <10	○ <10	○ >30
➢ Urine to plasma creatinine ratio	○ >30:1	○ >30:1	○ <20:1
➢ Urine osmolality	○ At least 100m Osm >plasma osmolality	○ At least 100m Osm> plasma osmolality	○ Equal to plasma osmolality
➢ Urine sediment	○ Normal	○ Normal	○ Casts, debris

Abbreviation: Osmp, osmolality of plasma; Osmu, osmolality of urine

Useful background: Diagnosis and management strategy in spontaneous bacterial peritonitis (SBP)

- ➢ Diagnosis
  - ○ Consider SBP and perform diagnostic paracentesis if:
    - Symptoms/signs (abdominal pain, fever, chills)
    - Patient is in emergency room or admitted
    - Worsening renal function or encephalopathy
  - ○ SBP present if ascites PMN count >250 cells/ul (if fluid bloody, subtract 1PMN per 250 RBC/ul
- ➢ General management
  - ○ Avoid therapeutic paracenteses during active infection
  - ○ Intravenous albumin (1g/kg of body weight) if BUN>30mg/dl, creatinine >1mg/dl, bilirubin >4 mg/dl, repeat at day 3 if renal dysfunction persists
  - ○ Avoid aminoglycosides
- ➢ Specific management
  - ○ Cefotaxine (2 g i.v every 12h) or
  - ○ Ceftriaxone (2g every 24h) or
  - ○ Ampicillin/sulbactam (2g/1g i.v every 6h)
- ➢ Follow up
  - ○ Continue therapy for 7 days
  - ○ Repeat diagnostic paracentesis at day 2
  - ○ If ascites PMN count decreases by at least 25% at day 2, intravenous therapy can be switched to oral

	therapy (quinolone such as ciprofloxacin or levofloxacin 250mg p.o b.i.d) to complete 7 days of therapy

Abbreviations: b.i.d, twice a day; BUN, blood urea nitrogen; i.v intravenous; PMN, polymorphonuclear (neutrophil) cell count; p.o, orally; RBC, red blood cell count.

Printed with permission: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1806-1829, Table 4, page 1811.

Useful background: Management strategy in the prevention of recurrent SBP

➢ Recommended therapy	○ Oral norfloxacin 400mg p.o q.d (preferred) or ○ Oral ciprofloxacin 250-500 mg q.d* or ○ Oral levofloxacin 250 mg q.d*
➢ Alternative therapy	○ TMP-SMX 1 double strength tablet p.o q.d ○ Patients who develop quinolone resistant organisms may also have resistance to TMP-SMX
➢ Duration	○ Prophylaxis should be continued until the disappearance of ascites or until liver transplantation

Abbreviations: p.o: Orally; SBP: Spontaneous bacterial peritonitis; TMP-SMX: Trimethoprim sulfamethoxazole, q.d: Once daily
*Empirical doses

Source: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1806-1829.

Useful background: Management strategy for refractory ascites

➢ Definitions	○ Ascites that is not eliminated even with maximum diuretic therapy ○ Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic induced complications
➢ Recommended therapy	○ 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
- PVS for patients who are not TIPS or liver transplant candidates
- Liver transplantation

Abbreviations: CTP, Child Turcotte Pugh; I.V., intravenous; TIPS, transjugular intrahepatic portosystemic shunt; PVS, peritoneovenous shunt

Source: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829.

Useful background: Diagnosis and management strategy of hepatorenal syndrome (HRS)

➢ Diagnosis
- Consider HRS in a patient with cirrhosis and ascites and a creatinine level of >1.5 mg/dl
- Because HRS is a diagnosis of exclusion, before making the diagnosis, the following need to be ruled out and treated:
  - Sepsis (patient needs to be pancultured)
  - Volume depletion (hemorrhage, diarrhea, overdiuresis)
  - Vasodilators
  - Organic renal failure (urine sediment, kidney ultrasound)
- Diuretics should be discontinued and intravascular volume expanded with i.v albumin
- If renal dysfunction persists despite above, diagnose HRS

➢ Recom-mended therapy
- Liver transplant (priority dependent on MELD score)
- If patient is on transplant list, MELD score should be updated daily and communicated to transplant center, if patient is not on transplant list, packet should be prepared urgently

➢ Alternative (bridging therapy)	○ Vasoconstrictors plus albumin for ≥ 7 days	Octreotide PLUS Midodrine or Terlipressin[a]	100-200 mcg s.c t.i.d 5-15 mg p.o t.i.d	Goal : ↑ MAP by 15

		mm Hg
	0.5 – 2.0 mg i.v every 4-6 h	
	50-100 g i.v q.d	

Abbreviations: I.V., intravenous; HRS, hepatorenal syndrome; MAP,mean arterial pressure; MELD, model for end stage liver disease; t.i.d thrice a day; s.c subcutaneously

Adapted from: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829.

Esophageal varices

152. Give the factors in a person with liver disease and known esophageal varices which predict a high risk for the first variceal bleeding in the future.

- Clinical
  - Child's class/ MELD score > 15
  - Previous variceal bleed
  - Alcohol consumption
- Endoscopic
  - Large esophageal varices
  - Red colour sign
  - Presence of gastric or proximal esophageal varices
  - Presence of portal hypertensive gastropathy
- Hemodynamic
  - Intra-esophageal variceal pressure
  - ↑ HVPG > 12 mm Hg
- Blood tests
  - Platelets < 140-150 k
    - Ratios spleen diameter/platelets
    - Liver span/albumin
  - collateral flow on Doppler ultrasound
  - Flow reversal in PV
- Ultrasound
  - Congestion index of the portal vein
  - Portal vein size > 10-13 mm

Adapted from: Franchis de, R, and Dell'Era A. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 11.

153. Give the management strategy for esophageal varices after the initial screening endoscopy in patients with cirrhosis.

➢ No varices	○ Repeat endoscopy in 3 years (sooner if decompensation occurs)		
➢ Small varices	○ In a CTP B/C patient or varices with red signs	○ Non selective ß-blockers (propranolol or nadolol)	○ Start propranolol (20 mg b.i.d) or nadolol (20 mg q.d) ○ Titrate to maximal tolerable dose or a heart rate of 55-60 b.p.m ○ No need to repeat EGD
	○ In a CTP A patient, without red signs	○ Non selective ß-blockers optional ○ If no. ß-blockers are given, repeat endoscopy in 2 years (sooner if decompensation occurs)	○ Same as above
➢ Medium/ large varices	○ All patients independent of CTP class	○ Non selective ß-blockers (propranolol, nadolol), or ○ Endoscopic variceal ligation*	○ Same as above ○ Ligate every 1-2 weeks until variceal obliteration ○ First surveillance endoscopy 1-3 months after obliteration, then every 6-12 months indefinitely

*Choice depends on patient characteristics and preferences, local resources

Abbreviations: CTP, Child Turcotte Pugh ; EGD, esophagogastroduodenoscopy

Printed with permission: Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104: 1806.

154. Give the diagnosis and management strategy of patients with acute variceal hemorrhage.

- Diagnosis
  - Any of the following findings on upper endoscopy performed within 12h of admission:
  - Active bleeding from a varix or stigmata of variceal hemorrhage (white nipple sign) or
  - Presence of gastroesophageal varices without another source of hemorrhage
- General management
  - Cautious transfusion of fluids and blood products, aiming to maintain a hemoglobin of ~8g/dl
  - Antibiotic prophylaxis (3-7 days) with:
    - Ciprofloxacin 500 mg b.i.d (p.o) or 400 mg b.i.d (i.v), or

      Ceftriaxone 1g/day (i.v) particularly in facilities with known quinolone resistance and in patients with two or more of the following: malnutrition, ascites, encephalopathy, serum bilirubin >3 mg/dl
- Specific initial management
  - Pharmacological therapy initiated as soon as diagnosis is suspected; Octreotide 50 mcg i.v bolus, followed by continuous infusion 50 mcg/h (3-5 days), and endoscopic therapy (ligation preferable) performed at time of diagnostic endoscopy (performed within 12 h of admission)
- Rescue management
  - Considered in patients with bleeding esophageal varices who have failed pharmacological and endoscopic therapy or in patients with bleeding gastric fundal varices who have failed one endoscopic therapy: TIPS or Shunt therapy (CTP A patients where available)

Abbreviations: BID, twice a day; CTP, Child Turcotte Pugh; PO, orally.

Printed with permission: Garcia Tsao, et al. The *American Journal of Gastroenterology* 2009; 104:1808.

155. Give the first and second line management strategy in the prevention of recurrent variceal hemorrhage (secondary prophylaxis).

- First line therapy
  - Nonselective ßblockers (propranolol, nadolol)
    - Start propranolol (20 mg b.i.d) or nadolol (20 mg q.d)
    - Titrate to maximum tolerable dosage or a heart rate of 55-60 b.p.m
    - No need for repeat endoscopy

  or

  - Endoscopic variceal ligation
    - Ligate every 1-2 weeks until variceal obliteration is achieved
    - First surveillance endoscopy 1-3 months after variceal obliteration, then every 6-12 months
- Second line therapy
  - TIPS *or*
- (if combined pharmacologic + endoscopic treatment has failed)
  - Shunt surgery (CTP class A patients, where available)

Abbreviations: BID, twice daily; BPM, beats per minute; CTP, Child Turcotte Pugh; QD, once daily

Printed with permission: Garcia-Tsao G, et al. *The American Journal of Gastroenterology*: 1809.

Useful background: Esophageal varices

- In persons withhepatic cirrhosis, esophageal varices develop in 2.5% of persons per year
- About 30% of varices will bleed, with the risk increasing with longer varices, the presence of red unle?? marks on the varices, or in the person with more extensive liver dysfunction
- Variceal hemorrhage recurs at the rate of 70% per year
- The mortality rate for each episode of variceal bleeding is 30%
- Primary (before the first bleeding episode) or secondary (after the first esophageal variceal bleed) prophylaxis with either non-selective beta-blockers or EVBL (endoscopic variceal band ligation) is recommended in Class A cirrhotic patients with medium or large varices, or Child Class B and C patients with varices of any size
- If EVBL cannot control the bleeding, the patient may benefit from a distal splenorenal shunt procedure or TIPS
- Occult infection from spontaneous bacterial peritonitis (SBP) may increase the rate of early rebleeding
- Antibiotics are used on an empirical basis in cirrhotic patients with a variceal bleed or ascites

Abbreviations: EVBL, endoscopic variceal band ligation; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt

156. Give the King's College criteria for liver transplantation in fulminant liver failure*.

- Fulminant liver failure due to Wilson's disease or Budd-Chiari syndrome
- Acetaminophen-induced if either of the following are met:
  - pH<7.3 24 hours after overdose
  - Creatinine >3.4 mg/dL and prothrombin time>100 seconds and grade 3-4 encephalopathy
- Nonacetaminophen if either
  - INR>6.5 *or*
  - Any three of the following: INR>3.5, more than 7 days from jaundice to encephalopathy, indeterminate or drug-induced cause, age<10 years, age >40 years, bilirubin >17.5 mg/dL

INR, international normalized ratio
*Any of the three criteria

157. Compare the outcomes of endoscopic band ligation (endoscopic variceal ligation, EVL) versus beta-blockers for primary prophylaxis of esophageal variceal bleeding.

Ligation versus beta-blocker	RR
➢ Variceal bleeding	0.57
➢ Gastrointestinal bleeding (all types)	0.69
➢ Bleeding-related mortality	0.84
➢ Mortality (from all causes)	1.03
➢ Severe adverse event	0.34

Abbreviations: RR, relative risk

Source: Klebl, F.H., and Schölmerich, J. *Best Practice & Research Clinical Gastroenterology* 2008; 22(2): pg. 373-387.

Useful background: Endoscopic treatment of varices

- EVL is the endoscopic method of choice to treat esophageal varices.
- No beneficial effects have been observed combining endoscopic sclerotherapy (EST) and EVL.
- Proton pump inhibitors may enhance the safety of EVL

- Variceal bleeding is markedly reduced when the HVPG decreases to <12 mm Hg or by >20% from baseline

- EVL may reduce variceal size until variceal obliteration

- EVL has no effect on portal pressure

- Variceal oblitern with tissue adhesives (eg cyanoacrylates) is effective in the treatment of gastric varices

Abbreviations: EVL, endoscopic variceal ligation; EST, endoscopic sclerotherapy; HVPG, hepatic venous pressure gradient

Adapted from: Villanueva, Candid., et al. *Best Practice & Research Clinical Gastroenterology* 2008;22(2): pg. 263

Useful background: Persistent hepatic encephalopathy (HE)

- General management
  - Diet
    - No longterm protein restriction
    - Protein from dairy or vegetable sources is preferable to animal protein
  - Drugs
    - Avoid sedatives and tranquillizers
  - Bowel habit
    - Avoid constipation
- Specific therapy
  - Lactulose dosage that produces 2-3 soft, formed bowel movements per day, starting at 15-30 ml p.o b.i.d
- Antibiotics
  - Rifaximin 400 mg p.o t.i.d in patients who cannot tolerate lactulose
  - Consider metronidazole if rifaximin not available
  - Avoid neomycin for concern for nephrotoxicity and ototoxicity

Abbreviations: BID, twice a day; HE, hepatic encephalopathy; PO, orally; TID, thrice daily

Adapted from: Garcia Tsao, et al. The *American Journal of Gastroenterology* 2009; 104:1821.

Useful background: Management strategy after results of screening endoscopy for esophageal varices in patients with cirrhosis

Varices	Patient	
➢ None	○ Repeat endoscopy (EGD) in 3 years (sooner if decompensation occurs)	
	Drugs and repeated EGD	
➢ Small varices	○ In a CTP B/C patient, or varices with red signs	- Non selective ß-blockers (propranolol or nadolol)
	○ In a CTP A patient, without red signs	- Non selective ß-blockers optional - If no. ß-blockers are given,

		repeat endoscopy in 2 years (sooner if decompensation occurs)
➢ Medium/large	○ All patients independent of CTP class	- Non selective ß-blockers (propranolol, nadolol) - Or*, Endoscopic variceal ligation

Abbreviations: CTP, Child Turcotte Pugh; EGD, esophago-gastroduodenoscopy

Adapted from: Garcia Tsao et al. *Am J Gastroentero* 2009; 104:1806-1829.

Useful background: Diagnosis and management strategy of patient with acute variceal hemorrhage

➢ Diagnosis
- ○ Any of the following findings on upper endoscopy performed within 12h of admission:
  - Active bleeding from a varix or stigmata of variceal hemorrhage (white nipple sign), or
  - Presence of gastroesophageal varices without another source of hemorrhage

➢ Management
- ○ Cautious transfusion of fluids and blood products, aiming to maintain a hemoglobin of ~ 8 g/dl
- ○ Antibiotic prophylaxis (3-7 days) with:
  - Ciprofloxacin 500mg b.i.d (p.o) or 400 mg b.i.d (i.v) or
  - Ceftriaxone 1 g/day (i.v) particularly in facilities with known quinolone resistance and in patients with two or more of the following: malnutrition, ascites, encephalopathy, serum billirubin > 3mg/dl
  - Octreotide 50mcg i.v bolus, followed by continuous infusion 50 mcg/h (3-5 days) and
  - Endoscopic therapy (ligation preferable) performed at time of diagnostic endoscopy (performed within 12h of admission)

➢ Rescue management
- ○ Failed pharmacological and endoscopic therapy, or
- ○ Patients with bleeding gastric fundal varices who have failed one endoscopic therapy:
  - TIPS or
  - Shunt therapy (CTP A patients where available)

Abbreviations: b.i.d twice a day; CTP, Child Turcotte Pugh; i.v, intravenous; p.o,orally; TIPS, transjugular intrahepatic portosystemic shunt.

Adapted from: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829

Useful background: Management strategy in the prevention of recurrent variceal hemorrhage (secondary prophylaxis)

➢ First line therapy	○ Nonselective B blockers (propranolol, nadolol)	- Start propranolol (20mg b.i.d) or nadolol (20 mg q.d) - Titrate to maximum tolerable dosage or a heart rate of 55-60 b.p.m - No need for repeat endoscopy
	○ Endoscopic variceal ligation	- Ligate every 1-2 weeks until variceal obliteration - First surveillance endoscopy 1-3 months after obliteration then every 6-12 months
➢ Second line therapy (if combined pharmacologic and endoscopic treatment has failed)	○ TIPS or ○ Shunt surgery (CTP class A patients, where available)	

Abbreviations: b.i.d twice a day; BPM, beats per minute; CTP, Child Turcotte Pugh; TIPS, transjugular intrahepatic portosystemic shunt; q.d, once daily

Printed with permission: Macmillan Publishers Ltd: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829, Table 3, page 1809.

HE; Hepatic encephalopathy (aka PSE, portosystemic encephalopathy)

158. The finding of an elevated serum ammonia concentration is not specific for the diagnosis of hepatic encephalopathy.Give 15 causes of hyperammonemia

- Liver/GI tract
  - Acute liver failure
  - Cirrhosis
  - Gastrointestinal bleeding

- Renal
  - Chronic kidney disease

- Inborn errors of metabolism
  - Proline metabolism disorders
  - Urea cycle disorders (e.g carbamyl phosphate synthetase I deficiency, ornithine transcarbamylase deficiency, argininosuccinate lyase deficiency, *N*-acetyl glutamate syntehtase deficiency)

- Medications
  - Alcohol
  - Diuretics (e.g. acetazolamide)
  - Narcotics
  - Valproic acid

- Muscle exertion and ischemia

- Blood sampling
  - Tourniquet use
  - High body temperature
  - High protein diet

- Diet

- Cigarette smoking

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, Table 92-1, page

159. Outline the contribution of the small and large intestine, liver, skeletal muscle, kidney and brain in patients with liver failure and HE.

- Small bowel and large intestine
  - Dietary amino acids and urease-positive bacteria → glutamine
  - Uptake of glutamine

	glutaminase (deamination)	
glutamine	→	glutamate +
	←	glutamine synthetase NH_3

  - Activity of gut glutaminase increased in liver disease

- Gut
  - Increased production of ammonia by urease-producing bacteria in GI tract
  - Increased production of ammonia and glutamate from increased action of intestinal glutaminase

- Liver
  - Portosystemic shunting, by-passing portovenous system with less hepatic detoxification of ammonia via the urea cycle
  - NH_3 → urea, periportal hepatocytes → glutamine, perivenous hepatocytes
  - In presence of hyponatremia, myoinositol falls, with less compensation for ↑ intracellular glutamine

- Skeletal muscle
  - Atrophy of skeletal muscles, with reduced muscle synthesis of glutamine, large nuclei and nucleoli, margination of chromatin→ Alzheimer type II astrocytes
  - uptake of 50% of NH_3

	glutamine↓	
NH_3	→	
	glutamine synthetase↓	

- Kidney
  - increased NH_3 production in presence of hypokalemia

- Brain
  - Ammonia and glutamate normally converted to and detoxified to glutamine by glutamine synthetase in astrocytes
  - In cirrhosis, increased brain blood flow and increased blood brain barrier permeability: ↑ brain ammonia system

- Abnormal form and function of astrocytes, with reduced glutamine synthetase and peripheral type benzodiazepine receptors (PTBR)
- Increased brain glutamine increases mitochondrial permeability, which leads to brain edema
- Glutamate normally taken up by synaptic excitatory amino acid transporters; reduced glutamate uptake leads to the accumulation of extracellular brain levels of glutamate, with impairment of the glutamatergic neurotransmitter system
- Hyperammonemia activates N-methyl-D-aspartate-nitric oxide-C-granylate cyclase (NMDA-NO-C6MP) signal transduction pathway, impairing memory, learning and sleep
- ↑NH_3 ↑glutamate cross BBB, and causes asteocyte swelling and cerebral edema
- in presence of hypokalemia and metabolic alkalosis, $NH_4 \rightarrow NH_3$, which crosses BBB
- plasma NH_3 > 150 µmol is associated with brain herniation
- CNS neurotransmitter disorder

Neurotransmitter system	HE
○ Glutamate (neuro-excitation)	▪ ↓ glutamatergic function ▪ ↓ receptors
○ GABA/BZ (Neuro-inhibition)	▪ ↑endogenous BZs
○ Dopamine/Noradrenaline (motor/cognitive)	▪ ↓false neurotransmitters
○ Serotonin (Arousal)	▪ ↑ serotonin turnover, synaptic defect

Abbreviations: BZ, benzodiazepine; GABA-γ-aminobutyric acid

160. Give a grading of the mental state of persons with HE.

Grade	Criteria
➢ 0 (MHE, sub clinical HE)	Impaired mental tasks (psychometric testing speed of visual perception, and attention)
➢ I	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition; sleep-wake disorder; tremor
➢ II	Lethargy or apathy; minimal disorientation of time or place; subtle personality changes; inappropriate behavior; impaired performance of subtraction
➢ III	Somnolence to semi-stupor, but responsive to verbal

stimuli; confusion, gross disorientation

- IV Coma (unresponsiveness to verbal or noxious stimuli)

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1966.; and 2010, pg. 1545.

161.

a) Give the clinical neurological deficits in MHE.

- Affective/ emotional
- Behavioural
- Cognitive/ memory/ attention
- Language and verbal skills are relatively spared

b) Give 4 important areas of assessment of the patient with possible MHE.

- Exclude other causes of metabolic encephalopathy
- Exclude possible precipitating factors of HE
- Altered neuropsychiatric testing
- Number conection tests (Trailmaking)
- Visuomotor skills
- Mental tracking and concentration
- Digit symbol test
- Block design test
- Standardised test battery, the psychometric HE score (PHES)
- Digit span test (Weschler adult intelligence scale – passive auditory, working attention)
- Critical flicker frequency (correlates with PHES [Psychometric hepatic encephalopathy score])
- Quality of life measures: SE-36, chronic liver disease questionnaire (CLDQ)

c) List 4 reasons to treat MHE.

- Improved cognitive function
- Quality of life
- Driving performance
- Performance in workplace
- Sleep

- Survival
- Prevent development of overt clinically evident HE

Adapted from: Ortiz M, et al. *J Hepatol* 2005;42 Suppl(1):S45-53. Epub 2004 Dec 28.

162. Give the treatment of episodic and persistent HE, and provide the rationale for each treatment.

- Treat precipitants
  - Increased ammonia production - excessive protein intake, constipation, GI bleed (20%), azotemia (30%), hypokalemia
  - Increased protein catabolism - surgery, diuretics, arterial hypotension/hypovolemia,
  - Malnutrition - skeletal muscle wasting, less muscle metabolism of NH_3
  - Increased diffusion across BBB – alkalosis
  - Synergistic effects of cytokines – infection (SBP) (10%)
  - Altered brain function – sedative drugs, psychotropics, analgesics, benzodiazepines; hyponatremia; astrocyte swelling
  - Dehydration – fluid restriction, diuretics, excessive paracentesis, vomiting, diarrhea (mechanism unknown)
  - Hypoxia, anemia, fever, sepsis
  - Metabolic-:K+↓ (50%), ↑BS, alkalosis; ↓hypoxemia, thyroid, dehydration
  - Drugs (30%) - benzodiazapines, analgesics, interferon, alcohol, NSAIDs, acetaminophen
  - Surgery shunting, anesthetic, TIPS
  - Liver decompensation, HCC, PVT
  - Surgery

- Lactulose (beta-galactosidofructose), lacitol beta-galactosidosorbitol (traps NH_3) - enter colon, broken down by colonic bacteria to lactic acid, acetic acid acidification of stool pH < 5

$$NH_3 \xrightarrow{pH < 5} NH_4^+ \text{ (non-absorbable)}$$

  - Hyperosmolar purgation, ↑ stool volume, loss of nitrogen compounds

- Neurotransmitters: flumazenil (a competitive GABA-benzodinzepine receptor antagonist) or bromocriptine

- Branched chain amino acids

- Measure and manage cerebral blood flow (CSF)
  - Intracranial pressure (ICP) monitoring, transcranial Doppler, jugular venous oximetry
  - Manage lactic acidosis and sepsis
  - 45˚ elevation of head of bed
  - Moderate hypothermia to reduce ICP and CBF, reduce arterial NH_3 and reduce cerebral NH_3 uptake

- Manage circulatory effects
  - Fluid management, consider CVP monitoring
  - Perform short synacthen test, and give GCS if adrenal insufficiency is present
  - Inotropes: terlipressin (a vasopressin analog) or norepinephrine
  - Albumin

- 'Biotics (pre-, pro- and synbiotics)
  - ↑ bacterial NH_3 utilization
  - ↓ pro-inflammatory response
  - ↓ gut permeability
  - ↓ bacterial translocation

- Extracorporeal liver assist devices (ELADs)
  - MARS (molecular absorbent recirculating system): providing counter-current hemodiolysis against albumin and biocarbonate circuits
  - SPAD (single-pass albumin dialysis): counter-current albumin dialysis against high blood flow in a fibre hemodinfilter, and continous veno-venous hemofiltration
  - Prometheus R system, direct albumin adsorption through a specific polysulfur filter
  - Enteral feeding/TPN

- Orthoptic liver transplantation
  - ↑ lactobacillus spp., ↓ urease-containing bacteria, ↓ NH_3 production by replacing urease-positive bacteria
  - ↓ production of potentially toxic SCFA (proprionate, butyrate, violerate)
  - Removes shunted (non-detoxified blood)

- Driving license – psychometric testing

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1971-1972.

