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GASTROENTEROLOGY AND HEPATOLOGY

Efficient Refresher for the Busy Clinical Gastroenterologist

Volume 6

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The editors wish to thank the trainee and staff contributors who maintain the excellence of the Division of Gastroenterology at Western University.

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DEDICATION

We dedicate this book to the persons and families

Who lost loved ones due to Covid-19 infection.

We also dedication this to all frontline workers

Who so generously gave us their wisdom, care and skill in

these difficult times.

Nilesh Chande

Karim Quaroni

Alan Thomson

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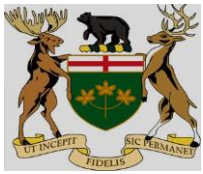
ESOPHAGUS

ESOPHAGEAL MOTILITY DISORDERS (EMD)

Alan Thomson



- Definition
  - A patient is said to have an esophageal motility disorder if their findings on motility study are two standard deviations beyond normal.

- Classification
  - There are multiple classifications shown here but the most widely used are based upon high resolution esophageal manometry (HREM), and used now in most examination and clinical settings.
  - Esophageal motility disorders may be primary or secondary to (associated with) another disease process.

- Give a simple classification of esophageal motility disorders (EMD).

Primary EMD	Secondary EMD	Manometric Variants
○ Achalasia (three subtypes)	– Pseudo-achalasia	▪ Hypertensive peristalsis
○ Diffuse/distal esophageal spasm (DES)	– Chagas disease	▪ Hypertensive LES
○ Nutcracker esophageal	– Scleroderma esophagus	▪ Ineffective esophageal motility
○ Absent peristalsis	– Parkinson disease	
○ Gastroesophageal reflux disease (GERD)	– Infiltrative disorders	

- Give the classification of esophageal motor abnormalities based upon conventional manometry.

Upper Esophageal Sphincter (UES)	Esophageal Body (EB)	Lower Esophageal Sphincter (LES)
↑ Contraction ○ Zenker 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 disease ○ Cricopharyngeal bar ○ Belch dysfunction	**↓ Co-ordination** – Diffuse esophageal spasm (DES) – Achalasia (absent or simultaneous contractions)	**↓ Co-ordination** ▪ (relaxation*) ▪ Achalasia, type I ▪ Atypical LES 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; MCTD, mixed connective tissue disease; UES, upper esophageal sphincter

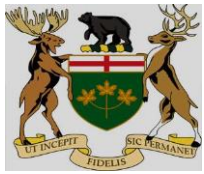
- Give the advantages of high-resolution esophageal manometry (HREM), and high resolution esophageal pressure topography (HREPT).
    - High quality, uniform format
    - Greater reproducibility
    - Viewing simultaneous contractions of the entire esophagus
    - Standardized objective metrics
    - Topographic patterns easily learned and recognized
    - Allows for subclassification of achalasia, and of DES.

- **Give classification of** esophageal motor abnormalities based on high-resolution manometry.
    - Normal
        - Normal EGJ pressure (10-35 mm Hg) and relaxation (see below)
        - Peristaltic velocity <8 cm/s in >90% of swallows
        - ↑ intra-bolus pressure at <8 cm/s to <30 mm Hg in > 90% of swallows
        - Normal velocity, <8 cm/s in > 90% of swallows; normal peristaltic amplitude; (≥7 peristaltic contractions with an intact wave progression [amplitude >30 mmHg])
        - Mean distal contractile index (DCI) <5000 mm Hg·s·cm**

- Peristaltic dysfunction
  - Mild
    - 3-6 swallows with failed peristalsis or
    - >2 cm defect in the 30 mm Hg
    - Isobaric contour of the distal esophageal peristalsis (15 mm Hg in proximal-mid esophagus)
  - Severe
    - 7 swallows with either failed peristalsis or
    - >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)
    - Absent or simultaneous contractions (<30 mmHg)
- 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
    - LOS after-contraction: mean DCI 5000-8000 mm Hg·s·cm

❖ Spastic esophageal motility disorders

- Nutcracker esophagus
  - Nutcracker esophagus may be a hypercholinergic condition which leads to a loss of the normal synchrony between the inner



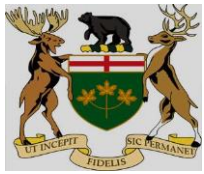
circular and other longitudinal smooth muscle layers of the esophagus.

- Average peristaltic amplitude >180 mmHg over pressure sensors 3 and 8 cm above LES
- Modest ↑ amplitude → better transit (less dysphagia) plus NCCP
- ≥ 20% simultaneous contractions with an amplitude of > 30 mm Hg
- 1/3 of DES patients also have ↑ LES pressure a ↓ LES relaxation
- This latter subgroup of DES may actually have achalasia (on HREPT, distal latency plus DES may be spastic achalasia).
- Barium sallow in DES
  - May be normal, or show corkscrew esophagus
  - Low sensitivity and specificity
- The average amplitude in the distal 10 cm of esophagus from ≥ 10 5 mL liquid swallows, ≥ 220 mm Hg
- HREPT defines 2 subgroups of nutcracker esophagus, based on the DCI
- DCI (distal contractile integral) is an integration of the amplitude, duration and length duration of a contraction.
- DCI is expressed as mm Hg.s.cm
- Values of DCI on HREPT
  - Normal ≤ 5000 mm Hg.s.cm
  - Nutcracker 5000 to 8000 mm.Hg.s.cm
  - Spastic nutcracker 8000 mm.Hg.s.cm
- May be associated with ↑ LESP pressure and ↓ LES relaxation.
- The manometric diagnosis of a motility disorder may change if it is performed at a time the patient is having symptoms.

- Hypertensive LES (lower esophageal sphincter)
  - Resting LES > 45 mm Hg
  - ~ 50% have ↓ LES (> 35 mm Hg on HREPT) relaxation and ↑ amplitude distal esophageal contraction amplitude, as high as ≥ 220 mm Hg.
- The relationship between a manometric event and the patient's symptoms may be poor, and association indices have been developed to establish the probability of a cause and effect relationship between a motility event, e.g., gastroesophageal reflux or DES, and patient symptoms, e.g., heartburn or NCCP (non-cardiac chest pain).

- 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 esophagitis, 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
    - The nutcracker esophagus and a hypertensive LES may be seen in persons with GERD



- Hypertensive peristalsis ("nutcracker esophagus") is defined by high-amplitude peristaltic contractions and can be associated with dysphagia and/or chest pain.
- Nutcracker esophagus is relatively common heterogeneous condition encountered in normal controls, dysphagic, and reflux disease patients.
- Esophageal hypercontractility is defined in esophageal pressure topography (EPT) by the occurrence of propagated swallow-induced contractions with distal contractile integral (DCI) > 8,000 mm Hg-s-cm (a magnitude never encountered in control subjects).
- Hypercontractility, ("Jackhammer Esophagus") is associated with multi-peaked contractions, is rare, and is usually associated with dysphagia.
- Subsets of patients with "Jackhammer Esophagus" had this as an apparent primary abnormality of hypercontractility or in association with EGJ outflow obstruction or reflux disease.
- DES (diffuse [or distal] esophageal spasm)
  - In DES (distal or diffuse esophageal spasm), there is an uncertain relationship between symptoms and the DES motility changes
  - Contractile velocity >8 cm/s mmHg over pressure sensors 3 and 8 cm above LES in $\geq$2 swallows

Abbreviations: DES, distal or diffuse esophageal spasm; DSRS, distal splenorenal shunt; EHT, endoscopic hemostatic therapy; LES, lower esophageal sphincter; MCTD, mixed connective tissue diseases; MII, multichannel intraluminal impedence; TIPS, transjugular intrahepatic postoperative shunt; 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 Pract Res Clin Gastroenterol* 2007;21(4): pg. 575-576.

Achalasia

- Definition
  - Primary achalasia is associated with loss of ganglion cells in the myenteric plexus of the esophagus.
  - In order to make the diagnosis of achalasia, there must be standard manometric or HREPT evidence of
    - Loss of peristalsis in distal esophagus (GBA)
    - Loss of relaxation ± opening of LES (lower esophageal sphincter), plus (Impaired deglutative EGJ relaxation and/or opening)
    - There may also be ↑LES pressure (not required for diagnosis)
  - ↑ intra-esophageal bolus pressure due to resistance to flow at EGJ
    - *Classic*
      - Aperistalsis with no identifiable contractile activity
    - *Vigorous (compression: compartmentalized pressurization)*:
      - Persistent contractile activity (spasm)
      - ↑ intra-esophageal bolus pressure, +/- esophageal shortening
    - *Variant*
      - Preserved peristalsis in the distal esophagus in ≥20% swallows

Abbreviations: EGJ, esophagogastric junction; LES, lower esophageal sphincter

- Give subtypes of achalasia made by high-resolution manometry (HRM) and compare the treatment responses with each type.

	Type I (Classic)	Type II (Compression)	Type III (Spastic)
○ 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%

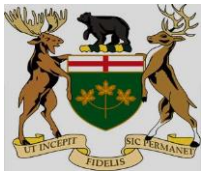
○ Response to achalasia treatment varies by subtypes.

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

➢ Causes

- Give causes of secondary achalasia (**pseudoachalasia**).
  - Infection/Infiltration
    - Sarcoidosis
    - Sjogren syndrome
    - Amyloidosis
    - Fabry disease
    - Chagas disease (↓ infection with Trypanosoma cruzi)

- Cancer
  - GI
    - Squamous cell carcinoma (SCC) of the esophagus
    - Adenocarcinoma of the esophagus (EAC)
    - Hepatocellular carcinoma (HCC)
    - Pancreatic adenocarcinoma
  - Non-GI (Paraneoplastic syndrome)
    - Lung carcinoma (non-small cell)
    - Metastatic prostate carcinoma
    - Metastatic renal cell carcinoma
    - Breast adenocarcinoma
    - Leiomyoma
    - Lymphoma
    - Reticulum cell sarcoma
    - Lymphangioma
    - Mesothelioma
- Motility abnormalities
  - Achalasia with associated Hirchsprung disease
  - Familial achalasia
  - Fundoplication
  - Hereditary hollow visceral myopathy
  - Parkinson disease
- Surgical
  - Post-fundoplication
  - Post-vagotomy



- Miscellaneous
  - Allgrove syndrome (AAA syndrome) – (Alacidygia, Addisons disease, Achalasia)
  - Hereditary cerebellar ataxia (HCA)
  - Autoimmune polyglandular syndrome type II
  - MEN IIb (Sipple Syndrome)

Adapted from: *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2016, 10th edition, page 721.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Achalasia is rare, and an even rarer condition is achalasia secondary to a tumour (e.g., small cell lung cancer).

- Give the molecular basis for the paraneoplastic syndrome which may case secondary achalasia, gastroparesis, small intestinal pseudo-obstruction, or colonic intertia.
  - An epitope on the cancer forms an antibody (anti-Hu) which attaches to the myenteric plexus of different portions of the GI tract, resulting in dysmotility.

- Diagnostic imaging
  - Esophageal dilatation
  - Poor esophageal emptying
    - Retention of food/fluids
  - Bird-beak deformity of EGJ

- Absent gastric air bubble (on chest x-ray)
  - Retention of barium on esophagogram (height of barium column may be useful directly to severity of obstruction)

➢ Treatment

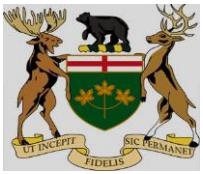
❖ Smooth muscle relaxation (relaxants taken 15 to 30 min before meals)

- Calcium channel blockers
  - Nifedipine
  - Nitrates
- Botulinum toxin injection into the area of LES
  - ↓ acetylcholine-releasing excitatory neurons innervating the smooth muscle of the LES (lower esophageal sphincter), which thereby lowers the LES pressure.

❖ Smooth muscle damage

- Esophageal dilation
  - Bougie
  - Forceful balloon dilation (BD; tears some of the smooth muscle fibres)
  - Success rates

Months	%
6	74%
12	~75%
24	86%
≥ 36	58%



- Post-procedure
  - Perforation, 2 to 4%
  - Heartburn, 45%
  - Repeated dilations if dilation fails (there may be risk of complications from subsequent surgical myotomy)
  - Note that if BD fails and surgical myotomy is required, the adverse outcomes are more severe

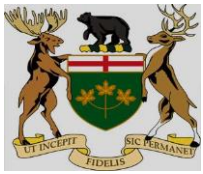
- Surgical myotomy (Heller myotomy, thoracic, or abdominal approach)
  - Success rate higher (70% to 90%), and recurrence rate lower at 10 yr, 70% to 85%; 20-30 yr, 65% to 75% lower than forceful pneumatic dilation
    - The 5 yr likelihood of being asymptomatic after laparoscopic myotomy for achalasia is 87%.
  - Short-term complications
    - Esophageal perforation ~5%
    - Mortality < $1/10^3$
  - Long-term complications include
    - GER (gastroesophageal reflux) (heartburn, strictures, BE and adenocarcinoma of esophagus)
    - With fundoplication, risk of GER falls from 32% to 9%
- Laparoscopic myotomy

- Give the influence (approximate %) of endoscopic procedures performed for achalasia (pneumatic dilation or injection of botulinum toxic) which fail and are followed by surgical myotomy, as compared with surgical myotomy not proceed by endoscopic treatment.

Adverse Outcomes	Surgical Myotomy Alone	Surgical Myotomy Proceeded by Endoscopic Therapy
○ Complications		
– Intraoperative	4%	10%
– Post-operative	5%	10%
○ Persistent or recurrent symptoms	10%	20%

- Give the pre-operative factors which are associated with a higher risk of failure from laparoscopic myotomy.
  - LES pressure > 30 mm Hg (high)
  - Dilated S (sigmoid) shape esophagus
  - Chest pain
  - Peroral endoscopic myotomy [a POEM form of NOTES: natural orifice transluminal endoscopic surgery])
  - > 90% clinical success rate, improved Eckhard symptom score, as well as improved manometry outcomes.

Source: von Rentein D, et al. Am J Gastroenterol 2012; 107: 411-417.



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

- Pharmacological

Comparative Feature	Smooth Muscle Relaxants	Botulinum Toxin Injection
○ Response		
– Early (<1 yr)	- 50%-70%	▪ 90% at 1 mon
– Late (>1-5 yr)	- <50%	▪ 60% at 1 yr
○ Morbidity	- Headache, hypotension (30%)	▪ Rash ▪ Transient chest pain (20%)
○ 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
○ Response			
– Early (< 1 yr)	– 60%-90%	– >90%	– >90%
– Later (> 1-5 yr)	– 60%	– 75% (at 20 yrs)	– 85%
○ Morbidity	– Rare – Techinique-related – 3%-5% perforation	– <10% at 1 yr – Symptomatic reflux (<10 % at 1 yr) – Dysphagia (10%) Mortality (<2%)	– Symptomatic reflux (10%) – NR
○ Advantage	– Good response durability	– Best response rate and durability	– Avoids thoracotomy, result is likely equivalent to open myotomy technique
○ Disadvantage	– See Morbidity	– Thoracotomy required – Severe reflux may develop	– Long-term outcome unknown, small conversion to open procedure

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.

Diffuse/Distal Esophageal Spasm (DES), Nutcracker Esophagus, and Hypertensive LES

- Treatment of DES, nutcracker esophagus and hypertensive LES
  - Calcium channel blocker
    - Diltiazem 60 mg to 90 mg po qid
  - Anti-depressive
    - Trazodone 100 mg to 150 mg/day
    - Imipramine 50 mg/day at bedtime
  - Anticholinergic
    - Bethanechol
  - Anti-phosphodiesterase
    - Sildenafil (50 mg prn); tadalafil; vardenafil
  - Nitrates
    - Isosorbide 10 mg
  - Peppermint oil 3 drops per day
  - Botulinum toxin endoscopic injection
    - 20 units/mL injection at the Z-line 5 circumferential injections
    - Inhibits the acetylcholine-releasing excitatory neurons innervating the smooth muscle of the LES, which thereby lowers the LES pressure.
  - Warm/hot water
  - Pneumatic dilation management of any associated psychological symptoms
  - Surgical myotomy

Adapted from: Roman S, et al. Am J Gastroenterol 2012; 107: 27-45.

Zenker Diverticulum (ZD)

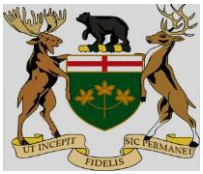
- Definition
  - A protrusion of the mucosa of the upper esophagus through Killian triangle (oblique muscle of the inferior pharyngeal constrictor muscle and the cricopharyngeal sphincter), producing a false diverticulum with its neck proximal to the cricopharyngeal muscle.

- Pathophysiology
  - Motor abnormalities of upper esophagus
    - ↑ degeneration of skeletal muscle fibres in upper esophagus
    - ↑ replacement of degenerated muscle with fibrous and adipose tissue
    - ↓ opening of UES (upper esophageal sphincter)
    - ↑ intrabolus pressure upon swallowing
    - ↑ hiatus hernia (possibly from ↑ GER)
    - ↑ GER (gastroesophageal reflux > 50%,
      - BE [Barrett epithelium] in ~20%)
      - ↑ risk of squamous cell carcinoma in the diverticulum

Clinical Alert

While videofluoroscopy may be a good test to detect a small ZD, video capsule endoscopy is not! Give why.

- Because the device may become trapped in the pseudodiverticulum.

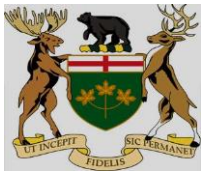


- Diagnostic imaging
  - Cricopharyngeal bar
    - A prominent cricopharyngeal bar from hypertrophy of the cricopharyngeal muscle may occur in patients with Zenker diverticulum and contribute to the symptoms of the diverticulum.
    - However, a crycopharyngeal muscle may appear to be prominent on an upper GI barium swallow performed in persons with a variety of neuromuscular disorders.
      - Amyotrophic lateral sclerosis (ALS)
      - CVA (stroke)
      - Multiple sclerosis (MS)
      - Myasthenia gravis (MG)
      - Myopathies

- Treatment
  - Endoscopic (flexible) or surgical (internal) myotomy of crycopharyngeal muscle (sphincterotomy), plus diverticulopexy
  - ESED (endoscopic stapler esophagodiverticulostomy)
  - One-or-two-step excision of ZD
  - External sphincterotomy

Scleroderma Esophagus

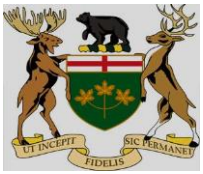
- Give the effects of scleroderma (systemic sclerosis [SSc] on the GI tract.
  - Mouth xerostomia
    - Facial exercises (small mouth)
    - Difficult hygiene
    - Erosion of lower teeth
  - Esophagus
    - SSc associated loss of LES and of peristalsis leads to ↑ risk of symptoms and esophagitis, including severe (LA C-D) disease
    - Treat the GERD as per usual (non-SSc), remembering the higher risk of:
      - Need for higher dose PPI
      - NAB (nocturnal acid breakthrough)
      - Strictures
      - ENT complications, especially aspiration
      - Pill-associated esophagitis
  - Stomach
    - Delayed gastric emptying (may worsen GERD)
    - Bleeding from telangiectasia
  - Small intestine
    - Small intestinal bacterial overgrowth (SIBO)
      - Slow small intestinal transit in SSc from ↓ MMCs (migrating motor complexes) leads to stasis and to SIBO
      - Antibiotic therapy (7 to 10 days); intermittent, episodic, continuous, or rotational
        - Tetracycline 250 mg po qid
        - Trimethoprim 200 mg po bid
        - Amoxicillin-clavulanate po tid
        - Metronidazole 250 mg to 500 mg tid to qid



- Dysmotility, pseudo-obstruction, nutritional risk
  - Home parenteral nutrition (HPN)
  - Octreotide
  - Percutaneous endoscopically-placed gastrostomy or jejunostomy feeding tube (PEE/PEJ)
  - Total parenteral nutrition (TPN)

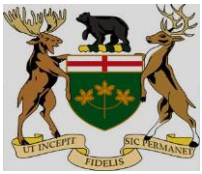
- Colon
  - Constipation
  - Fecal incontinence
  - Wide-mouthed colonic diverticula
- Liver
  - Primary biliary cirrhosis (PBC)

SMALL BOWEL



CLINICAL PHARMACOLOGY IN INFLAMMATORY BOWEL DISEASE

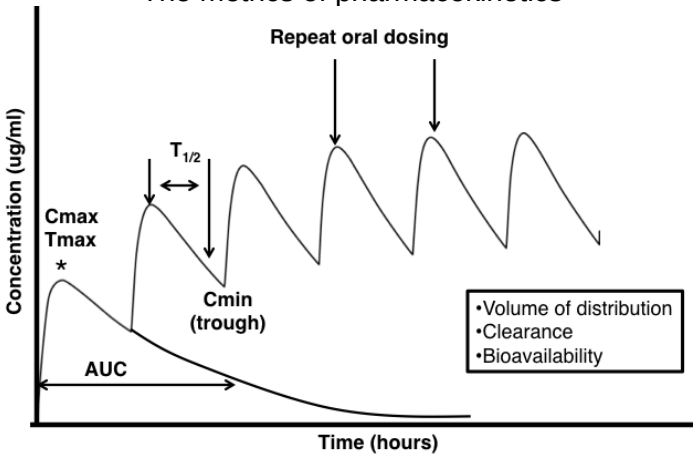
Aze Wilson



Clinical Pharmacology

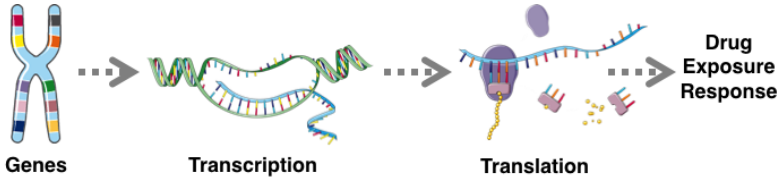
- Definition
  - The study of drugs in humans
    - Includes the basic science of pharmacology with the application of pharmacological principles and methods in the real world
      - Discovery of new target molecules
      - Evaluation of a drug's effect in a population

- Terminology
  - **Pharmacokinetics** (PK)
    - What happens to a drug while it is in the body
    - The study of how an organism affects a drug
    - Components
      - Absorption
      - Distribution
      - Metabolism (biotransformation or inactivation)
      - Excretion
    - The metrics of pharmacokinetics



    - therapeutic drug monitoring (TDM)

- Pharmacodynamics (PD)
  - Clinical endpoints
- Drug-drug interactions
  - What drugs do to each other in the body
- Pharmacogenomics
  - The effect of gene patterns on drugs
  - *"The study of how our genetic makeup affects drug response"*
    - Variation in key genes (metabolism, transport, regulation) may affect gene expression



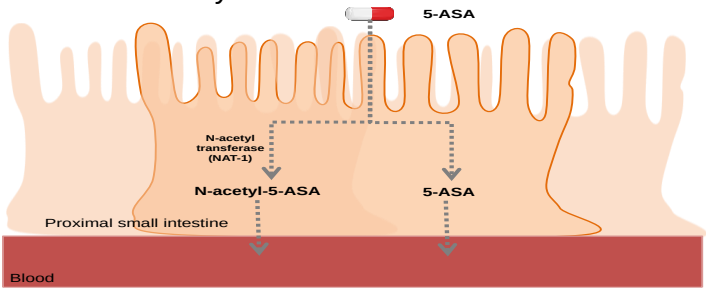
Artwork from http://smart.servier.com

  - Most drugs mimic or inhibit physiological or pathological processes in animals, or
  - Inhibit vital processes of microbial organisms

➢ Treatment challenges
- Multiple disease phenotypes
- Pathogenesis remains a mystery
- Drug exposure **DOES NOT EQUAL** response
- Significant inter- and intra-patient variability
- Risk of significant/severe adverse drug effects
- Biomarkers predicting efficacy or failure of biologics and small molecule drugs in the hope of personalized therapy.