163. Give the management of an episodic and persistent HE.

a) Episodic

- General Management
  - Identify and treat precipitating factor (GI hemorrhage, infection, pre-renal azotemia, constipation, sedatives)
  - Short term (<72h) protein restriction may be considered in severe HE
- Specific therapy
  - Lactulose enemas (300 ml in 1L of water) in patients who are unable to take it p.o; or Lactulose ml p.o every 1-2 h until bowel evacuation, then adjust to a dosage that will result in 2-3 formed bowel movements per day (usually 15-30 ml p.o b.i.d). Lactulose can be discontinued once the precipitating factor has resolved

Printed with permission: Garcia Tsao, et al. *The American Journal of Gastroenterology* 2009; 104: 20.

164. Give 5 management options for MHE.

- Reverse any precipitants
- Cathartics: Lactulose
- Antibiotics: Flagyl, vanesmycin, ampicillin, rifimaxin
- Probiotics
- High calorie, high protein diet

Adapted from: Holstege A, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 541.

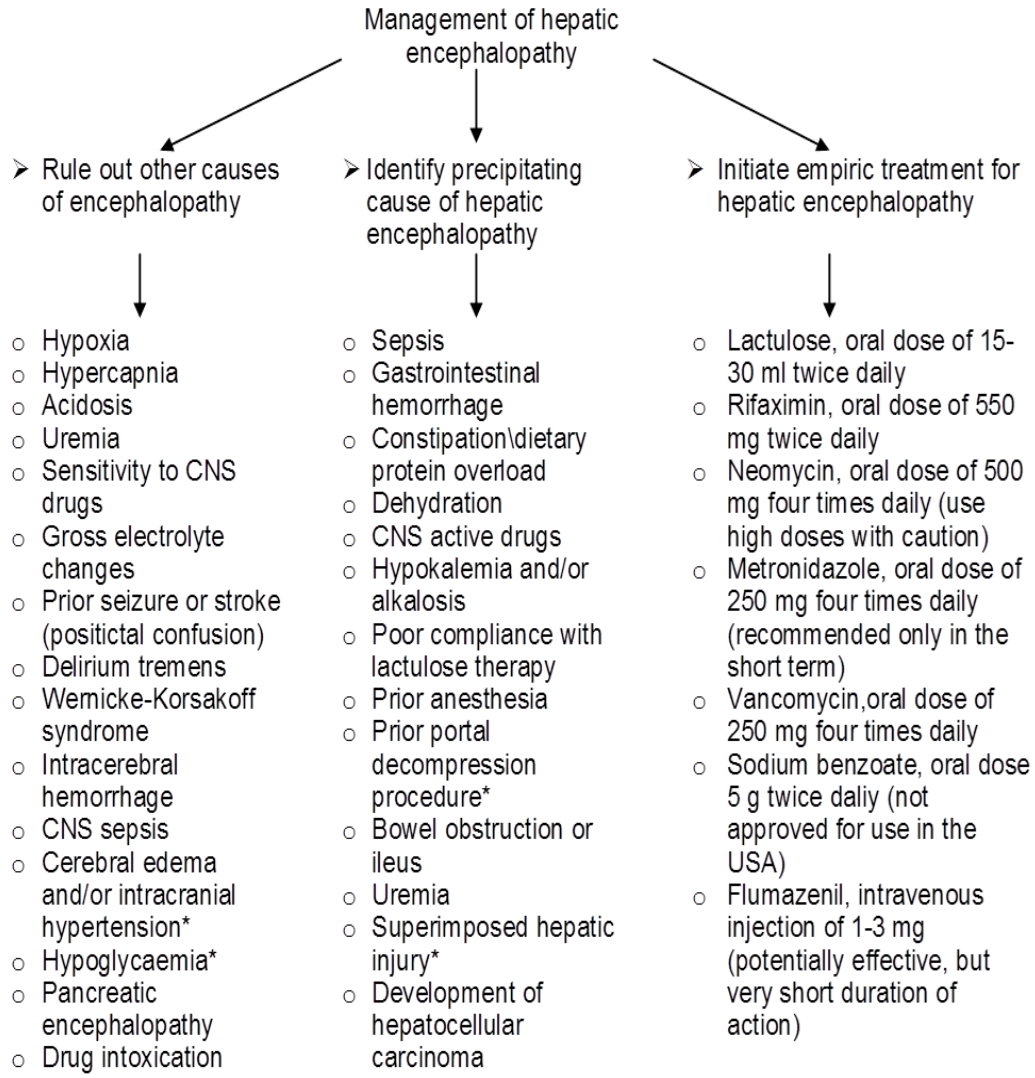
"Rewarding anticipation activates a reward network: that is the success of the not-so-common random acts of kindness."

Useful background: Grading system for portal systemic encephalopathy

Grade of encephalopathy	Level of consciousness
0	Normal
1	Trivial lack of awareness
	Personality change
	Day-night reversal
2	Lethargic
	Inappropriate behaviour
3	Asleep but arousable
	Confused when awake
4	Unarousable

165. Give the survival rate and etiological factors for the 3 types of hepatic encephalopathy (HE) (acute liver failure, cirrhosis with precipitant, and chronic HE).

Type of HE	Approximate Survival	Etiolgogical factors
➢ Acute liver failure	~ 20%	○ Viral hepatitis ○ Alcoholic hepatitis ○ Drug reactions and overdose
➢ Cirrhosis w/precipitant	~ 80%	○ Drugs/ Toxins - Diuretics - Alcoholic excess - Sedatives ○ Infection - Any type, including SBP ○ Volume loss - Hemorrhage - Paracentesis - Diarrhea/vomiting ○ Surgery ○ Constipation
➢ Chronic HE	~100%	○ Portal-systemic shunting ○ ↑ Dietary protein intake ○ Intestinal bacteria



*predominantly observed in patients with acute liver failure.

Useful background: Management of hepatic encephalopathy (HE)

- Precipitation
  - Treat precipitating factors (GI hemorrhage, infection, pre-renal azotemia, constipation, sedatives)
  - Short term (<72h) protein restriction may be considered in severe HE

- No long term protein restriction

- Specific therapy
  - Lactulose enemas (300 cm^3 in 1L of water) in patients who are unable to take it p.o Or
  - Lactulose 30cm^3 p.o every 1-2 h until bowel evacuation, then adjust to a dosage that will result in 2-3 formed bowel movements per day (usually 15-30 cm^3 p.o b.i.d)
  - Lactulose can be discontinued once the precipitating factor has resolved

Abbreviations: b.i.d, twice a day; GI, gastrointestinal; p.o, orally

Source: Garcia Tsao et al. *The American Journal of Gastroenterology* 2009; 104:1802-1829.

- ICP monitoring for HE used in ½ of centres (to monitor intracranial pressure)

Liver transplantation

166. Outline the indications for liver transplantation.

- Acute liver failure (ALF; fulminant hepatic failure; King's College criteria)
- Complications of cirrhosis
  - Ascites
  - Encephalopathy
  - Synthetic dysfunction
  - Liver cancer
  - Refractory variceal hemorrhage
  - Chronic gastrointestinal blood loss due to portal hypertensive gastropathy
  - INR
  - Na
  - HCC
  - OILI
  - Cr
  - MELD >13
  - PSE
  - Ascites
  - Hepatorenal syndrome
  - Vascular
  - Weber Rendir (intractable bleed)
  - GAVE; Budd-Chiari

- Systemic complications of chronic liver disease
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension

- Liver-based metabolic conditions causing systemic disease, and which may also cause liver disease
  - Primary oxaluria
  - Familial Amyloidosis
  - α_1-antitrypsin deficiency
  - Wilson's disease
  - Urea cycle enzyme deficiencies
  - Glycogen storage disease
  - Tyrosemia

Adapted from: Lilly LB, Girgrah N, and Levy GA. *First Principles of Gastroenterology* 2005: pg. 634.

167. Give the 6 most common primary liver diseases in North America representing indications for liver transplantation.

- Chronic HCV
- Alcoholic liver disease (ALD)
- Cryptogenic cirrhosis (NASH)
- PSC
- PBC
- Chronic HBV
- ALD + HCV
- Hepatoma
- AIH
- α, AT deficiency
- Drug induced liver disease
- Hemochromatosis, Budd-Chiari syndrome, Wilson's disease

Adapted from: Martin P, and Rosen HR. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 2037; and 2010, pg. 1594.

168. Outline the protocol for evaluation of potential living-related liver donors.

Stage 1
- Complete history and physical examination
- Laboratory blood tests: liver biochemical test, blood chemistry, hematology, coagulation profile, urinalysis,

alpha-fetoprotein, carcinoembryonic antigen, and serologic tests for hepatitis A, B, and C, cytomegalorvirus, Epstein-Barr virus, and human immunodeficiency virus
- Imaging studies: abdominal ultrasound examination, chest x-ray

Stage 2
- Complete psychiatric and social evaluation
- Imaging studies: computed tomography scan of the abdomen
- Other studies: pulmonary function tests, echocardiography

Stage 3
- Histology: liver biopsy
- Imaging studies: celiac and superior mesenteric angiography with portal phase

Stage 4
- Imaging studies: magnetic resonance cholangiogram
  Informed consent

Printed with permission: Ghobrial RM, et al. *Clin Liver Dis* 2000; 4: pg. 553.

169. Give 15 possible contraindications to liver transplantation.

- Patient
  - Ongoing alcohol or drug abuse
  - Non-adherence
  - Lack of social support
  - Serious underlying symptomatic illness
  - Advanced cardio-pulmonary disease
  - Sepsis
  - Marked psychiatric impairment
  - HIV/ AIDS
  - Diabetes mellitus
  - Advanced age
  - Obesity
  - Multi-organ failure
  - Increased intracranial pressure
  - Jehovah Witness
  - Non-adherence

- Anatomy
  - Metastatic cancer
  - Anatomical abnormalities
  - PV thrombosis (large size)
  - Outside Milan criteria for HCC (1 lesion <5 cm, 3 lesions <3 cm)
  - Cholangiocarcinoma

- Liver
  - Mild liver disease (Child <7, or MELD <9)

- Co-morbidity
  - Pulmonary hypertension
  - Right heart dysfunction
  - Extrahepatic cancer

Adapted from: Hay J. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 433.

170. Give 20 early and/or late complications arising after liver transplantation.

- Surgery-related
  - Non-specific
  - Cannot get off of ventilator
  - Dehiscence
  - Ileus
  - DVT
  - Atelectasis

- Metabolic
  - Hypertension
  - Hypercholesterolemia
  - Diabetes mellitus
  - Obesity

- Abdominal bleeding
  - Anastomoses (immediate)
  - Site of implantation (immediate)

- Vascular complications
  - Suprahepatic/infrahepatic vena caval obstruction (immediate)
  - Hepatic artery thrombosis (early)
  - Portal vein thrombosis (early)
  - Hepatic artery stenosis (late)

- Biliary complications
  - T-tube insertion (early)
  - Anastomosis (early)
  - Stenosis of papilla vateri (early)
  - T-tube removal (late)

- Anastomosis, extrahepatic (late)
- Multiple strictures, intra-hepatic, abscesses

- Renal failure (adverse effects of treatment)

- Vascular
  - Coronary artery disease (dyslipoproteinemia)
  - Cerebrovascular
  - Peripheral vascular

- CNS/PNS
  - Depression
  - Neuropathy
  - Seizures

- Malignancy
  - Lymphoma
  - EBV-PTLD (Ebstein-Barr virus – post transplant lymphoproliferative disorder)
  - Pre-existing malignancies (within 5 years)
  - Acquired donor malignancy
  - Skin cancers (non melanoma)
  - Cervical cancer (HPV), as per usual standard of care
  - Prostate cancer, as per usual standard of care
  - Pharyngeal cancer
  - Lung cancer
  - Increased risk of all malignancies

- Infections
  - Viral (HSV, CMV, EBV)
  - Bacterial (lines, wound)
  - Fungal (PCP, Candida - catheters)

- Drug reactions
- 1° graft failure
- Rejection
- Recurrence of disease
- Death

Adapted from: Mueller AR, Platz KP, and Kremer B. *Best Practice & Research Clinical Gastroenterology* 2004;18(5): pg. 882.

171. Give 7 examples of liver disorders which can recur in the liver following liver transplant (recurrence rates in brackets).

- HBV (100%)
- HCV (more virulent; cholestatic type often fatal)
- NASH
- PBC, AIH, PSC (20%)
- Hemochromatosis (late)
- Alcoholic liver disease (~50%)
- 2° amyloid
- HCC

Adapted from: Lilly LB, Girgrah N, and Levy G.A. *First Principles of Gastroenterology* 2005: pg. 642.

Useful background: The UNOS listing criteria for status 1, 2A, 2B and 3 for liver transplantation.

- Status 1
  - Fulminant hepatic failure. Onset within 8 weeks of initial symptoms and one of the following:
    - Stage 2 encephalopathy
    - Bilirubin > 15 mg/dl
    - INR > 2.5
    - Hypoglycemia (glucose level < 50 mg/dl)
  - Primary non-function of graft transplanted within 7 days
  - Hepatic artery thrombosis occurring within 7 days of transplantation
  - Acute decompensated Wilson's disease

- Status 2A
  - Patient with chronic liver failure and a Child-Pugh score $\geq$10, in the critical care unit, with a life expectancy without a liver transplant of less than 7 days, with at least one of the following criteria:
    - Unresponsiveness active variceal hemorrhage with failure or contraindication of surgical or transjugular intra-hepatic shunt
    - Hepatorenal syndrome
    - Refractory ascites/hepatorenal syndrome (hydrothorax)
    - Stage 3-4 encephalopathy unresponsive to therapy
  - Contraindications to status 2A listing:
    - Extrahepatic sepsis unresponsive to antimicrobial therapy
    - Requirement for high dose or two or more pressor agents to maintain an adequate blood pressure

- Severe, irreversible multi-organ failure

- Status 2B
  - Patients with chronic liver disease and a Child-Pugh score ≥10, or ≥7 and one or more of the following clinical considerations:
    - Unresponsive variceal hemorrhage
    - Hepatorenal syndrome
    - Spontaneous bacterial peritonitis
    - Refractory ascites/hepatorenal syndrome (hydrothorax)
  - Liver transplant candidates with hepatocellular carcinoma can be registered as status 2B if they meet the folowing criteria:
    - Thorough assessment has excluded metastatic disease
    - Recipient has one nodule ≤5 cm or three or fewer nodules all ≤3cm
    - Patient is not a resection candidate

- Status 3
  - Patients with chronic liver disease and a Child-Pugh score ≥7

Adapted from: United Network Organ Sharing. *UNOS policy 3.6* June 23, 2009.

Useful background: Definitions of hyperacute, acute and chronic liver allograft rejection

- Hyperacute rejection
  - Hyperacute rejection (also known as massive hemorrhagic necrosis) seldom occurs, but when it does it results in rapid graft destruction with coagulative parenchymal necrosis owing to widespread endothelial dysfunction. Endothelial cells are primarily targeted by a pre-existing anti-donor humoral immune response that leads to the deposition of antibodies, platelets, fibrin and erythrocytes within the portal venules and hepatic sinusoids. Lymphocytes are usually absent and bile ducts unaffected. This form of rejection is seen more commonly in recipients with ABO incompatible grafts.

- Acute rejection
  - Acute rejection (also known as cellular rejection) is more common than hyperacute rejection, and usually occurs in the first 3 months post-transplantation: it is characterized by portal tracts that are heavily infiltrated with lymphocytes, bile duct damage and venular inflammation. Early acute rejection (within the first 3 months post-transplantation) generally responds well to increased doses of

immunosuppressive agents, with resolution of biliary inflammation and stable long-term allograft function. The degree of inflammation and graft damage does not correlate with either the response to increased immunosuppression or with long-term outcome. By contrast, late acute rejection, recurrent rejection and steroid-resistant rejection are more likely to develop into chronic rejection.

- Chronic rejection
  - Chronic rejection (also known as ductopenic rejection or vanishing bile duct syndrome) affects a small minority of liver allograft patients and may lead to graft loss. A central late feature of chronic rejection is a loss of bile ducts (ductopenia), and pruning of the distal branches of the portal venous system owing to persistent inflammation and arterial foam cell infiltration and the presence of arterial foam cells. Vanishing bile duct syndrome eventually ensues, with progressive cholestasis and liver dysfunction and, ultimately, graft failure.

Printed with permission: Eksteen and Neuberger. *Nature Clinical Practice Gastroenterology & Hepatology* April 2008;5(4): pg 210.

172. Give 10 gastrointestinal complications of transplant immunosuppression.

- Infections
  - Viral: CMV (especially for MMF), HSV
  - Fungal: Candida albicans, candida tropicalis
  - Bacterial: versinia enterocolitica, Clostridium difficile
  - Parasites: microspordia, Strongyloides, *H. pylori* (70% in renal transplant recipients, and 60% in hemodialysis patients)

- Mucosal injury and ulceration
  - Diarrhea, constipation dyspepsia (especially tacrolimus and MMF)
  - Ulcerations: stress/NSAID ulcers
    - Giant gastric ulcers (>3cm, lung transplant recipients)
  - Diverticular disease: complicated diverticulitis (perforation, abscess, Phlegmon, fistula); especially with polycystic kidney disease
  - Perforations: early, late (especially from diverticulitis or CMV colitis)
- Biliary tract disease
  - Cholecystectomy (often as an emergency, high mortality [MR])
  - Cholelithiasis

- Pancreatitis
  - 5% in liver, Tx, MR 64%

- GI malignancy

- Lymphomas, Kaposi sarcomas, skin cancer
- Gastric MALT lymphomas; may be associated with *H. pylori*
- Colorectal cancer (liver Tx, RR, CRC 12.5)
- Post transplantation Lymphoproliferative disorder (PTLD) (10% of Tx pts; acute perforation, obstruction, bleeding; associated with EBV)

Printed with permission: Helderman JH, and Goral S. *J Am Soc Nephrol* 2002; 13: pg. 277-287.

Useful background: Allograft dysfunction

- Acute early cellular rejection of graft occurs in the first few weeks after liver transplantation, especially for REC and AH
- Chronic rejection occurs in 10% of liver transplant recipients, especially in HCV or AH
- Chronic hepatitis of graft develops in 5-10% of liver transplanted patients, and may lead to cirrhosis in the allograft
- Liver diseases that may recur in the transplanted graft include PBC, DSC and AH
- Strictures of biliary tree occur in 20-35% of patients post liver transplantation, especially at the duct-to-duct anastamosis, or at the Roux-en-Y
- Post transplant biliary strictures result from hepatic artery occlusion, chronic allograft rejection, or prolonged cold ischemia time

Useful background: Post-transplant diabetes and cardiovascular disease

- Early after liver transplantation, transient hyperglycemia occurs in 40% of patients, and 9-21% have persistent hyperglycemia (new onset diabetes)
- Hyperlipidemia occurs in 20-50% of liver transplant patient, with a 2.6 fold higher risk of coronary artery disease (CAD) and 20% of deaths occurring 3 years after liver transplantation coming from CAD
- Squamous cell and basal cell skin cancer is 12-90 times more common in transplanted patient
- There is a 10-fold increased risk of non-Hodgkins lymphoma (B-cell related to EBV) after liver transplantation, giving a relative risk of 3%
- In patients given a liver transplant for PSC in the settling of associated UC, the incidence of CRC is 1% per year, with a cumulative risk of colonic mucosal dysplasia of 15% at 5 years and 21% at 8 years

Abbreviation: CAD, coronary artery disease

What's new: Post liver transplantation steatosis

- Steatosis occurs in as many as a third of persons following a liver transplantation (LT), with a histological diagnosis of NASH occurring in about 10% of these persons.
- Multivariant analysis has shown that seven factors predict the risk for post-LT steatosis: post-LT obesity, diabetes mellitus, hyperlipidemia, arterial hypertension, a tacrolimus-based immunosuppression regimen, and alcoholic cirrhosis as the primary indication for LT (Dumortier et al., AJG 2010; 105: 613-620). The more of these risk factors that are present, the higher their rate for steatosis: for example; 3 factors, 30% risk; 4-66%; 5-82%; 6 risk factors, 100% ped LT steatosis.

173. Suggest 10 quality assurance measures that you should consider to continuously monitor in your clinical practice.

Clinical Condition	Selected Quality Measures
➢ Acute coronary syndrome	○ Aspirin at arrival & discharge ○ B-blocker at arrival & discharge ○ ACE inhibitor for LVSD ○ Assessment for hypertension, hyperlipidemia, metabolic syndrome, smoking cessation, exercise program
➢ Congestive heart failure	○ Left ventricular function assessment ○ ACE inhibitor for LVSD ○ Smoking cessation advice & counseling
➢ Community-acquired pneumonia	○ Oxygenation assessment within 24 h ○ Pneumococcal screening & vaccination ○ Antibiotic timing (first dose in < 4 h) ○ Smoking cessation advice & counseling

Abbreviation: ACE, angiotensin-converting enzyme; LVSD, left ventricular systolic dysfunction

- Colorectal cancer (CRC) screening
  - Surveillance if screening is positive
  - Age > 50 years
  - Family or personal history history of CRC or adenomatous polyps
  - Site land marks
  - Preparation
  - Sedation/ patient comfort

- Withdrawal time
- Miss-rate on consent form
- Screening polyp detection rate

Adapted from: *Mayo;*Table 13-2: pg 505.

Useful background: Sexual function and pregnancy after liver transplantation

- Decreased libido in 25% of men and women after liver transplantation
- Erectile dysfunction in 30% of men after liver transplanation
- Post-transplant, pregnancy is associated with increased fetal loss (18%), low birth weight (31%), and premature delivery (39%), pre-eclampsia (21%), and the need for caesarian section (47%)
- Allograft rejection occurs in 10-20% of women during pregnancy, with increased risk of miscarriages and premature labour

Useful background: Performance characterstics for mortality by PNED cutoff score point

Cutoff score point	Sensitivity (%)	Specificity (%)	PLR
(≥0)	100	0	1.0
(≥1)	99	24	1.3
(≥2)	94	45	1.7
(≥3)	86	58	2.0
(≥4)	80	74	3.0
(≥5)	64	83	3.7
(≥6)	49	89	4.3
(≥7)	38	93	5.4
(≥8)	30	96	8.3
(≥9)	21	99	16.1

Abbreviation: PNED, Progetto Nazionale Emorragia Digestiva

Source: *American Journal of Gastroenterology* 2010; 1289.

Useful background: The most common adverse effects of immune-suppressive drugs frequently used after orthotopic liver transplantation.

Adverse effect	Cyclo sporin	Tacro-limus	Gluco-Corticoids	Azathio-prine	Mycophenolate Mofetil	mTOR Inhibitors
Alopecia	-	+	-	+	+	-
Arterial hypertension	+++	++	+++	-	-	+
Bone marrow suppression	+	+	-	+++	+++	++
Dermatitis	-	+ (rash, pruritus)	+	-	-	++ (oral ulcers,acne)
Gastrointestinal Toxicity	+	+	+	+ (pancreatitis)	+++ (gastritis and/or diarrhea)	++
Hirsutism and/or gingival hyperplasia	+	-	-	-	-	-
Hyperglycemia and diabetes mellitus	-(?)	+	+++	-	-	-
Hyperlipidemia	++	+	++	-	-	+++

Adverse effect	Cyclo sporin	Tacro-limus	Gluco-Corticoids	Azathio-prine	Mycophenolate Mofetil	mTOR Inhibitors
Impaired wound healing	-	-	+	+	+	++
Lymphoma or malignancy	++	++	-	?	?	-
Myalgia and/or arthralgia	-	-	+	+	-	++
Nephrotoxicity	+++ (K+, Mg^{2}+)	+++ (K+,Mg^{2} +)	-	-	-	+ (proteinuria)
Neurotoxicity[a]	++[a]	++[a]	+ (psy-chiatric)	-	+ (headache)	-
Osteoporosis	+	+	+++	-	-	-
Pneumonitis	-	-	-	-	-	+

It should be noted that each agent has other specific adverse effects in addition to those listed in the table. [a]Neurotoxicity includes mainly peripheral neuropathy, headaches, tremor, convulsions, akinetic mutism, and insomnia.

? , Incidence unknown; - not reported; + rarely reported; ++ commonly reported; +++ very frequently reported adverse effect limiting usage of the drug.
Printed with permission: Benten D, et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;6:1:23-36.

Inherited disorder

174. Give 8 inherited disorders that involve the liver.

- Alagille's syndrome
- Benign intrahepatic cholestasis
- Cholesterol ester storage disease
- Cystic fibrosis
- Dubin-Johnson syndrome
- Gilbert's syndrome
- Hemochromatosis
- Pharmacogenetics/pharmacogenomics
- Progressive familial intrahepatic cholestasis
- Wilson's disease
- Wolman's disease
- Zellweger's syndrome

Printed with permission: Wright TL. *2007 AGA Institute Postgraduate Course*. pg. 44.

175. Give 5 hereditary liver diseases, and outline their diet therapy (always avoid alcohol).

Disorder	Dietary intervention
➢ Hemochromatosis	○ Avoidance of excess dietary iron, selection of foods containing phytates or tannins to reduce iron absorption (together with appropriate phlebotomy treatment)
➢ Wilson's disease	○ Low-copper diet, zinc supplementation (together with chelating agent); green tea
➢ Cystic fibrosis	○ High-fat diet, pancreatic enzyme supplements, fat-soluble vitamin supplements, medium chain triglycerides (MCT)
➢ Hereditary fructose intolerance	○ Low fructose, low sucrose diet
➢ Galactosemia	○ Galactose-free diet
➢ Tyrosinemia	○ Low phenylaline and tyrosine diet
➢ Glycogen storage disease	○ Continuous glucose feeding
➢ Cerebrotendinous xanthomatosis	○ Deoxycholic acid supplementation

Adapted from: Thapa BR. *Indian J Pediatr*. 1999; 66(1 Suppl): S110-9.

Useful background: The meaning of selected genetic terms.

Terminology	Meaning
○ Polymorphism	- Variation in DNA sequence present in an allele with a frequency of 1% or greater in a population
○ Single nucleotide polymorphism (SNP)	- Most common form of DNA sequence variation
○ Missense mutation (non-synonymous)	- Base pair substitution that results in an amino acid change
○ Sense mutation (synonymous)	- Base pair substitution that does not alter the coded amino acid
○ Insertions and deletions	- One or more base pairs are inserted or deleted into the genome (rare)
○ Cosmopolitan SNPs	- Present in all ethnic groups

- Population-specific SNPs - Occur in specific ethnic groups
- Haplotype - Group of variants or SNPs that occur together on a single chromosome
- Linkage disequilibrium - Variants that are linked to one another
- Recombination - Cross-over events that occur during meiosis that result in unlinking of genes or variants

Printed with permission Wright TL. *2007 AGA Institute Postgraduate Course*. pg. 45.

176. Give the classification of porphyria.

- Acute
  - Neuroporphyria - *Acute intermittent porphyria*
  - Neurocutaneous - *Hereditary coproporphyria*
    Variegate porphyria
- Non-acute (cutaneous) - *Porphyria cutanea tarda*
  Erythropoietic protoporphyria
  Congenital erythropoietic porphyria

Adapted from: Leonis MA, and Balistreri WF. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management* 2006; pg. 1621-22; and 2010, pg. 1267.

Miscellaneous

177. Give 6 hepatobiliary complications of sickle cell disease.

- Liver diseases
  - Acute sickle hepatic crisis
  - Hepatic sequestration
  - Sickle cell intra-hepatic cholestasis
  - Hepatic infarction
  - Hepatic iron overload
  - Viral hepatitis
- Biliary diseases
  - Cholelithiasis and choledocholithiasis
  - Acute cholecystitis and cholangitis
  - Ischemic cholangiopathy

Printed with permission: Ahmed S, et al. *Best Practice & Research Clinical Gastroenterology* 2005;19(2): pg. 299.

178. Give the causes and features of mitochondrial cytopathies.

- Causes
  - Acute fatty liver of pregnancy
  - Reye's syndrome
  - Genetic defects in mitochondrial function
  - Drug-related

- Features
  - Vomiting and apathy
  - Lactic acidosis
  - Hypoglycemia
  - Hyperammonemia
  - Microvesicular fat in organs

Adapted from: Leonis, Mike A and Balisteri, William F. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1621-1622.

179. Liver disease is a common cause of death in HIV-infected persons in the post-HAART era. List 7 liver diseases/conditions/presentations in such persons.

  - HCV (coinfection in 25%) - faster development of fibrosis, poorer response to HCV treatment
  - HBV, HBV-associated ↑ mortality
  - Alcohol liver disease (associated life style)
  - NAFLD (fat redistribution from HAART [lipodystrophy]))
  - Cholangiopathy (intra- and extra-hepatic)
  - Asymptomatic ↑ in transaminases, alkaline phosphatase
  - Kaposi's sarcoma
  - Opportunistic infection:
    - Cholangiopathy: mycobacterium
    - Fungal: cryptological, histological, coccidiomycosis, extra pulmonary pneumacystitis carcinoma
  - Nodular regenerative hyperplasia (vasculopathy)

Adapted from: Wilcox, C. Mel. Gastrointestinal Consequences of Infection with Human Immunodeficiency Viurs. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/Management* 2006; pg.676-79.

180. Give 4 post-cholecystectomy complications.

- CHD, CBD leak
- Stricture
- Choledocholithias
- Persistent pain – SOD, IBS

Abbreviations: CHD, common hepatic duct; CBD, common bile duct; SOD, sphincter of Oddi; IBS, irritable bowel syndrome.

Adapted from: Glasgow, Robert E. and Mulvihill, Sean J. Treatment of Gallstone Disease. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006; pg. 1424--36.

Useful background: Liver and biliary diseases following stem cell transplantation, the timing of onset and method, and making a diagnosis

Disease	Timing	Diagnosis
Sinusoidal obstruction syndrome	Onset before day 20	○ Typical clinical features plus exclusion of other causes of jaundice and weight gain ○ Imaging (Doppler ultrasound or CT) ○ Transvenous measurememnt of wedged hepatic venous pressure gradient and liver biopsy ○ Note atypical presentations (acute hepatitis, anasarca)
○ Cholestasis of infection (cholangitis lenta)	Following sepsis or neutropenic fever (usually before day 30)	○ Exclude other causes of cholestasis ○ Inferential diagnosis in a patient with cholestatic jaundice
○ Acute GVHD	Day 15-50	○ Confirm GVHD in skin, gut ○ Exclude other causes of cholestasis ○ Liver biopsy
○ Acute viral hepatitis ○ Sludge, stones	○ HSV, day 20-50 ○ Adenovirus, day 30-80 ○ VZV, day 80-250 ○ HBV and HCV, during immune reconstitution	Pre-transplant blood test (antigen, antibodies, PCR results) Isolation of virus from other sites (stool and urine for adenovirus) PCR of serum for specific virsuses

Disease	Timing	Diagnosis
○ Fungal abscess	Day 10-60	○ Liver biopsy histology/PCR/immunostains
○ Bacterial infection	Day 10-80	○ Hepatic pain, fever ○ Liver imaging (MRI>CT) ○ Serum fungal antigen(s)
○ Drug-liver injury	Day 0-100	○ Hepatic pain, fever ○ Liver imaging ○ Liver biopsy, culture
○ Ischaemic liver disease	Day 0-30	Clinical evidence linking elevations of serum ALT or alkaline phosphatase to drugs known to cause liver injury
○ Biliary obstruction	Day 15-60	Clinical evidence linking shock to subsequent rises in serum ALT
	Day 10-50	○ History, examination ○ Biliary ultrasound
○ Idiopathic hyper-ammonemia	After day 80	○ ERCP>magnetic resonance cholangiography ○ Unexplained confusion, coma
○ Chronic hepatitis C	○ Pre-transplant ○ Long-term follow-up after transplant	○ Blood ammonia ○ HCV RNA in serum ○ Elevation of serum ALT after immune reconstitution
○ Iron overload	After day 80	Transferrin saturation ○ Marrow iron qualification ○ Liver iron quantification (Ferriscan MRI, liver biopsy quantification)
○ Chronic GVHD		○ Prior acute GVHD history ○ Chronic GVHD in other organs
Nodular regenerative hyperplasia	Years after transplant	○ Consistent elevations of serum ALT, alkaline phosphatase ○ Note hepatitis presentation ○ Liver biopsy ○ Signs of portal hypertension but preserved liver function
		Liver biopsy histology (reticulin stain), laparoscopic appearance of the liver

Printed with permission: McDonald, G.B., and Frieze, D. *Gut* 2008; 57:987-1003, Table 3 pg. 995.

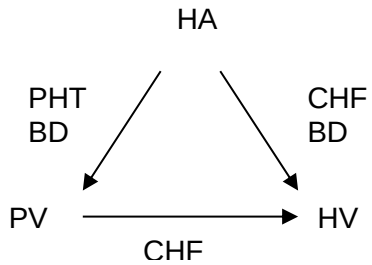
181. List 4 possible causes for failure to achieve pain relief after biliary sphincterotomy for presumed sphincter of Oddi dysfunction (SOD).

- Sphincter
  - Inadequate initial sphincterotomy (remaining ↑ SOD pressure)
  - Restenosis
- Pancreatitis
  - Chronic pancreatitis with a normal pancreatogram
  - Nonpancreaticobiliary pain (beware functional gastrointestinal disease)

Source*:* Elta, Grace H. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*:* pg. 1365*.*

182. In hereditary hemorrhagic telangiectasic liver disease, clinical manifestations are the result of the development of shunts between the hepatic artery (HA), hepatic vein, or portal vein. Give the clinical presentations in HHT the associated pathophysiology.

- Type of disorder arising from shunting between HA, HV and PV in HHT



- High-output congestive heart failure (CHF) (hepatic artery and/or portal vein to hepatic vein shunt)
  - Shortness of breath on exertion
  - Orthopnea
  - Ascites
  - Edema

- Portal hypertension (PHT) (hepatic artery to portal vein shunt)
  - Esophageal varices
  - Nodular regenerative hyperplasia

- Biliary disease (hepatic artery to hepatic vein and/or portal vein shunt)
  - Severe cholestasis
  - Recurrent cholangitis

- Hepatic disintegration

Abbreviation:BD, biliary disease; HA, hepatic artery; HV, hepatic vein; PHT, portal hypertension ; PV, portal vein.

Adapted from: Sabbà C, Pompili M. Review article: The hepatic manifestations of hereditary haemorrhagic telangiectasia. *Aliment Pharmacol Ther* 2008;28(5):523-33. Epub 2008 Jun 20.

Biliary tree

Useful background: Imaging tests for diagnosis of acute cholangitis

Parameter	Abdominal ultrasonography	CT	MRCP	EUS	ERCP
➢ Availability	Widely available	Helical CT is rare	Available	Limited	Available
➢ Portability	Portable	No	No	Limited	Limited
➢ Invasiveness	Non-invasive	Non-invasive	Non-invasive	Invasive	Invasive
➢ Need for sedation	No	No	Some patients	Yes	Yes
➢ Sensitivity for detection of stones	Low	High (best for helical CT)	High	As good as, if not better than ERCP	Gold standard in most studies
➢ Sensitivity for detection of strictures	Low	Fair	Best non-invasive method	Good	Excellent
➢ Sensitivity for detection of tumours	Low	Good	Good	Excellent	Fair
➢ Advantages	Widely available and non invasive	Widely available and accurate	Accurate without radiation exposure	Excellent for small stones, can be done at same time as ERCP	Therapeutic capability

Parameter	Abdominal ultrasonography	CT	MRCP	EUS	ERCP
➢ Disadvantage	Low sensitivity	Effects on renal function, poor detection of small stones, not portable	Not compatible in patients with implanted metal devices, poor detection of small stones, not portable	Invasive, poor imaging of intrahepatic ducts	Invasive, possible worsening of condition owing to contrast injection

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography

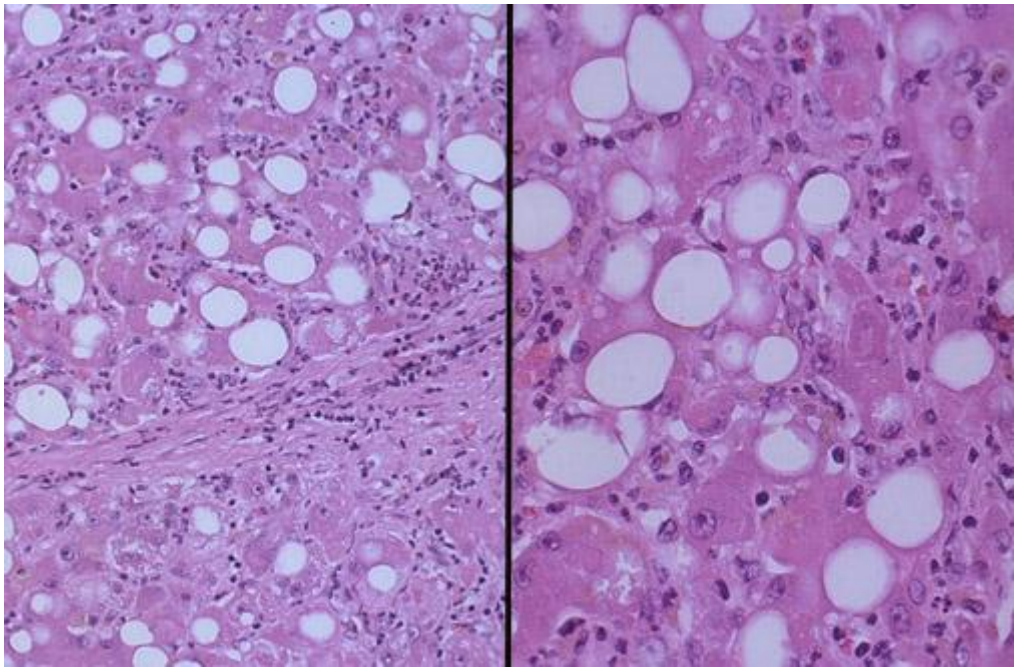
Printed with permission: John G. Lee. *Nature Reviews Gastroenterology and Hepatology* 2009;6:533-541, page 535.

Case 1. Clinical vignette: A 55-year-old sales executive presents for a physical examination pertaining to an insurance policy application. He has consumed 4 bottles of beer a day for 30 years. Past history, symptoms review, and physical examination is non-contributory. You suspect Alcoholic Liver Disease.

The typical pathological features of Alcoholic Liver Disease include:

- Hepatocyte swelling and necrosis
- Macrovesicular fatty change in centrilobular area
- Mallory's hyaline
- Neutrophils, portal lymphocytes and macrophages
- Sclerosing hyaline fibrosis

Identify these features on the following slides.



Reference: Colombat M, et al. Portal lymphocytic infiltrate in alcoholic liver disease. *Hum Pathol*. 2002;33;1170-4.

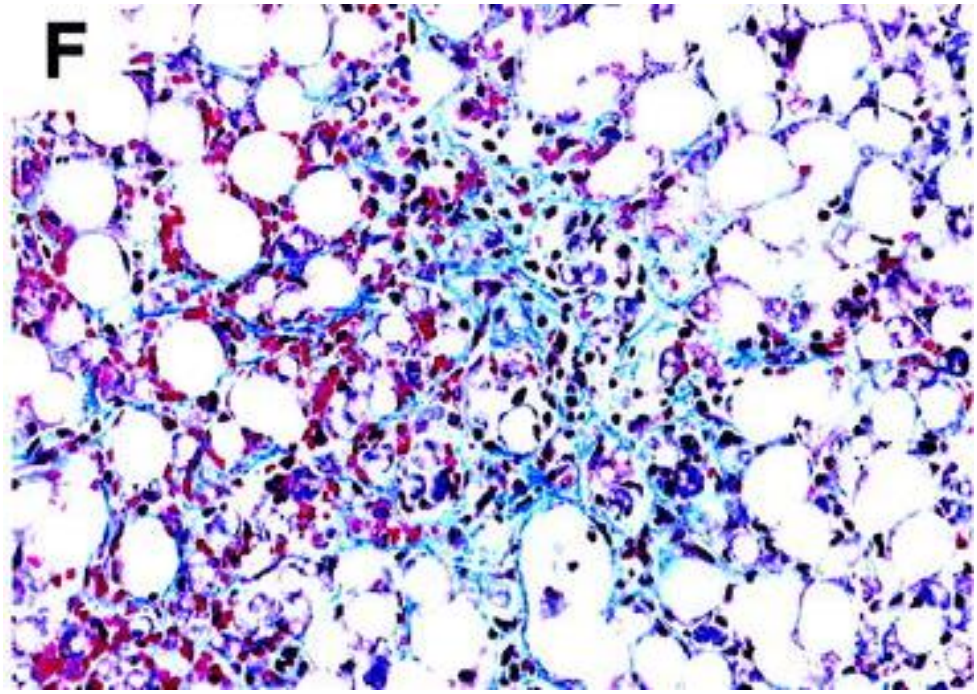
Case 2. Clinical vignette: A 45-year-old type II diabetic with a BMI of 35 from Brandon, Manitoba presents with 2 x normal increased AST. There is no alcohol intake. This is a routine follow-up for mild hypertension, and she is otherwise well except for hypercholesterolemia. You suspect non-alcoholic steatohepatitis.

The typical pathological features of non-alcoholic steatohepatitis include:

- Micro- and macrovesicular steatosis
- Lobular plasma cell and lymphocyte infiltrate
- Ballooning degeneration

Reference: Mod Path 2003;16:86

Identify these features on the following slide.



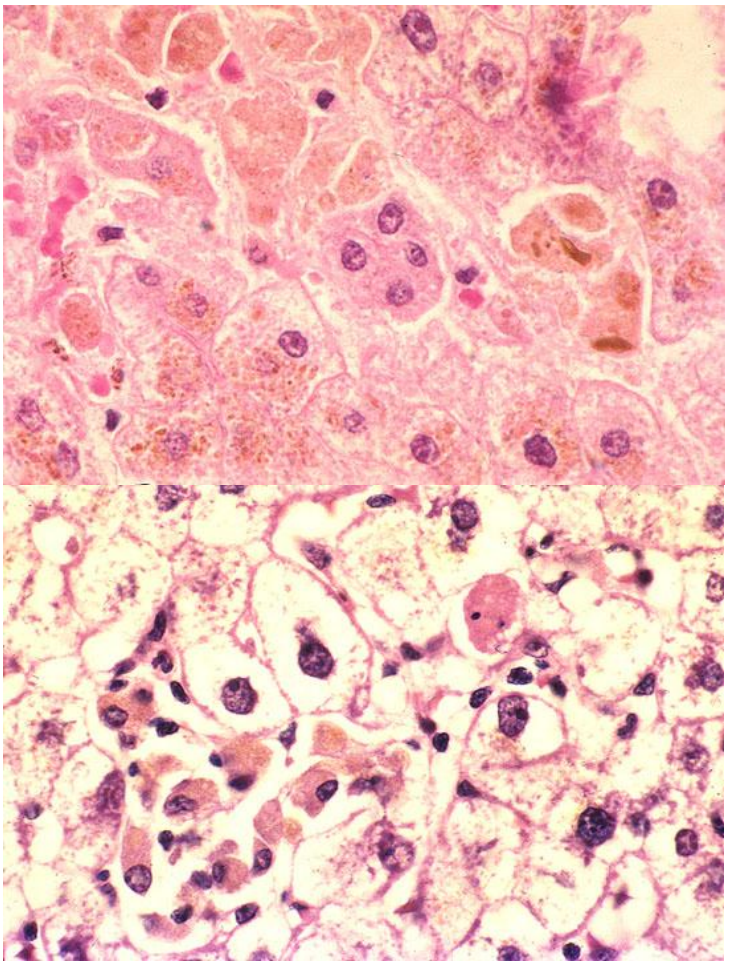
Reference: Paik SY, et al. Expression of transforming growth factor-beta1 and transforming growth factor-beta receptors in hepatocellular carcinoma and dysplastic nodules. *Mod Pathol*. 2003;16:86-96.

Case 3. Clinical vignette: A 19-year-old young man from White Rock, BC, traveling in SE Asia presents with fatigue and jaundice. You suspect hepatitis A.

The typical pathological features of Hepatitis A include:

- Portal and periportal inflammation
- Ballooning degeneration
- Acidophil bodies or cytolysis (hydropic degeneration)
- Bridging necrosis
- Interface haptitis
- Relative sparing of centrilobular hepatocytes

Identify these features on the following slides.



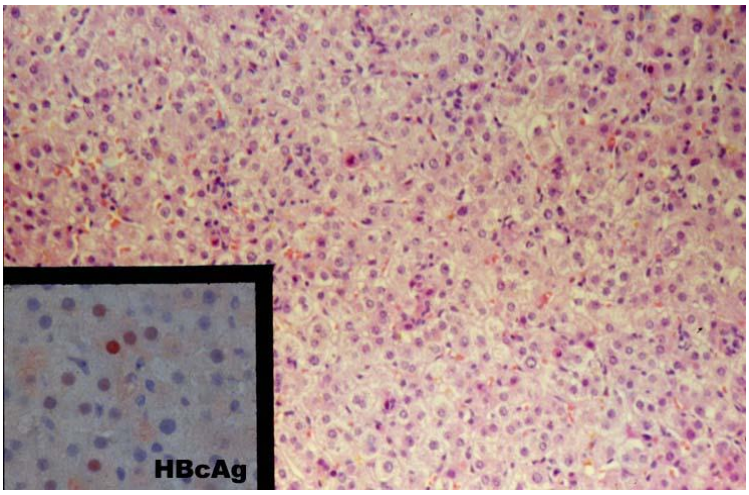
Reference: Colombat M, et al. Portal lymphocytic infiltrate in alcoholic liver disease. *Hum Pathol*. 2002;33;1170-4.

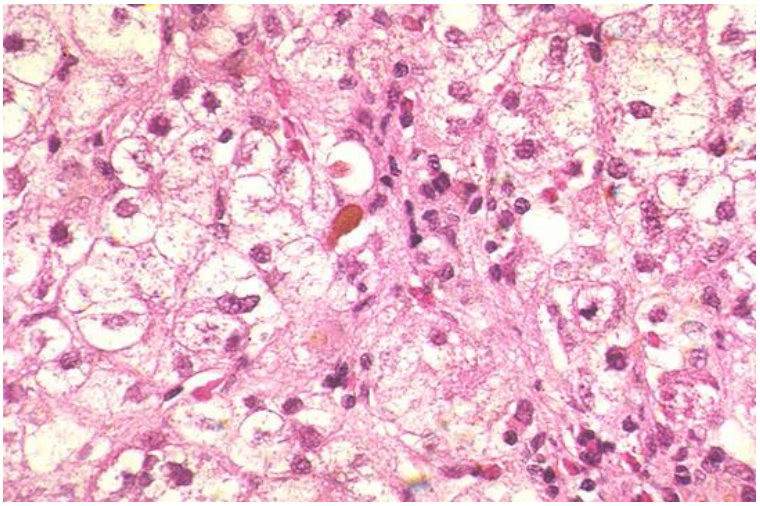
Case 4. Clinical vignette: A 62-year-old businessman from Elk Point, AB, presents with recent onset of malaise and transaminitis. He denies alcohol intake. His younger brother died from HCC. You suspect Hepatitis B.

The typical pathological features of Hepatitis B include:

- Piecemeal necrosis
- Ground glass hepatocytes

Identify these features on the following slides.