- Pharmacokinetics

- 5-aminosalicylates

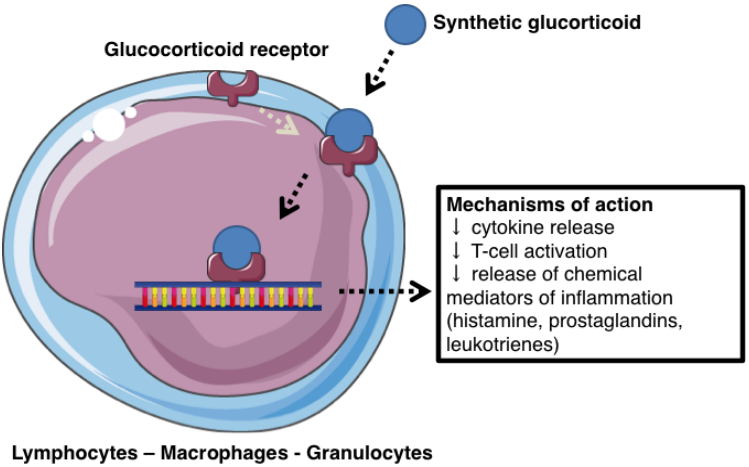


  - 5-ASA converted to acute agent, N-acetyl-5-ASA, by N-acetyltransferase (NAT-1) in enterocytes and colonocytes
  - Plasma concentrations are variable in both IBD patients and in healthy persons
  - Systemic bioavailability is low (20%) vs 80% available at TI and colon (topical benefit)
    - ↑ with multiple daily dosing
    - ↓ with higher doses
    - Steady state at 5 days
      - Note that since the action of n-acetyl-5-ASA is topical in the enterocytes and colonocytes, a lower concentration in the clood (bioavailability) reflects more active drug in the mucosa, or unabsorbed non-active drug (5-ASA) in the gut lumen
  - Interact with pathways of inflammation and apoptosis
    - "Interferes" with TNF-α, TGF-β, NFκB
    - Scavenger for reactive oxygen species (ROS)
    - Alter fecal bacteria profiles
    - ↓ leukocyte motility

- Effective for inducing remission and preventing relapse in UC
- Combined oral and topical therapy is superior to oral therapy alone for induction of remission in mild to moderate UC
- ADRs: flatulence, abdominal pain, nausea, diarrhea, rash, headache

Abbreviation: ADR, adverse drug reaction

❖ Glucocorticoids

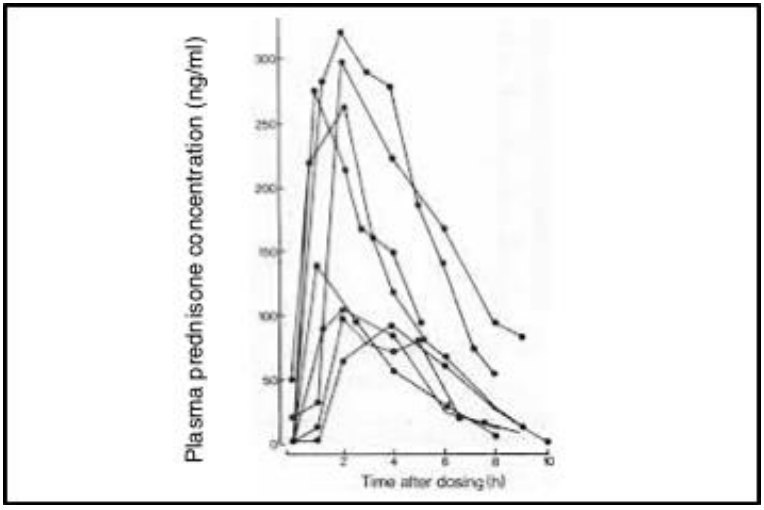


Artwork from http://smart.servier.com

❖ Prednisone

- Absorption:
  - Proximal jejunum
- Cmax
  - 1-3 hr
  - ~75% systemic bioavailability
- Significant inter-patient variability

- Exposure

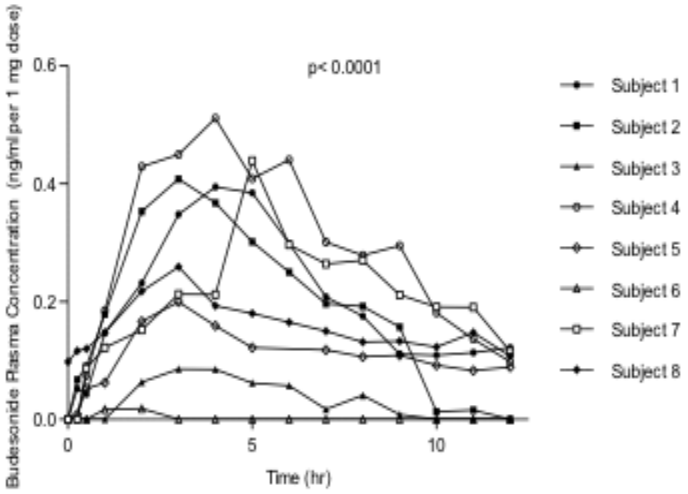


Source: Wilson CG, et al. Br J Clin Pharmacol 1975;2(4):321-5.

❖ Budesonide
  - Topical potency is 5x > Prednisone
  - Release pattern
    - Jejunum
      - Entocort, pH > 5.5)
    - Colon
      - Cortiment, pH > 7
  - 1st pass metabolism by CYP3A4 and P-glycoprotein in the
    - Liver and intestine (90%)
    - Systemic exposure (10-15%)
  - Large interpatient variability in budesonide plasma concentrations in a CD cohort, inversely reflecting variable delivery of drug to target tissue (GI tract, liver)

- Exposure

Budesonide plasma concentrations in a CD cohort



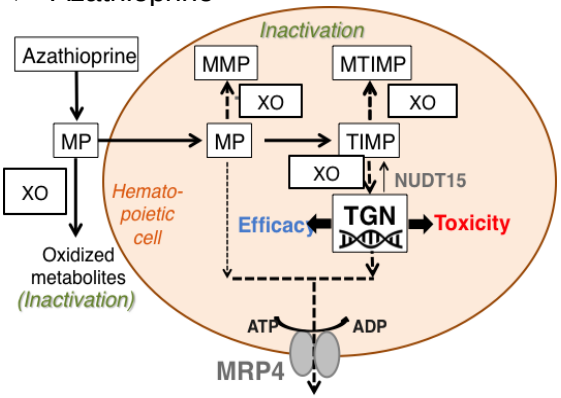
Source: Wilson A, et al. Inflamm Bowel Dis 2017; 23(5): 804-13.

- Response

Cochrane Review: Budesonide more effective than placebo in CD for inducing remission
Core II study:
MMX budesonide x 8 wks = remission (17.4% vs 4.5%) = histo healing (16.5% vs 6.7%)
Low to minimal risk of adrenal suppression and infection

Rezaie A, et al. Cochrane Database Syst Rev. 2015; 6 :CD000296.
Travis SP, et al. Gut 2014; 63(3): 433-41.

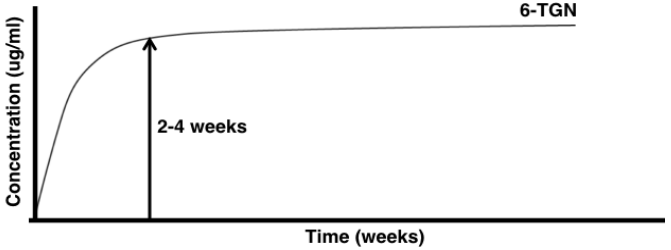
❖ Azathioprine



Abbreviation: XO, xanthine oxidase

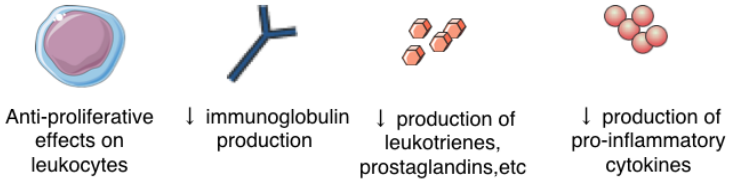
Source: Schwarz et.al. Western University Resident Research Day May 2019 poster

- Bioavailability ranges widely (27-83%)
- Biologically active component is 6-TGN
- Erythrocyte 6-TGN concentrations rise to a plateau after 2-4 wks of oral dosing



- Biological benefit may take 2-3 mon to achieve therapeutic role remains controversial
  - Slow onset of action
  - Weak evidence to support efficacy
  - High rate of adverse events (AEs, ~30%)
  - Up to 30% of patients discontinue treatment due to AEs or lack of benefit

- Methotrexate (MTX)
  - DHFR regenerates folate co-factors essential for purine synthesis
  - MTX and its polyglutamated metabolites inhibit activity of dihydrofolate reductase (DHFR)
  - Mechanism of action



Artwork from http://smart.servier.com

  - Absorbed in the proximal jejunum
  - Bioavailability ranges from 50-90%
  - IM/SC absorption is rapid
    - peak concentrations seen at 1 hr
  - T1/2 = 44-55 hr
  - Metabolism
    - Oxidation in the liver
    - 7-OH MTX metabolite is excreted renally
  - Crohn disease
    - Moderate quality evidence suggests SC MTX (15-25mg wkly) is superior to placebo for maintenance of remission
  - UC
    - No evidence for efficacy
  - Use of anti-TNF therapy
    - ↓ immunogenicity and formation of antibodies

Hemperly A, et al. Inflamm Bowel Dis 2018;24(12): 2527-42.

- Monoclonal antibodies
  - Large (~150 kDa) vs small (<900 Da) molecule drug
  - IgG class
  - T1/2
    - Chimeric 10-14 d
    - Humanized 10-20 d
  - Catabolized in the hostile proteolytic environment GI tract
  - Target soluble or membrane-bound antigen (or both)
  - No renal clearance (due to large size)

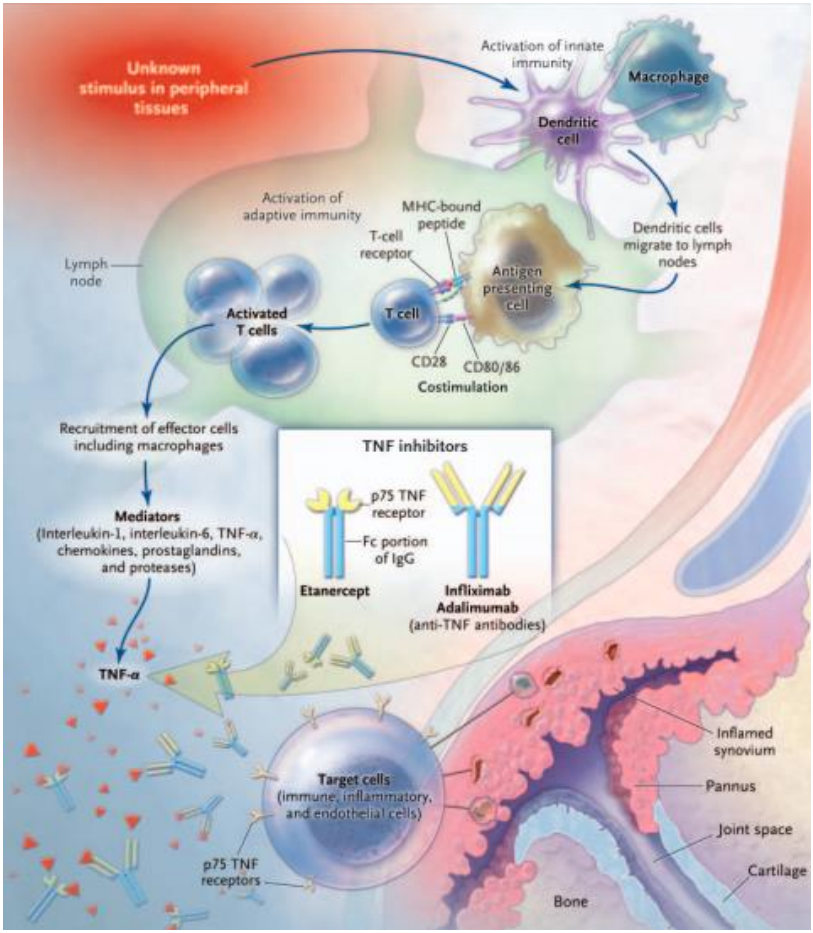
Ferri N, et al. Pharmacol Res. 2016;111:592-599.

Modulate the signaling pathway

- Antibodies made by identical immune cells that are clones of a unique parent cell
- Bind to the same or a single epitope
- Block the function of the target molecule
  - Induce apoptosis of the target-expressing cell
- Bioavailability dependent on
  - Antigen distribution
  - Concentration
  - Antibody structure (chimeric vs human)
  - Host factors (body weight, inflammatory state)
  - Concurrent medications
  - Immunogenicity
- Clearance from the circulation by catabolism dependent on
  - Proteolysis
    - Internalization in phagocytic cells of the reticulo-endothelial system (mediated via FCγR)

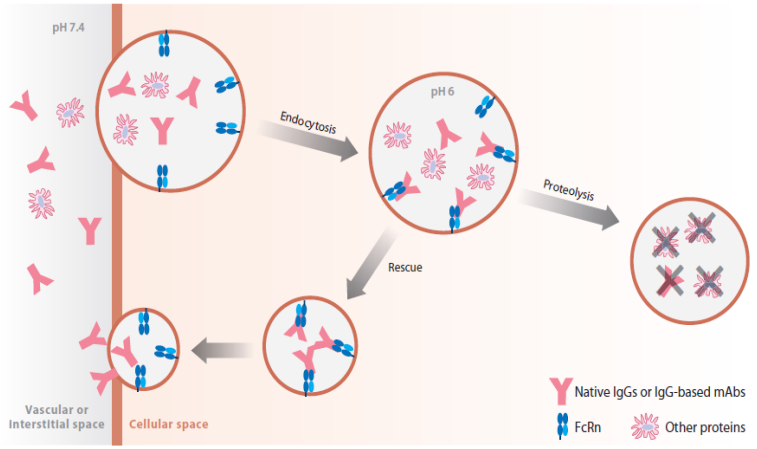
- "Antibody salvage" via Fc neonatal receptor (FcRn aka "Brambell receptor)

- Can be specific (membrane-bound antigen) or non-specific (soluble antigen)



Printed with permission: Scott DL and Kingsley GH. NEJM 2006; 355(7): 704-12.

Role of FcRn



Printed with permission: Zhou H and Mascelli MA. Annu Rev Pharmacol Toxicol 2011; 51: 359-72.

Monoclonal antibodies (mAb) targeting soluble antigen

- Ustekinumab: p40subunit IL-12/23
- Rizankizumab: p19 subunit IL-23

Infliximab (IFX)

- Murine variable region grafted into human IgG1 scaffold
- Small volume of distribution (3-6L) (confined to blood stream)
- T1/2
  - 11-19 days
- Exposure to infliximab correlates with clinical, biochemical and endoscopic outcomes
- Clearance = 0.230L-0.407L/d
- ↑ clearance → ↓ blood levels → ↓ clinical benefit

- Patient factors associated with changes in clearance of infliximab and changes in biological activity
  - ↓ albumin and infliximab clearance
    - IgG and albumin share a common elimination pathway
    - High fecal load day 1; low blood concentration at wk 2
  - ↓ anti-infliximab antibodies
    - Formation of anti-drug antibodies (ADAs) is associated with
      - Drug clearance (2.5x)
      - ↓ response and i
      - ↑ infusion reaction
    - Incidences range from 6-73%
    - Transient ADAs are less likely to affect infliximab effect vs sustained ADAs (5x risk of stopping infliximab due to LOR or ADR)
    - There is no defined cutoff for low or high ADA titre, but
      - ADA 8 AU/mL
      - ↓ duration of infliximab response
  - ↓ body weight
  - ↑ biological activity
    - GI inflammation → ↓ barrier function / ↑ "leakiness" and → ↑↑ loss of albumin pool (up to 60%)
      - In acute colitis this affects other large proteins
  - ↓ concomitant immunosuppression
    - A concurrent immunomodulator ↓ infliximab clearance (↑ biological activity)
    - In patients with combination therapy infliximab peak concentration is (↑ 1.44x compared to monotherapy
    - Withdrawal of an immunomodulator has been associated with loss of response

- ↑ inflammation (CRP)
- Therapeutic drug monitoring (TDM)
  - Reactive monitoring
    - ↓ exposure is associated with ↓ response
    - Maintain Infliximab trough concentration >5ug/mL
  - Crohn disease
    - ↑ exposure (> 10.1 ug/mL) is associated with fistula closure
    - Based on combined analysis of patient-level data from four studies that evaluated 483 patients with Crohn disease using a fluid phase mobility shift assay, IFX trough concentrations > 2.79 ug/mL during maintenance therapy were associated with remission as measured by C-reactive protein concentration (Vande Casteele NV, et al. Gut. 2015; 64(10): 1539-45)
    - AGA recommends reactive TDM to guide treatment changes in the active IBD patient with active IBD
  - Ulcerative colitis
    - Infliximab concentrations >10.6 ug/mL in UC predicts endoscopic healing in the maintenance phase
    - Infliximab concentration ≥ 23.1 ug/mL at 2-wk interval predicts endoscopic healing at 8 wks
  - Proactive TDM
    - ↑clinical remission with ↑ drug concentration (3-7ug/mL) in optimization phase
    - Proactive infliximab TDM no better than reactive TDM/clinical symptoms, when IFX concentration targeted at > 13 ug/mL (D'Haens G, et al. Gastroenterology 2018; 154: 1343-1351)

- Overall correlation between tissue and serum drug concentration in quiescent disease
- "serum concentration-tissue concentration mismatch"
- Subjects with active IBD more likely to have ↓ tissue infliximab (IFX) concentrations despite normal serum IFX concentrations (Yarur AJ, et al. Gut 2016; 65(2): 249-55)

Adalimumab

- Fully human IgG1
- In healthy volunteers (40mg dose)
  - Cmax
    - 4.7ug/mL
  - Bioavailability
    - 64%
- IBD maintenance current guidelines recommend an adalimumab TC > 7.5 ug/mL (maintenance)
  - If loss of response at this concentration, consider switching drug

Ustekinumab

- Fully human mAb against IL12/23 p40 subunit
- IV induction, SC maintenance
  - Peak concentration following IV administration 125 ug/mL
    - Trough concentration = 2.5 ug/mL
    - Small volume of distribution (4L) (mAb is confined to blood stream)
- Association between serum concentrations and remission
  - Trough concentrations > 0.8 ug/mL associated with clinical remission
- Low rates of immunogenicity (0.2-2.3%)

- Antibodies targeting membrane-bound antigens
  - Vedolizumab (α4β7 integrin)
  - Natalizumab (α4β1/β7 integrin)

- Antibodies targeting soluble and membrane-bound antigen
  - Anti-TNF agents:
    - Infliximab
    - Adalimumab
    - Certolizumab
    - Golimumab

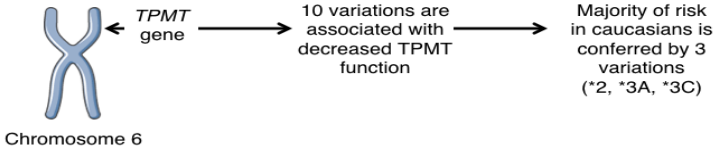
Vedolizumab

- Targets α4β7 integrin
- Prevents interaction of α4β7 integrin with MAdCAM-1 and extravasation of T-cells into inflamed intestinal tissues
- T1/2 = 15-22 days
- Gemini I:
  - Evaluated exposure-efficacy relationship
  - Positive association in UC for response, remission and mucosal healing
  - Induction trough concentrations <17ug/ml were associated with clinical remission similar to placebo
  - More data needed to confirm role of TDM
- Infusion-related reactions < 5%
- No ↑ risk of infection with vedolizumab exposure
- No cases of PML detected
- Malignancy risk $1/10^3$ person-yr (similar to IBD patients in general)

- ❖ Janus Kinase Inhibitor (Tofactinib)
  - ↓ phosphorylation / activation of JaK associated with the cytokine receptor
  - Regulate cytokine signaling and activation of pro-inflammatory genes
  - Small molecule drugs (<900Da)
  - Benefits over monoclonal antibodies
    - Short half-life
    - Lack of immunogenicity
    - High bioavailability when orally delivered
    - Large volume of distribution ~ 115 L
    - High clearance (hepatic CYP3A4) ~ 25 L

- ➢ Pharmacogenomics

- ❖ Azathioprine
  - TPMT



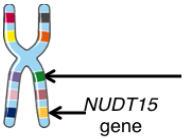
Artwork from http://smart.servier.com

  - Pattern of inheritance:
    90% wild type
    11% heterozygous variant carrier
    0.3% homozygous variant carrier
  - Risk of severe myelosuppression:
    Wild-type 3%
    - Carriers 1 variant allele 30-60%
    - Carriers 2 variant alleles 100%

- Benefit to variant carriers is established
  - 10-fold reduction in myelotoxicity in individuals who underwent TPMT testing

Relling et.al. CPIC guidelines 2005; Dean Med Gen Summ 2016; Coenen et.al. Gastro 2015

- Other emerging genetic determinants of azathioprine toxicity



HLADQA1-DRB1 gene
- HLA-DQ1 – HLADRB1 polymorphism is a major predictor of azathioprine-induced pancreatitis in patients with inflammatory bowel disease
- Association of genetic variations in NUDTIS with thiopurine-induced myelosuppression in patients with inflammatory bowel disease

Artwork from http://smart.servier.com

"Having potential is great if you're 12"

The Economist

MESENTERIC ISCHEMIA

Waleed Alghamdi

- Demography
  - Frequency
    - AMI > CMI
      - Acute mesenteric ischemia (AMI) is more common than chronic (CMI)
    - AD > VD
      - Arterial disease (AD) is more common than venous disease (VD)
  - Seriousness (area of impact)
    - AMI
      - Intestinal viability
    - CMI
      - Functional demand

Source: Reinus JF, et al. *Gastroenterol Clin North Am*. 1990;19(2):319-43; Cappell MS. *Gastroenterol Clin North Am*. 1998;27(4):783-vi; Acosta S. *Curr Opin Crit Care*. 2015;21(2):171-178; and Kärkkäinen JM, Acosta S. *Best Pract Res Clin Gastroenterol*. 2017;31(1):15-25.

- Diagnosis
  - The diagnosis of mesenteric ischemia may be missed until late, when the bowel is necrotic or perforates.
    - Prognosis once intestinal infarction has occurred
      - Mortality rate ~80%
  - To encourage us all to have this diagnostic possibility at the front of our mind, this topic is often tested.
  - In the MCQ stem, look for
    - Severe abdominal pain with minimal findings on abdomen examination

- Risk factors for low flow, thrombosis or embolism causing mesenteric ischemia
  - Atrial fibrillation
  - Athrosclerosis
  - Vasculitis
  - Drugs, such as
    - Digitalis
    - Cocaine
    - 5-HT3 antagonists / 5-HT4 agonists
    - Vasopressors
    - Octreotide

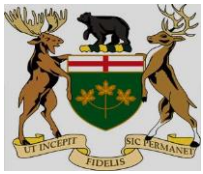
Source: Gnanapandithan K, Feuerstadt P. Review Article: Mesenteric Ischemia. *Curr Gastroenterol Rep*. 2020;22(4).

- Types

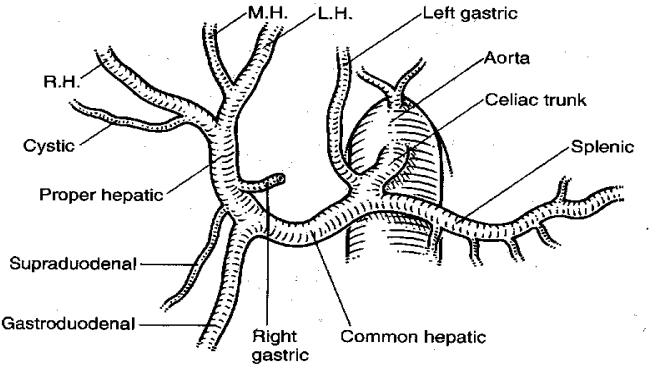
Type	Frequency (%)
Colon	
– Colonic ischemia*	75
Small intestine	
– Acute mesenteric ischemia*	25
– Focal segmental ischemia of the small intestine*	<5
– Chronic mesenteric ischemia	<5

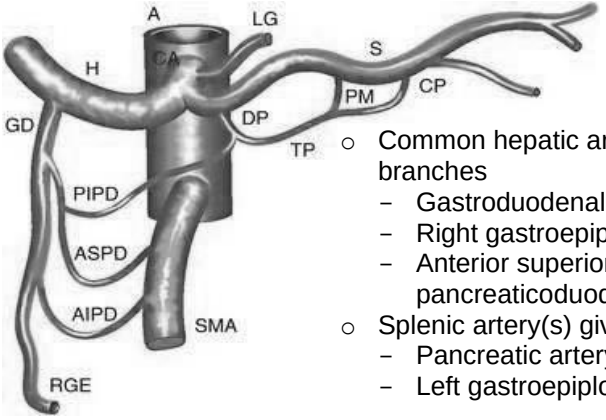
***** Includes mesenteric venous thrombosis, which can manifest as colon ischemia, acute mesenteric ischemia, or focal segmental ischemia.

- Anatomy (Splanchnic Circulation)
  - Almost all blood to the GI tract comes from 3 vessels
    - Celiac access (CA)
    - Superior mesenteric artery (SMA)
    - Inferior mesenteric artery (IMA)



- Celiac Artery (CA) Trunk
  - Supplies stomach, duodenum, pancreas and liver.
  - Three major branches:
    - Left gastric artery
    - Common hepatic artery (CHA)
    - Splenic artery (SA)



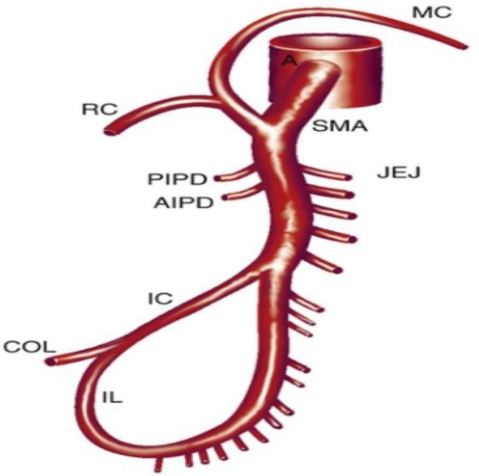


  - Common hepatic artery gives off branches
    - Gastroduodenal (GD)
    - Right gastroepiploic (RGE)
    - Anterior superior pancreaticoduodenal (ASPD)
  - Splenic artery(s) gives branches:
    - Pancreatic artery
    - Left gastroepiploic artery

Adapted from: Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: pathophysiology, diagnosis, management. 10th ed. Philadelphia: Saunders/Elsevier, 2016; and Abdeldayem RSCE-H. Essential Functional Hepatic and Biliary Anatomy for the Surgeon. In: Rijeka: IntechOpen; 2013: Ch 2.

- Note that there are abundant collaterals between the CA and SMA

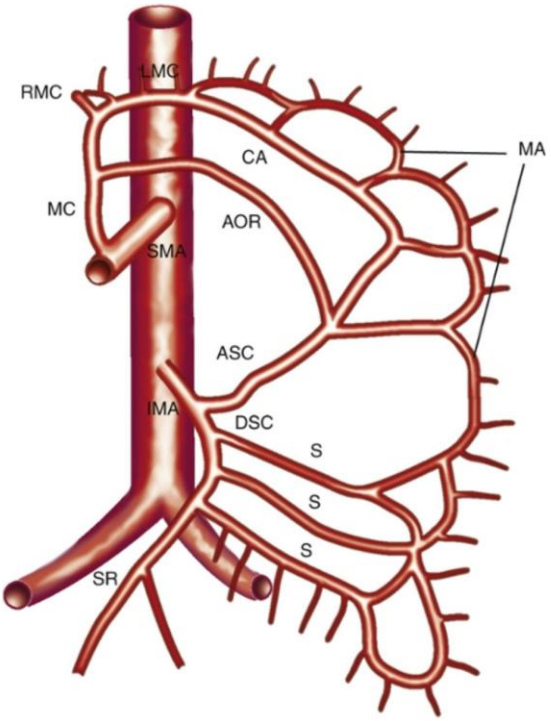
❖ Superior Mesenteric Artery (SMA)
- Originate from the anterior aorta near the neck of the pancreas
- 5 branches
  - The anterior and posterior inferior pancreaticoduodenal vessels
  - Middle colic
  - Right colic
  - Ileocolic arteries
  - Series of jejunal and ileal branches



- Note that there are abundant collaterals between SMA and CA, and between SMA and IMA

Source: Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: pathophysiology, diagnosis, management. 10th ed. Philadelphia: Saunders/Elsevier, 2016.

- Inferior Mesenteric Artery (IMA)
  - Arises 3 to 4 cm above the aortic bifurcation close to the inferior border of the duodenum
  - Branches
    - Left colic artery
    - Multiple sigmoid branches
    - Terminates as the superior rectal artery
  - Distal rectum is supplied by branches of the internal iliac (hypogastric) (IA[HE]) artery



Source: Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: pathophysiology, diagnosis, management. 10th ed. Philadelphia: Saunders/Elsevier, 2016.

- Note that there are abundant collaterals between IMA and SMA

- Give why is it less likely to have ischemic events in certain parts of the GI tract stomach, duodenum or rectum.
  - Stomach, duodenum
    - Blood supply from CA and SMA
  - Rectum
    - Blood supply from IMA (superior rectal artery, and sigmoid arteries) and from internal iliac (hypogastric) artery

➢ Pathophysiology and Pathology

- Bowel can tolerate a 75% ↓ mesenteric blood flow / ↓ oxygen consumption for 12 hr (1/5 of the mesenteric capillaries are open at any time)
- Deprivation of oxygen and nutrients necessary for cellular integrity → bowel adapts by ↑ oxygen extraction → below a critical level of blood flow, compensatory mechanisms become overwhelmed
- Occlusion → ↓↓ arterial pressure distally → P_{vas} < MAP → ↑ Collaterals blood flow → Persist (hr) → vasoconstriction (vascular bed) → ↑↑↑↑ P_{vas} → ↓↓ Collateral blood flow → → irreversible and persist even after correction of cause! (e.g., OR)

Abbreviations: MAP, mean arterial pressure; OR, operating room (i.e., surgery); P_{vas}, pressure in intestinal vascular bed

Source: Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: pathophysiology, diagnosis, management. 10th ed. Philadelphia: Saunders/Elsevier, 2016.

- How does our body maintainsbowel blood flow?

- α-adrenergic receptors
  - Maintaining splanchnic arteriolar tone
- Vasoactive substances
  - Angiotensin II, vasopressin, and prostaglandins

- Reperfusion injury (RPI) occurs following restoration of blood flow after a period of ischemia
- RPI is a complex response characterized by release of free oxygen radicals, toxic byproducts of ischemic injury, and neutrophil activation which can lead to multisystem organ failure

➢ Reperfusion Injury

- In non-ischemic tissue → xanthine dehydrogenase (XDH), which uses NAD instead of O_2 during nucleic acid oxidation → no free radicals
- Ischemia →
  XDH → Xanthine oxidase (XO)
  → Free radicals → platelet-activating factor (PAF)
  Neutrophils → → leukotriene B_4 (LTB4)
  Migration
  Adherence → proteases+endothelial injury
  microvascular injury

Source: Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: pathophysiology, diagnosis, management. 10th ed. Philadelphia: Saunders/Elsevier, 2016.

Acute Mesenteric Ischemia (AMI)

- Demography
  - 0.1% of admissions to tertiary care centers (↑ in recent decades, ↑ recognition)
  - ↑ with age
  - ↑ with seriousness of condition (e.g., ICU)

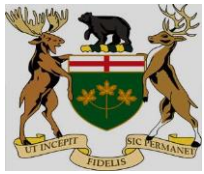
- Causes

Cause	Frequency (%)
SMA thrombosis (SMAT)	54-68
SMA embolus (SMAE)	26-32*
Non-occlusive mesenteric ischemia (NOMI)	10*
Mesenteric venous thrombosis (MVT)	5*
Focal segmental ischemia of the small intestine (FSI)	5

* ↓ current incidence of SAME and NOMI

Source: Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: pathophysiology, diagnosis, management. 10th ed. Philadelphia: Saunders/Elsevier, 2016.

- Performance
  - Arterial
    - Embolus (SMAE), 50%
    - Non-occlusive (NOMI), 25%
    - Thrombus (SMAT), 10%
    - Focal, 5%
  - Venous thrombosis (MVT), 10%



- Types
  - Arterial
    - **SMAE** (SMA embolus; 50%)
      - Thrombus in SMA distal to the takeoff of the ileocolic artery is minor, proximal is major
      - If no peritonitis, consider TTT (transcatheter thrombolytic therapy)
    - **NOMI** (non-occlusive mesenteric ischemia; 25%)
      - Splanchnic vasoconstriction
      - Seen in hypoperfusion (shock, MI, CCF, arrhythmia, digitalis); CABG; chronic renal failure, hemodialysis, peritoral dialysis
      - Treat with infusion of papaverine
    - **SMAT** (SMA thrombosis; 10%)
      - Occurs in area of narrowing from atherosclerosis
      - May occur on top of CMI (chronic mesenteric ischemia)
      - Important to distinguish between acute versus chronic thrombosis: “the absence of collateral vessels or the presence of collaterals with inadequate filling of the SMA indicates an acute occlusion and demands prompt intervention” (Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2035), i.e., SMA infusion of papaverine followed by surgery for peritoneal signs
    - **FSI** (focal segmental ischemia; 5%)
      - Note: approximate frequency of causes of AMI are given in brackets

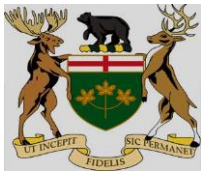
- Venous (Mesenteric Venous Thrombosis, 10%)

Types of Emboli	Site of Supply from Branches of SMA
○ Major (proximal to origin of ileocolic artery)	– MCA (middle colic artery) ▪ Transverse colon – RCA (right colic artery) ▪ Distal ascending colon
○ Minor (distal to origin of ileocolic artery)	– Ileocolic ▪ Terminal ileum, cecum, plus proximal ascending colon

- Give the anastomotic circulation between the CA (celiac axis) and the SMA (superior mesenteric artery), and between the SMA and the IMA (inferior mesenteric artery).

CA ↔ SMA	SMA ↔ IMA
○ Superior pancreaticoduodenal artery (comes off CA)	– Margina artery of Drummond
○ Inferior pancreaticoduodenal artery (comes off SMA)	– Central anastomotic artery – Arc of Riolan

  - The central anastomotic artery or the arc of Roilan may be called the “meandering artery” when SMA or IMA are obstructed.



- Pathophysiology

- Give the mechanisms of tissue injury which occurs with reperfusion following a period of ischemia (reperfusion injury).
  - During ischemia, the enzyme XDH (xanthine dehydrogenase) becomes XO (xanthine oxidase)
  - During reperfusion, XO produces reactive oxygen radicles
  - Reactive oxygen radicals cause
    - ↑ permeability of microvessels
    - ↑ necrosis of epithelial cells
    - ↑ LT (leukotriene) B4 release
    - ↑ PAF (platelet-activating factor)
  - LTB4 and PAF → neutrophil adherence/migration → ↑ proteases → ↑ damage to endothelium

- Clinical
  - Severe abdominal pain out of keeping with minimal findings on abdominal examination
  - Abdominal distention, guarding; rebound, ↓ bowel sounds) → suggests small intestinal
    - Necrosis
    - Infarction
    - Gangrene
    - Perforation
  - Sudden onset of severe abdominal pain in person > 50 yr, with cardiovascular risks
    - May be unexplained/persistent/chronic
  - Chronic heart failure, porrly controlled
  - Recent mycocardial infarction
  - Arrhythmias
  - Hypotension

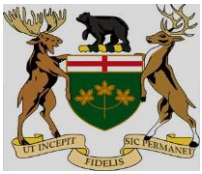
- Mental confusion (30%)
- Rectal bleeding (15%)
- Abdominal distention (15%)
  - Increasing tenderness / rebound tenderness
  - Abdominal muscle guarding
- Clinical course may indolent with MVT

MCQ Tricks

- Give the type of AMI in which there may be no/minimal abdominal pain.
  - NOMI
- Give the type of AMI in which there may be chronic (wks-months) postprandial abdominal pain which preceds the onset of acute severe abdominal pain.
  - SMAT
- Give the relationship between the symptoms and signs of AMI.
  - The severity of pain is out of proportion to the severity of the abdominal findings

More MCQ Tricks

- Usually AMI is a disorder of persons > 50 yr. Give when AMI should be suspected in young persons.
  - Younger patients:
    - Vasoactive medications (e.g. Phenylephrine, amphetamines, tryptans)
    - Cocaine
    - Thrombophilia



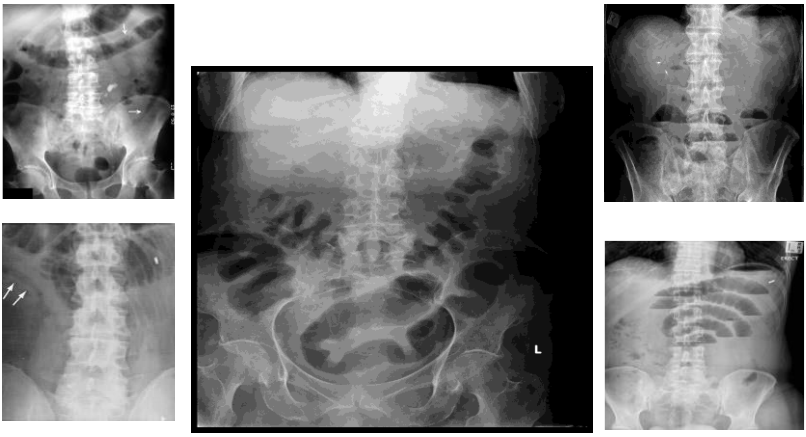
- Causes/associations

- Give factors which are associated with ↑ risk of AMI (acute mesenteric ischemia) in young persons.
  - Vasoactive drugs (e.g., amphetamine, phenylephrine)
  - Cocaine use
  - Thrombophilia

- Laboratory
  - ↑ LDH
  - Metabolic acidosis
  - ↑ WBC, “shift to the left”

- Diagnotic imaging (30%)
  - Even if AMI is diagnosed clinically, imaging is helpful
  - Plain films of the abdomen
    - Poor sensitivity and specificity
  - Abdominal ultrasound (Duplex scanning and Doppler flowmetry):
    - Assess peripheral but not central splanchnic vasculature
    - Occlusions
      - Not diagnostic
    - Blood flow through the SMA
      - Highly variable
    - NOMI
      - Cannot be diagnosed

- CT scan abdomen
  - Findings are non-specific and late
    - Colon dilatation
    - Bowel wall thickening
    - Abnormal bowel wall enhancement
    - Lack of enhancement of arterial vasculature with timed intravenous contrast injections
    - Arterial occlusion
    - Venous thrombosis
    - Engorgement of mesenteric veins
    - Intramural gas and mesenteric or portal venous gas
    - Infarction of other organs,
    - Ascites
    - Cause of the infarcted bowel, such as hernia



  - CT angiography (CTA):
    - Imaging modality of choice in the diagnosis of AMI
    - Diagnostic accuracy of 96%
    - Good for occlusive diseases
    - Superior to selective mesenteric angiography
    - Not as reliable for NOMI

- Selective mesenteric angiography (papaverine infusion):
  - 90-100% Sensitivity and 100% specificity
  - CTA is more feasible/easier
- Magnetic resonance angiography (MRA) and venography (MRV)
  - Takes a long time to perrform

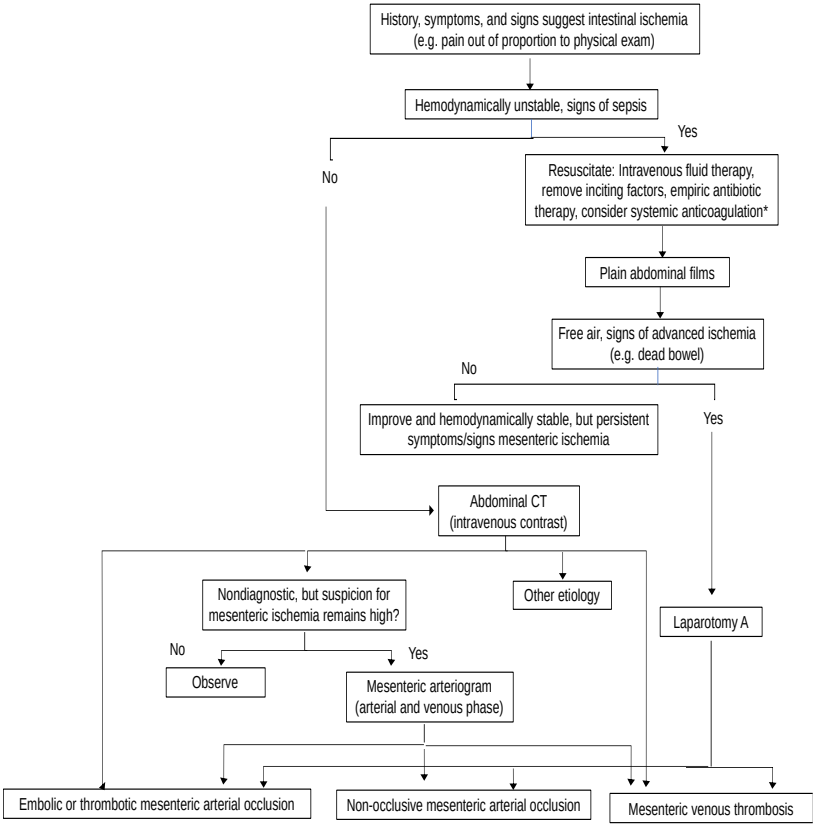
SO YOU WANT TO BE A GI RADIOLOGIST!