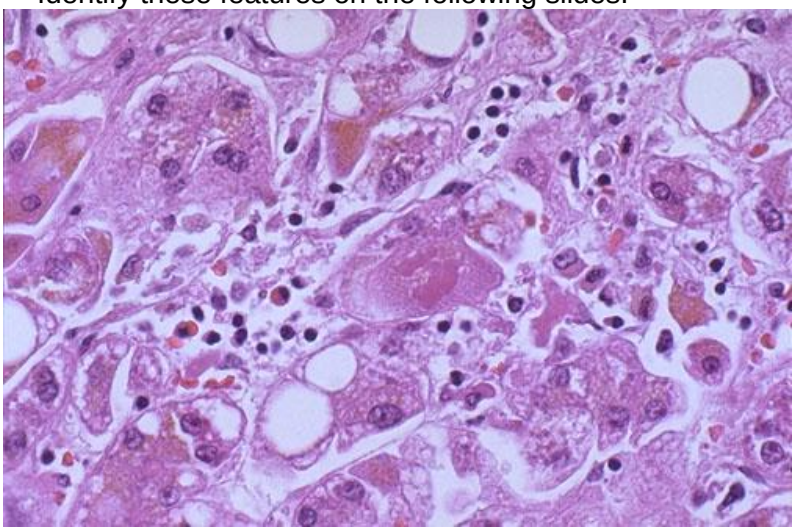
Reference: Colombat M, et al. Portal lymphocytic infiltrate in alcoholic liver disease. *Hum Pathol*. 2002;33;1170-4

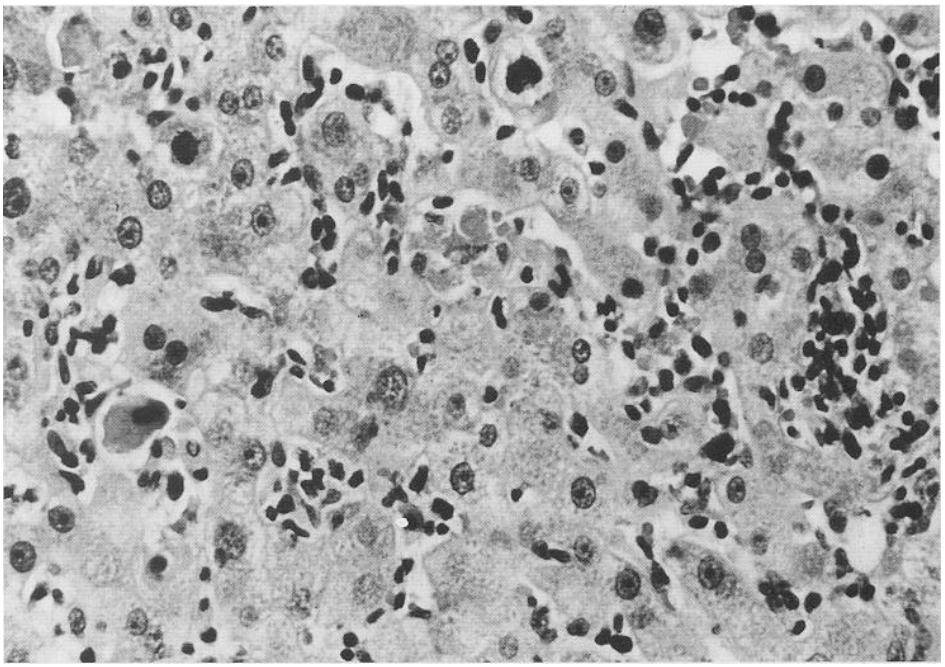
Case 5. A 39-year-old hemophiliac physician from Brookville, ON, presents with fatigue and mild jaundice. You suspect Hepatitis C.

The typical pathological features of Hepatitis C include:

- Sinusoidal lymphocytic infiltrate
- Mallory's hyaline
- Macrovesicular steatosis
- No/minimal plasma cells or eosinophils

Identify these features on the following slides.





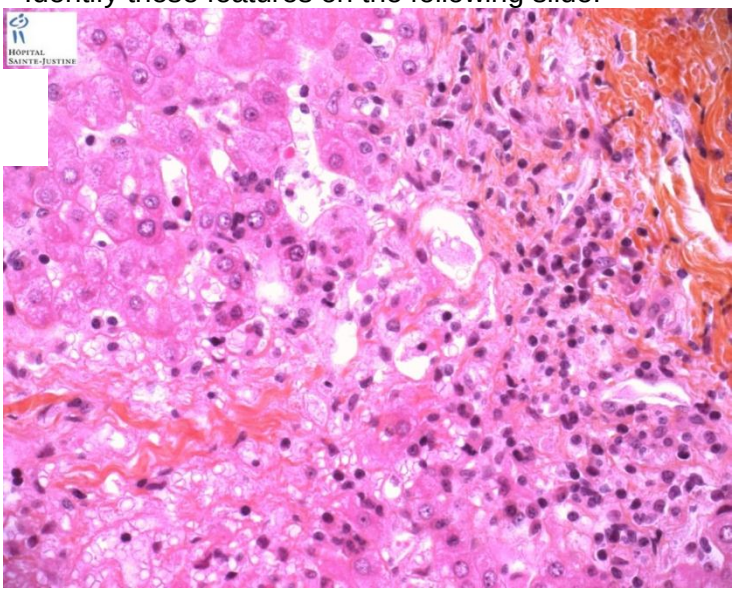
Reference: Ohmori S, et al. High expression of CD34-positive sinusoidal endothelial cells is a risk factor for hepatocellular carcinoma in patients with HCV-associated chronic liver diseases. *Hum Pathol*. 001;32(12):1363-70; Allory Y,et al. Impact of human immunodeficiency virus infection on the histological features of chronic hepatitis C: a case-control study. The MULTIVIRC group. *Hum Pathol*. 2000;31(1):69-74; Pol S, et al. Reversibility of hepatitis C virus-related cirrhosis. *Hum Pathol*. 2004;35(1):107-12; Fontaine H, et al. Hepatitis activity index is a key factor in determining the natural history of chronic hepatitis C. *Hum Pathol*. 2001;32(9):904-9; and Nuovo GJ, et al. Correlation of histology, viral load, and in situ viral detection in hepatic biopsies from patients with liver transplants secondary to hepatitis C infection. *Hum Pathol.* 2002 Mar;33(3):277-84.

Case 6. Clinical vignette: A 45-year-old high school principal from Trois-Riviera, QC, with treated hypertension presents with a 6 month history of pruritis. The GGT and AP are increased twice normal. You suspect Autoimmune Hepatitis.

The typical pathological features of Autoimmune Hepatitis include:

- Portal infiltrate with abundance of plasma cells
- Bridging necrosis
- Central necrosis with plasma cells

Identify these features on the following slide.



Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34:1127-36.

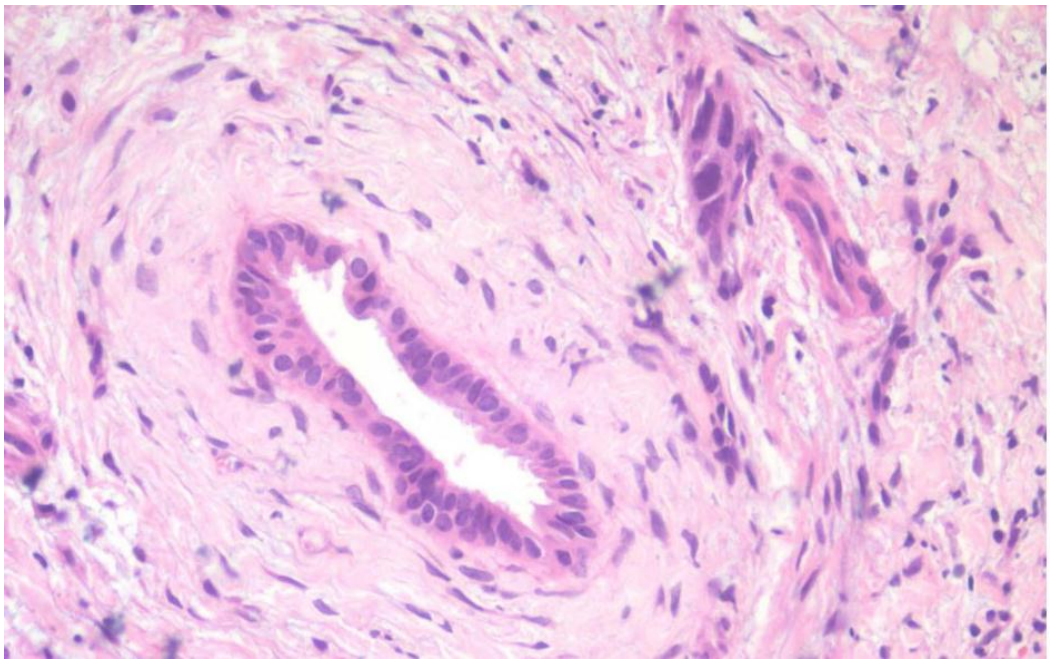
Case 7. Clinical vignette: A 24-year-old male nurse from Red Earth, SK, with a 10 year history of ulcerative colitis presents with abnormal LFTs. You suspect Primary Sclerosing Cholangitis (PSC).

The typical pathological features of PSC include:

- "Onion skin" fibrosis

Reference: *Hum Path* 2003;34:1127

Identify this feature on the following slide.



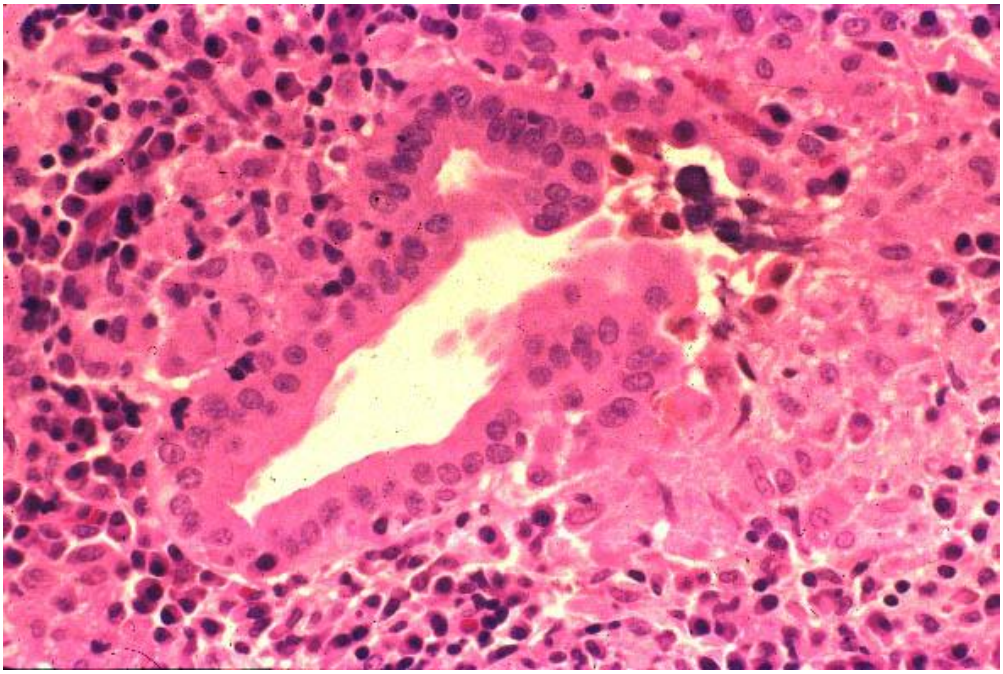
Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34:1127-36.

Case 8. Clinical vignette: A 50-year-old woman from Halifax, NS, presents with an asymptomatic elevation in her GGT and AP at the time of routine follow up of her dyslipoproteinemia. You suspect Primary Biliary Cirrhosis (PBC).

The typical pathological features of PBC include:

- Dense lymphocytic infiltrate in portal tracts
- Granulomatous destruction and loss of medium sized interlobular bile ducts
- Minimal neutrophils
- Destruction of bile ductules within the liver

Identify these features on the following slide.



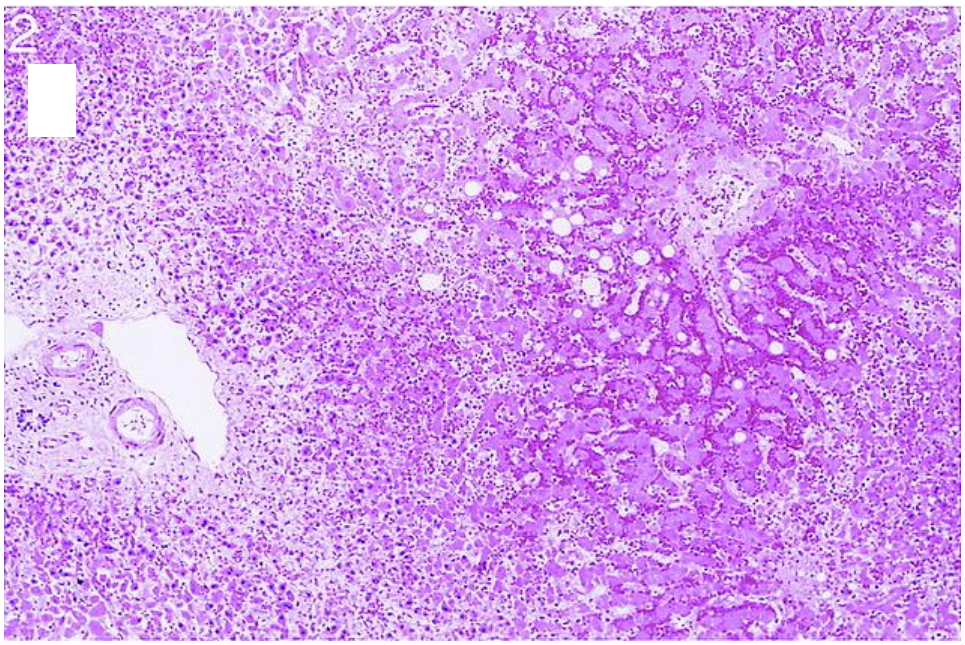
Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34:1127-36.

Case 9. A distraught 19-year-old student from Mitchell, ON, consumed a bottle of unknown OTC pills, and presents to the ER with confusion and jaundice. You suspect Massive Hepatic Necrosis (MHN).

The typical pathological features of MHN include:

- Massive necrosis of hepatocytes in all zones
- Reticulin collapse
- Minimal inflammatory reaction

Identify these features on the following slide.



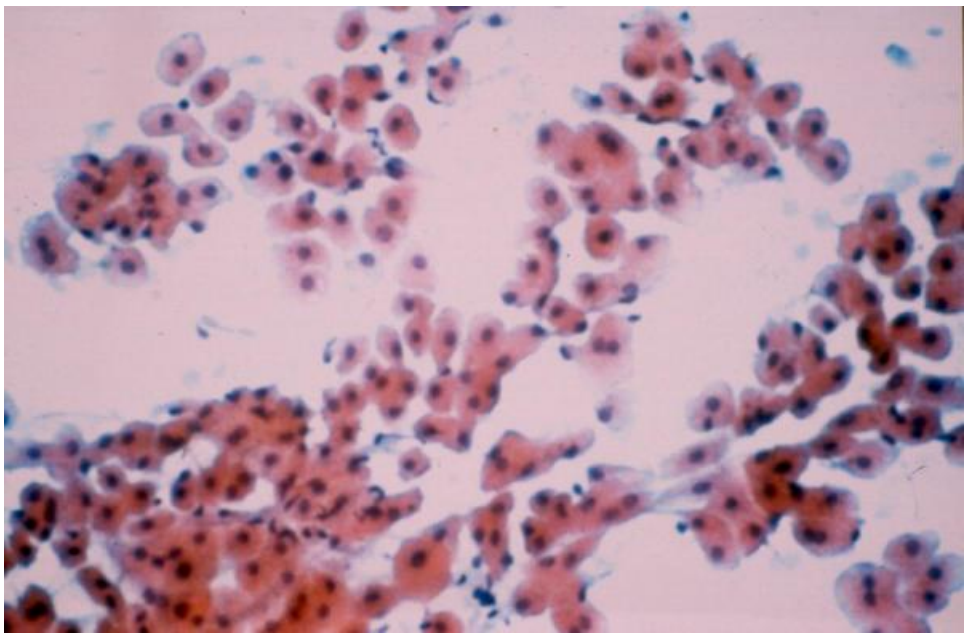
Reference: Khettry U, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol.* 2003;34:1127-36.

Case 10. A 30 year old woman presents with abnormal liver enzymes. You suspect Focal Nodular Hyperplasia (FNH).

The typical pathological features of FNH include:

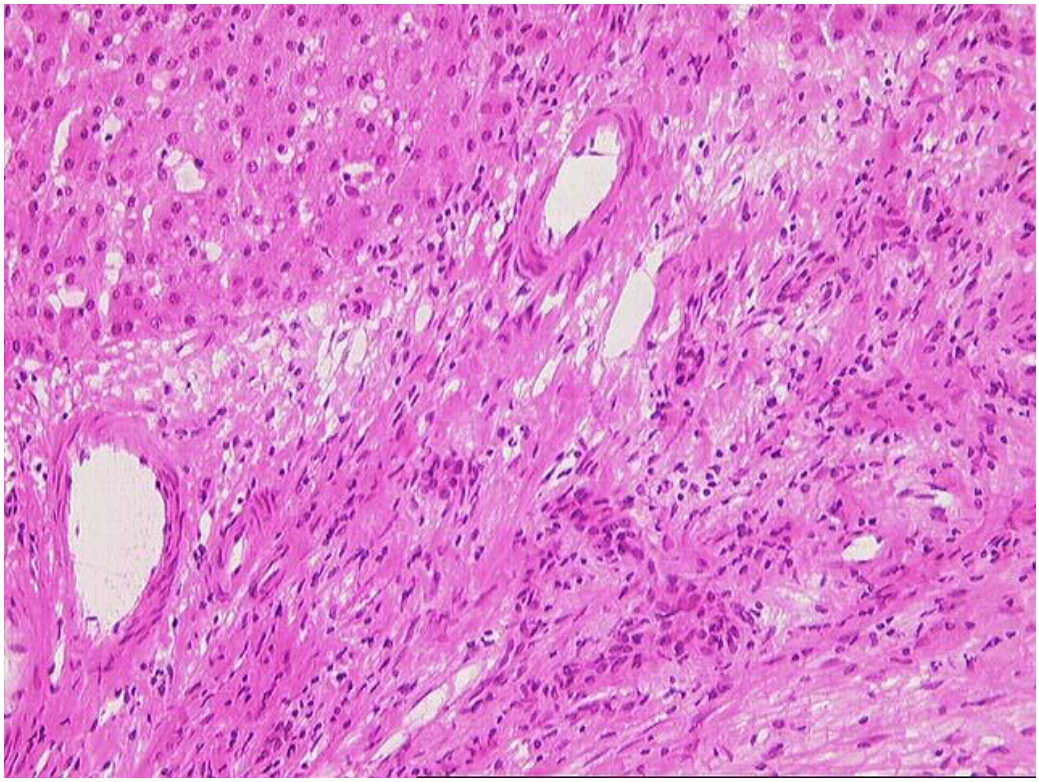
- Hepatocyte nodules surrounded by fibrous septa
- Foci of intense lymphocytic infiltrates

Identify these features on the following slide.



Reference: Gräntzdörffer I, et al.Angiotensin I-converting enzyme (CD143) is down-regulated in focal nodular hyperplasia of the liver. *Am J Surg Pathol.* 2004 Jan;28(1):84-8; Wanless IR. Epithelioid hemangioendothelioma, multiple focal nodular hyperplasias, and cavernous hemangiomas of the liver. *Arch Pathol Lab Med.* 2000 Aug;124(8):1105-7.

Case 11. Clinical vignette: A patient with known HIV and HBV from Calgary, AB, presents with worsening ascites and cachexia. You suspect hepatocellular carcinoma (HCC).

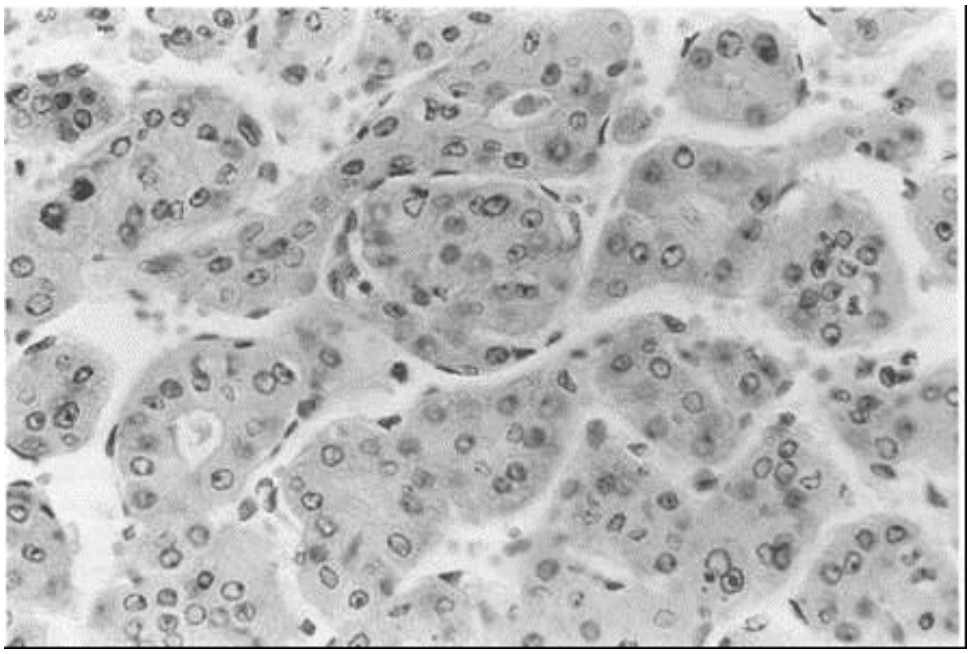


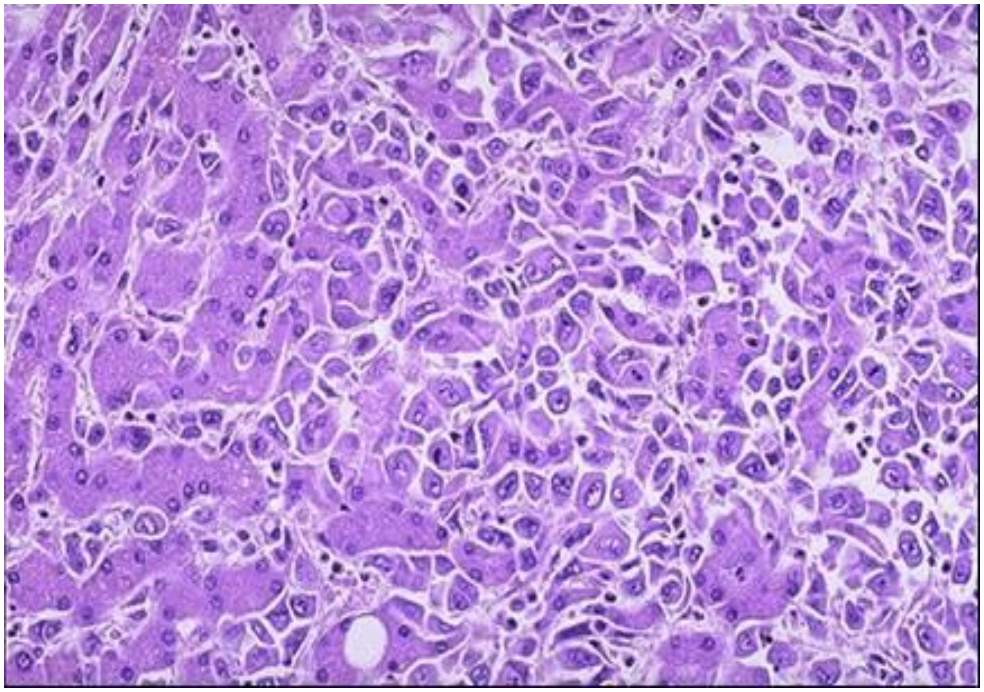
The typical pathological features of HCC include:

- Trabecular patterns
- Cells surrounded by layer of flattened endothelial cells
- Pseudoglandular
- Giant cells
- Sarcomatoid and clear cell patterns
- Sinusoidal vessels surrounding tumour cells
- Scanty stroma
- Well differentiated to bizarre
- Polygonal cells with distinct cell membranes
- Higher N/C ratio
- Granular eosinophilic cytoplasm
- Round nuclei with coarse chromatin and thickened nuclear membrane
- Vascular invasion

Reference: Fan Z, et al. Hep par 1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumours tested using tissue microarrays and conventional tissue sections. *Mod Patho*l. 2003;16:137-44; Itoh T, et al., Immunohistochemical detection of hepatocellular carcinoma in the setting of ongoing necrosis after radiofrequency ablation. *Mod Pathol*. 2002;15:110-5.