- Give the findings suggestive of acute MVT on CT scanning and on selective mesenteric arteriography.
  - CT (MRI or abdominal ultrasound)
    - Bowel wall
      - Thick
      - Enhanced
    - SMV
      - Dilated
      - Thrombus (lucency) in lumen of the vein
    - Collaterals
      - Wall of vein shows ↑ density
      - Dilated
  - Selective mesenteric arteriography of acute superior mesenteric venous thrombosis
    - SMV
      - Thrombus in lumen
      - No visualization of SMV or portal vein
      - Slow/no filling of mesenteric veins
    - SMA
      - Spasm
      - Arterial arcades slow to empty
      - Blush

- Laparoscopy
  - Normal serosal appearance in early ischemia
  - Do not insuflate excessive CO_2
    - ↓ SMA blood flow when intraperitoneal pressure > 20 mm

- Suggested diagnostic algorithm

Diagnosis and initial management of intestinal ischemia



Source: Tendler DA, Lamont JT. Overview of intestinal ischemia ina adults. In: Post TW, et al. (Eds.), *UptoDate*. 2020.

- Treatment
  - Mandatory treatment for infarction to ↓ mortality rate (~80%)
  - Multidisciplinary approach has survival benefit
    - 30 days, 95%
    - 2 yr 89%
  - Papaverine (phosphodiesterase inhibitor) through an angiography catheter in the SMA (↓ mesenteric vasoconstriction preoperatively and postoperatively)
  - Endovascular techniques
    - Aspiration embolectomy, SMA thrombolysis, and stenting) based on mechanism, length and appearance of distal arteries
  - Aspiration embolectomy
    - Proximal SMA emboli, antegrade approach
  - SMA thrombolysis (tPA via catheter)
    - Rarely used as sole therapy
    - ↑ risks propagation, GI bleeding if necrosis present
  - Percutaneous transluminal angioplasty (PTA) with stenting (P-gradients)
  - Laparotomy
  - Use of oral contraceptive pill after treatment (except for NOMI)
    - Wait 48 hr after embolectomy or arterial reconstruction, when thrombosis is common

Superior Mesenteric Artery Embolus (SMAE)

- Pathology
  - Origin
    - Mural thrombi in left atrium or ventricle (LA, LV)
  - Emboli
    - Major emboli: proximal to origin of ileocolic a.
    - Minor emboli: distal
  - Angiography: rounded filling-defect (embolus) with near complete obstruction of blood flow

- Treatment
  - Oral anticoagulation (OAC)
  - Surgical revascularization (SR)
  - Intravascular, intra-arterial perfusion (thrombolysis)
    - Intravascular papaverine; best survival rate; pre, during and post-operative of no 2nd look planned

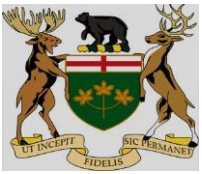
Non-occlusive Mesenteric Ischemia (NOMI)

- Origin
  - Splanchnic vasoconstriction 2 yr to previous CV event

- Causes
  - Acute MI, CHF, arrhythmia, shock, CKD, cirrhosis, CABG, meds (Tryptans, Cocaine)

Angiography: 4 +1 criteria:

1. Narrow SMA branches origins
2. Intestinal branches irregularities
3. Arcades spasm
4. Intramural vessels impaired filling
5. No shock, no vasopressors and no pancreatitis



- Managament
  - SOC angiography with intravascular papaverine

Acute Thrombosis of the Superior Mesenteric Artery

- Origin (severe ATH vascular narrowing)
  - CT Angiography: focal stenosis of the vessel +/- vascular calcification
  - Flush Aortography: occlusion of SMA + distal filling of SMA via collaterals
  - Acute thrombosis vs chronic occlusion? collaterals indicate chronic SMA block

Mesenteric Venous Thrombosis (MVT)

- Demography
  - 5-10% of AMI
- Definition
  - Acute, subacute or chronic at one time, acute mesenteric venous thrombosis was thought to be the principal cause of acute mesenteric ischemia
- Pathophysiology
  - Almost always involves the distal small intestine (superior mesenteric venous drainage) and rarely involves the colon (inferior mesenteric venous drainage).
  - Most common locations: ileum (83%) or jejunum (81%)
  - Reduces perfusion pressure due to increased resistance in the mesenteric venous bed → stagnation of blood → efflux of fluid to tissues → bowel wall edema → can progress to submucosal hemorrhage or infarction → sequestration → low BP → worsening ischemia

- Common risk factors
  - Abdominal mass (e.g., tumor, pseudocyst) leading to venous compression
  - Abdominal inflammatory processes (eg, acute pancreatitis, diverticulitis)
  - Myeloproliferative disorders (eg, *JAK-2* V617F mutation)
  - Portal hypertension (increased portal venous pressure)
  - Personal or family history of venous thromboembolism
  - Acquired thrombophilia (eg, malignancy, oral contraceptives)
  - Inflammatory bowel disease
  - Mesenteric adenopathy/viral infection (eg, influenza)
  - Inherited thrombophilia – Factor V Leiden mutation, prothrombin G20210A mutation, protein S deficiency, protein C deficiency, antithrombin-III deficiency, activated protein C resistance, and antiphospholipid syndrome
  - Endoscopic sclerotherapy

- Clinical Presentation
  - Average age 45 and 60 yr
  - Slight male to female predominance
  - Depends on location and time

Acute:

- Colicky, periumbilical abdominal pain
- Few hr duration
- Out of proportion to the abdominal findings on physical examination (initially)
- Presents similar to AMI

Subacute: (ischemia that is compensated)

- More insidious
- Days to wks before diagnosis
- Non-specific abdo pain
- Venous occlusion sufficient to produce ischemia, but adequate compensation through collateral vessels to allow recovery

Chronic:

- Asymptomatic
- Incidental on imaging
- Intermittent post-prandial pain (minority) >> acute/chronic usually

- Diagnosis
  - MRV is the most accurate imaging study
  - CT abdomen is still recommended (feasibility, r/o other acute abdomen causes)
  - Ext would be (MRA, CTA or catheter-based study)

- Management
  - Operative (signs of infarction)
  - Non-operative
  - Abdominal pressures (e.g. bladder pressure) should be monitored in acute setting (compartment syndrome)

Oral Anticoagulation (OAC)

- For patients with acute or subacute mesenteric venous thrombosis without indications for surgery, we initiate systemic anticoagulation to minimize extension of thrombus
- Chronic mesenteric venous thrombosis, anticoagulation is individualized and depends upon symptoms, location and extent of thrombosis, and risk for bleeding
- If no identifiable risk factors, or transient or correctable acquired risk factors (eg, pancreatitis), we anticoagulate for six months of anticoagulation, rather than long-term anticoagulation
- Risk factors that cannot be corrected (malignancy, inherited condition), we anticoagulated long term

- Prognosis
  - Acute mesenteric venous thrombosis: mortality 10-20%
  - 75% for those with intestinal infarction

Focal Segmental Ischemia of the Small Intestine (FSI)

- Definition
  - Vascular insults to short segments of small intestine
  - Less prevalence of life-threatening complications

- Causes
  - FSI can manifest as acute enteritis, chronic enteritis, or a stricture
  - Radiographic findings can also resemble those of Crohn disease (anywhere in the small bowel)

- Most common presentation is chronic small bowel obstruction from a stricture with intermittent abdominal pain, distention, and vomiting
- Blind loop syndrome (if SIBO)

- Treatment
  - Resection of the involved bowel

Colon Ischemia (CI)

- Demography
  - 9-24% of all patients hospitalized for acute LGIB (2nd to CRC)
  - Annual incidence rate of 16.3-17.7 cases/100,000
  - CI is more common in women than in men (up to 76%)
  - Mortality rates 4-12%

- Definition
  - A condition that results when blood flow to the colon is reduced to a level insufficient to maintain cellular metabolic function

- Pathophysiology
  - Alterations in the systemic circulation or from anatomic or functional changes in the mesenteric vasculature
  - Proximate cause is thought to be local hypo-perfusion and reperfusion injury
  - 2 entities:
    - Type I (no cause, small vessel disease) – broader Rx/supportive
    - Type II (etiology identified) like low BP or CO or aortic surgery – Targeted Rx

- Risk Factors
  - Comorbid CV disease and DM
  - A history of IBS and constipation
  - Selective cardiology consultation is justified in patients with CI, particularly if a cardiac source of embolism is suspected
  - Chronic kidney disease (increased mortality)
  - Evaluation for thrombophilia (young patients with CI, recurrent CI)
  - Surgical procedures in which the inferior mesenteric artery (IMA) has been sacrificed, such as AAA repair and other abdominal operations
  - In patients suspected of having CI, a history of medication and drug use is important, especially constipation-inducing medications, immunomodulators, and illicit drugs

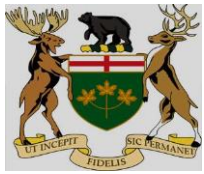
- Clinical Presentation
  - The diagnosis of CI is usually established in the presence of symptoms including sudden cramping and mild abdominal pain; an urgent desire to defecate; and passage within 24 h of BRBPR or maroon blood or bloody diarrhea (Strong recommendation, very low level of evidence)
  - A diagnosis of non-isolated right colon ischemia (non-IRCI) should be considered when patients present with hematochezia (Strong recommendation, very low level of evidence)
  - (Mosli, 2013) Analysis of 72 Canadian patients with biopsy-proven CI showed: abdominal pain (77.8%), hematochezia (58.3%), bloody diarrhea (34.7%), and non-bloody diarrhea (19.4%)

- Segmental Nature of CI:
  - Segmental blood supply of colon (SMA, IMA, superior hemorrhoidal a.)
  - L colon (32.6%) is more common in involvement than R colon (25.2%)
  - Pancolonic pattern of CI portends a similarly poor prognosis to that of IRCI
  - IRCI: associated with high mortality >> 30-day mortality (22.5% vs 11.9%, p = 0.03). Abdominal pain more common than bleeding (<50%)
  - Combination of these two disease distributions was associated with a HR of 14.6 (p <0.001) for CI that required surgery or led to death

- Laboratory Investigations and Diagnosis
  - Predictors of CI severity: (Montoro, 2011)
    - Decreased hemoglobin levels
    - Low serum albumin
    - Metabolic acidosis
  - Abnormal lab values in CI vs Control: Retrospective Data (Mosele, 2010)
    - Serum white blood cell count (WBC, p < 0.0001)
    - Creatinine (Cr, p = 0.003)
    - Urea (p = 0.008)
    - Lactate dehydrogenase (LDH, p < 0.0001)
  - Imaging in CI
    - CT with intravenous and oral contrast should be ordered as the imaging modality of choice for patients with suspected CI, to assess the distribution and phase of colitis (strong recommendation, moderate level of evidence)

- The diagnosis of CI can be suggested based on CT findings (e.g., bowel wall thickening, edema, and thumb-printing) (strong recommendation, moderate evidence)
- Multiphasic CT angiography (CTA) should be performed on any patient with suspected IRCI or in any patient in whom the possibility of AMI cannot be excluded (strong recommendation, moderate level of evidence)
- CT or magnetic resonance imaging (MRI) findings of colonic pneumatosis and portomesenteric venous gas can be used to predict the presence of transmural colonic infarction (strong recommendation, moderate level of evidence)
- In a patient in whom the presentation of CI may be a heralding sign of acute mesenteric ischemia (AMI; e.g., IRCI, severe pain without bleeding, and atrial fibrillation), and the multiphasic CT is negative for vascular occlusive disease, traditional splanchnic angiography should be considered for further assessment (conditional recommendation, low level of evidence)

- Colonoscopy in the Diagnosis of CI:
  - Early colonoscopy (within 48 h of presentation) should be performed in suspected CI cases to confirm the diagnosis (strong recommendation, low level of evidence)
  - When performing colonoscopy on a patient with suspected CI, the colon should be insufflated minimally (conditional recommendation, very low level of evidence)
  - In patients with severe CI, CT should be used to evaluate the distribution of disease. Limited colonoscopy is appropriate to confirm the nature of the CT abnormality (i.e., diagnostic



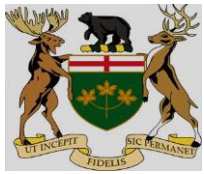
flex sig). The endoscopic procedure should be stopped at the distal-most extent of the disease (strong recommendation, low level of evidence)
- Biopsies of the colonic mucosa should be obtained except in cases of gangrene (strong recommendation, very low level of evidence)
- Colonoscopy should not be performed in patients who have signs of acute peritonitis or evidence of irreversible ischemic damage (i.e., gangrene and pneumatosis) (strong recommendation, very low level of evidence)

Chronic Mesenteric Ischemia (Intestinal Angina)

- Demography
  - < 5% of intestinal ischemic diseases
  - Can be associated with mesenteric artery stenosis (MAS) but not diagnostic (mainly CA stenosis 86%)
  - (Moawad, 1997) 75% of patients with CMI have a history of smoking
  - (Poole, 1987) Abdominal pain is the most typical symptom (classically postprandial in 78%) – onset at 30 min, gradual, resolves in 1-3 hrs – lead to sitophobia
  - Pain can be continuous >>> think infarction!
  - Nausea, bloating, constipation, diarrhea or malabsorption and weight loss

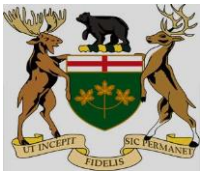
- Definition
  - Uncommon presentations (acalculous cholecystitis, antral PUD that is -ve for H. pylori and PPI-unresponsive, gastroparesis)
  - Physical exam: Limited, benign abdomen, possible bruits

- Diagnosis
  - Post-prandial lactate and D-dimer (elevated in CMI)
  - Radiographic films and CT scan: can be normal, vascular calcifications
  - Endoscopy + biopsy: normal, non-specific abnormalities
  - US, MRA, mesenteric angiography: they don't diagnose ischemia but etiologies if present
  - Gastric tonometry exercise testing (GTET): accuracy 87% vs angiography. Requires:
    - NG tube (gastric juice)
    - Peripheral arterial catheter (arterial gas)
    - Acid suppression pre-treatment
    - Standard exercise protocol
      - Gastric-arterial PCO_2 gradient (before, during and after exercise)
      - Diagnosis: post-exercise increase in gradient
      - Best diagnostic workup strategy: combined duplex US + GTET (Otte, 2007)
      - 24-hr tonometry (catheters in stomach and jejunum) also had good results
  - In most patients, 2 out of 3 splanchnic vessels are occluded or severely stenotic
- Treatment
  - Doesn't require urgent intervention
  - Best algorithm: Clinical suspicion → r/o other causes (screening imaging) → if abnormal → mesenteric angiography → if abnormal → treat after risk stratification
    - Outcomes: percutaneous transluminal mesenteric angioplasty PTMA +/- stenting = surgical revascularization (SR)
    - SR vs PTMA >> higher patency and lower recurrence, no head-head prospective trials



SMALL INTESTINE BACTERIAL OVERGROWTH

Anshul Arora

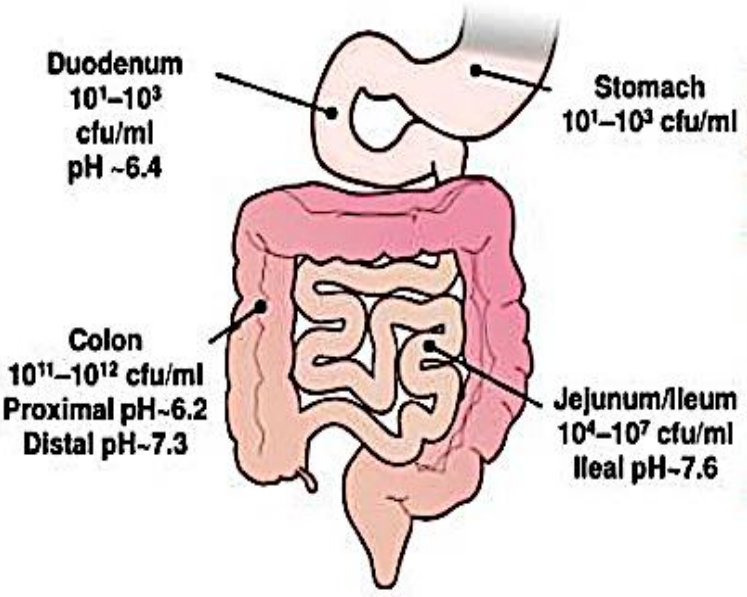


- Definition
  - Small intestinal bacterial overgrowth (SIBO) is a condition in which there is excess proliferation of colonic bacteria in the small intestine (> 10^5 /CFU), leading to gastrointestinal symptoms and nutrient deficiencies

Abbreviation: CFU, colony forming units

- Demography
  - Associations of SIBO (50%) with
    - Celiac disease
    - IBS

- Intestinal Microbiome Overview
  - Concentration and species of bacteria follow characteristic pattern in health in GI tract
  - The stomach and proximal small intestine contain few bacteria due to acidity and peristalsis
  - Ileum represents intermediary zone between small intestine and colon
  - Stomach, duodenum and proximal jejunum = gram positive aerobes
  - Mid-jejnum, ileum and colon = coliforms and anaerobes



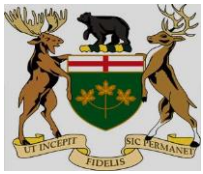
Adapted from: O'Hara AM and Shanahan F. EMBO Rep. 2006;7(7):688-693.

- Mechanisms preventing overgrowth
  - In health, normal gut microflora is maintained by 5 major mechanisms:
    - Gastric acid secretion
      - ↓ bacterial numbers in food and suppresses growth in proximal small intestine
    - Pancreatic enzyme secretion
      - Antimicrobial in proximal small intestine
    - Small intestinal motility (MMC/migrating motor complex phase III)
      - Preventing stasis
    - Structural integrity of GI tract – intact ileocecal (IC) valve
    - Intact gut immune system

- Causes/Associations
  - Stomach
    - Achlorhydria
    - Acid suppression medication
    - Atrophic gastritis
    - Chronic alcohol use
  - Small bowel
    - Crohn disease
    - Enteroenteric fistula
    - Mechanical obstruction
    - Post ileocecal valve surgery
    - Radiation enteritis
    - Small intestinal diverticulosis
    - Radiation enteropathy
    - Diabetic enteropathy
    - Celiac disease
    - Systemic sclerosis
  - Pancreas
    - Pancreatic insufficiency
  - Liver
    - Cirrhosis
  - Migrating Motor Complex (MMC)
    - The distinct pattern of electromechanical activity that occurs in the GI smooth muscle in the period between meals
    - Serves “housekeeping” role and sweeps residual undigested material through digestive tract
  - Cycle recurs every 1.5 to 2 hr:
    - Phase I: resting phase, between 90 to 120 min
    - Phase II: irregular spikes and sporadic peristalsis, 30-45 min
    - Phase III: most important phase. Large # spikes and regular, frequent peristalsis, lasting 5-15 min
    - Phase IV: transition period, about 5 min

- Pathogenesis
  - SIBO can lead to direct and indirect effects on gut mucosa and luminal microenvironment
  - Three studied and recognized mechanisms:
    - Direct mucosal injury via bacterial adherence to mucosa or production of enterotoxins.
      - ↓ brush border enzyme disaccharidases and ↑ permeability of small intestine (protein-losing enteropathy)
    - ↑ bacterial metabolism and fermentation →compete with host for nutritionally valuable substrates like vitamin B12 → production of undesirable by-products like ammonia
    - ↑ bile acid deconjugation/dehydroxylation by bacterial hydrolase enzymes → malabsorption of fat, and fat-soluble vitamins (A, D, E, K)

- Clinical
  - Symptoms
    - Non-specific
      - Abdominal pain/discomfort
      - Flatulence
      - Distension
      - Diarrhea
      - Constipation
    - Systemic symptoms
      - ↑ intestinal permeability → hypoalbuminemia→ edema/malnutrition/ immune dysfunction
  - Malabsorption
    - Macronutrients
    - Micronutrients



- Laboratory
  - Blood
    - ↓ Hg
    - ↓ Fe
    - ↓ B12
    - Electrolyte disorders
    - ↑ folic acid
    - ↑ vitamin K → ↓ effect of Coumadin
  - Urine
    - Schilling test
  - Stool
    - ↑ fat
    - ↑ bile acids
    - ↑ protein
  - Breath
    - C13/14 / H2 tests using mono-/disaccharide / amino acid / conjugated bile acid probes
  - Tissue
    - Small bowel biopsies for associatec celiac disease
  - Intestinal lumen
    - Jejunal
      - Bacteria
      - 1^o/ 2^o bile acids
      - Decongested bile acid
      - ↑ 2^o / ↓ 1^o bile acids

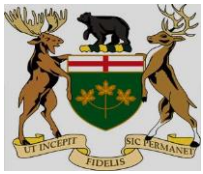
- Breath Test
  - Probe
    - Depends upon chemical question
      - SIBO
      - Malabsorption
      - Disaccharide deficiency

- Print out
  - Depends upon available equipment
    - C13 / C14
    - H2
- Breath test diet
  - Meat/fish/poultry, white rice, eggs, hard cheese, clear beef or chicken broth, salt and pepper
  - No option for vegetarians/vegans since starches and fermentable sugars in those diets can ↑ basal hydrogen/methane levels →false positive results
- Antibiotics
  - Hold for 4wks prior to testing
- Prokinetic drugs/laxatives
  - For 1 wk prior to testing

Diagnosing SIBO – Breath Test

- The lactulose/glucose breath test is diagnostic of SIBO if any one of the following criteria are met:
  - An absolute ↑ hydrogen by ≥20 ppm above baseline within 90 minutes
  - Methane level ≥10 ppm
- Lactulose breath test
  - Sensitivity: 17-68%
  - Specificity: 44-86%
- Glucose breath test
  - Sensitivity: 20- 93%
  - Specificity: 45-86%

Sources: Riordan SM, et al. Am J Gastroenterol 1996;91(9):1795-1803; Ghoshal UC, et al. Indian J Gastroenterol 2006;25(1):6-10.