Identify these features on the following slides.



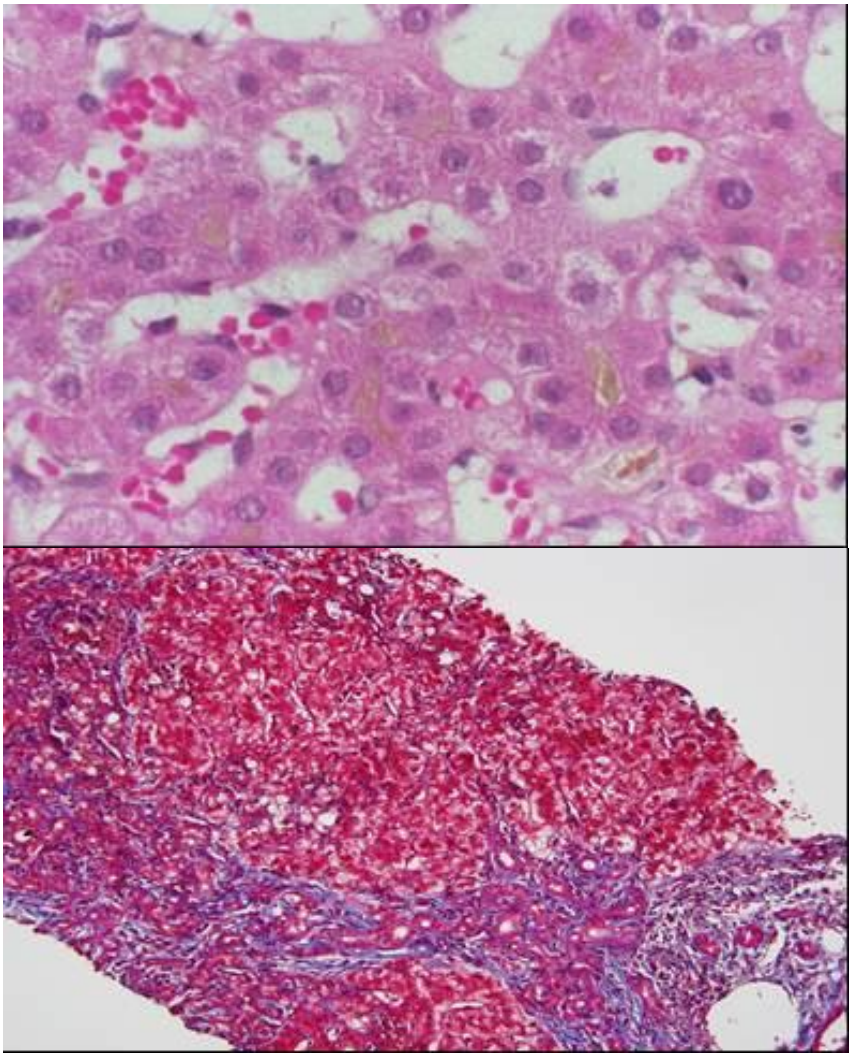


Case 12. Clinical vignette: On a Royal College OSCE exam, this slide was presented for interpretation, with the only history being “jaundice of unknown origin.” You suspect Cholestasis syndrome.

The pathological features of Cholestasis syndrome include:

- Bile plugs
- Canalicular cholestasis
- Ductular cholestasis
- Cholangiolar proliferation

Identify these features on the following slides.

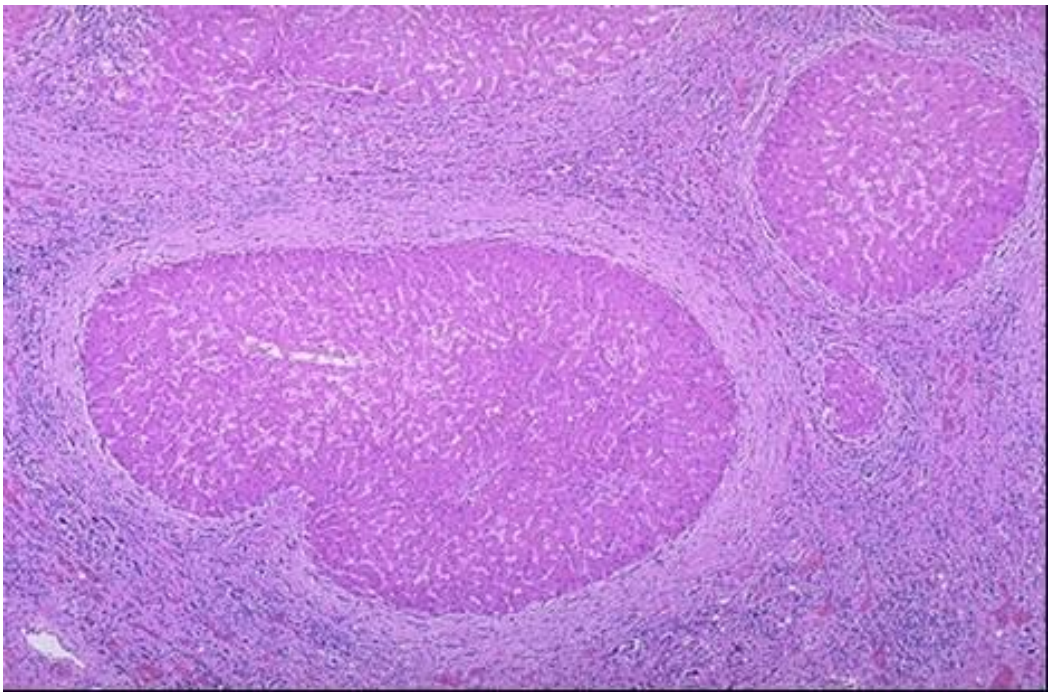


Case 13. Clinical vignette: A 58-year-old man from P.E.I. with known alcoholic liver disease presents with resent onset abdominal distension and confusion. You suspect Cirrhosis.

The typical pathological features of Cirrhosis include:

- Disruption in architecture of entire liver
- Bridging fibrous septa
- Rounded parenchymal nodules of regenerating hepatocytes without central veins

Identify these features on the following slide.

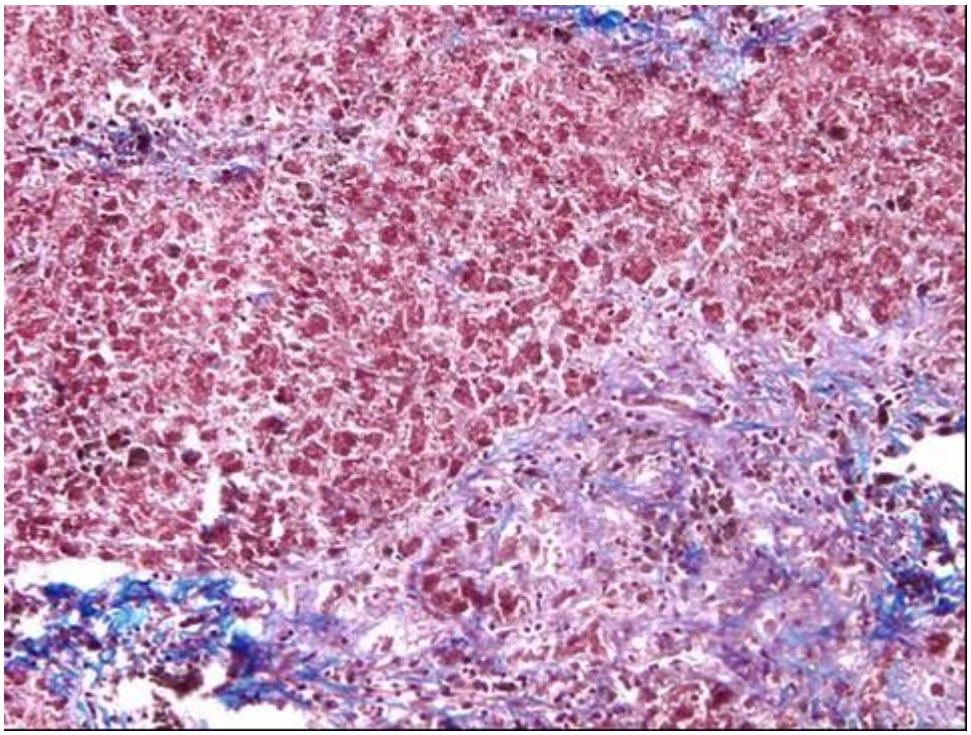


Case 14. Clinical vignette: A 55-year-old Caucasian man from Yellowknife, N.W.T., with a family history of diabetes and heart disease, presents with abnormal liver enzymes on LFT on routine annual examination. You suspect Hemochromatosis.

The typical pathological featues of Hemochromatosis include:

- Iron within hepatocytes
- Heavy periportal parenchymal iron
- Deposition with sparing of Kupffer cells
- No inflammation

Identify these features on the following slide.



Abbreviations

^{99m}Tc-MAA	Perfusion body scan with ^{99m} Technetium-labeled macroaggregated albumin
$AaPO_2$	Alveolar-arterial pressure gradient for oxygen
AFLP	Acute fatty liver of pregnancy
AFP	Alpha- fetoprotein
AH	Autoimmune hepatitis
ALD	Alcoholic liver disease
ALF	Acute liver failure
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibodies
ANA	Antinuclear antibodies
ARBs	Angiotensin receptor blockers
ASA	Anti-smooth muscle antibody
AST	Aspartate aminotransferase
ATN	Acute tubular necrosis
BID	Twice a day
BMI	Body mass index
BNP	Brain natriuretic peptide
BPM	Beats per minute
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CAT	Computerized axial tomography
CBD	Common bile duct
CEE	Contrast enhanced echocardiography
CHD	Common hepatic duct
CLT	Cadaveric liver transplatation
CT	Computerized tomography

CTP	Child Turcotte Pugh
E	Hepatitis B e antigen
E/A ratio	Ratio of early to late (arterial) phases of ventricular filling
ECG	Electrocardiogram
EGD	Esophagogastroduodenoscopy
ELISA	Enzyme linked immunosorbent assay
ERCP	Endoscopic retrograde cholangiopancreatography
ESLD	End-stage liver disease
EUS	Endoscopic ultrasonography
EVBL	Endoscopic variceal band ligation
EVL	Endoscopic variceal ligation
EVR	Early virologic response
FH	Family history
FNH	Focal nodular hyperplasia
GAVE	Gastric antral vascular ectasia
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
H	Hemalysis
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HH	Hereditary hemochromatosis
HOMA	Homeostatic model assessment
HRS	Hepatorenal syndrome
HRT	Hormone replacement therapy
HSC	Hepatic stellatecells
HVPG	Hepatic venous pressure gradient
IBS	Irritable bowel syndrome

ICP	Intracranial pressure
ICP	Intrahepatic cholestasis of pregnancy
INR	International normalized ratio
IV	intravenous
IVC	Inferior vena cava
IVDU	IV drug use
LCHAD	Long chain 3-hydroxyacyl-CoA-dehydrogenase
LDLT	Live donor liver transplantation
LP	Thrombocytopenia
MAP	Mean arterial pressure
MCV	Mean corpuscular volume
MDA	Malondialdehyde
MELD	Model for end stage liver disease
MPAOP	Mean pulmonary artery occlusion pressure
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MTOR	Mammalian target of rapamycin
NA	Not available
NAS	NASH activity score
NASH	Non alcoholic steatohepatitis
NNFL	Non-NASH fatty liver
NP	Not applicable
NRH	Nodular regenerative hyperplasia
NVR	No virologic response
OGIS	Oral glucose insulin sensitivity index
OLT	Orthotopic liver transplantation
OR	Odds ratio
PA	Pulmonary artery
PaO_2	Partial pressure gradient for oxygen
PBC	Primary biliary cirrhosis

PCLD	Polycystic liver disease
PCR	Polmerare chain reaction
PEI	Percutaneous ethanol injection
PFT	Pulmonary function testing
PHG	Portal hypertensive gastropathy
PHT	Portal hypertension
PMN	Polymorphonuclear (neutrophil) cell count
PNH	Proxysmal nocturnal hemoglobulinuria
PO	Orally
PPH	Portopulmonary hypertension
PS	Performance status
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
PV	Pulmonary vein
PVR	Pulmonary vascular resistance
QD	Once daily
QUICKI	Quantitative insulin-sensitivity check index
RBBB	Right bundle branch block
RBC	Red blood cell count
RFA	Radiofrequency ablation
RIBA	Recombinant immunoblot assay
RV	Right ventricular
RVR	Rapid viral response
SAAG	Serum ascites albumin gradient
SBP	Spontaneous bacterial peritonitis
SC	Subcutaneously
SMA	Smooth muscle antibodies
SMR	Standard mortality ratio
SOD	Sphincter of Oddi
SS	Simple steatosis

SVR	Sustained viral response
TACE	Transarterial chemoembolization
TAE	Transarterial embolization
TID	Thrice a day
TIPS	Transjugular intrahepatic portosystemic shunt
TMP-SMX	Trimethoprim sulfamethoxazole
UDCA	Ursodeoxycholic aid
ULN	Upper limit of normal
US	Ultrasound
VR	Viral response

Suggested reading list and references

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PANCREAS

TABLE of CONTENTS

Acute pancreatitis

Useful background: Classification of drugs associated with induction of acute pancreatitis

- Class I: implicated in > 20 reports, at least one documented case following reexposure
  - Asparaginase
  - Azathioprine
  - Cytarabine
  - Didanosine
  - Estrogen preparations
  - Furosemide
  - Mercaptopurine
  - Mesalamine
  - Opiates
  - Pentamidine
  - Pentavalent antimonials
  - Steroids
  - Sulfasalazine
  - Sulindac
  - Tetracycline
  - Trimethoprim/sulfamethoxazole
  - Valproic acid
- Class II: implicated in > 10 reports
  - Acetaminophen
  - Carbamazepine
  - Cisplatin
  - Cyclopenthiazide
  - Enalapril
  - Erythromycin
  - Hydrochlorothiazide
  - Interferon Alfa-2b
  - Lamivudine
  - Octreotide
  - Phenformin
  - Rifampicin

Printed with permission: Keller J, et al. *Best Pract Res Clin Gastroenterol* 2007;21(3):519-33.

1. Give 20 complications of acute pancreatitis.

- Local
  - Sterile necrosis
  - Infected necrosis
  - Abscess

- Pseudocyst
- Gastrointestinal bleeding

- Pancreatitis-related:
  - Splenic artery rupture or splenic artery pseudoaneurysm rupture
  - Splenic vein rupture
  - Portal vein rupture
  - Splenic/portal vein thrombosis, leading to gastroesophageal varices with rupture
  - Pseudocyst or abscess hemorrhage
  - Postnecrosectomy bleeding

- Non-pancreatitis-related:
  - Mallory-Weiss tear
  - Alcoholic gastropathy
  - Stress-related mucosal gastropathy

- Splenic injury
  - Infarction
  - Rupture
  - Hematoma

- Fistulization to or obstruction of small or large bowel

- Right-sided hydronephrosis

- Systemic (systemic cytokine response, aka “cytokine” storm)
  - Respiratory failure
  - Renal failure
  - Shock (circulatory failure)
  - Hyperglycemia
  - Hypoglycemia
  - Hypocalcemia
  - Hypomagnesemia
  - Disseminated intravascular coagulation
  - Subcutaneous nodules due to fat necrosis
  - Retinopathy
  - Psychosis
  - Malnutrition
  - Death

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 524.

Chronic pancreatitis

2. Give 20 causes of chronic pancreatitis.

- Duct obstruction
  - Benign pancreatic duct obstruction
    - Traumatic stricture
    - Stricture after severe acute pancreatitis
    - Duodenal wall cyst
    - Pancreas divisum
  - Malignant pancreatic duct stricture
    - Ampullary or duodenal carcinoma
    - Pancreatic adenocarcinoma
    - Intraductal papillary mucinous neoplasm

- Hereditary
  - CT (cationic trypsinogen) gene
  - Autosomal dominant
    - Hereditary pancreatitis (PRSS1 mutations)
  - Autosomal recessive or modifier genes
    - CFTR mutations
    - SPINK1 mutations
    - IgG4 associated

- Autoimmune
  - Associated with autoimmune diseases (eg. Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis)

- Tropical
  - Tropical calcific pancreatitis
  - Fibrocalculous pancreatic diabetes

- Metabolic
  - Diabetes
  - Alcohol
  - Hypercalcemia
  - Hyperlipidemia
  - Hypertriglyceridemia
  - Lipoprotein lipase deficiency
  - Apolipoprotein C-II deficiency

- Postnecrotic chronic pancreatitis

- Idiopathic
  - Early-onset

- Late-onset
- Asymptomatic pancreatic fibrosis
  - Chronic alcoholism
  - Old age
  - Chronic renal failure
  - Radiotherapy

Adapted from: Chari ST. *Mayo Clinic Gastroenterology and Hepatology Board Review:* pg 470.; Forsmark CE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1274.; and 2010: pg. 988; and Keller J, and Layer P. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): pg. 106.

3. What tests would you do to seek a cause of pancreatitis prior to diagnosing the patient as having idiopathic pancreatitis?

- Structural (ERCP/MRCP, CT)
  - Pancreas Divisum, chronic pancreatitis, ampullary stenosis, juxta-ampullary diverticulum, or other anatomic abnormalities.
  - ERCP with bile aspiration, centrifugation and examination of pellet for biliary crystals
  - SOD (Sphincter of Oddi) dysfunction (pressure measurement)

- Hereditary
  - CFTR gene
  - cationic trypsinogen (CT) gene
  - SPINK gene
  - Test for autoimmune pancreatitis (IgG4 level)
  - Sphincter of Oddi pressure measurement for SOD (sphincter of Oddi dysfunction)

Printed with permission: Dite P, et al. *Best Pract Res Clin Gastroenterol.* 2008;22(1):131-43.

Useful background:

- Accuracy of detection on abdominal ultrasound: gallstones, > 90%; dilated CBD, 55-91%; CBD stones, 20-75%

- Contract enhanced CT useful to grade pancreatitis, and to detect necrosis as well as neoplasm; equivalent to gadolinium-enhanced dynamic MRCP (but contrast-enhanced MRCP is superior to contrast

enhanced CT to detect CBD stones) (Arvanitakis M, et al. *Gastroenterology* 2005:715-23.

- Microlithiasis occurs in 37-89% of persons with idiopathic acute pancreatitis, and some experts recommend cholecystectomy for associated symptoms

- Definitions
  - Microlithiasis, stones < 3 mm
  - Biliary sludge, a suspension of crystals, mucin, glycoproteins, cellular debris, and protein acrous material
  - Biliary crystals, crystals of calcium bilirubinate, calcium carbonate, or cholesterol monohydrate; the use of duodenal drainage to assess the presence of biliary crystals has a sensitivity of 65%, and a specificity of 94-100%
  - The risk of pancreatitis following ERCP is high in persons with IAP (ideopathic acute pancreatitis), sphincter of Oddi dysfunction (SOD), or a post history of pancreatitis (12.5% risk)

Abbreviations: IAP, ideopathic acute pancreatitis; SOD, Sphincter of Oddi dysfunction

4. Give the histological and diagnostic imaging features, serology and pancreatic organ involvement, and response, to steroid therapy in autoimmune pancreatitis (AIP).

Category	Criteria
➢ Histological features	Diagnostic: a) Periductal lymphoplasmacytic infiltrate with obliterative phlebitis (LPSP) in pancreatic tissue b) High (>10 cells/hpf) igG4 positive cells in the pancreas c) Lymphoplasmacytic infiltrate with fibrosis in the pancreas
➢ Diagnostic imaging	1. CT/MR: diffusely enlarged gland with delayed enhancement 2. ERCP: diffusely irregular, attenuated main pancreatic duct Atypical imaging features: pancreatitis, focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy

Category	Criteria
➢ Serology	Elevated serum IgG4 level
➢ Other organ involvement	Persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
➢ Steroid therapy	Resolution of pancreatic/extrapancreatic manifestation with steroid therapy

Printed with permission: Dite, Petr., et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): pg. 138.

5. Compare and contrast the diagnostic imaging of autoimmune chronic pancreatitis (AIP) versus alcoholic chronic pancreatitis (ACP).

	ACP	AIP
○ Duct	Duct dilation	Duct narrowing
○ Pseudocyst	Common	Rare
○ Calcification or stone	Common	Rare
○ Pancreatic parenchyma	Atrophy	Enlargement

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6. Give 5 causes for failure to achieve pain relief after biliary sphincterotomy for pancreatic pain.

- Nonpancreaticobiliary pain, especially functional gastrointestinal disease
- Subtle chronic pancreatitis with a normal pancreatogram
- Inadequate intitial sphincterotomy
- Ductal edema post sphincterotomy
- Restenosis
- Residual pancreatic sphincter hypertension (SOD)
- Failure in SOD types II, or III

7. Give 20 current approaches to the management of pain in the patient with chronic pancreatitis.

- General measures
  - Manage associated/causative factors
  - Cessation of alcohol intake
  - Analgesics
  - Gabbapentum
  - SSRIs, TCAs

- Neural interruption
  - Percutaneous or endoscopic (EUS) nerve blocks
  - Surgical (thorascopic) splanchic nerve resection

- Reduction of intrapancreatic pressure
  - Suppression of enzyme secretion
  - Anticholinergics, PPI, somatostatin, pancreatic enzyme replacement
  - Decompression techniques
    - Sphincterotomy, endoscopic dilation and stenting
    - Stone removal (endoscopic or ESWL)
  - Surgical drainage, if pancreatic duct dilated (Peustow)
  - Organ resection
    - Partial, complete, with/without pancreatic islet cell transplant

Adapted from: Forsmark CE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg 1288-1294.

8. Give indications for surgery in persons with chronic pancreatitis.

- Intractable pain
- Suspicion of malignancy
- Common bile duct obstruction
- Symptomatic duodenal obstruction
- Symptomatic pseudocysts[a]
- Vascular obstruction[b]
- Pancreatic duct obstruction[b]

[a]Both surgical and endoscopic drainage procedures are possible
[b]If present with other complications

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Cystic fibrosis (CF)

9. Give 10 non-GI/Hepatobiliary manifestations of cystic fibrosis in the adult.

- Respiratory
  - Sinusitis
  - Nasal polyposis (secondary to mucous membrane hypertrophy)
  - Lower respiratory infections
  - Bronchiectasis

- GU
  - Male infertility (sterility; congenital absence of vas deferens, epididymis, and seminal vessels)
  - Female infertility (increased viscosity of vaginal mucous)

- Nutrition
  - Clubbing
  - Short stature

- Premature death
- Reproductive
  - Female gender
    - Increased viscosity of vaginal mucus and decreased fertility
  - Male gender
    - Sterility: absence of ductus deferens, epididymis and seminal vesicles

- Skeletal
  - Retardation of bone age
  - Demineralization
  - Hypertrophic pulmonary osteoarthropathy

- Ophthalmic
  - Venous engorgement
  - Retinal hemorrhage

- Other
  - Salt depletion through excessive loss of salt via the skin
  - Heat stroke
  - Hypertrophy of apocrine glands

Adapted from: Whitcomb DC. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1214.

Cysts and tumours

10. Provide a classification of cystic and cystic-appearing lesions of the pancreas.

- Congenital true cysts
  - Polycystic disease
  - Von Hippel-Lindau disease
  - Cystic fibrosis
  - Dermoid cysts

- Inflammatory
  - Pseudocysts
  - Abscess
  - Hydatic cyst

- Angiomatous cysts

- Cystic neoplasms
  - *Mucinous tumours*
    - Mucinous cystadenoma (macrocystic adenoma) and cystadenocarcinoma
    - Intraductal mucin hypersecreting neoplasm; "Mucinous ductal ectasia"
  - *Non-mucinous tumours*
  - Serous cystadenoma (microcystic adenoma)
    - Papillary cystic tumour
    - Cystic cavitation of pancreatic adenocarcinoma or lymphoma

- Acquired cysts
  - Central cavitary necrosis
  - Pseudocyst
  - Parasitic cyst

- Misdiagnosed nonpancreatic lesions
  - Splenic artery aneurysm
  - Choledochal cyst
  - Mesenteric cyst
  - Duodenal duplication cyst or diverticulum
  - Lesser sac biloma
  - Lymphangioma
  - Hypoechoic solid tumour

- Metastases, with cystic component

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11. Compare and contrast pancreatic serous cystadenoma, mucinous cystadenoma (MCN), IPMT (Intraductal papillary mucinous tumour) and pseudocyst from the perspective of patient age, gender, alcohol use, pancreatic history, location, malignant potential, as well as locularity and presence of calcifications.

	Serous cystadenoma (SCA)	Mucinous cystadenoma (MCA)
○ Sex	Female (2-3:1)	Female (~100%)
○ Age	60s	Adenocarcinoma (50s-60s) Carcinoma (60s-70s)
○ Ethanol abuse	No association	No association
○ Pancreatic history	Yes (uncommon)	Yes (uncommon)
○ Malignant potential	No (rare)	Yes
○ Location	Evenly distributed body/tail	Body/tail
○ Locularity	Multiple small	multilocular
○ Calcifications	Yes (central sunburst or stellate)	Yes (peripheral, curvilinear)

	IPMT	Pseudocyst (PC)
○ Sex	Male (3-4:1)	Male
○ Age	60s	Variable
○ Ethanol abuse	no association	Yes
○ Pancreatic history	yes (uncommon)	Yes (uncommon)
○ Malignant potential	yes	No
○ Location	head	Head
○ Locularity	multilocular	Unilocular
○ Calcifications	no	No, unless associated with chronic pancreatitis

Adapted from: Scheiman JM. *AGA Institute Postgraduate Course* 2006: pg. 586.

Useful background: Intraductal papillary mucinous neoplasms (IPMN)

- Lesions of main or bronchial pancreatic ducts, with proliferation of the mucinous epithelium leading to ductal and cystic dilation
- Three types of IPMN, including main, branched or main plus branched (mixed) pancreatic ducts
- 20-30% of IPMNs are multifocal, arising from a field defect in the entire pancreas that can cause multiple primary neoplasms (Brugge 09)
- Range histologically from benign, low grade (LGD), or high grade dysplasia to invasive cancer, with various grades of histology, probably being present with the same specimen
- Main branch IPMNs are more likely to become malignant and to grow faster: 63% develop HGD/cancer in 5 years, vs 15% for branched chain IPMNs
- As compared with pancreatic adenocarcinoma, in IPMN there are more frequent molecular changes in SKT 11/LKB1 inactivation and PIK3CA mutation, and less frequent mutations in K-ras and P53 tumour suppressor genes, P16 and DPC4
- In IPMN, overexpression of fascin (an actin-bundling protein), methylated PPENK, and human telomerase reverse transcriptase
- Male: female ration 1-2.4, mean age of diagnosis is 65 years; symptoms arise from mucin distending involved pancreatic duct; (may see mucus extruding from ampulla on ERCP)
- Increased serum bilirubin predicts the presence of malignancy
- Grape-like cluster of cysts, localized or diffuse dilation of main pancreatic duct, patulous ampulla of Vater
- Diagnosis: MDCT (multidetectable CT), MRCP, breath-hold MRCP, MRCP with secretin (S-MRCP), CT using pancreatic protocol (detects IPMN in 97% of cases), EUS, ERCP
- ↑ CEA in 80-95% of IPMNs
- PET scanning sensitivity, 57-90%; specificity, 85-97%

- MRCP is superior to CT to demonstrate communication between ducts, and cyst morphology

- Exclude pancreas divisium (MRCP, 100% accurate; CT, sensitivity 90%, specificity, 97%)

- Main duct IPMN or branching chain IPMN > 3 cm are more likely to be malignant. Cyst ablation with ethanol or paclitaxel (a chemotherapeutic agent which inhibits the disassembly of microtubules and induces apoptosis with complete resolution of cysts in 79%, may be reasonable for IPMNs with low risk of malignancy:
  - No symptoms
  - < 3 cm size
  - Main duct < 6 mm
  - No mural nodules, thickness or septations

- After surgical resection, invasive > 40%, non-invasive > 70%; resections recur in a median of 20 months, and 58% of these recurrences involve distal sites.

Abbreviations: HGD, high grade dysplasia; IPMN, intraductal papillary mucinous neoplasms; LGD, low grade dysplasia; MDCT, multidetectable CT; S-MRCP, MRCP with secretin

12. List 8 indications for treatment of a person with a pancreatic pseudocyst.

- Pseudoaneurysm formation
- Fistula formation into adjacent viscera
- Expansion of the pseudocyst producing abdominal pain
- Expansion of the pseudocyst producing duodenal or biliary obstruction
- Abscess formation.
- Pancreatic ascites (tracking of pancreatic juice into the peritoneal cavity or pleural space)
- Pleural effusion
- Rupture
- >6 cm, 6 weeks after episode of pancreatitis
- Concern for malignant cystic lesion

Adapted from: Kim HC, et al. *Acta Radiol*. 2008;49(7):727-34; and Christensen NM, et al. *Am J Surg*. 1975;130(2):199-205.

13. The placement of temporary prophylactic pancreatic duct stents is suggested for high risk patients following ERCP. List 3 features giving a high risk of post-GERD pancreatitis and 3 features giving a low risk.

High	Low
○ Ampullectomy ○ Recent biliary sphincterotomy ○ Sphincter of Oddi dysfunction ○ Prior episode of post-ERCP pancreatitis	○ Female ○ Young ○ Non-dilated bile ducts ○ Trainee participation in procedure

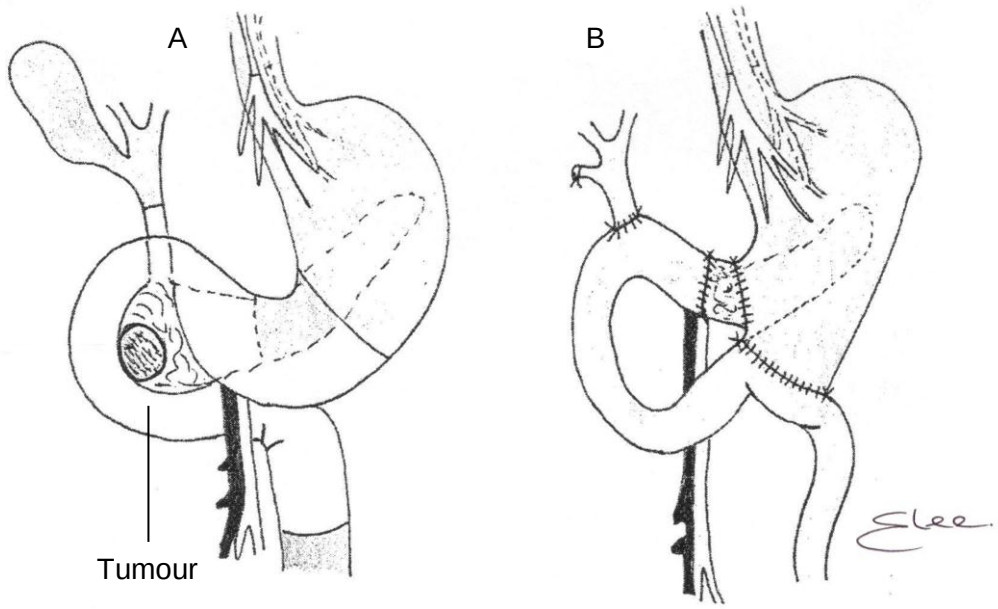
Adapted from: Elta GH. *Gastrointest Endosc* 2008;67(2):262-64.; and Freeman ML, et al. *Gastrointest Endosc* 2001;54(4):425-434.

14. Give the pros and cons of a nasogastric drains pancreatic stents.

Nasogastric drain	Stent
➢ Pros ○ Flushing and fluoroscopy at any time	Easy, quick, dislocation rare; not disabling, patients stay mobile, feel better
➢ Cons ○ Discomfort; easily dislocated; leads to immobilization of patients, nose-pain; flushing often futile and tedious, no direct control during flushing	No flushing; control needs endoscopic session

Printed with permission: Giovanni M. *Best Practice & Research Clinical Gastroenterology* 2004; 18(1): pg.192.

Whipple Procedure



A.
- An en bloc resection of the distal stomach, duodenum, common duct, and head of the pancreas containing the pancreatic neoplasm is performed (areas removed are not shaded).
- A cholecystectomy and truncal vagotomy are also done.

B.
- Gastrointestinal continuity is restored by performing a pancreaticojejunostomy, a choledochojejunostomy, and a gastrojejunostomy.

Adapted from: Reber, H.A and Way, L.W: The pancreas. In Dunphy, J.E, and Way, L.,W [eds.]. *Current Surgical Diagnosis and Treatment*, 3rd Ed. Los Altos, Calif. Lange Medical Publications, 1977. ; Printed with permission: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* F82-8: page 106.

What's new: Differentiate focal autoimmune pancreatitis from pancreatic cancer

- It may be difficult to distinguish between autoimmune pancreatitis (especially the focal variety) and pancreatic cancer. An antibody to a PBP-like protein of H.Pylori is found in over 90% persons with autoimmune pancreatitis, and in less than 10% of those with pancreatic cancer (NJEM 2009, 361: 2135-2142)

Useful background: Pancreatic neuroendocrine tumours

- Gastrinoma
  - 1 per year/10^6 population
  - Malignant ~ 66%
  - 20% associated with MEN I
  - > 50% of sporadic and > 70% of hereditary gastrinomas are in the duodenum
  - Resection of all sporadic gastrinomas and in MEN I if > 2.5 cm

- Insulinoma
  - 1 per year/10^6 population
  - Benign in ~90%
  - Solitary in 95%
  - <2 cm in 85-90%
  - 4% are MEN I
  - In MEN I patients insulinomas are multiple in 90%
  - Enucleation if solitary; pancreatectomy if multiple

- Non-functioning pancreatic neuroendocrine tumours
  - > 50% are malignant
  - Mostly in pancreas head and often large
  - Have worse survival compared to functioning pancreatic neuroendocrine tumours
  - Resection of all sporadic tumours, or if > 2 cm in MEN I and if > 2-3 cm in VHL

- Pancreatic neuroendocrine tumours in VHL
  - Occur in 10-15% of patients
  - Frequently multiple (>30%)
  - Tumours >3 cm are aggressive (metastases)
  - Resect lesion if > 3 cm in the body/tail and if > 2 cm in the pancreas head
  - Tumours < 1 cm require yearly follow-up by CT or MRI from an early age

- Local treatment – liver metastases
  - Liver resection
  - Chemoembolization
  - Radiofrequency ablation

- Systemic therapy
  - Somatostatin analogues
  - Somatostatin receptor radionuclide therapy
  - MIBG radionuclide therapy

- Chemotherapy, especially for poorly differentiated tumours

Printed with permission: Alexakis N, and Neoptolemos JP. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): pg. 199.

15. Give 10 genetic diseases/associations of pancreatic cancer.

- Hereditary pancreatitis
  - Cationic trypsinogen (CT)
  - CF
  - SPINK

- Polyp syndromes
  - FAP
  - HNPCC-Lynch mismatch MLH1, MSH2, BRCH2
  - HNPCC
  - Peutz-Jeghers syndrome
  - Cowden syndrome

- Genetic abnormalities
  - Familial atypical mole and multiple melanoma (FAMMM): germline p16 mutation
  - Hereditary breast cancer: germline BRCA2 mutation
  - Oncogenes - K-RAS mutations (90%) and p53 (70%) indicate tumour induction by exogenous carcinogens
  - Inactive tumour suppression gene (p59, p16 [DKN2A])
  - Familial pancreatic cancer
  - Familial ovarian and breast cancer

- Drugs/Diet
  - Risk factors are smoking, alcohol, and high-saturated fat/low vegetable/low vitamin diet
  - 7-fold increased risk after exposition to dichlorodiphenyltrichloroethane or deviates (e.g. ethylene)

- Metabolic
  - Chronic pancreatitis
  - Diabetes
  - Partial gastrectomy

- Miscellaneous
  - Diabetes mellitus
  - Cystic fibrosis
  - Fanconi anemia
  - Familial adenomatons polyposis

- Ataxia telangiectasia
- Neurendocrine tumours

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 522.

Additional information

16. List 6 causes of an elevated serum amylase/lipase.

- GI causes
  - Small bowel obstruction
  - Intestinal ischemia
  - Bowel perforation
  - Cholecystitis, appendicitis
  - Salivary gland disease, e.g. mumps
  - Peptic ulcer disease with penetration
  - Pancreatic cancer
  - Celiac disease
  - Appendicitis
  - Pancreatitis

- Non-GI causes
  - Tubo-ovarian disease, e.g. fallopian tube inflammation (salphingitis), ectopic pregnancy
  - Renal failure
  - Diabetic ketoacidosis
  - HIV infection
  - IgA deficiency
  - Anorexia, bulimia

Adapted from: Vissers RJ, et al. *J Emerg Med* 1999;17(6):1027-37.

17. Inadvertent activation of trypsin in the pancreas is prevented by several protective mechanisms. Give the four main mechanisms that have been suggested to prevent autodigestion.

- Separation of zymogen granules and lysosomes within the acinar cell
- Trypsin inhibitors (spink) within the acinar cells and the pancreatic duct
- The digestive enzymes secreted as precursors
- Activation of trypsin actually occurs OUTSIDE the pancreas by duodenally secreted enterokinases (pepsinogen activated kinase)

Adapted from: Hirota M, et al. *J Gastroenterol* 2006;41(9):832-6.

18. Describe the risk stratification and management of the patient with acute pancreatitis.

- Risk stratification
  - Clinical criteria-based scoring systems: Ranson, Glasgow, Apache (not accurate until 48 hours)
  - Atlanta symposium criteria: Pancreatic necrosis (seen in 20% of acute pancreatitis)
  - SIRS (systemic inflammatory response syndrome) leading to organ failure: cardiovascular, pulmonary, renal, GI bleeding
  - Laboratory Hematocrit, urinary TAP (trypsinogen activation peptide; not surrogate markers of inflammation)
  - Diagnostic imaging: CT, MR – sensitive for necrosis (the amount of necrosis does not correlate with the development fo organ failure; necrosis may not develop for 24-48 hours)

- Management
  - IV fluids 72 suuc/h
  - Pain control
  - NG/NJ tube feeding
  - Antibiotics only if infected necrosis suspected (usually after day 10), do not give prophylactically since only 1/3 of patients with necrosis can develop infected necrosis
  - Early ERCP for gallstone pancreatitis (ALT 3XULN, PPV- 95%; ↑bilirubin on day 2); sphincterotomy and stone extraction
  - US not sensitive to detect gb/cbd stones in acute pancreatitis; MR, EUS
  - CT guided FNA for culture
  - Debridement by surgery, endoscopy, radiology

Abbreviation: EUS, endoscopic ultrasound; FNA, fine needle aspiration; NG/NJ, nasogastric/ nasojejunal; ULN, upper limit of normal; US, ultrasound

Adapted from: Forsmark CE, and Baillie J. *Gastroenterology* 2007;132(5):2022-44.

19. Give 10 risk factors associated with the development of post-ERCP pancreatitis.

- Operator related
  - Lower ERCP volume

- Patient related
  - Suspected sphincter of Oddi dysfunction (SOD)
  - Younger age

- Normal bilirubin
- Prior post-ERCP pancreatitis
- Female sex (possible)

- ERCP method related
  - Difficult cannulation
  - Pancreatic duct injection
  - Pancreatic sphincterotomy
  - Precut sphincterotomy (by endoscopists of mixed experience)
  - Balloon dilation of biliary sphincter
  - Acinarization (possible)
  - Absent common bile duct stone (possible)

Abbreviation: CCK, cholecystokinin

Adapted from: Slivka A. *AGA Institute Postgraduate Course* 2006; pg.211-213.

20. Give 6 tests of exocrine pancreatic functions.

- Direct invasive intubation tests
  - CCK/secretin stimulation
  - Lundh meal
  - ERCP and pancreatic aspiration

- Indirect non-invasive tests
  - Stool fats and nitrogen
  - Stool trypsin and chymotrypsin
  - Breath tests
  - Oral function tests (benitiromide test and pacnreaolauryl test)

- Blood determinations
  - Trypsinogen
  - Lipase
  - Pancreatic amylase

Adapted from: Pandol SJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1197-1199; and 2010: pg. 928.

21. Give the Mayo Clinic criteria for the diagnosis of autoimmune pancreatitis (AIP), and the features characteristic for the diagnostic groups.

- Diagnostic criteria
  - Histology
    - At least one of the following:

        - Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis
        - Lymphoplasmacytic infiltrate with storiform fibrosis with abundant IgG4 cells (>10 IgG4 cells/HPF)
    - Imaging
        - Typical: diffusely enlarged gland with delayed 'rim' enhancement, diffusely irregular, attenuated main pancreatic duct
        - Other: focal pancreatic mass/enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis
    - Serology
        - Elevated serum IgG4 level (normal 8-140 mg/dl)
    - Other organ involvement
        - Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
    - Response to steroid therapy
        - Resolution or marked improvement of pancreatic /extrapancreatic manifestation with corticosteroid therapy

Abbreviations: HPF, high power field; IgG4, immunoglobulin G4

- Japan pancreas society criteria for the diagnosis of AIP

Diagnostic criteria: for diagnosis, criterion I must be present together with criterion II and/or III

I. Imaging criterion: diffuse narrowing of the main pancreatic duct with irregular wall (more than one third the length of the entire pancreas) and enlargement of the pancreas

II. Laboratory criterion: abnormally elevated levels of serum gammaglobulin and/or IgG, or the presence of autoantibodies

III. Histopathologic criterion: marked lymphoplasmacytic infiltrate and dense fibrosis

Abbreviations: AIP, autoimmune pancreatitis; IgG, immunoglobulin G

Printed with permission: Gardner, et al. *AM J Gastroenterol* 2009; 104: 1620-1623.

- Diagnostic groups of AIP
    - Group A: diagnostic pancreatic histology
        - Presence of one or more of the following criteria:
            - Specimen demonstrating the full spectrum of LPSP

        - >10 IgG4 cells/HPF on immunostatin of pancreatic lymphoplasmacytic infiltrate
    - Group B: typical imaging and serology
        - Presence of all the following criteria:
            - CT or MRI scan showing diffusely enlarged pancreas with delayed and 'rim' enhancement
            - Pancreatogram showing diffusely irregular pancreatic duct
            - Elevated serum IgG4 levels
    - Group C: response to corticosteroids
        - Presence of all the following criteria:
            - Unexplained pancreatic disease after negative workup for other etiologies
            - Elevated serum IgG4 and/or other organ involvement confirmed by presence of abundant IgG4 positive cells
            - Resolution or marked improvement of pancreatic and/or extrapancreatic manifestations with corticosteroid therapy

Abbreviations: AIP, autoimmune pancreatitis; CT, computed tomography; HPF, high power field; IgG, immunoglobulin G; LPSP, lymphoplasmacytic sclerosing pancreatitis; MRI, magnetic resonance imaging

Printed with permission: Gardner, el. *AM J Gastroenterol* 2009; 104: 1620-1623.

Useful background: Autoimmuine pancreatitis (AIP)

- IgG4-associated systemic disease (ISD) (Chari 09)

- Focal, but usually diffuse involvement of pancreas with irregular narrowing of pancreatic duct, swelling of parenchyma, from periductive lymphoplasmacytic, infiltration, storiform fibrosis, obliterative phlebitis (infiltrative surrounds venules but not arteriols), and IgG4 positive immunostaining of $\underline{\geq}$ IgG4 positice cells per HPF

- Type I, lymphoplasmacytic sclerosing pancreatitis, and type II idiopathic duct centric pancreatitis

- ISD may affect pancreas, bile ducts, salivary glands, kidneys, retroperitoneum, and lymph nodes

- More frequently males (80%), over 50 years (80%)

- Pain is not a prominent feature

- CT/MRI shows “sausage-shaped” enlargement of pancreas, peripheral (RIM) enhancement, and delayed enhancement; ERCP shows characteristic diffusely irregular and narrowed pancreatic duct

- Elevated serum IgG4 is 75% sensitive and 93% specific for AIP; IgG4 > 2XULN are highly specific, but ↑ IgG4 may also be seen in 1.5% of pancreatic cancers

- Consistent response to 30-40 mg prednisone, tapering with improvement in serum IgG4 and imaging

Abbreviation: IgG4-associated systemic disease

22. 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 Steinberg, William M. *Sleisenger & Fordtran’s Gastrointesintal and Liver Disease: Pathophysiology/ Diagnosis/Management* 2006: 1241-1270.

23. Give 8 clinical, diagnostic imaging and laboratory features that distinguish pseudocysts from cystic neoplasms of the pancreas.

Feature	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 multiocular - 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: Forsmark, Chris E. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:1297.

Useful background: The clinical and laboratory findings in patients with Pancreatic (Pan) and intestinal (Int) somatostatinomas.(the approximate frequency of symptoms is shown)

	Somatostatinoma	
	Pancreatic	*Intestinal*
○ Diabetes mellitus	95	20
○ Gallbladder disease	94	40
○ Diarrhea	75	25
○ Weight loss	50	35
○ Steatorrhea	85	10
○ Hypochlorhydria	85	15

24. Give six tests used for the detection of large and small duct disease in persons with chronic pancreatitis.

Diagnostic test	Possible findings in 'big duct' disease	Findings in 'small duct' disease
➢ Fecal elastase	○ Usually low (<100/g of stool)	○ Usually normal
➢ Serum trypsin	○ Usually low (<20 ng/mL)	○ Usually normal
➢ Abdominal ultrasonography	○ Pancreatic atrophy, pancreatic duct dilation, pancreatic calcifications, pseudocyst	○ Usually normal
➢ Computerized tomography	○ Pancreatic atrophy, pancreatic duct dilation, pancreatic calcifications, pseudocyst	○ Usually normal or equivocal
➢ MRCP	○ Pancreatic atrophy, pancreatic duct dilation, irregularity or stricture, pancreatic calcifications, pseudocyst	○ Usually normal or equivocal
➢ Endoscopic ultrasonography	○ Abnormal (>4 features of chronic pancreatitis	○ May be abnormal
➢ ERCP	○ Abnormal	○ Normal of minimally abnormal

➢ Direct hormonal stimulations test (e.g. secretin test)	○ Abnormal	○ Usually abnormal

Abbreviations: MRI, magnetic resonance imaging, MRCP, magnetic resonance cholangiopancreatography.

Source: Lieb JG II, and Forsmark CE. Aliment Pharmacol Ther. Review: Pain and Chronic Pancreatitis. *Journal Compilation* 2009;29:713.

25. Give 20 causes of acute pancreatitis.

- ➢ Idiopathic
  - ○ Pancreas divisum
  - ○ Choledochocele
- ➢ Inherited
  - ○ CFTR, SPINK 1 & 2, CT gene and other mutations
- ➢ Infection
  - ○ Viral (mumps, Coxsackie, CMV, HSV, HIV)
  - ○ Bacterial (Mycoplasma, Legionella, Leptospira, Salmonella)
  - ○ Fungal (Aspergillus)
  - ○ Parasitic (toxoplasma, cryptosporidium, Ascaris)
- ➢ Inflammation
  - ○ Penetrating gastroduodenal ulcer
  - ○ Crohn's disease
- ➢ Ischemic
  - ○ Ischemia
  - ○ Vascular bypass surgery
  - ○ Vasculitis
- ➢ Immune
  - ○ Idiopathic autoimmune pancreatitis
- ➢ Obstruction
  - ○ Gallstones
  - ○ Biliary sludge
  - ○ ERCP
  - ○ Juxta-ampullary diverticulum
  - ○ Ampullary neoplasms
  - ○ Pancreatic neoplasms
  - ○ Ampullary stenosis
  - ○ Sphincter of Oddi dysfunction
- ➢ Trauma
  - ○ Blunt trauma
  - ○ Penetrating trauma
  - ○ Post ERCP

- Metabolic
  - Hypertriglyceridemia
  - Hypercalcemia
- Medications/ toxin
  - Ethanol
  - Methanol
  - Scorpion venom
  - Pentamadine, DDI, furosemide, thiazides, sulfasalazine, 5-ASA, alicylates, L-asparaginase, azathioprine, valproate, estrogen, sulindac, and others (see next question please)

26. Give 5 methods used to estimate the severity of acute pancreatitis.

- Clinical
  - Apache II > 8
  - Apache 0 >10
  - Ranson $\geq$ 3
  - Glasgow scope $\geq$ 3
  - Evidence of systemic complications
- Laboratory
  - Hematocrit $\geq$ 44
  - $\uparrow$ CRP
- CT scan
  - CT $\geq$ 30% pancreatic necrosis

Source: Vege Santhi Swaroop, and Baron Todd H. *Mayo Clinical Gastroenterology and Heptalogy Board Review*: page 461.