- Treatment
  - Manage associated
    - Disorders
    - Deficiencies
  - Antibiotics po generally for at least 10 days

Antibiotic	Adult dose
Preferred	
Rifaximin	550 mg tid
Alternative	
Trimethroprim-sulfamethaxole	1 double strength tablet bid
Amox-Clav	875 mg bid
Ciprofloxacin	500 mg bid
Metronidazole	250 mg tid
Tetracycline	250 mg qid

  - If SIBO primarily methane positive, then add neomycin 500 mg po bid for 14 days
  - Prokinetics (↑ MMC)
    - Domperidone
    - Erythromycin 50 mg po qhs
    - Naltrexone 2.5 mg po qhs/bid
  - Diet
    - No benefit from probiotics / FOMAP diet / gluten-free diet

Antibiotics: Treatment response and recurrence

- Response ~40%
  - Persistent symptoms after initial antibiotic treatment
  - Recurrent SIBO
- Empirically treat with second course of a different antibiotic if partial improvement in symptoms and early recurrence (< 3 mon)
- Antibiotic prophylaxis for patients with
  - ≥4 distinct / well-documented episodes within 1yr
  - Risk factors for recurrent SIBO (eg, short bowel syndrome, jejunal diverticulosis)

Source: Pimentel M, et al. Am J Gastroenterol 2020; 115:165.

Diet in treating SIBO

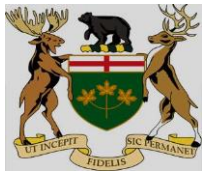
- No one size fits all diet for SIBO
- Most common are specific carbohydrate diet (SCD) and low FODMAPs diet
  - However, no clear evidence of benefit in SIBO
- Elemental diet
  - Effective in inducing remission but costly and poor taste

Source: Dionne J, et al. Am JGastroenterol 2018;113:1290-300.

❖ Probiotics

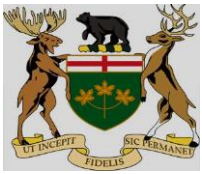
- No clear evidence identified for use of probiotics
- 2017 meta-analysis with 18 studies showed no significant difference in incidence of SIBO in patients on probiotics compared with control group

Source: Zhong C, et al. J Clin Gastroenterol 2017;51(4):300-11.



MALDIGESTION AND MALABSORPTION

Cassandra Townsend



- Definitions
  - Maldigestion
    - Defective intraluminal hydrolysis of nutrients
  - Malabsorbtion
    - Defective mucosal absorption
  - Clinical presentation and symptoms of these two conditions can be similar
  - Can be caused by many diseases

- Give the diseases which cause nutrient malabsorption.

Gastric Diseases
- Atrophic gastritis
- Autoimmune gastritis (pernicious anemia)
- Gastric resection or bypass surgery

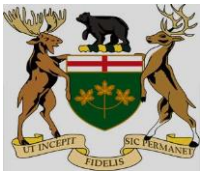
Biliary Tree (obstruction)
- Biliary tumors
- Primary and secondary sclerosing cholangitis

Liver Diseases
- Inborn errors of bile acid biosynthesis and transport
- Cirrhosis and other liver diseases
- Portal hypertension

Pancreatic Diseases
- Congenital pancreatic enzyme deficiencies:
  - Colipase deficiency
  - Lipase deficiency
  - Trypsinogen deficiency
- Pancreatic insufficiency:
  - Chronic pancreatitis
  - Cystic fibrosis
  - Johanson-Blizzard syndrome
  - Pearson marrow-pancreas syndrome
  - Shwachman syndrome
- Pancreatic tumors

Intestinal Diseases

- Amyloidosis
- Autoimmune enteropathy
- Celiac disease
- Collagenous sprue
- Congenital intestinal defects
- Crohn disease
- Enteroendocrine cell deficiency:
  - Autoimmune polyglandular syndrome type 1
  - Enteric anendocrinosis
- Enterokinase deficiency
- Eosinophilic gastroenteritis
- Fistulas
- Food allergy
- Graft-versus-host disease
- Hypolactasia
- Ileal bile acid malabsorption
- Intestinal infections:
  - Giardiasis
  - Helminthic infections
  - HIV infection: cryptosporidiosis, Mycobacterium avium complex infection, viral infections
  - Tuberculosis
  - Whipple disease
- Immunoproliferative small intestinal disease
- Intestinal ischemia/lymphoma
- Intestinal resections or bypass
- Mastocytosis
- Nongranulomatous chronic idiopathic enterocolitis
- Postinfection malabsorption
- Primary immunodeficiency diseases
- Radiation enteritis
- Refractory sprue
- Sarcoidosis
- Small Intestinal Bacterial Overgrowth (SIBO)
- Tropical sprue



Lymphatic Diseases
- Primary intestinal lymphangiectasia
- Secondary intestinal lymphangiectasia:
  - Lymphoma
  - Solid tumors
  - Thoracic duct trauma, damage, or obstruction

Neuroendocrine Tumors
- Carcinoid syndrome
- Glucagonoma
- Somatostatinoma
- Zollinger-Ellison syndrome

Cardiac and Vascular Diseases
- Constrictive pericarditis
- Heart failure

Endocrine Causes
- Addison's disease
- Diabetes mellitus
- Hyperthyroidism
- Systemic Diseases
- Cronkhite-Canada syndrome

Mixed connective tissue disease
- Neurofibromatosis type 1
- Protein-calorie malnutrition
- Scleroderma
- Systemic Lupus Erythematosis (SLE)

- Pathophysiology
  - Normal uptake of nutrients, vitamins and minerals by the GI tract requires several steps
    - Solubilization
      - Needed to absorb fat or calcium
        - Fat and fat-soluble vitamins are solubilized by the formation of micelles
        - Calcium is solubilized through acidification in the GI lumen
        - Can also contribute to absorption of increased oxalate

- Digestion
  - Macromocecular components like polysac-charides, triglycerides, and proteins to their molecular components—monosaccharides, fatty acids, and amino acids, respectively
- Liberation of substrates from binding sites in food or binding to factors allows absorption to take place (eg Vit B12)
- Chemical changes to nutrients may be required for absorption, such as reducing the charge of iron from Fe+3 to Fe+2.
- Mucosal absorption can occur by active or passive carrier-mediated transport or simple or facilitated diffusion.
  - Postmucosal transport of absorbed substrates occurs in blood vessels and lymphatic vessels
- Intestinal sensory and motor function permits detection of the presence of nutrients, facilitates adequate mixing of nutrients with intestinal secretions and delivery to absorptive sites, and provides adequate time for nutrient absorption
- Neural and hormonal functions are required to stimulate and coordinate digestive secretions, mucosal absorption, and intestinal motility

Mechanisms of Malabsorption, Malabsorbed Substrates, and Representative Causes

Pathophysiological Mechanism	Malabsorbed Substrate(s)	Representative Causes
❖ Maldigestion		
○ Conjugated bi acid deficienc	– Fat – Fat-soluble vita – Calcium – Magnesium	▪ Hepatic parenchymal disease ▪ Biliary obstruction ▪ SIBO with bile acid deconjugation ▪ Ileal bile acid malabsorption ▪ CCK deficiency
○ Pancreatic insufficiency	– Fat – Protein – Carbohydrate – Fat-soluble vita – Vitamin B12 (cobalamin)	▪ Congenital defects ▪ Chronic pancreatitis ▪ Pancreatic tumours ▪ Inactivation of pancreatic enzymes (e,g., ZES)
○ ↓ mucosal digestion	– Carbohydrate – Protein	▪ Congenital defects ▪ Acquired lactase deficiency ▪ Generalized mucosal disease (e.g., celiac disease, Crohn disease)
○ Intraluminal consumption o nutrients	– Vitamin B12 (cobalamin)	▪ SIBO ▪ Helminthic infections (e.g., Diphyllobothrium latum infection)

- Malabsoption
  - ↓ mucosal absorption
    - Fat
    - Protein
    - Carbohydrate
    - Vitamins
    - Minerals
    - Congenital transport defects
    - Generalized mucosa disease (e.g., celiac disease, Crohn disease)
    - Previous intestinal resection or bypass
    - Infections
    - Intestinal lymphoma
  - ↓ transport from the intestine
    - Fat
    - Protein
    - Intestinal lymphangiectasia
    - Primary
    - Secondary (e.g., solid tumours, Whipple disease, lymphomas)
    - Venous stasis (e.g., from heart failure)

- Other Mechanism
  - ↓ gastric acid and/or intrinsic factor secretion
    - Vitamin B12
    - Pernicious anemia
    - Atrophic gastritis
    - Previous gastric resection
  - ↓ gastric mixing and/or rapid gastric emptying
    - Fat
    - Calcium
    - Protein
    - Previous gastric resection
    - Autonomic neuropathy
  - Rapid intestinal transit
    - Fat
    - Autonomic neuropathy
    - Hyperthyroid

Fats

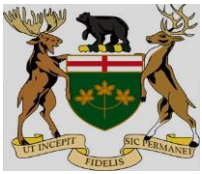
- Defective Mixing
  - For adequate absorption, fats must mix with digestive secretions
    - Restrictions on secretions or GI motility causing rapid gastric emptying or intestinal transit causes fat malabsorption
- Reduced solubilization of Fat
  - Fat malabsorption resulting from decreased formation of micelles occurs if the luminal concentrations of conjugated bile acids are lower than the critical concentration required for forming micelles

➢ Pathophysiologic Mechanisms That Result in Deficiency of Luminal Conjugated Bile Acids

Pathophysiologic Mechanism	Causes
○ ↓ synthesis and/or secretion of conjugated bile acids	– Parenchymal liver disease (e.g., cirrhosis, PBC) – Biliary obstruction (e.g., tumour) – Biliary fistulas – Inborn errors of bile acids synthesis – CCK deficiency
○ ↑ intestinal loss of conjugated bile acids	– Ileal resection – Severe ileal mucosal disease – Congenital defects of the ileal sodium bile acid cotransporter

Pathophysiologic Mechanism	Causes
○ Luminal deconjugation of bile acids	– SIBO
○ Binding of bile salts or insolubilization of bile salts as a result of low luminal pH	– Cholestyramine (binding) – ZES (low pH) – Exocrine pancreatic insufficiency (low pH)

- ○ ↓ Lipolysis
  - Exocrine pancreatic function is severely reduced, impairment of pancreatic lipase and colipase secretion results in decreased luminal hydrolysis of dietary fat
  - Chronic pancreatitis, cystic fibrosis, pancreatic duct obstruction by pancreatic and ampullary tumors, and pancreatic resection are the most common causes of pancreatic insufficiency
  - Even when pancreatic enzyme concentrations are normal, reduced pancreatic lipase activity resulting from low luminal pH, excessive calcium ingestion, or ingestion of the specific lipase inhibitor orlistat can cause pancreatic steatorrhea
  - Selective congenital lipase or colipase deficiency is a rare cause of pancreatic fat malabsorption.
- ○ ↓ Mucosal Absorption and Chylomicron Formation
  - Generalized mucosal diseases like celiac disease are often associated with fat malabsorption
  - Defective uptake of free fatty acids and monoglycerides results from reduced mucosal surface area secondary to villus shortening,



reduced enterocyte function, and mucosal inflammation
- Intestinal fat absorption is also impaired in diseases that result in dis-turbance of intracellular formation of chylomicrons and accumulation of lipids within the enterocytes, including abetalipoproteinemia, hypobetalipoproteinemia, and chylomicron retention disease

- ↓ Lymphatic Transport of Chylomicrons
  - Impairment of lymphatic transport of chylomicrons is a cause for postmucosal malabsorption of dietary fat
  - Decreased lymphatic transport can result from congenital diseases such as primary intestinal lymphangiectasia or from obstruction of lymphatic vessels as a result of metastatic solid tumors, lymphoma, Whipple's disease, retroperitoneal fibrosis, or trauma
  - Usually, lymphatic vessels in the mucosa become dilated (lymphangiectasia), and chylomicrons are lost postprandially into the intestinal lumen and also in the fasting state; steatorrhea in these situations usually is only mild to moderate

Proteins and Amino Acids

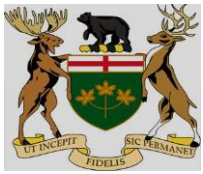
- ↓ intralumial proteolysis
  - Protein digestion may be impaired in patients who have undergone partial or total gastric resection, presumably as a result of poor mixing with digestive secretions, although gastric pepsin deficiency could be contributory
  - Impaired activation of pepsin due to acid inhibition by PPIs can result in an increased risk of food allergy like childhood asthma,

owing to decreased gastric digestion of proteins
- Defective proteolysis also occurs with exocrine pancreatic insufficiency
- In congenital diseases, pancreatic proteolysis can be impaired by inborn errors in the synthesis of proteolytic enzymes (trypsinogen deficiency) or by defective activation of pancreatic proenzymes resulting from congenital deficiency of intestinal enterokinase

- ↓ Mucosal Hydrolysis of Peptides and ↓ Absorption of Oligopeptides and Amino Acids
  - Generalized mucosal diseases, such as celiac disease, result in global malabsorption, which includes malabsorption of oligopeptides and amino acids secondary to lack of mucosal hydrolysis of oligopeptides and defective mucosal absorption
  - Reduction of intestinal absorptive surface, as in short bowel syndrome or jejunoileal bypass, also results in protein and amino acid malabsorption
  - Congenital defects of amino acid transporters on the enterocytes (e.g., Hartnup's disease, lysinuric protein intolerance) can lead to selective malabsorption of a subgroup of amino acids

Carbohydrates

- ↓ intraluminal hydrolysis of carbohydrates
  - Pancreatic α-amylase is normally secreted in excess into the intestinal lumen
  - In mild forms of pancreatic insufficiency, carbohydrate digestion usually is at least partially preserved, but severe pancreatic insufficiency results in clinically apparent carbohydrate malabsorption and diarrhea due to decreased luminal hydrolysis of ingested starch



- Mucosal Defects of Carbohydrate Digestion and Absorption
  - Most common cause of carbohydrate malabsorption is late-onset lactose malabsorption due to decreased levels of the intestinal brush border enzyme lactase (adult-type hypolactasia, acquired primary lactase deficiency)
    - Depending on ethnic background, lactase is present in less than 5% to more than 90% of the adult population
  - Acquired malabsorption of carbohydrates occurs commonly after extensive intestinal resections, in diffuse mucosal diseases like celiac or Crohn disease, or temporarily after self-limited GI infections
  - Pathophysiology reduction of surface area and reduced activity or expression of disaccharidases or transport proteins for monosaccharides
  - Congenital disaccharidase deficiencies (lactase, sucrase-isomaltase, trehalase) and congenital deficiency or malfunction of transport molecules, as in congenital glucose-galactose malabsorption, can cause early onset of malabsorption of mono- or disaccharides

Vitamins

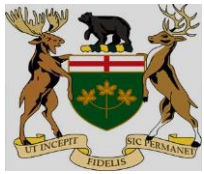
- Fat Soluble Vitamins (A, D, E, K)
  - Diseases that cause malabsorption of dietary fat commonly cause malabsorption of fat-soluble vitamins because they require similar absorptive mechanisms
    - Especially in conditions that result in impaired micelle formation due to bile salt deficiency

- Fat-soluble vitamins also are malabsorbed in diffuse diseases of the mucosal surface area, in diseases affecting chylomicron formation and transport, and in exocrine pancreatic insufficiency

- Water-soluble vitamins
  - Vitamin B12
    - ↓ dietary release from food sources
    - Impaired pepsin and acid secretion
      - Atrophic gastritis, PPI
    - Intrinsic factor deficiency
      - Seen in autoimmune gastritis or pernicious anemia
      - Usually results in more severe malabsorption with clinical consequences
      - Parietal cell destruction and production of autoantibodies that inhibit binding of IF to Vit B12
    - ↓ proteolytic release from R protein
      - Zollinger Ellison, pancreatic insufficiency
    - Ileal resection
      - Reduction of IF-vit B 12 complex
      - Ileal resection >60 cm

- Folate
  - Seen in conditions that affect proximal small intestine
    - Celiac disease, Whipple disease
  - Common in chronic alcoholism
    - Decreased dietary intake and intestinal absorbtion

- Other water-soluble vitamins, such as ascorbic acid and the B-complex vitamins, are absorbed in the small intestine either by carrier-mediated transport or passive diffusion



- Generalized malabsorption syndromes from intestinal causes impair the absorption of these vitamins, thereby leading to deficiency states

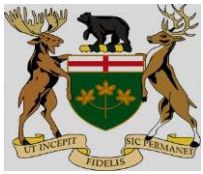
Minerals

- Calcium
  - Absorption is reduced due to reduction of surface area
    - Celiac, exocrine pancreatic insufficiency
  - Diseases that causes deficiency in long chain fatty acid can also cause calcium malabsorption
    - Bile acid deficiency
  - Vitamin D deficiency
  - Renal Disease, hypoparathroidism, and inborn defects in formation of 1, 25 vitamin D or in the intestinal vitamin D receptor
  - PPI therapy
- Magnesium
  - Magnesium deficiency due to magnesium malabsorption results from a reduction in mucosal absorptive surface area and luminal binding of magnesium by malabsorbed fatty acids
- Iron
  - Seen following gastric resection or celiac disease (loss of surface area)
  - Intestinal loss from GI bleeding is most common (most common)
  - Hookworm infection is the most common world wide
- Zinc
  - Malabsorbed in generalized mucosal diseases of the small intestine

- Copper
- Selenium
- Unsure whether malabsorptive diseases result in chromium and manganese deficiency

➢ Mechanisms that Compensate for Malabsorption

- Colonic Salvage of incompletely absorbed carbohydrates
  - Colon has the capacity to absorb a limited number but wide variety of substances and nutrients including sodium, chloride, water, oxalate, short-chain fatty acids, calcium, water-soluble vitamins (biotin, folate, pantothenic acid [B5], pyridoxine [B6], riboflavin [B2], thiamine [B1]), and vitamin K
  - In healthy people, between 2% and 20% of ingested starch escapes absorption in the small intestine; pancreatic insufficiency or severe intestinal disorders further increases this amount
  - Carbohydrates that reach the colon cannot be absorbed by the colonic mucosa but can be metabolized by colonic bacteria. Metabolism by anaerobic bacteria results in breakdown of oligosaccharides and polysaccharides to mono- and disaccharides, which are further metabolized to lactic acid, short-chain (C2 to C4) fatty acids (SCFAs)
  - Rate limiting step is the conversion of monosaccharides to SCFAs colonic absorption of SCFAs results in reduction in osmotic load and reduction in osmotic diarrhea

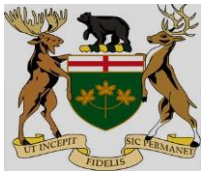


- In normal subjects, more than 45 g of carbohydrates must reach the colon to cause diarrhea, and up to 80 g of carbohydrates per day can be metabolized by bacteria to SCFAs; approximately 90% of these SCFAs are absorbed by colonic mucosa
- Chronic carbohydrate malabsorption causes adaptive changes in bacterial metabolic activity that result in even higher efficiency of the bacterial microbiota to digest carbohydrates, but at the expense of increased flatus production
- Can contribute positively to caloric intake
  - SCFAs have caloric values between 3.4 and 5.95 kcal
- Impaired colonic salvage of carbohydrates has been suggested to contribute to the diarrhea in Crohn's disease and UC
- Bacterial carbohydrate metabolism may be lessened by antibiotic treatment
  - In some patients, antibiotic-associated diarrhea may be the result of impaired colonic salvage of carbohydrates that are not normally absorbed or the result of dietary fiber that can accumulate in stool because of decreased bacterial fermentation

- Role of Colon in Fat Malabsorption
  - Long-chain triglycerides or fatty acids, which constitute most dietary fat, cannot be absorbed by the human colon. Long-chain fatty acids bind calcium in the colon, thereby increasing the amount of oxalate that is absorbed bound to sodium
  - Fatty acids with chain lengths longer than 12 carbons can cause diarrhea because they

increase mucosal permeability and inhibit colonic absorption of fluid and electrolytes
    - Increased mucosal permeability may also be the reason for increased oxalate exposure in patients with steatorrhea and hyperoxaluria
- Patients with short bowel syndrome can gain caloric energy from colonic absorption of medium-chain fatty acids coming from medium-chain triglyceride supplementation if they have at least part of the colon in continuity with the remaining small intestine

- Colonic Salvage of Calcium
    - Preservation of at least half of the colon in patients with extensive small bowel resection improves calcium absorption by about 40
    - Absorption of calcium requires solubilization of calcium salts. Bacterial metabolism of dietary fiber or incompletely absorbed carbohydrates can help solubilize calcium by causing a decrease in the pH of luminal contents in the colon. Once calcium is solubilized, it can contact the cecal mucosa, which, in the rat, has the highest calcium absorption rate per surface area of intestine
    - Calcium solubilization in the colon from bacterial fermentation of malabsorbed lactose can also occur in patients with lactose malabsorption; in this condition, the bioavailability of calcium from milk is greater than that from mineral water
    - SCFAs acetate and propionate, which are products of bacterial metabolism of lactose, have been shown to directly enhance calcium absorption in the human colon

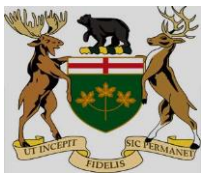


- Clinical

Symptoms and Signs of Malabsorption

Symptoms or Sign	Pathophysiologic Explanation
○ Gastrointestinal	
– Diarrhea	▪ Osmotic activity of carbohydrates or short-chain fatty acids ▪ Secretory effect of bile acids and fatty acids ▪ ↓ absorptive surface ▪ Intestinal loss of conjugated bile acids ▪ Ileal resection ▪ Severe ileal mucosal disease ▪ Congenital defects of the ileal sodium-bile acid cotransporter
– Abdominal distention, flatulence	▪ Bacterial gas production from carbohydrates in colon, SIBO
– Foul-smelling flatulence or stool	▪ Malabsorption of proteins or intestinal protein loss
– Pain	▪ Gaseous distention of intestine
– Ascites	▪ Protein loss or malabsorption
○ Musculoskeletal	
– Tetany, muscle weakness, paresthesias	▪ Malabsorption of vitamin D, calcium, magnesium, and phosphate
– Bone pain, osteomalacia, fractures	▪ Protein, calcium, or vitamin D deficiency, secondary hyperparathyroidism
○ Cutaneous and Mucosal	
– Easy, bruisability, escchymoses, petechiae	▪ Vitamin K deficiency, vitamin C deficiency (scurvy)

Symptoms or Sign	Pathophysiologic Explanation
– Glossitis, cheilosis, stomatitis	▪ Vitamin B complex, vitamin B12, folate, or iron deficiency
– Edema	▪ Protein loss or malabsorption
– Acrodermatitis, scaly dermatitis	▪ Zinc and essential fatty acid deficiency
– Follicular hyperkeratosis	▪ Vitamin A deficiency
– Hyperpigmented dermatitis	▪ Niacin deficiency (pellagra)
– Thin nails with spoon-shaped deformity	▪ Iron deficiency
– Perifollicular hemorrhage	▪ Malabsorption of vitamin C
– Spiral or curly hair	▪ Malabsorption of vitamin C
○ Other	
– Weight loss	▪ Nutrient malabsorption
– Growth and weight retardation, infantilism	▪ Nutrient malabsorption in childhood and adolescence
– Anemia	▪ Iron, folate, or vitamin B12 deficiency
– Kidney stones	▪ Increased colonic oxalate absorption
– Amenorrhea, impotence, infertility	▪ Multifactorial (including protein malabsorption, secondary hypopituitarism, anemia)
– Night blindness, xerophthalmia	▪ Vitamin A deficiency
– Peripheral neuropathy	▪ Vitamin B12 or thiamine deficiency
– Fatigue, weakness	▪ Calorie depletion, iron, and folate deficiency, anemia
– Neurologic symptoms, ataxia	▪ Vitamin B12, vitamin E, or folate deficiency



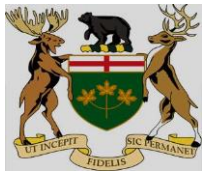
- Laboratory Findings
  - Blood cell count
    - Hematocrit, hemoglobin
      - ↓ iron, vitamin B12, and folate malabsorption or with blood loss
    - Mean corpuscular hemoglogin or mean corpuscular volume
      - ↓ iron malabsorption; ↑ folate and vitamin B12 malabsorption
    - White blood cells; differential
      - ↓ vitamin B12 and folate malabsorption; low lymphocyte count in lymphangiectasia
  - Biochemical Tests (serum)
    - TGs
      - ↓ severe fat malabsorption
    - Cholesterol
      - ↓ bile acid malabsorption or severe fat malabsorption
    - Albumin
      - ↓ severe in malabsorption, lymphangiectasis, protein-losing enteropathy
    - Alkaline phosphatase
      - ↑ calcium and vitamin D malabsorption (severe steatorrhea, ↓ zinc deficiency)
    - Calcium phosphorus, magnesium
      - ↓ extensive small intestinal mucosal disease, after extensive intestinal resection, or in vitamin D deficiency
    - Zinc
      - ↓ extensive small mucosal disease or intestinal resection
    - Iron, ferritin
      - ↓ celiac disease, in other extensive small intestinal mucosal diseases, and chronic blood loss

- Other Serum Tests
  - Prothrombin time
    - Prolonged in vitamin K malabsorption
  - Beta carotene
    - ↓ fat malabsorption from hepatobiliary or intestinal diseases
  - Immunoglobulin
    - ↓ lymphangiectasia, diffuse lymphoma
  - Folic acid
    - ↓ extensive small intestinal mucosal diseases, with anticonvulsant use, in pregnancy; may be increased in SIBO
  - Vitamin B12
    - ↓ after gastrectomy, in pernicious anemia, terminal ileal disease, SIBO, and infection with *Diphyllobothrium latum*
  - Methylamalonic acid
    - Marked elevated in vitamin B12 deficiency
  - Homocysteine
    - Marked elevated in vitamin B12 or folate deficiency
  - Citrulline
    - May be decreased in destructive small intestinal mucosal disease or intestinal resection
- Stool tests
  - Fat
    - Qualitative or quantitative increase in fat malabsorption
  - Elastase, chymotrypsin
    - ↓ concentrations and output in exocrine pancreatic insufficiency
  - pH
    - Less than 5.5 in carbohydrate malabsorption
- Quantitative fecal fat measurement followed by measurement of fecal chymotrypsin or elastase concentration may be helpful, both in establishing malabsorption and in differentiating between pancreatic and intestinal causes of malabsorption

- Low levels of serum β-carotene, cholesterol, triglycerides, and calcium and a prolonged prothrombin time suggest malabsorption of fat and fat-soluble vitamins
- Low levels of vitamin B12, folate, iron, and albumin suggest malabsorption of water-soluble substances and therefore indicate intestinal disease rather than pancreatic or biliary disease
- Severe deficiency of fat-soluble vitamins might indicate intestinal or biliary disorders
- Low levels of plasma citrulline are associated with destructive small intestinal disease (e.g., celiac disease) or can follow intestinal resection, although fasting plasma citrulline tests are poor predictors of enterocyte dysfunction in clinical practice. An oral citrulline generation test has been proposed to improve its predictive value

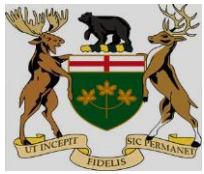
- Differential diagnosis
  - Adrenal insufficiency – Skin darkening, hyponatremia, hyperkalemia
  - Amyloidosis – Renal disease, nephrotic syndrome, cardiomyopathy, neuropathy, carpal tunnel syndrome, macroglossia, hepatosplenomegaly
  - Bile acid deficiency – Ileal resection or disease, liver disease
  - Carcinoid syndrome – Flushing, cardiac murmur
  - Celiac disease – Variable symptoms: dermatitis herpetiformis, alopecia, aphthous mouth ulcers, arthropathy, neurologic symptoms, and (life-threatening) malnutrition; elevated liver biochemical test levels, mild iron deficiency

- Crohn's disease – Arhtritis, aphthous mouth ulcers, episcleritis, uveitis, pyoderma gangrenosum, erythema nodosum, abdominal mass, fistulas, perianal laboratory signs of inflammation
- CF – Chronic sinopulmonary disease, meconium ileus, distal intestinal obstruction syndrome (DIOS), elevated sweat chloride
- Cystinuria, Hartnup disease – Kidney stones, dermatosis
- Diabetes melitus – Long history of diabetes complications
- Disaccharidase deficiency – Bloating and cramping, intermittent diarrhea
- GI fistulas – Previous intestinal surgery or trauma, Crohn disease
- Glucagonoma – Migration necrolytic erythema, enlarged gallbladder
- Hyperthyroidism, hypothyroidism – Symptoms and signs of thyroid disease
- Hypo-gammaglobulinemia – Recurrent infection
- Intestinal ischemia – Other ischemic organ manifestations; abdominal pain with eating (chronic mesenteric ischemia)
- Lymphoma – Enlarged mesenteric or retroperithneal lymph nodes, abdominal mass, abdominal pain, fever



- Mastocytosis – Urticaria pigmentosum, peptic ulcer
- Mycobacterium avium complex infection – AIDS
- Pancreatic insufficiency – History of pancreatitis, abdominal pain, or alcoholism; large-volume fatty, oily stools; passage of orange oil
- Parasitic infection – History of travel to endemic areas
- PBC – Jaundice, itching
- Scleroderma – Dysphagia, inability to open the mouth widely, Raynaud phenomenon, skin tightening
- SIBO – Previous intestinal surgery, motility disorder (scleroderma, pseudo-obstruction), small intestinal diverticula, strictures
- Tropical sprue – History of travel to endemic area
- Tuberculosis – Specific history of exposure, living in or travel to endemic area, immunosuppression, abdominal mass or intestinal obstruction, ascites
- Whipple disease – Lymphadenopathy, fever, arthritis, cerebral symptoms, heart murmur (pulmonary valve), oculomasticatory myorhythmia
- ZES – Peptic ulcers, diarrhea

- Approach to Investigations
  - Weight loss, osteomalacia, osteopenia, diarrhea, steatorrhea, or deficiency of fat-soluble vitamins
  - First line
    - Abdominal and small intestinal US
    - Chymotrypsin or elastase concentration in stool
    - EGD with small intestinal biopsies
    - Endomysial or tissue transglutaminase antibodies
    - Laboratory tests (CBC, white blood cell differential, cholesterol, TGs, electrolytes, calcium, magnesium, serum ALT, AST, AP, bilirubin levels, prothrombin time, serum albumin level, erythrocyte sedimentation rate and C-reactive protein, TSH)
    - Ova, parasites, calprotectin and leukocytes in stool
  - Second line
    - Abdominal CT, MRI
    - Endoscopic examination of the terminal ileum, including ileal biopsies
    - Enteroscopy, including biopsies
    - ERCP/MRCP
    - More extensive laboratory investigation (immunoglobulins, HIV ELISA, antinuclear antibodies, ferritin, food allergen–specific IgE, ACTH cortisol, chromogranin A, gastrin, urinary 5-HIAA)
    - Quantitative fecal fat
    - Quantitative small intestinal culture or breath tests for SIBO
    - Small bowel series/small bowel MRI
    - Special staining of small intestinal biopsies (e.g., Congo red for amyloid, PAS for Whipple's disease)
    - Therapeutic trial of pancreatic enzymes, antibiotics (tetracycline, metronidazole), cholestyramine, or a gluten-free diet
    - Video capsule endoscopy



- Third line
  - Mesenteric angiography
  - Antienterocyte antibodies
  - EUS
  - MRA
  - PET
  - Serum or plasma glucagon, somatostatin
  - Somatostatin (octreotide) scan
  - Special tests of intestinal biopsies (e.g., flow cytometry of intraepithelial lymphocytes for lymphoma and refractory celiac disease, PCR for Tropheryma whipplei or other infective organisms, chromogranin A stain for enteroendocrine cells)
  - Spiral CT of the pancreas
  - Tests for bile acid malabsorption
  - Tube test for exocrine pancreatic secretion (secretin, CCK, or Lundh test)
- Bloating with or without Diarrhea
  - First-Line Tests
    - Fructose H2 breath test
    - Lactose H2 breath test
    - Lactose tolerance test
  - Second-Line Tests
    - Chymotrypsin or elastase concentration in stool
    - EGD with duodenal biopsies
    - Endomysial or tissue transglutaminase antibodies
    - Genetic testing for hypolactasia
    - Quantitative small intestinal culture or breath tests for SIBO
    - Stool pH (in patients with diarrhea)

- Anemia and Suspected Malabsorption:
  - Microcytic or hypochromic anemia (low MCV, MCH)
    - EGD with duodenal biopsies
    - Endomysial and tissue transglutaminase antibodies
    - Iron, ferritin, and transferrin in serum
    - Ova and parasites in stool
    - Video capsule endoscopy
    - Calprotectin
    - FOBT
- Macrocytic anemia (high MCV, MCH)
- First-Line Tests
  - Folic acid in serum or red blood cells
  - Vitamin B12 in serum
- Second-Line Tests in Cases of Vitamin B12 Deficiency
  - CT, small bowel series, enteroclysis, video capsule endoscopy
  - EGD with gastric and duodenal biopsies
  - Endomysial and tissue transglutaminase antibodies
  - Evaluation of ileum (e.g., colonoscopy to ileum with biopsy, balloon enteroscopy with biopsy)
  - Ova and parasites in stool
  - Quantitative small intestinal culture or breath tests for SIBO
  - Calprotectin
  - Schilling test (with and without intrinsic factor)
  - Second-Line Tests in Cases of Folate Deficiency
  - EGD with duodenal biopsies
  - Endomysial or tissue transglutaminase antibodies

- AP, alkaline phosphatase; CBC, complete blood cell count; FOBT, fecal occult blood test; 5-HIAA, 5-hydroxyindoleacetic acid; IgE, immunoglobulin E; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PAS, periodic acid–Schiff; TSH, thyroid-stimulating hormone.

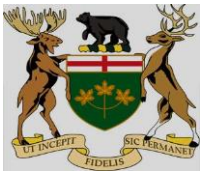
- Endoscopy
  - Appearance of duodenal mucosa can provide some clues to etiology of malabsorption
  - Mosaic like scalloping of duodenal folds and reduction in number of duodenal folds
    - Suggestive of celiac disease
  - Can enhance appearance of villous atrophy using magnification and chromoendoscopy
  - Apthous ulcers in Crohn's Disease
  - Small, diffuse, white-yellowish, punctate lesions can be seen in primary or secondary lymphangiectasia
  - Ampullary tumors – gastrinomas, somatostatinomas or ampullary tumors

- Causes of Malabsorption Diagnosed on Small Bowel Biopsy

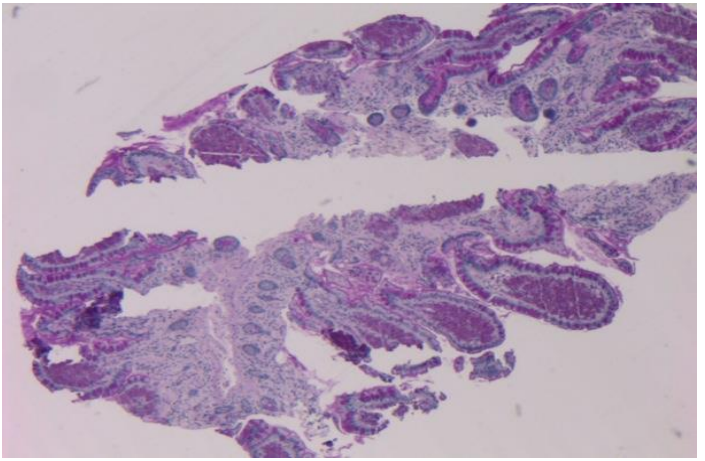
Cause	Main Histologic Features
Generalized histologic abnormalities	
– Abetalipoproteinemia hypobetalipoproteinemia	▪ Lipid accumulation and vacuolization of enterocytes
– Collagenous sprue	▪ Collagenous band below atrophic epithelium
– Mycobacterium avium complex infection	▪ Acid-fast bacilli, foam cells
– Whipple disease	▪ Foamy macrophages with PAS-positive inclusion bodies

Cause	Main Histologic Features
○ Patchy histologic abnormalitis	
– Amyloidosis	▪ Congo red-stained deposits with green-apple birefringence in polarized light
– Crohn's disease	▪ Epitheloid granulomas and characteristic focal inflammation
– Eosinophilic gastroenteritis	▪ Eosinophilic infiltration
– Lymphangiectasia	▪ Ectatic lymph vessels
– Lymphoma	▪ Clonal expansion of lymphocytes
– Mastocytosis	▪ Diffuse infiltration with mast cells
– Parasites and worms (Giardia lamblia, Strongyloides stercoralis, coccidia)	▪ Some parasites may be seen on histologic examination

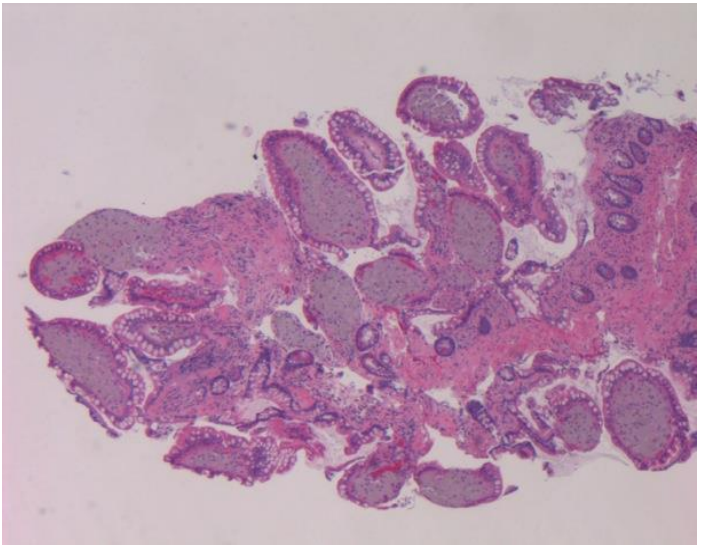
- Diagnostic yield of biopsy is influenced by the dis-tribution of histologic abnormalities
  - Tropical diarrhea and malabsorption syndrome, abetalipoproteinemia, and immunodeficiency usually result in a diffuse alteration of small intestinal mucosa
    - Normal biopsy rules out these conditions
  - Primary lymphangiectasia and celiac disease have a patchy distribution, so a single mucosal biopsy might not rule out the disorder
  - Other possible sources of error and misdiagnosis include poorly oriented specimens and those obtained proximally, where confounding peptic injury can be the cause of mucosal alterations
  - May have histologic features specific for certain conditions



Whipple Disease, Small Bowel Biopsy



Whipple Disease, Small Bowel Biopsy



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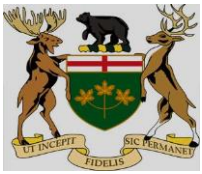
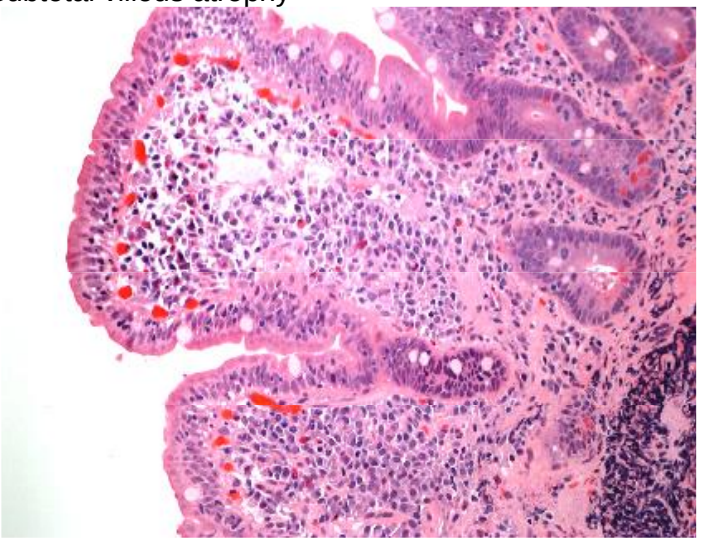
Malabsorptive Diseases with Abnormal but Nondiagnostic Small Intestinal Histologic Findings

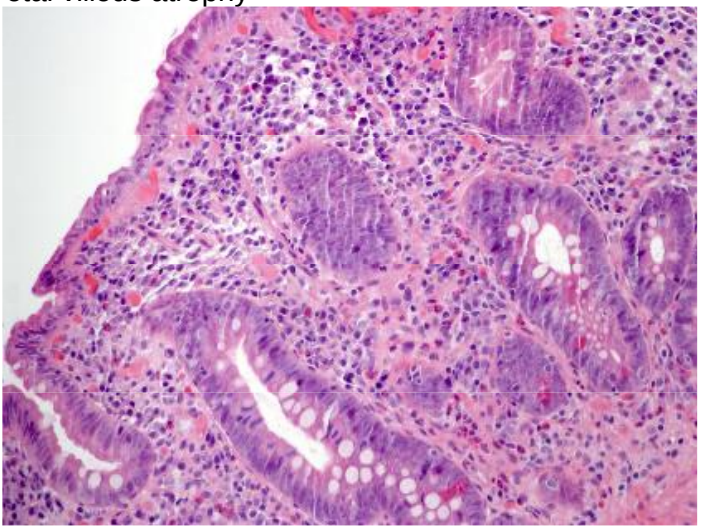
- Increased Lymphocyte Infiltration with or without Crypt Hyperplasia
  - AIDS enteropathy
  - Celiac disease
  - Infection (due to Giardia lamblia, Cryptosporidium, viral enteritis)
  - Tropical sprue
- Atrophic Lesion
  - Chronic radiation damage
  - Cicatrizing Crohn disease
  - Diffuse lymphoma
  - Idiopathic diarrhea of infancy (microvillus inclusion disease) Unresponsive gluten sensitivity (lymphoma or ulcerative jejunitis)
- Flat Lesion with or without Mucosal Inflammation
  - Celiac disease
  - Drug-induced enteropathy (NSAIDs, colchicine, neomycin)
  - Food protein hypersensitivity (rye, barley, egg, fish, rice, poultry)
  - Immunodeficiency (hypogammaglobulinemia)
  - Immunoproliferative small intestinal disease (IPSID)
  - Infection (due to Giardia lamblia, Cryptosporidium)
- Intestinal transplantation
- Lymphoma
- Nongranulomatous chronic idiopathic enterocolitis
- Autoimmune enteropathy
- Prolonged folate or cobalamin deficiency
- Protein-calorie malnutrition
- Traumatic injury
- Tropical sprue