27. Give 20 GI/hepatobiliary clinical manifestations of cystic fibrosis.

- Esophagus
  - Gastroesophageal reflux
- 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: Whitcomb, David C. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006: pg. 1214,; and Castillo, Carlos Fernandez-del., and Jimenez, Ramon E. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006: pg.1322.

28. Compare and contrast the viscosity, amylase, concentration, CEA and CA2-4 levels, and cytological findings in pancreatic serous cystadenoma, benign and malignant mucinous cystic neoplasm (MCN), intraductal papillary mucinous tumour and pseudocyst.

Parameter analyzed	Serous cystaden-oma	MCN-Benign	MCN-Malignant	IPMT	Pseudocyst
➢ Viscosity	↓	↑	↑	↑	↓
➢ Amylase	↓	↓	↓	↑	↑
➢ CEA	↓	↑	↑	↑	↑
➢ CA 2-4	↓	↓/↑	↑	?	↓
➢ Cytologic findings	Usually negative, rarely cuboidal cells	Occasionally mucinous epithelial cells	Benign – occasional mucinous epithelial cells Malignant - adenocarcinoma cells	Papillary cluster of mucinous cells	Histiocytes

Adapted from: Castillo, Carlos Fernandez-del., and Jimenez, Ramon E. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:1322.

29. Give the features of the insulinoma and glucagonoma syndromes.

- Features of the insulinoma syndrome
  - Neuroglycopenia (90%)
    - Amnesia or coma (47%)
    - Confusion (80%)
    - Visual changes (59%)
    - Convulsions (17%)
    - Altered consciousness (38%)
  - Sympathetic overdrive (60-70%)
    - Weakness (56%)
    - Sweating (69%)
    - Tremors (24%)
    - Palpitations (12%)
    - Hyperphagia (14%)
  - Obesity (<50%)

- Features of the glucagonoma syndrome
  - Migratory necrolytic erythema (70-90%)

- Weight loss (80%)
- Glucose intolerance (40%-90%)
- Normochromic, normocytic anemia (35%-90%)
- Hypoaminoacidemia (80%)
- Diarrhea (25%)
- Thromboembolism (15%-25%)
- Glossitis, chelitis (15%-40%)
- Psychiatric symptoms (0%-17%)

Adapted from: Metz, D.C., and Jensen, R.T. *Gastroenterology* 2008; 135: pg. 1469-1492.

Useful background: Mayo Clinic HISORt criteria for the diagnosis of AIP

- Diagnostic criteria
  - Histology
    - At least one of the following:
    - Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis
    - Lymphoplasmacytic infiltrate with storiform fibrosis with abundant IgG4 cells (>10 IgG4 cells/HPF)
  - Imaging
    - Typical: diffusely enlarged gland with delayed 'rim' enhancement, diffusely irregular, attenuated main pancreatic duct
    - Other: focal pancreatic mass/enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis
  - Serology
    - Elevated serum IgG4 level (normal 8-140 mg/dl)
  - Other organ involvement
    - Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
  - Response to steroid therapy
    - Resolution or marked improvement of pancreatic /extrapancreatic manifestation with corticosteroid therapy

- Diagnostic groups: patients meeting criteria for one or more of the groups have AIP
  - Group A: diagnostic pancreatic histology
    - Presence of one or more of the following criteria:
      - Specimen demonstrating the full spectrum of LPSP
      - >10 IgG4 cells/HPF on immunostain of pancreatic lymphoplasmacytic infiltrate

- Group B: typical imaging and serology
  - Presence of all the following criteria:
    - CT or MRI scan showing diffusely enlarged pancreas with delayed and 'rim' enhancement
    - Pancreatogram showing diffusely irregular pancreatic duct
    - Elevated serum IgG4 levels
- Group C: response to corticosteroids
  - Presence of all the following criteria:
    - Unexplained pancreatic disease after negative workup for other etiologies
    - Elevated serum IgG4 and/or other organ involvement confirmed by presence of abundant IgG4 positive cells
    - Resolution or marked improvement of pancreatic and/or extrapancreatic manifestations with corticosteroid therapy

Abbreviations: AIP, autoimmune pancreatitis; CT, computed tomography; HP, high power field; IgG4, immunoglobulin G4; IgG, immunoglobulin G; LPSP, lymphoplasmacytic sclerosing pancreatitis; MRI, magnetic resonance imaging

Printed with permission: Macmillan Publishers Ltd: Gardner el, *AM J Gastroenterol* 2009; 104: 1620-1623, Table 1: page 1621.

30. In the era of the use of diagnostic imaging (MRCP), give 3 therapeutic indications for the use of ERCP and EUS in pancreatic disease.

- ERCP in pancreatic disease
  - Evaluation of recurrent pancreatitis (Avoid in chronic pain syndromes)
  - Pancreatic duct disruptions or leaks
  - Symptomatic pancreatic pseudocysts
  - Drainage of pancreatic necrosis

- EUS
  - Diagnostic procedure in acute and chronic pancreatitis
  - Consider before transmural drainage of pancreatic fluid collection/necrosis/pseudocyst
  - Celiac plexus block

Useful background: Pancreatic cysts

- Cyst fluid CGA < 3.1 mg/ml suggests serious cystadenomas, whereas CEA > 480 mg/ml suggest mucinous fluid

a) Traditional therapeutic approach to the management of cystic lesions

	Mucinous	Malignant	Serous	Pseudocyst
➢ Head	○ Monitor	○ Resect	○ Monitor	○ Drain
➢ Body	○ Resect	○ Resect	○ Monitor	○ Drain
➢ Tail	○ Resect*	○ Resect	○ Resect*	○ Resect

*Approach varies with risk of surgery

Printed with permission: Brugge WR. *2009 ACG Annual Postgraduate Course*:231-234.

Useful background: Diagnostic features of pancreatic cysts

Cyst type	EUS features	Fluid appearance	Cytology	CEA	Amylase
➢ SCA	○ Microcystic, honeycombed, 20% macrocystic	○ Thin, clear, some-times bloody	○ Cuboidal cells, clear glycogen-positive cytoplasm	○ Low	○ Low
➢ MCN	○ Macrocystic	○ Viscous, clear	○ Mucin-rich fluid, columnar mucin-positive cells, variable atypia	○ High	○ Low

Cyst type	EUS features	Fluid appearance	Cytology	CEA	Amylase
➢ PMN	○ Cystic branch duct dilation	○ Viscous, clear	○ Mucin-rich fluid, columnar mucin-positive cells, variable atypia	○ High	○ High
➢ Cystic	○ Variable	○ Variable,	○ Small cells,	○ Un-	○ Low

	PET			typically non-mucinous		scant cytoplasm, monomorphic nuclei		unknown	
➢	SPT	○	Mixed solid and cystic	○ Bloody	○	Papillary structures, macrophages, myxoid strona, monomorphic neoplastic cells	○	Low	○ Low
➢	LEC	○	Solid, heterogen-eous, subtle posterior enhancement	○ Thick milky, gray or frothy	○	Anucleated squamous cells, lymphocytes	○	Variable	○ Low
➢	PP	○	Macrocystic, thick wall, unilocular, internal debris	○ Thin, dark, non-mucinous	○	Inflammatory cells without evidence of mucin or epithelial cells	○	Variable	○ High

Abbreviations: EUS: Endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm; LEC, lymphoepithelial cysts; MCN, mucinous cystic neoplasmas; PD: Pancreatic duct; PET, pancreatic endocrine tumour; PP, pancreatic pseudocysts; SCA, serous cystaderma; SPT, solid pseudopapillary tumours

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Abbreviations

AIP	Autoimmune pancreatitis
CCK	Cholecystokinin
CT	Computed tomography
CT	Cationic trypsinogen
EUS	Endoscopic ultrasound
FNA	Fine needle aspiration
HGD	High grade dysplasia
HPF	High power field
IAP	Ideopathic acute pancreatitis
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
IPMN	Intraductal pancreatic mucinous neoplasia
ISD	IgG4-associated systemic disease
LEC	Lymphoepithelial cysts
LGD	Low grade dysplasia
LPSP	Lymphoplasmacytic sclerosing pancreatitis
MCN	Mucinous cystic neoplasmas
MDCT	Multidetectable CT
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NG/NJ	Nasogastric/ nasojejunal
PD	Pancreatic duct
PET	Pancreatic endocrine tumour
PP	Pseudopapillary tumours
S-MRCP	MRCP with secretin
SOD	Sphincter of Oddi dysfunction
ULN	Upper limit of normal
US	Ultrasonography

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NUTRITION

TABLE of CONTENTS

Increased body mass index

1. Give 5 methods of nutritional assessment.

- Subjective global assessment
  - History
    - Changes in weight (< 90% IBW [ideal body weight])
    - Changes in dietary intake
    - Gastrointestinal symptoms
    - Functional capacity
    - Stress of disease
  - Physical examination
    - Loss of subcutaneous fat
    - Muscle wasting: deltoids, quadriceps, biceps, supra/subscapular muscles
    - Edema: ankles, sacrum, ascites
    - Skin rashes
    - Eye changes
    - Neurological changes
    - Indirect calorimetry
  - Classification
    - Well nourished: no history or physical findings of malnutrition
    - Moderately malnourished: weight loss 5-10% of usual body weight (UBW), mild Signs of malnutrition
    - Severely malnourished: weight loss 10% of UBW, severe signs of malnutrition

- Laboratory determinations
  - Albumin, pre-albumin, transferrin, retinol-binding protein, lymphocyte count, WBC
  - 24-hour urinary urea nitrogen, nitrogen balance
  - Creatinine-height index
  - Delayed cutaneous hypersensitivity
  - Muscle function

- Anthropometric measurements
  - Height, weight, ideal body weight (IBW), usual body weight (UBW), BMI
  - Weight as percent IBW or UBW; % weight loss
  - Triceps skinfold thickness, mid-arm circumference, and others

- Techniques to assess body composition
  - Bio-impedance

- Imaging: DEXA, CT scan
- Dilution radioisotope methods, whole body counting (total body K^+)

Abbreviations: BMI, body mass index (kg/ m^2); IBW, ideal body weight; UBW, usual body weight

Adapted from: De Legge MH. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg. 357-359.

2. Give a classification, and state the effect, of adult obesity.

Classification	BMI (kg/m^2)	Risk of comorbidities
➢ Normal range	18.5-24.9	Average
➢ Overweight	≥ 25.0	
➢ Preobesity	25.0-29.9	Increased
➢ Obesity class I	30.00-34.9	Moderate
➢ Obesity class II	35.00-39.9	Severe
➢ Obesity class III	≥ 40.0	Very severe

Printed with permission: Formiguera X, and Canton A. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): pg 1126.

3. Give the diagnostic criteria for the "Metabolic Syndrome".

Risk factor		Abnormal level
➢ Waist circumference	– Men – Women	>102 cm >88 cm
➢ Fasting blood glucose		≥100 mg/dl
➢ Serum triglycerides		≥ 150 mg/dl, or under fibrates
➢ Serum HDL cholesterol	– Men – Women	<40 mg/dl <50 mg/dl
➢ Arterial blood pressure		≥ 130/≥85 mm Hg, or under pharmacologic treatment

Printed with permission: Cortez-Pinto H, and Camilo ME. *Best Practice & Research Clinical Gastroenterology* 2004;18(6): pg 1092.

4. Classify 6 classes of drugs used to treat obesity in addition to behavior modification (diet, exercise) for weight reduction.

- Sympathomimetric
- Serotonergic (sibutramine) blocks orexigenic and stimulates anorexigenic systems
- Pancreatic lipase inhibition: orlistat (Xenical®)
- Endocannaboids: CB-1 antagonists
- Metformin
  - ↓ hepatic glucose production
  - ↑ insulin sensitization in peripheral tissue
  - ↑ anorexic effect
- GLP-1 mimetic
  - ↑ glucose-dependent insulin secretion
  - ↓ appetite
  - Slows gastric emptying
- NPY antagonists
- Anti-ghrelin agents
- GH (growth hormone) fragment

Adapted from: Palamara KL, et al. *Cardiol Rev* 2006;14(5):238-58.

5. List 6 GI side effects of orlistat (Xenical®) therapy for obesity.

- Nausea
- Fatty/oily stools/spotting 12-48 hours after a high fat meal
- Increased defecation frequency
- Liquid stools
- Fecal urgency
- Flatulence
- Flatus with fecal discharge
- Fecal incontinence
- Low plasma vitamin concentrations (vitamins A, D, K, and E)
- Weight loss

Adapted from: Klein S. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006; pg 417-418.

Micronutrients

6. Outline the principal causes of micronutrient deficiencies.

- Reduced intake
  - Sitophobia
  - Complicated meals
  - Underlying disease (tumour)
- Impaired absorption
  - Rapid emptying
  - Poor mixing of food and duodenal juice
  - Pancreaticocibal asynchrony
  - Bacterial overgrowth
  - Rapid transit
- Disturbed distribution/metabolism
  - Enterohepatic circulation ↓
  - Enteropancreatic circulation ↓
  - Micronutrient interactions
- Increased loss
  - Occult bleeding
  - Disturbed protein binding
  - Increased renal elimination

Printed with permission: Schölmerich J. *Best Practice & Research Clinical Gastroenterology* 2004; 18(5): pg.917-933.

Malnutrition

7. Give a classification of the causes of malnutrition, and indicate how these could be suspected from a directed history.

Etiologies	History
➢ Decreased diet intake and decreased assimilation	○ Unintentional weight loss >10% body wt ○ Decreased food intake - Socioeconomic - Anorexia - Self-restricted diets e.g. alcoholism
➢ Increased metabolism ○ Critical acute illness ○ Chronic inflammation	○ Critical illness
➢ Increased losses	○ Gastrointestinal symptoms - Dysphagia - Nausea/vomiting - Chronic diarrhea - Abdominal pain (sitophobia [fear
➢ Mixed metabolic abnormality ○ HIV/ AIDS ○ Cancer	

- Chronic liver disease of eating])
- COPD
- Chronic infection(e.g. TB)

Abbreviation: COPD, chronic obstructive pulmonary diesase

Printed with permission: Alberda C, et al. *Best Practice & Research Clinical Gastroenterology* 2006; 20(3): pg.427.

8. Give 10 GI/liver complications of obesity.

- Esophagus - GERD, Barrett's epithelium, adenocarcinoma
- Stomach – retention, adenoma carcinoma, gastric cardia cancer
- Colon – Hemorrhoids, diverticulosis, colorectal cancer (CRC), non-specific abdominal pain
- Liver (NAFLD, SS/NASH), cirrhosis, hepatocellular cancer (HCC)
- Pancreas - Pancreatitis, cancer
- Gallbladder – Stones, cancer

Abbreviations: NAFLD, non-alcoholic fatty liver dieaseas; NASH, non-alcoholic steatohepatitis; SS, simple steatosis

Printed with permission: Freeman HJ. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): pg 1169.

Appetite and food intake

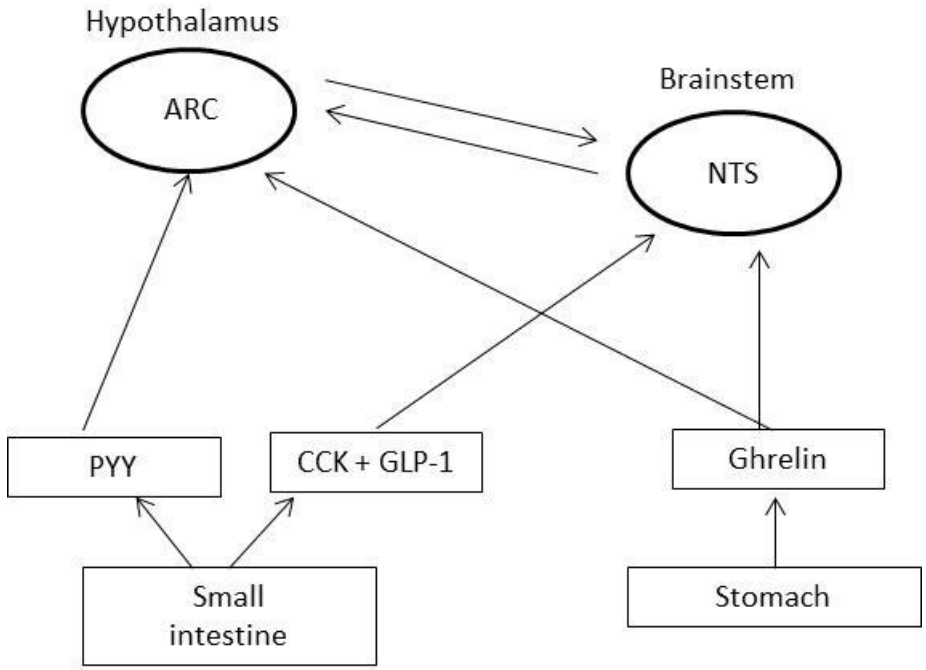
9. Give 8 central (CNS) and peripheral (non-CNS/GI) signals which influence food intake.

- GI
  - Stomach - ghrelin, leptin
  - Small bowel - PYY, CCK, GLP
  - Pancreas – insulin

- CNS
  - First order neurons
    - Arcuate nucleus – NPY, AGRP, POMC, CART
    - Paraventricular nucleus (PVN) – CRF, TRH, GLP-I
    - Lateral hypothalamic nucleus (LVN) – MSH, Orexin A, B
  - Cortex – Orexigenic, anorexigenic pathways

Abbreviations: AGRP, agouti-related protein; ARC, arcuate nucleus; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CRF, corticotrophin releasing factor; GLP-1, glucagon-like peptide; LHA, lateral hypothalamic area; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; NTS, solitary nucleus; POMC, proopiomelanocaortin; PYY, peptide YY3-36.

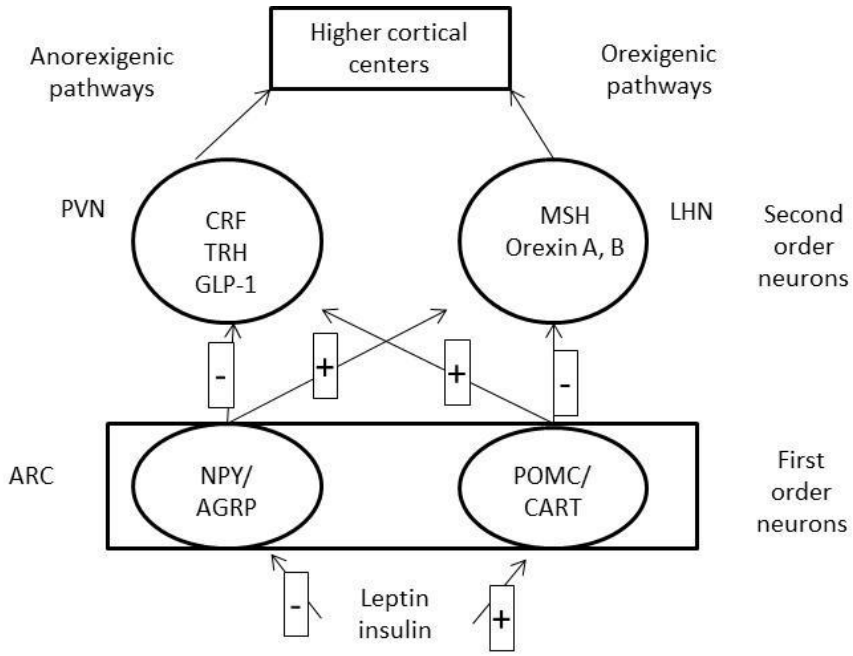
Useful background: Sites of action of non-CNS signals influencing food intake.



Abbreviations: ARC, arcuate nucleus; CCK, cholecystokinin; GLP-1, glucagon-like peptide; NTS, solitary nucleus; PYY, peptide YY3-36.

Printed with permission: Foxx-Orenstein AE. *2008 ACG Annual Postgraduate course book:* pg. 148.

Useful background: CNS networks implicated in the control of food intake



Abbreviations: AGRP, agouti-related protein; ARC, arcuate nucleus; CART, cocaine and amphetamine regulated transcript; CNS, central nervous system; CRF, corticotrophin releasing factor; GLP-I, glucagon-like peptide; LHN, lateral hypothalamic nucleus; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; NS, nervous system; POMC, proopiomelanocaortin; PVN, paraventricular nucleus; TRH, thyrotrophin-releasing hormone.

Printed with permission: Foxx-Orenstein AE. *2008 ACG Annual Postgraduate Course Book:* pg. 148.

10. Give 5 gastrointestinal hormones, and their behavioural brain effects on food intake.

Gastrointestinal hormone	Behavioural brain effects on Intake
➢ Foregut	
○ Leptin	↓
○ Ghrelin	↑
○ Obestatin	?
○ Pancreatic polypeptide (PP)	↓
➢ Hindgut	

- Cholecystokinin (CCK) ?
- Gastric inhibitory polypeptide (GIP) ↓
- Glucagon-like peptide-1 (GLP-1) ↓
- Peptide YY (PYY) ↓

Printed with permission: Vincent, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008 May; 5(5): pg 270.

Eating disorders

11. Give the diagnostic criteria for anorexia nervosa.

- Refusal to maintain minimal normal body weight
- Intense fear of weight gain
- Body-image disturbance (e.g. feeling fat when emaciated)
- Absence of three consecutive menstrual cycles
- Specific type
  - Restricting type: Person does not regularly engage in binge eating or purging behaviour (e.g. self-induced vomiting, use of laxatives)
  - Binge-eating/purging type: Person regularly engages in eating or purging behaviour (e.g. self-induced vomiting, use of laxatives)

Note: this table was adapted from the DSM-IV diagnostic criteria for anorexia nervosa

Printed with permission: Williamson DA, et al. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): pg 1074.

12. Give the diagnostic criteria for bulimia nervosa.

- Episodes of compulsive binge eating
- Lack of control over eating binges
- Use of extreme methods for controlling weight (self-induced vomiting, laxative abuse, diuretic abuse, restrictive dieting, or excessive exercise)
- At least two binge eating episodes per week for at least 3 months
- Obsessive overconcern with body shape, body weight, and body size
- Specific type
  - Purging type: Person regularly engages in purging behaviour (e.g. self-induced vomiting, use of laxatives, use of diuretics, or enemas)

- Non-purging type: Person does not engage in purging behaviour (e.g. self-induced vomiting, use of laxatives, use of diuretics, or enemas)

Note: this table was adapted from the DSM-IV diagnostic criteria for bulimia nervosa

Printed with permission: Williamson DA., et al. *Best Practice & Research Clinical Gastroenterology* 2004; 18(6): pg 1080.

13. Give 10 guidelines for the use of enteral tube feeding (ETF) in the adult patient.

- Conditions where tube feeding should be a part of routine care
  - Protein-energy malnutrition (greater than 10% weight loss) with little or no oral intake for 5 days
  - Less than 50% of the required oral nutrient intake for previous 7-10 days
  - Severe dysphagia or swallowing-related difficulties, e.g. head injury, strokes, motor neurone disease
  - Major, full-thickness burns
  - Massive small bowel resection (in patients with 50-90% small bowel resection, ETF is given to hasten gut regeneration and return to oral intake, often in combination with parenteral nutrition)
  - Low-output enterocutaneous fistulae* (<500 ml/day)

- Conditions where tube feeding would normally be helpful
  - Major trauma
  - Radiation therapy
  - Mild chemotherapy

- Conditions where tube feeding is of limited or undetermined value
  - Immediate postoperative period or post-stress period if an adequate oral intake will be resumed within 5-7 days
  - Acute enteritis
  - Less than 10% of the small intestine remaining (parenteral nutrition is usually indicated)

- Conditions/situations in which tube feeding should not be used
  - Complete mechanical intestinal obstruction
  - Ileus or intestinal hypomotility
  - Severe uncontrollable diarrhoea
  - High-output fistulae
  - Severe acute pancreatitis
  - Shock
  - Aggressive nutritional support not desired by the patient or legal guardian, in accordance with hospital policy and existing law

- Prognosis not warranting aggressive nutritional support

**If the fistula is proximal, the feeding should be distal. If the fistula is distal, sufficient proximal length must be present to allow sufficient absorption. Fistuale due to malignancy, radiation and distal obstruction are unlikely to close spontaneously*

Printed with permission: Stratton RJ, and Smith TR. *Best Practice & Research Clinical Gastroenterology* 2006; 20(3): pg. 457.

14. Give 10 complications of enteral tube feeding (ETF).

- Mechanical
  - Tube blockage by feed or tube kinking
  - Tube malposition (e.g. into trachea)
  - Insertion trauma
  - *Nasogastric* damage to nasal septum, esophagus, stomach, perforation (rare)
  - *Gastrostomy/enterostomy* damage to stomach, small bowel, bleeding, peritonitis, leakage, irritation and infection around site
  - Loss of tube into GI tract
- Feed/flow related
  - Diarrhea or constipation, bloating, cramps
  - Aspiration pneumonia/regurgitation
- Metabolic
  - Fluid and electrolyte disturbances
  - Hypo- and hyper-natremia, kalemia, phosphatemia, glycemia
- Infections
  - Infection around ostomy site
  - Infection of feed or administration set (very rare if commercial feed and set used according to guidelines)
- Organ dysfunction
  - Aspiration pneumonia may precipitate respiratory distress
- Psychological
  - Effects on self-image
  - Anxiety and depression
  - Social isolation (if unable to eat, if confined to bed/home)

Printed with permission: Stratton RJ, and Smith TR. *Best Practice & Research Clinical Gastroenterology* 2006; 20(3): pg. 459.

Food intolerances

15. Give 8 examples of immunological reactions to foods (food allergy, eg. immune-mediated mechanisms).

- Skin
  - Immediate gastrointestinal hypersensitivity
  - Oral allergy syndrome
  - Acute urticaria
  - Atopic dermatitis
  - Acute angioedema

- Lung
  - Acute bronchospasm
  - Asthma

- Gut
  - Celiac disease
  - Dermatitis herpetiformis (DH)
  - Cow's milk enteropathy
  - Food protein-induced enterocolitis
  - Food protein-induced proctocolitis or proctitis
  - Eosinophilic esophagitis, gastroenteritis

Adapted from: Klein S. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006:pg 467-483.

16. Give 8 examples of adverse reactions to food or food additives (not including immunological reactions to food).

- Eosinophilic esophagitis
- Allergic eosinophilic gastroenteritis
- Food protein-induced enterocolitis syndromes
- Food intolerance (non-immune mechanisms)
- Food toxicity or food poisoning
- Pharmacological reactions
- Metabolic reactions
- Idiosyncratic reactions
- Psychological reactions

- Physiological reactions

Adapted from: Klein S. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg 467-483.

17. Outline a management approach to the patient with suspected food allergies as a cause of GI symptoms.

- Establish foods and food additives that reproducibly cause symptoms
  - Careful history, including diet history
  - Elimination diet
  - Skin testing and/or RAST
  - Food antigen challenge
- Exclude and manage other disorders that may mimic GI food allergy
- Initiate treatment for food allergies
  - Elimination diet
  - Avoidance of specific foods
  - Medications for after accidental exposure (antihistamines, epinephrine, corticosteroids)
  - Preventive measures (oral cromoglycate, avoid co-precipitating factors, e.g., medications)
  - Education about hidden sources of antigens and cross-reacting foods

Adapted from: Ferreira CT, and Seidman E. *J Pediatr* (Rio J) 2007;83(1):7-20.

18. The psychiatric eating disorder bulimia nervosa may be associated with the misuse of laxatives. Give three clinical features that could confirm your suspicions of laxative abuse.

- Hypothermia
- Bradycardia
- Arrhythmia
- Dry skin
- Languor
- Hair loss
- Scars or calluses on the dorsum of hand
- Loss of dental enamel
- Large parotid glands
- Pedal edema

Abbreviations

AGRP	Agouti-related protein
ARC	Arcuate nucleus
BMI	Body mass index
CART	Cocaine and amphetamine regulated transcript
CCK	Cholecystokinin
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRF	Corticotrophin releasing factor
GLP-1	Glucagon-like peptide
IBW	Ideal bodyweight
LHA	Lateral hypothalamic area
LHN	Lateral hypothalamic nucleus
MSH	Melanocyte-stimulating hormone
NPY	Neuropeptide Y
NAFLD	Non-alcoholic fatty liver dieaseas
NASH	Non-alcoholic steatohepatitis
NPY	Neuropeptide Y
NS	Nervous system
NTS	Solitary nucleus
POMC	Proopiomelanocaortin
PVN	Paraventricular nucleus
PYY	Peptide YY3-36
SS	Simple steatosis
TRH	Thyrotrophin-releasing hormone
UBW	Usual body weight

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MISCELLANEOUS

TABLE of CONTENTS

GI therapy and pregnancy

1. For the following GI conditions, list the medications to avoid during attempts to become pregnant.

- Nausea/vomiting
  - Cisapride

- Dyspepsia, GERD
  - Sodium bicarbonate, Omeprazole, bismuth subsalicyclate for *H. pylori* eradication, misoprostol (PGE_2)

- EGD/colonoscopy
  - Avoid EGD in first trimester (T1) because you can't monitor the fetus
  - Full colonoscopy rarely indicated
  - Avoid diazepam, propofol in T1

- Liver disease
  - Interferon, ribavarin, B blockers, peniciliiamine

- Liver transplant
  - Mycophenolate, Sirolimus

- Constipation
  - Castor oil, mineral oil, Tegaserod

- Diarrhea
  - Kaopectate, Alosetron

- IBD
  - Methotrexate, ciprofloxacin

- IBS
  - Amitriptyline, nortriptyline, imipramine, SSRIs, bismuth

Adapted from: Kane S. *AGA Institute 2007 Spring Post Graduate Course Syllabus* pg. 511-513.

GI and neuromuscular diseases

2. Give 10 common causes of diarrhea in patients receiving oncological therapy.

- Fluoropyrimidines
  - 5-Fluorouracil
  - Capecitabine
- Irinotecan hydrochloride
- Oxaliplatin
- Small-molecule EGFR inhibitors
  - Erlotinib
- Small-molecular VEGF inhibitors
  - Sorafenib
- Monoclonal antibodies directed against EGFR
  - Cetuximab
- Radiation therapy
- Graft-versus-host disease
- *Clostridium difficile* infection
- Chemotherapy
- Radiotherapy
- Acute/chronic graft-versus-host disease
- *Cl. Difficile*
- Neutropenic enterocolitis

Abbreviations: ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; BMT, bone marrow transplantation; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; GH, growth hormone; GI, gastrointestinal; HSV, herpes simplex virus; LES, lower esophageal sphincter; MCT, medullary carcinoma of the thyroid; MEN, multiple endocrine neoplasia; SOS, sinusoidal obstruction syndrome; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal polypeptide

Printed with permission: Davila M, and Bresalier RS. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(12): pg.

Microbiology

3. Give the advantages and disadvantages of 4 common microbiological techniques.

Technique	Method	Advantage	Disadvantage
➢ Culture	○ Bacteria grown on selective mediums	- Cheap, widely available, and easy to use	- Grossly underestimates fecal populations
➢ PCR-T/DGGE denaturing/temperature gradient gel electrophoresis	○ Using either temperature or a denaturing agent to separate DNA strands, which are then run on a gel	- Very useful in detecting difference in bacterial populations	- Does not identify bacteria unless bands on the gel are cut and sequenced
➢ FISH (fluorescent *in situ* hybridization)	○ Oligonucleotide probes designed to hybridize with specific species	- Allows spatial organization of microbiota to be studies	- Slow, will only detect the bacteria probed for
➢ Quantitative PCR	○ Specific primers detect either individual species or genus	- Can detect small number of bacteria and quantify them	- Laborious
➢ 16S rDNA sequencing	○ Bacterial DNA isolated and ribosomal DNA cloned and then sequenced	- Enormous quantities of data at individual species level	- Very costly, available in only a few specialist centers

Printed with permission: Parkes GC, et al. *AJG* 2008;103: pg. 1561.

Abdominal pain

4. Give five causes of RUQ pain.

- ➢ Peptic ulcer disease (gastric or duodenal ulcer)
- ➢ Pancreatitis

- Hepatitis
- Cholecystitis
- Renal colic
- Pneumonia/pleurisy
- Empyema/pericarditis
- Coronary artery disease

5. Give four 'red flag' situations that indicate that surgery is necessary in the patient with an acute abdomen.

- Progressive abdominal distension
- Tender abdominal mass with fever and hypotension (abscess)
- Septicemia plus abdominal findings
- Suspected bowel ischemia (acidosis, fever, tachycardia)
- Deterioration of patient while on conservative treatment

6. Give 20 causes of abdominal pain in patients with HIV/AIDS, not including non-AIDS specific conditions.

Organ	Causes
➢ Stomach	
○ Gastritis	CMV, Cryptosporidia
○ Focal ulcer	CMV, PUD
○ Outlet obstruction	Cryptosporidia, CMV, lymphoma, PUD
○ Mass	Lymphoma, KS, CMV
➢ Small bowel	
○ Enteritis	Cryptosporidia, CMV, MAC
○ Obstruction	Lymphoma, KS
○ Perforation	CMV, lymphoma
➢ Colon	
○ Colitis	CMV, enteric bacteria, HSV
○ Obstruction	Lymphoma, KS, intussusception
○ Perforation	CMV, lymphoma, HSV
○ Appendicitis	KS, Cryptosporidia, CMV
➢ Liver, spleen	
○ Infiltration	Lymphoma, CMV, MAC

- Biliary tract
  - Cholecystitis — CMV, Cryptosporidia, Microsporidia
  - Papillary stenosis — CMV, Cryptosporidia, KS
  - Cholangitis — CMV

- Pancreas
  - Pancreatitis — CMV, KS, pentamidine,ddl
  - Tumour — Lymphoma, KS

- Mesentery, peritoneum
  - Infiltration — MAC, Cryptococcus spp., KS, lymphoma, histoplasmosis, tuberculosis, coccidioidomycosis, toxoplasmosis

Abbreviations: AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; ddl, didanosine; HSV, herpes simplex virus; KS, Kaposi's sarcoma; MAC, Mycobacterium avium complex; PUD, peptic ulcer disease

7. Give 15 causes of anorectal disease in patients with AIDS, not including non AIDS specific conditions.

- Infections
  - Bacteria
    - Chlamydia trachomatis*
    - Lymphogranuloma venereum
    - Neisseria gonorrhoeae*
    - Shigella flexneri
    - Mycobacterium tuberculosis
  - Viruses
    - Herpes simplex*
    - Cytomegalovirus*
  - Protozoa
    - Entamoeba histolytica
    - Leishmania donovani
  - Fungi
    - Candida albicans
    - Histoplasma capsulatum

- Neoplasms
  - Lymphoma*
  - Kaposi's sarcoma
  - Condyloma acuminatum
  - Squamous cell carcinoma (HPV)

- Cloacogenic carcinoma

- Other
  - Idiopathic ulcers*
  - Perirectal abscess
  - Fistula*

* More frequent diagnosis

Abbreviations: AIDS, acquired immunodeficiency syndrome. HPV, human papillomia virus.

8. Pain from injury to the viscera in the abdomen often presents as referred pain. In the following pathologies, where is the pain referred?

- Biliary colic- to right shoulder or scapula
- Renal colic- to groin
- Appendicitis- epigastric to RLQ
- Pancreatitis- to the back
- Perforated ulcer- to RLQ (right paracolic gutter)
- Ruptured aortic aneurysm- back or flank

Gum hypertrophy

9. Give 5 causes of gum hypertrophy.

- Gingivitis (e.g. from smoking, calculus, plaque, Vincent's angina (fusobacterial membranous tonsillitis)
- Drugs
- Phenytoin
- Pregnancy
- Scurvy (vitamin C deficiency: the gums become spongy, red, bleed easily and are swollen and irregular)
- Leukemia (usually monocytic)

Adapted from: Talley NJ and O'Connor S. 4th ed. Oxford. *Blackwell Science* 2001 .

Halitosis

10. Give 6 non-dental causes of halitosis.

- Infection
  - Poor oral hygiene
  - Putrid (due to anaerobic chest infections with large amounts of sputum)

- Metabolic
  - Fetor hepaticus (a sweet smell)
  - Ketosis (diabetic ketoacidosis results in excretion of ketones in exhaled air, causing a sickly sweet smell)
  - Uremia (fish breath: an ammoniacal odour)

- Drugs
  - Alcohol (distinctive)
  - Paraldehyde
  - Cigarettes, tobacco

Adapted from: Talley NJ and O'Connor S. 4th ed. Oxford. *Blackwell Science* 2001.

Useful background: The clinical features, diagnosis and treatment of sexually transmitted anorectal diseases

STI	Symptoms	Investigations	Treatment
Gonorrhea	Pruritis ani, mucopurulent anal disharge, rectal pain, tenesmus, bleeding	Culture and/or NAAT Anoscopy; rectal friability, erythema, ulceration and mucus	Ceftriaxone (250 mg intramuscularly) and doxycycline (100 mg orally twice daily) for 1 week
HSV	Vesicular lesions, anal pain, tenesmus, discharge, viremic symptoms, lymphadenopathy, pruritis ani, mucoid and/or bloody diarrhea, psychogenic	Viral culture and/or NAAT Anoscopy; perianal vesicles, rectal ulcers, rectal inflammation	Aciclovir (200 mg orally five times daily) for 5 days

	constipation, sacral paraesthesia, impotence		
Amoebiasis	Bloody diarrhea	Microscopy of stool Anoscopy; friable rectal mucosa, shallow ulcers with exudates and ring of erythema	Metroidazole (500-750 mg orally three times daily) for 5-10 days

STI	Symptoms	Investigations	Treatment
Shigellosis	Abdominal cramps, fever, bloody diarrhea	Culture of stool	Trimethoprim-sulfamethoxazole (double strength) orally twice daily for 7 days, or tetracycline 1.5g once and ampicillin 500 mg orally four times daily for 7 days
Non LGV chlamydia	Commonly asymptomatic but can involve pruritis ani, mucoid discharge, perianal pain	NAAT	Doxycycline (100 mg orally twice daily) for 1 week
LGV chlamydia	Purulent anal discharge, pain, tenesmus, fever, malaise genital ulcers/papules, lymphadenopathy (buboes)	NAAT Anoscopy; friable, ulcerated rectal mucosa with or without rectal mass	Doxycycline (100 mg orally twice daily) for 3 week
Primary syphillis	Anorectal chancres, anal pain, discharge, tenesmus, itching,	Dark field microscopy Serology tests	Procaine penicillin (750 mg intramuscularly

	bleeding, mucus membrane lesion, maculopapular rash	(eg RPR, TPPA, TPHA)	once daily) for 10 days or benzothine penicillin (2.4g intramuscularly once) or doxycycline (100 mg orally twice daily) for 14 days
Secondary syphillis	Snail track ulcers, perianal condylomata lata	Dark field microscopy Serology tests (eg RPR, TPPA, TPHA) Anoscopy; painful anal ulcer	Procaine penicillin (750 mg intramuscularly once daily) for 10 days or benzothine penicillin (2.4 g intramuscularly once) or doxycycline (100 mg orally twice daily) for 14 days

Abbreviations: HSV, Herpes simplex virus; LGV, lymphogranuloma venereum; NAAT, nucleic acid amplification testing; RPR, rapid plasma regain test; STI, sexually transmitted infection; TPHA, treponema pallidum hemagglutination assay; TPPA, treponema pallidum particle agglutination

Printed with permission: Siew C. Ng & Brian Gazzard. *Nat Rev Gastroenterol. Hepato* 2009;6:592-607, Table 1, page 594.

Useful background: Gastrointestinal manifestations of HIV infection

- Upper gastrointestinal tract
  - Esophagitis
  - Esophageal ulcers (eg caused by cytomegalovirus or candida spp.)

- Small intestine and colon
  - HIV associated enteropathy
  - HIV associated diarrhea

- Anorectal
  - Non-specific proctitis
  - Anal fistula and/or abscess and/or fissure
  - Rectal ulcers
  - Weight loss and wasting

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Useful background: Causes of HIV associated diarrhea

- Infectious pathogens
  - Viruses
    - Cytomegaloviruses
    - Adenoviruses
    - Herpes simpex virus
  - Bacteria
    - Shigella spp.
    - Salmonella spp.
    - Mycobacterium avium intracellulare
    - Clostridium difficile
    - Listeria monocytogenes
    - Enteroaggresive escherichia coli
  - Parasites
    - Microsporidia
    - Cryptosporidium parvum
    - Isopora belli
    - Entamoeba histolytica
    - Giardia lamblia
  - Fungi

- Non-infectious causes
  - Kaposi sarcoma
  - Intestinal lymphoma

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Useful background: Conditions that can cause systemic AA amyloidosis

- Inflammatory arthritis
  - Adult Still disease
  - Ankylosing spondylitis
  - Juvenile idiopathic arthritis
  - Psoriatic arthropathy
  - Rheumatoid arthritis

- Chronic infections
  - Bronchiectasis
  - Osteomyelitis
  - Tuberculosis
  - Skin abscesses (usually from injected drug abuse)

- Immunodeficiency states
  - Common variable immunodeficiency
  - HIV or AIDS

- Hereditary periodic fevers
  - Familial Mediterranean fever
  - Hyperimmunoglobulin D syndrome
  - Muckle Wells syndrome
  - TNF receptor associated periodic syndrome

- IBD
  - Crohn's disease
  - Ulcerative colitis

- Neoplasia
  - Castleman disease
  - Renal cell carcinoma
  - Adenocarcinoma of the lung, gut, and urogenital tract

- Systemic vasculitis
  - Behcet disease
  - Systemic lupus erythematosus

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Useful background: Treatment of systemic amyloidosis

Disease	Aim of treatment	Example of treatment
➢ AA amyloidosis	○ Suppress the acute phase response and, thereby, reduce the production of serum amyloid A protein	- Anti inflammatory and immunosuppressive therapy in patients with rheumatoid arthritis and Crohn's disease (e.g. anti TNF antibodies) Coichicine for patients with familial Mediterranean fever - Surgery for patients with osteomyelitis and rare cytokine producing tumours
➢ AL amyloidosis	○ Suppress production of monocional	- Chemotherapy directed at plasma cell dyscrasia

		immunoglobulin light chains	
➢ Hereditary amylodosis	○	Eliminate source of genetically variant protein	- Orthotopic liver transplantation for patients with familial amyloid polyneuropathy secondary to variant transthyretin or renal amyloidosis secondary to variant fibrinogen A chain
➢ B2 microglobulin amyloidosis	○	Reduce plasma concentration of B2 microglobulin	- Renal transplantation

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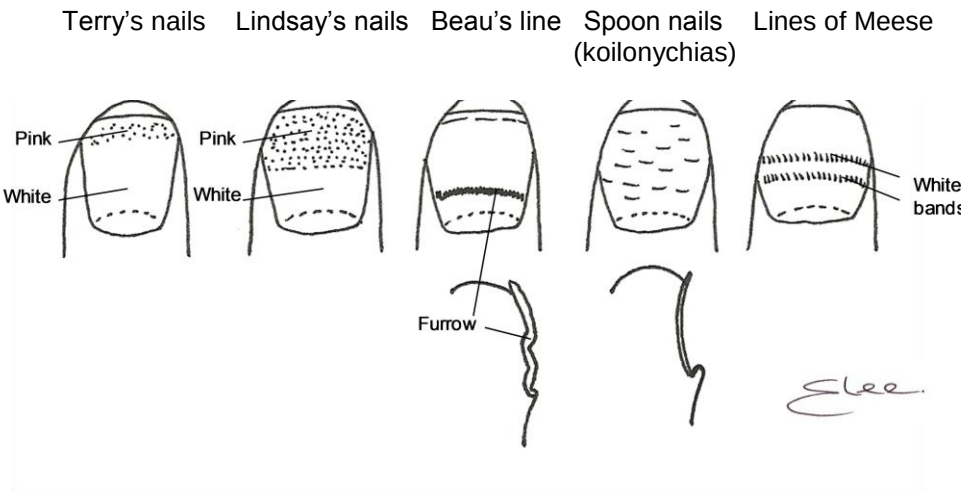
GI and rheumatological diseases

11. Give 5 conditions of alteration in the normal appearance of the nails of the hands.

- Terry's nails (from the British physician who first described them in 1954): characterized by whitening of the proximal 80% of the nail, leaving a small rim of peripheral reddening. They are seen in older people or patients with heart failure, cirrhosis, or non-insulin dependant diabetes.
- Red half moons in nail beds (variety of Terry's nails, also described by Terry): characterized by a lunula that is not white but red. They also are called the nails of cardiac failure.
- Azure half moons in nail beds: the nails of Wilson's disease (hepatolenticular degeneration). The lunulae are not white but light blue.
- Muehrcke's lines (from the American nephrologist who first described them in 1956): two arcuate white lines parallel to the lunula and separated by normal nail. Because they are located in the nail bed (not the nailplate). Muehrcke's lines do not progress with the growth of the nail. They are seen in patients with hypoalbuminemia (<2 gm/100 ml) and disappear with its resolution.

- Beau's lines: transverse grooves on the fingernails of patients recovering from a serious illness such as myocardial infarction. They were first described by the French physician Joseph H.S Beau (1806-1865).
- Mee's lines (also called Reynolds or Aldrich lines): transverse white lines distal to the cuticle. They are seen in arsenical or thallium poisoning, cancer chemotherapy, Hodgkin's lymphoma, and other systemic disorders, such as severe cardiac or renal disease. They were first described by the Dutch physician R.A Mees.
- Nail pitting: an early (but non-specific) sign of psoriasis.
- Yellow nail syndrome: characterized by a yellowish colour of the plates due to abnormal lymphatic circulation.
- Brittle nails: seen in various dysmetabolic states such as hyperthyroidism, malnutrition, and iron or calcium deficiency. They are characterized by irregular , frayed, and torn nail borders.
- Splinter hemorrhages: linear red hemorrhages, extending from the free margin of the nail bed toward the proximal margin. Traditionally considered a typical finding of subacute bacterial endocarditis or trichinosis, they result much more commonly from trauma.
- Leuconychia-white nails, beginning at the lunula-may be normal; seen in cirrhosis, leprosy, arsenic poisioning, vasomotor disturbance of fingers



Adapted from: Mangione S. Physical Diagnosis Secrets. *Hanley & Belfus*, Philadelphia, 2000, page 412.

Useful background: Mechanisms of HIV transmission into the gastrointestinal tract.

- Once released from the basal surface of the epithelial cell, HIV-1 infects CCR5+ lymphocytes in the lamina propria. The virus efficienctly replicates in activated CD4+ T cells of the lamina propria. The distribution of HIV coreceptors within the mucosa may also permit infection of cells central to antigen presentation such as macrophages and dendritic cells. Dendritic cells of the lamina propria express C type lectin that traps the virus and assists in the dissemination of HIV-1 from the gastrointestinal tract to secondary lymphoid organs. After 2 weeks of infection T cell death occur by cell lysis apoptosis and by cytotoxic lymphocytes, resulting in rapid depletion of lamina propria CD4+ T cells.

Abbreviation: CCR, CC-chemokine receptors

Source: Siew C. Ng & Brian Gazzard. *Nat Rev Gastroenterol. Hepato* 2009;6:592-607, page 594.

Abbreviations

ACTH	Adrenocorticotropic hormone
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
BMT	Bone marrow transplantation
CMV	Cytomegalovirus
CSS	Churg-Strauss syndrome
dDI	didanosine
EBV	Epstein-Barr virus
EGFR	Epidermal growth factor receptor
GH	Growth hormone
GI	Gastrointestinal
HSV	Herpes simplex virus
KS	Kaposis sarcoma
LES	Lower esophageal sphincter
LGV	Lymphogranuloma venereum
MAC	Mycobacterium avium complex
MCT	Medullary carcinoma of the thyroid
MCTD	Mixed connective tissue disease
MEN	Multiple endocrine neoplasia
NAAT	Nucleic acid amplifiction testing
PAN	Polyarteritis nodosa
PO	Orally
RPR	Rapid plasma regain test
SBP	Spontaneous bacterial peritonitis
SLE	Systemic lupus erythematous
SOS	Sinusoidal obstruction syndrome
STI	Sexually transmitted infection
TMP- SMX	Trimethoprim sulfamethoxazole
TPHA	Treponema pallidum hemagglutination assay
TPPA	Treponema pallidum particle agglutination
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal polypeptide

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