Subtotal villous atrophy



Total villous atrophy



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- Some disease states can be identified only with use of special histologic stains, such as
  - Congo red (intestinal amyloidosis)
  - Periodic acid–Schiff (PAS) (Whipple disease)
  - Immunohistochemical techniques for detecting refractory celiac disease
  - Small intestinal lymphoma
  - Enteroendocrine insufficiency

❖ Aspiration

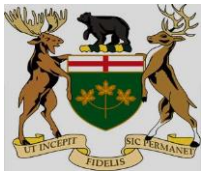
- Fluid aspirated from the descending part of the duodenum may be examined microscopically for Giardia lamblia or cultured to detect SIBO in patients with diffuse small intestinal motility disorders

❖ Capsule Endoscopy and Balloon Enteroscopy

- VCE appears to be superior to conventional radiologic imaging of the small intestine and CT enterography to detect subtle mucosal changes like aphthous or erosive lesions of the small intestine
- In refractory celiac disease, VCE can detect changes such as ulcerations and strictures that suggest T-cell lymphoma but that are missed by conventionnal techniques
- In some cases of malabsorption, balloon enteroscopy with biopsies of the jejunum and ileum can be helpful to establish the diagnosis. Compared with VCE, balloon enteroscopy has the advantage of being able to obtain biopsy specimens from altered mucosal areas, but it is time consuming and uncomfortable for the patient

❖ Abdominal Imaging – barium studies

- Small bowel follows through and small bowel enteroclysis



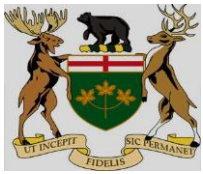
- The principal role of small bowel radiologic series in evaluating malabsorption is to identify focal or diffuse abnormalities that predispose to SIBO, such as diverticula, stagnant loops of intestine, generalized intestinal hypomotility or dilatation, intestinal fistulas, and tumors
- Small bowel enteroclysis is preferred to small bowel follow-through examination, because distention of the lumen results in better demonstration of the small bowel contour. Double-contrast enteroclysis, in which the upper jejunum is intubated for direct instillation of contrast material, has a higher sensitivity than small bowel series for detecting mucosal changes, although it is less acceptable to the patient and can miss focal changes in the duodenum, such as diverticula. Use of an intravenous agent such as glucagon to reduce motility enables overlapping loops of small intestine to be separated and imaged more distinctly

- Small bowel follow through and small bowel enteroclysis
  - Alterations associated with diffuse, localized, or distal mucosal changes that might have been missed by more proximal mucosal biopsy also may be identified
  - A normal small bowel series does not exclude intestinal causes of malabsorption and should not dissuade the clinician from performing biopsy of the small intestine
  - Ulcerations and strictures may be seen in various malabsorptive disorders, including Crohn’s disease, radiation enteritis, celiac disease, intestinal lymphoma, and tuberculosis. Aphthous ulcers and cobblestoning of the

mucosa, either alone or with thickened and distorted folds, are features of Crohn disease but can also be present in other conditions.
- Reduced numbers of jejunal folds and an increased number of and thickening of ileal folds can suggest celiac disease.
- Mass lesions can be found with intestinal lymphoma or, rarely, with hormone-producing tumors
- Disadvantage
  - Does not image the surrounding tissues
  - Can have overlapping bowel loops that obscure image

❖ Abdominal CT

- Abdominal CT for small bowel evaluation is performed after administration of oral or IV contrast agents
- Small intestinal CT scanning is useful to detect focal intestinal lesions, such as thickening of the small bowel wall in Crohn's disease or small intestinal lymphoma, intestinal fistula, and dilated bowel loops; however, mild mucosal changes like aphthae in Crohn's disease or villus atrophy from various causes are missed by this technique. Diffuse thickening of the small bowel may be seen in Whipple's disease and in graft-versus-host disease
- In some cases of celiac disease, reversal of the jejunoileal fold pattern is observed
- Evidence for pancreatic disease that may be detected on CT includes calcifications of the pancreas, dilatation of the pancreatic duct, and pancreatic atrophy. Tumors that obstruct the pancreatic duct or hormone-secreting neuroendocrine tumors can also be located by CT.



- MRI of Small Intestine
  - Can use oral contrast or enteroclysis
  - Segmental bowel wall thickening with inflammatory involvement of the mesentery, cobblestoning, and ulcerations may be seen in Crohn's disease; this method is very sensitive for demonstrating complications of Crohn's disease
  - In celiac disease, small bowel MRI with oral contrast can demonstrate small intestinal dilatation, mucosal thickening, and an increased number of folds in the ileum (ileal jejunization) with flattening of duodenal and jejunal folds reversal of pattern)
    - Findings more evident with active disease
    - Useful for identifying refractory celiac disease
      - Features: presence of less than 10 folds per 5 cm jejunum, mesenteric fat infiltration, and bowel wall thickening
  - Limitations
    - May miss subtle mucosal changes

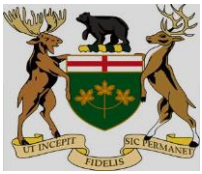
- US Examination
  - Advantage – no radiation exposure
  - Ultrasonography is often used to investigate the pancreas, although the sensitivity for detecting pancreatic tumors is lower than that of ERCP or CT
  - Inflammatory diseases of the small intestine like celiac disease, Crohn disease, mycobacterial infections, and Whipple disease, as well as small intestinal lymphomas, can exhibit thickening of the small bowel wall, loss of the small bowel layers, and enlarged mesenteric lymph nodes on US
    - In celiac disease, thickening of the small bowel wall (>3 mm) and dilatation of the bowel loops (>2.5 cm) have been suggested to be the most sensitive markers

- A hyperechoic appearance of the bowel wall may be suggestive for Whipple disease, AIDS enteropathy, or mycobacterial infections, and the presence of intraluminal abscesses in the ileocecal region for intestinal tuberculosis

❖ Other examinations
- Plain film abdomen
  - May be helpful to detect pancreatic calcifications, dilated small bowel loops that can predispose to SIBO
- ERCP
  - Can help establish cause of pancreatic insufficiency
  - Can also differentiate chronic pancreatitis from pancreatic tumor and can document pancreatic duct stones
- Suspected neuroendocrine tumor
  - Octreotide scan
  - PET
  - EUS

❖ Non-invasive testing
- Diagnostic accuracy limited
- Each lab has own cutoff values

Disease or Condition	Diagnostic Test(s)	Comment(s)
○ Lactose malabsorption	– Lactose hydrogen breath test – Lactose intolerance test	Tests do not differentiate between primary and secondary lactose malabsorption
○ Incomplete fructose absoption	– Fructose hydrogen breath test	



Disease or Condition	Diagnostic Test(s)	Comment(s)
○ SIBO	– ^{14}C-D-xylose breath test – Glucose hydrogen breath test – Schilling test with and without antibiotics	A predisposing factor should be sought if the result of any of the tests is positive
○ Bile acid malabsorption	– SeHCAT test, ^{14}C-TCA test	Does not differentiate between primary and secondary causes
○ Exocrine pancreatic insufficiency	– Quantitative fecal fat determination – Fecal elastase or chymotrypsin tubeless tests	Used to establish malabsorption in chronic pancreatitis Variable sensitivity and specificity, depending on the type of tests and stage of the disease
○ Vitamin B12 malabsorption	– Schilling test	The test is performed without intrinsic factor and, depending on the result with intrinsic factor, with antibiotics or pancreatic enzymes. Further tests are necessary if SIBO, terminal ileal disease, or pancreatic disease is suspected

- Fat Malabsorption
  - Fecal Fat Analysis
    - The van de Kamer method is the quantitative titration of fatty acid equivalents in which results are expressed as fecal output of fat in grams per 24 hr is considered the gold standard for fecal fat analysis
      - Modified versions have the extracted fats weighed rather than titrated – good correlation with this method
      - Still need 40-72 hr collection to eliminate confounding of day to day variability
    - Fecal fat excretion of less than 7 g/day with a fat intake of 100 g/day usually is considered normal
    - The volume effect of diarrhea may increase fecal fat output to levels of up to 14 g/day (secondary fat malabsorption) – if patient is having diarrhea 14g/day should be used as upper limit of normal
    - Limited clinical use overall:
      - Other tests could be used to evaluate diarrhea
      - Elevated fecal fat level usually cannot differentiate among biliary, pancreatic, and enteric causes of malabsorption
      - In many patients with severe steatorrhea, the stools have a very foul smell and a characteristic porridge-like appearance, and quantitative studies are not necessary to establish fat malabsorption
      - Fat absorption may be normal despite malabsorption of other nutrients, so a normal fat balance does not imply normal absorptive function of the GI tract

        - Accuracy depends on quantitative stool collections for 48 to 72 hr, adherence to a diet that contains 80 to 100 g of fat daily, and a diet diary to determine fat intake. Science aside, quantitative fecal fat analysis has never been popular among patients, physicians, or laboratory personnel performing the test
    - Despite drawbacks, can be used in some clinical situations
        - Estimate fecal calorie loss in patients with severe malabsorption syndromes
        - Monitor treatment in patients with established malabsorptive disorders
        - Quantitate fecal fat excretion in patients with diarrhea who have undergone ileal resection, thereby distinguishing steatorrhea due to bile acid deficiency from secretory diarrhea caused by bile acid loss

- Semiquantative Fat Analysis
    - Acid steatocrit test
        - Still is diluted and the amount of fat is calculated
        - <31% is normal
        - Can be used to detect steatorrhea
    - Qualitative Fecal Fat Analysis
        - Can not be used to exclude steatorrhea
        - Sample of stool is placed on a glass slide to which several drops of glacial acetic acid and Sudan III stain are added
        - Look for separation of lipid layer under microscope
        - Sensitivity of 78% and a specificity of 70% for the detection of steatorrhea
    - Breath test not used clinically

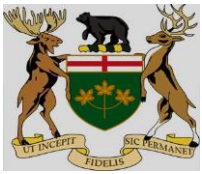
- Serum test
  - Beta-carotene: Values less than 100 mg per 100 mL suggest the presence of steatorrhea, and values less than 47 mg per 100 mL strongly indicate steatorrhea

❖ Carbohydrate Malabsorption

- Hydrogen breath test
  - Bacterial metabolism of carbohydrate results in accumulation of hydrogen
  - Diagnosis of lactose malabsorption is established if an increase in breath hydrogen concentration of greater than 20 parts per million over baseline occurs after ingestion of 20 to 50 grams of lactose
    - Elevation in the first 30 min can not be used as it may be due to degradation in the oral cavity
- Acquired lactase deficiency – SNP up stream of lactase gene
  - Caucasians only
  - CC genotype at −13910 C/T is associated with acquired primary lactase deficiency (adult-type hypolactasia), whereas TC and TT genotypes are linked with lactase persistence

❖ Protein Malabsorption

- Rarely used clinically, used in research settings
- Measurement of nitrogen in stool sample



- Vitamin B12 Malabsorption
  - Shilling Test
    - Used to distinguish between gastric and ileal causes of vitB12 def but rarely performed now
    - The Schilling test is performed by administering a small oral dose of radiolabeled vitamin B12 and, simultaneously or within 1 or 2 hr, a large intramuscular flushing dose of nonradiolabeled vitamin B12. The unlabeled B12 saturates vitamin B12 carriers, so any radioactive vitamin B12 absorbed by the intestine is excreted in the urine. If less than 7% to 10% of the administered dose is recovered in urine within 24 hr, vitamin B12malabsorption is confirmed
  - Serum Vit B12 and Folate
    - Sensitivity and specificity of these tests are unknown because no gold standard test has been established and because serum levels do not always correlate with body stores

Other Malabsorptive Testing

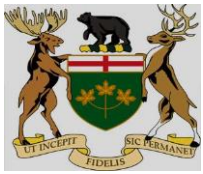
- SIBO
  - Gold standard – quantitative culture of small intestinal aspirate
- Exocrine Pancreatic Insufficiency
  - Non-invasive – fecal chymotrypsin or elastase concentration
  - Invasive – requires duodenal intubation to measure output after pancreatic stimulation
- Bile Sale Malabsorption
  - Measurement has limited clinical value
  - Can perform fecal bile acid output
  - Could also use therapeutic trial of cholestyramine - if no improvement, bile acid malabsorption is unlikely to be cause

- D-Xylose
  - Because D-xylose is susceptible to bacterial metabolism, absorption is diminished in patients with SIBO, although the test has a poor sensitivity for detecting bacterial overgrowth
  - The test is of limited clinical value has been replaced by small intestinal biopsy

❖ Malabsorption in Specific Situations and Disease States

- Lactose Malabsorption
  - Congential – present at birth
  - Acquired
    - Genetic: SNP −13910 T/C upstream of the gene that codes for lactase-phlorizin hydrolase (LPH gene)
    - Most often in patients with Western European descent
  - Main symptoms of lactose intolerance are bloating, abdominal cramps, increased flatus, and diarrhea
    - No clear relation between amount of lactose ingested and symptom severity
    - More severe with shorter intestinal transit time
    - Ingestion of as little as 3 g of lactose may be required to induce symptoms in persons with lactose malabsorption
  - Risk factor for osteoporosis
  - Treatment: lactose free diet, calcium supplementation

- Fructose Malabsorption
  - Fructose is found in modern diets either as a constituent of the disaccharide sucrose or as the monosaccharide, both of which are used as sweeteners in a variety of food items



- Average daily intake of fructose varies from 11 to 54 g
- The absorptive capacity for fructose that is not accompanied by glucose, however, is relatively small and dose dependent
  - Many individuals will have malabsorption and intolerance with intake of 50 g of fructose, can get symptoms with as little as 3 g
  - Ingesting fructose in excess of glucose can cause abdominal bloating and diarrhea
- Diagnosis – positive result on breath test after ingestion of 25-50g of fructose

- Bile Acid Malabsorption
  - Bile acid malabsorption (BAM) is usually present in patients who have undergone ileal resection or bypass operations or who have severe disease of the ileum, where specific bile acid transport proteins are located
    - Clinical consequences depend on whether bile acid loss can be compensated by hepatic synthesis
    - Ileal resection of >100cm usually results in BAM that can not be compensated for
  - Treatment
    - Cholestyramine will worsen in patients with BAM
    - Cholylsarcosine 2-3 g per meal (conjugated bile acid)

- Amyloidosis
  - Can get fat malabsorption, vitamin B12, D-xylose malabs, BAM, and protein losing enteropathy
  - Amyloid deposits are found in the muscle layers, the stroma of the lamina propria and the submucosa, the wall of mucosal and submucosal blood vessels

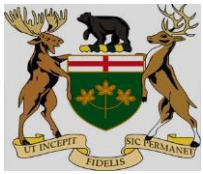
in the GI tract, and in enteric and extraenteric nerves
  - Mechanisms of malabs
    - Autonomic neuropathy causing rapid intestinal transit
    - Chronic mesenteric ischemia
    - Decreased absorption
    - SIBO
- Fails to respond to bile acid binding agents
- Endoscopic appearance of the GI mucosa may show a fine granular appearance, polypoid protrusions, erosions, ulcerations, atrophic changes, and mucosal friability
- Treatment
  - Prolong intestinal transit time
  - Treat amyloid

- Drugs and Dietary Products

Acarbose	– Carbohydrate	▪ Inhibition of glucosidase
Antacids	– Phosphate, iron, vitamin A	▪ Luminal binding of substrates
Azathioprine	– Genralized malabsorption	▪ Villus atrophy
Biguanide (metformin)	– Cobalamin, folate, glucose	▪ Reduce ileal absorption of intrinsic factor (IF) – cobalamin complex; inhibition of intestinal glucose or folate absorption
Carbamazepine	– Folate	▪ Inhibition of intestinal folate absorption

○ Cholestyramine	– Fat, fat-soluble vitamins, bile acided	▪ Binding of conjugated bile salts
○ Colchicine	– Fat, xylose, nitrogen, cobalamin, carotene	▪ Mucosal damage and villus atrophy at high doses (impaired processing of IF-cobalamin receptor (the cubilin-amnionless complex])
○ Contraceptives, oral	– Folate	▪ Inhibition of pteroylpolyglutamate hydrolase (folate conjugase)
○ Ethanol	– Xylose, fat, glucose, nitrogen, thiamine, cobalamin, folate	▪ Mucosal damage; decreased disaccharidase activity; decreased pancreatic exocrine function and bile secretion
○ Fiber, phytates	– Iron, calcium, magnesium, zinc	▪ Chelation
○ Glucocorticoids	– Calcium	▪ Inhibition of calcium absorption
○ H2Ras	– Cobalamin	▪ Impaired release of food bound B12, owing to reduced gastric acid and pepsin secretion (and reduced IF secretion)

○ Laxatives, irritant type (phenopphthalein bisacodyl, anthraquinones)	– Fat, glucose, xylose	▪ Washout effect; toxic effect on mucosa
○ Methotrexate	– Folate, fat, cobalamin, xylose	▪ Mucosal damage; inhibition of intestinal folate transport
○ Methyldopa	– Generalized malabsorption	▪ Mucosal damage
○ Neomycin	– Fat, nitrogen, fat-soluble vitamins, cobalamin, mono- and disaccharides, iron	▪ Mucosal damage; disruption of micelle formation
○ Olestra*	– Fat-soluble vitamins	▪ Binding of fat-soluble vitamins
○ Orlistat	– Fat, fat-soluble vitamins	▪ Inhibition of pancreatic lipase
○ Para-aminosalicylate	– Fat, cobalamin, folate	▪ Unknown
○ Phenytoin	– Folate, calcium	▪ Inhibition of folate and calcium absorption owing to luminal alkalinaization; impaired vitamin D metabolism

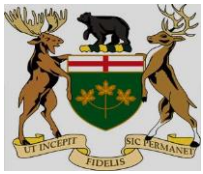


○ PPIs	– Cobalamin, calcium, magnesium	▪ Impaired release of food-bound cobalamin by pepsin owing to reduced gastric acid secretion; SIBO
○ Pyrimethamine	– Folate	▪ Competitive inhibition of intestinal folate absorption
○ Somatostatin analogs (e.g., octreotide)	– Fat	▪ Inhibition of hepatobiliary bile acid secretion; inhibition of pancreatic enzymes secretion; inhibition of CCK release
○ Sulfonamides and sulfasalazine	– Folate	▪ Inhibition of pteroyl-polyglutamate hydrolase and folate transport
○ Sulfonamides and sulfasalazine	– Folate	▪ Inhibition of pteroylpolyglutamate hydrolase and folate transport
○ Tetracycline	– Calcium	▪ Precipitation of luminal calcium
○ Thiazides	– Calcium	▪ Decrease 1, 25 dihydroxyvitamin D synthesis
○ Triamterene	– Folate	▪ Competitive inhibition of intestinal folate absorption

- Gastric Resection
  - Severe steatorrhea
    - Up to 15-20g/day
    - Suggested mechanisms for steatorrhea include defective mixing of nutrients with digestive secretions, lack of gastric acid and gastric lipase secretion, decreased small bowel transit time, SIBO, and pancreatic insufficiency
  - Vitamin E deficiency
    - Occurs when food does not pass through duodenum
  - Vitamin B12
    - Parietal cells loss result in diminished IF secretion
  - Iron malabsorption
    - Thought to be related to lack of acid secretion with decreased solubilization of iron salts
  - Calcium malabsorption

Bariatric Surgery

- Roux en Y
  - Severity of malabsorption varies and is correlated with the length of the biliopancreatic limb
  - Can develop fat malabsorption and protein malabsorption
  - Rarely cause deficiency of proteins, iron, calcium, folate, vitamin B12, and vitamin D. Deficiencies in vitamin B1
  - It has been suggested that after bariatric surgery, patients should have yrly measurements of a basic metabolic panel, magnesium, complete blood cell count, iron studies, vitamin D, parathyroid hormone, and bone density
  - Routine and lifelong use of multivitamins is considered necessary



- ❖ Aging
  - Evaluate for underlying malabsorptive disorder
  - Could be related to comorbidities (CHF, chronic intestinal ischemia)

- Connective Tissue Diseases
  - Systemic Sclerosis
    - Usually from SIBO, but decreased mucosal blood flow can contribute
  - Systemic Lupus Erythematosis
    - Excessive fecal fat excretion
    - If resolves following prednisone therapy could be linked to hypereosinophilic syndrome
- Congenital Defects
  - Malabsorption of Amino Acids
    - Hartnup's disorder
    - Cystinuria
    - Lysinuria protein intolerance
    - Isolated lysinuria
    - Iminoglycinuria
    - Blue diaper syndrome
    - Methionine malabsorption syndrome
    - Lowe oculocerebral syndrome
  - Malabsorption of Carbohydrates
    - Congenital lactase deficiency
    - Sucrase-isomaltase deficiency
    - Trehalase deficiency
    - Glucose-galactose malabsorption
  - Malabsorption of Vitamins
    - Congential IF deficiency
    - Imerslund-Gräsbeck syndrome (ileal B12malabsorption, megaloblastic anemia type I)
    - Transcobalamin II deficiency
    - Hereditary folate malabsorption

- Malabsorption of Minerals
  - Acrodermatitis enteropathica
  - Isolated magnesium malabsorption (hypomagnesemia with secondary hypocalcemia)
  - Menkes disease
  - Occipital Horn Syndrome
  - Iron-refractory iron deficient anemia
  - Hereditary deficiency of 1,25OH vitamin D
  - Hereditary resistence to 1,25OH vitamin D
- Other
  - Enterokinase deficiency
  - Congential bile acid malabsorption
  - Microvillus inclusion disease
  - Hyperinsulinism, with enteropathy and deafness
  - Immune dysregulation polyendocrinopathy and enteropathy, X-linked (IPEX)
  - Enteric anendocrinosis
  - Congenital proprotein convertase 1/3 deficiency
  - Congenital tufting enteropathy

- Primary Immunodeficiencies
  - Selective IgA Deficiency
    - Sprue-like small intestinal lesions that lead to severe diarrhea and malabsorption but are unresponsive to a gluten-free diet
    - Can improve with immunosuppressive therapy
    - Pernicious anemia, giardiasis, and secondary disaccharidase deficiencies are also seen with high frequency in patients with selective IgA deficiency
  - CVID
    - Clinically and genetically heterogeneous group of immunodeficiency disorders characterized by decreased serum IgG levels and variably decreased serum levels of other immunoglobulin subclasses with T-cell defects

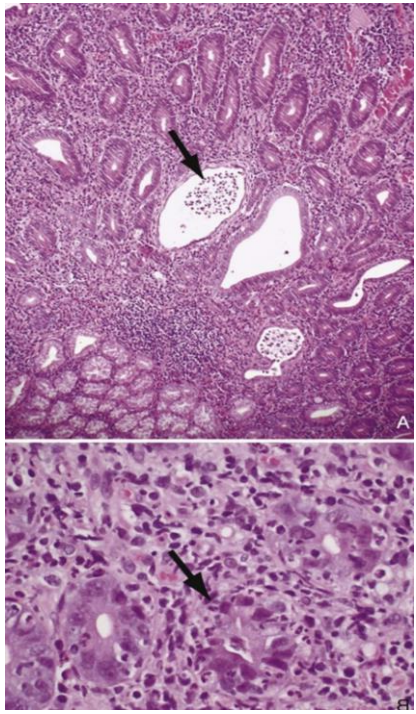
- Can develop malabsorption
  - Dietary fat, carbohydrates, vitamin B12, folate
- Small intestinal biopsy will show sprue like features – villous shortening, increased IEL, or a pattern similar to GVHD, can also get giardia or SIBO
- Higher incidence of atrophic gastritis and vitamin B12 malabsorption
- Treatment
  - Gluten free diet if sprue like syndrome
  - Antibiotics
  - Questionable benefit to IVIG
  - Increase risk of SB lymphoma

- Congenital Immunodeficiencies
  - X-Linked Infantile Agammaglobulinemia (Bruton's Agammaglobulinemia)
    - Manifests after the first 6 mon of life and is characterized by recurrent severe bacterial infections
    - Severe GI problems like malabsorption and chronic diarrhea are less common than in CVID
  - Immune Dysregulation-Polyendocrinopathy-Enteropathy–X-Linked Syndrome
    - Disorder of early childhood characterized by protracted diarrhea, dermatitis, insulin-dependent diabetes mellitus, thyroiditis, thrombocytopenia, and hemolytic anemia
    - Anti-enterocyte antibodies are commonly present. The enteropathy usually does not respond to a gluten-free diet, but immunosuppressive therapy has been shown to be of some benefit
    - Usually fatal in childhood

- Neurofibromatosis
  - Mechanisms of malabsorption include periampullary duodenal tumors, which are mainly somatostatin-containing neuroendocrine tumors, and pancreatic carcinomas with resultant pancreatic duct obstruction; tumors can cause exocrine pancreatic insufficiency and biliary obstruction
  - Could get gastrinomas as well

Nongranulomatous Chronic Idiopathic Enterocolitis and Autoimmune Enteropathy

- Distinct from refractory celiac disease and IBD
- Severe diarrhea and malabsorption occur as a result of diffuse villus atrophy, and ulcerations may be present in the small and large intestine
- Small intestinal villus atrophy and neutrophilic inflammation of the mucosa with crypt abscesses may be seen in biopsy specimens from the small intestine and colon
- Treatment
  - Prednisone
  - Cyclosporine



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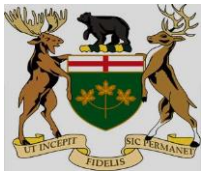
Endocrine and Metabolic Disorders

- Adrenal Insufficiency
  - Fat malabsorption
  - Pernicious anemia
- Autoimmune polyglandular syndrome type 1
  - Multiple endocrine failure due to autoimmune destruction
  - Can develop severe malabsorption
    - Hypoparathyrodism hypocalcemia
    - Absence of small intestinal enteroendocrine cells (lack of chromogranin A or CCK)
    - Autoimmune gastritis lack of vitamin B12
- Hyperthyroidism
  - Fat malabsorption
  - Decreased nutrient absorption with disturbed intestinal transit
- Diabetes
  - Chronic diarrhea is common
  - Can be linked to poor glycemic control an autonomic neuropathy
  - Rule out celiac, SIBO, pancreatic insufficiency
- Metabolic bone disease
  - Reduced bone mineral density is a common finding in patients with gastric resection, celiac disease, and lactose malabsorption.

ENDOSCOPIC INDEX OF SEVERITY IN IBD: UCEIS AND CDEIS

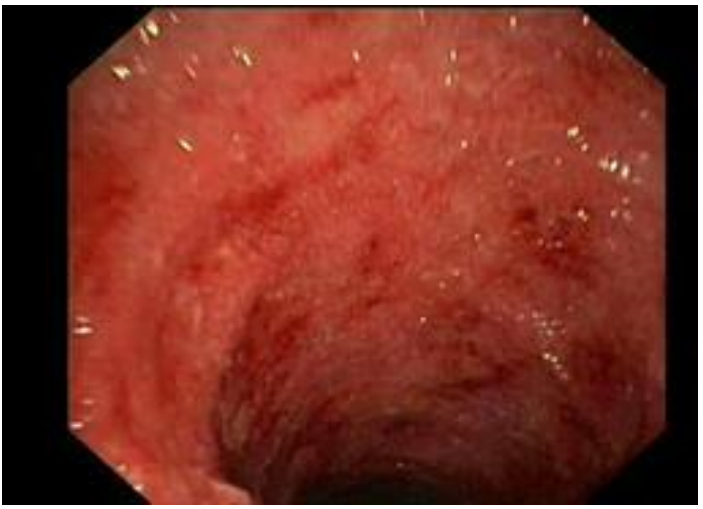
Majed Almaghrabi



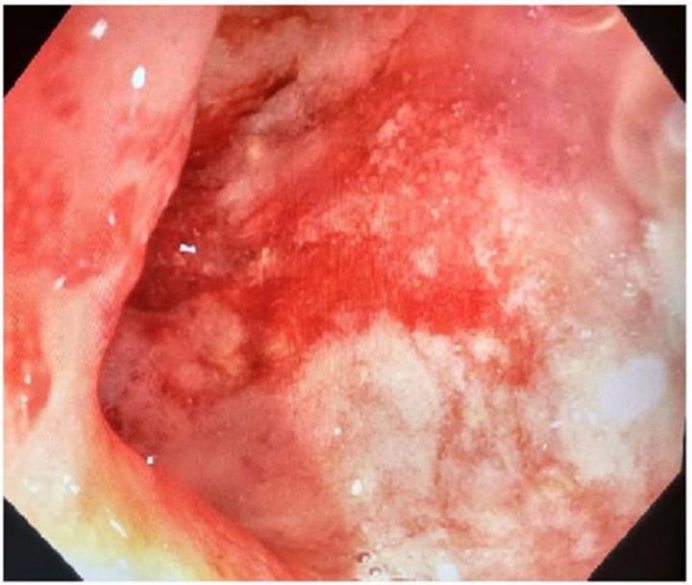
❖ Ulcerative Colitis Endoscopy Index and Severity (UCEIS)

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
○ Vascular pattern	– Normal	▪ Normal vascular pattern with arborization of capillaries clearly defined or with blurring or patchy loss of capillary margins
	– Patchy obliteration (1)	▪ Patchy obliteration of vascular pattern
○ Bleeding	– None	▪ No visible blood
	– Mucosal (1)	▪ Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away
	– Luminal mild (2)	▪ Some free liquid blood in the lumen
	– Luminal moderate or severe (3)	▪ Frank blood in the lumen ahead of the endoscopic or visible oozing from the mucosa after washing intraluminal blood or visible oozing from a hemorrhagic mucosa
○ Erosions and ulcers	– None	▪ Normal mucosa, no visible erosions or ulcers
	– Erosions (1)	▪ Tiny (≤ 5mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions but remain superficial
	– Deep ulcer (3)	▪ Deeper excavated defects in the mucosa with slightly raised edge

Acute Ulcerative Colitis



Acute Ulcerative Colitis



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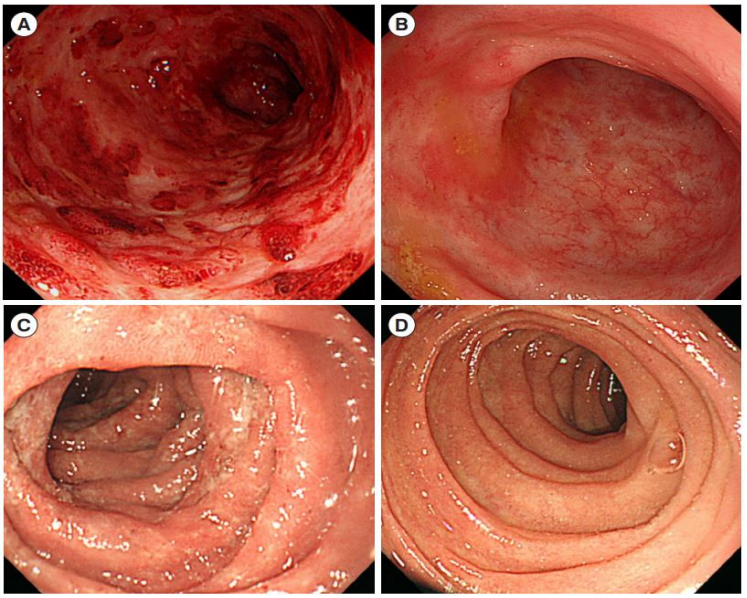
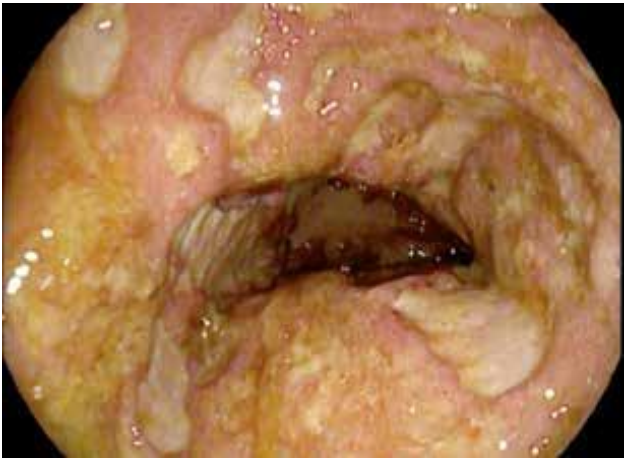
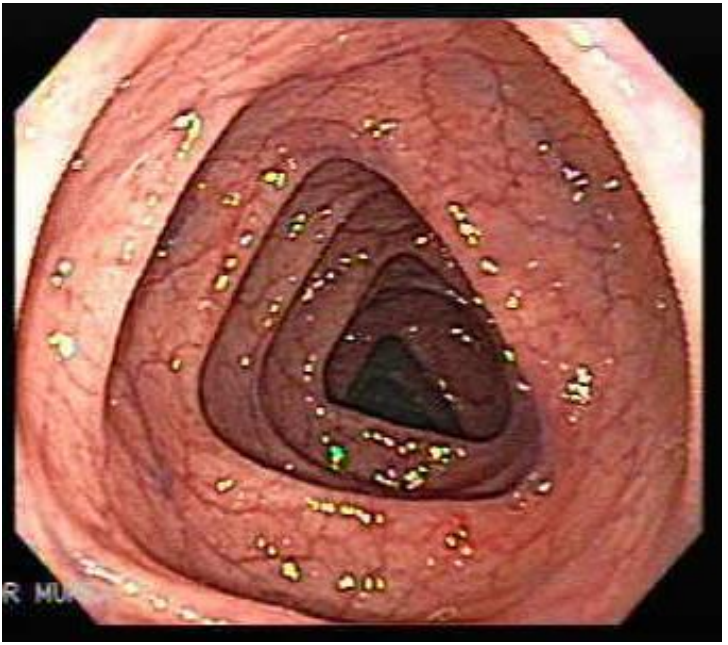


Acute Ulcerative Colitis



Ulcerative Colitis Remission



❖ Crohn Disease Endoscopy Index and Severity (CDEIS)

Crohn disease endoscopic index of severity

	Rectum	Sigmoid and left colon	Transverse Colon	Right Colon	Ileum		Total
○ Deep ulceration (12 if present in the segment, 0 if absent	0	0	0	0	0	0	1
○ Superficial ulceration (6 if present in the segment, 0 if absent)	0	0	0	0	0	0	2
○ Surface involved by the disease (cm)	0	0	0	0	0	0	3
○ Ulcerated surface measured (cm)	0	0	0	0	0	0	4
Total 1 + total 2 + total 3 + total 4					=	0	A
Number (n) of segments totally or partially explore					=	0	n
Total A divided by n					=	0	B
3 if ulcerated stenosis anywhere, 0 if not					+	0	C
3 if non ulcerated stenosis anywhere, 0 if not					+	0	D
Total score = B + C + D							

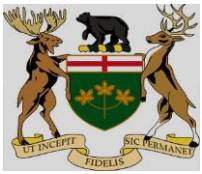
Score range: 0-44

Severe disease:	Moderate disease:	Mild disease:	Remission CDEIS
CDEIS ≥ 12	CDEIS 9-12	CDEIS 3-9	0-3

COLON

HEREDITARY COLORECTAL POLYPS AND CANCERS

Zoya Bahreini and Alan Thomson



Colonic Polyps

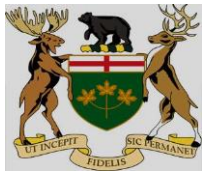
- Definition: “A gastrointestinal polyp is a discrete mass of tissue that protrudes into the lumen of the bowel”

Caution: An adenoma is neoplastic, because it shows cellular dysplasia.

- Background
  - All cancers have genetic components that may be inherited or acquired to varying degrees
  - Familiar (hereditary) CRC (<10%)
    - Born with an altered genome + environmental genotoxic event -> malignant phenotype
  - Sporadic (non-hereditary) CRC (70-80%)
    - Multiple somatic mutations contributed by environment

- Demography: Some approximate percentages to remember
  - Age 50, asymptomatic, average risk
    - Likelihood of finding
      - Adenomatous polyp, ~30% (5:3 M to F)
      - AAP (adenoma with advanced pathology, ~8%)
    - Greater risk of large or right-sided adenoma in African Americans > 60 yr
    - Adenoma recurrence, ~20% per yr
    - Incidence
      - Adenomas, 5% per yr
      - AAP, 0.4% per yr

- Terminology
  - Deminative polyp
    - ≤ 5 mm
    - 1/3 to ½ have adenomatous changes
    - Few have severe dysplasia/villous changes
    - 0.1% have carcinoma
  - Advanced adenomatous polyps, aka adenoma with advanced pathology)
    - Villous architecture, or
    - HGD, or
    - Carcinoma
  - Flat adenoma
    - Flat, or slightly raised
    - May be multiple
    - D > 2x T (diameter is more than two times the thickness) of the lesion
    - Usually < 1 cm (T < 0.5 cm)
    - Represent ~10% of adenomas (% depends on techniques used for detection, e.g., chromoendoscopy shows that 7% to 36% of all adenomas are flat!)
    - More HGD/cancer risk
  - Serrated adenomas
    - Histopathological features for both adenomatous plus hyperplastic polyp

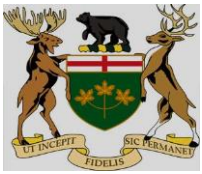


- Aberrant crypts
  - Small, raised foci of irregularly shaped crypts when viewed from lumen by magnifying endoscopy
  - Hyperplastic or adenomatous (when adenomatous, are preneoplastic)
- "multiple". e.g., multiple polyps or multiple CRCs ≥ 2
- Synchronous
  - Two polyps or one identified at the same time e.g., the index polyps is seen in the descending polyp, and a second polyps seen in the cecum at the time of the same colonoscopy
  - About 40% of colons with one polyp will have one or more synchronous polyp
- Metachronous
  - A polyp or CRC is identified at the index colonoscopy, and a polyp or CRC identified six months later is metachronous.
- Malignant
  - The term malignant polyp refers to an adenoma in which a focus of carcinoma has invaded beyond the muscularis mucosae into the submucosal
  - Note that some non-adenomatous polyps (e.g., hamartoma, juvenile [when polyps are multiple]) may also become malignant (i.e., the above definition refers to "adenoma", but when non-adenomatous polyps develop CRC, they are still referred to as being "malignant".
  - Colonic cancers which have a polypoid appearance may also be called a "malignant polyp".

- Mucosal
  - Submucosa pushes mucosa to appear as a small bump
  - Seen in ~10% of screening colonoscopies
- Inflammatory
  - Inflammation and granulation tissue resulting from regeneration of ulcerative tissue
- Juvenile (retention)
  - ↑ lamina propria, with edema
  - Dilated cystic glands filled with mucus
  - Inflammatory cells
  - ↑ vascularity
- Peutz-Jegher
  - Hamartomatous lesion characterized by glandular epithelium supported by an arborizing framework of well-developed smooth muscle that is contiguous with the muscularis mucosae

➢ Pathology

- Give a classification of colorectal polyps.
  - Neoplastic
    - Adenoma
    - Carcinoma
  - Non-neoplastic
    - Hyperplastic
    - Mucosal
    - Juvenile
    - Inflammatory
  - Hamartomas
    - ↑ vascularity
    - Peutz-Jegher Syndrome
    - Juvenile



- Another useful classification of colorectal polyps

➢ Mucosal lesions
  - Adenoma
    - Tubular
    - Tubulovillous
    - Serrated villous
  - Histopathological features
    - Immature goblet or columnar cell
    - ↑ cellularity of crypts
    - ↑ mucin
    - ↑ hyperchromatic (↑ basophilia)
    - Elongated nuclei
    - “picket fence” pattern of nuclei
  - Carcinoma
    - Carcinoma in situ
    - Intramucosal
  - Invasive
  - Hyperplastic
  - Inflammatory
  - Juvenile (retention)
  - Peutz-Jegher syndrome (hamartomas)
  - Normal mucosa in a polypoid configuration

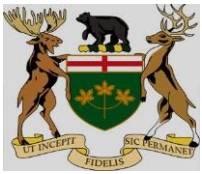
➢ Submucosal Lesions
  - Carcinoid
  - Colitis cystica profunda
  - Lipoma
  - Lymphoid polyp (benign and malignant)
  - Metastic neoplasms
  - Pneumatosis cystoides intestinalis

Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Box 126-1, page 2214.

- And a futher alternate approach to a classification of colonic polyps, based on predominant glandular pattern (may be mixed, e.g., serrated adenoma)
    - Epithelial cells
        - Adenomatous, hyperplastic, serrated
        - Mucosal
        - Inflammatory
    - Hamartomas
        - Juvenile
        - Peutz-Jegher syndrome
        - Cowden disease
        - BRR syndrome
        - Neurofibromatous
    - Submucosal
    - Colitis cystica coli
    - Pneumatosis cystoides coli

"The superior person is modest in his (her) speech, but exceeds in his action."

Confucius



- Give the histopathological findings of mild, moderate and severe dysplasia.

Feature	Mild (70%)	Moderate (20%)	Severe (5%)
○ Nuclei	Basal position Hyperchromatic Elongated Uniform size	Stratified Pleomorphic	↑↑ ↑↑
○ N/C ratio	Normal	Normal	↑
○ Nucleoli	Normal	Normal	↑↑
○ Cribriform**	-	+/-	+
○ Mucin	↓	↓↓	
○ Distribution of changes in crypt	Partial	Entire	Entire
○ Architecture	Branching Budding Crowding	↑	↑↑↑

*cribriform appearance, aka glands within glands

- Note:
  - Common practice
    > LGD – Includes mild plus moderate dysplasia
    > HGD – Includes severe dysplasia plus carcinoma in situ

- Recall that if an adenomatous polyp has HGD, cancer, or a villus architecture, it is considered to meet the criteria for being called an AAP (**adenoma with advanced pathology**)

Abbreviations: HGD, high grade dysplasia; LGD, low grade dysplasia; N/C ratio, ratio of nucleus to cytoplasm

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the anatomical reason why carcinoma in situ and intramucosal carcinoma are considered to be non-invasive lesions, with no potential to metastasize.
  - Carcinoma in situ and intramucosal cancer of the colon are contained in the mucosa, which lacks lymphatics, and thus there is no potential to metastasize.

- Give the histopathological characteristics of an AAP (adenoma with advanced pathology):
  - AAP are adenomatous polyps which have one or more of the following:
    Villous architecture
    Presence of high-grade dysplasia (HGD)
    Carcinoma

- Give the histopathological terms used to describe non-invasive and invasive colonic cancer.

Name	Through Basement Membrane	Into Lamina Propria	Through Muscularis Mucosae
○ Non-invasive			
– Carcinoma in situ	-	-	-
– Intramucosal cancer	+	+	-
○ Invasive			
– Malignant polyp	+	+	+

➢ Size: For purposes of considering their malignant potential, colonic polyps are categorized as

- ○ Diminutive < 5 mm
- ○ Small > 0.5 < 1 cm
- ○ Medium 1 to 2 cm
- ○ Large > 2 cm

Clinical recommendation:

Rather than using an adjective to describe the size of a polyp in a colonoscopy dictation (e.g., small, medium, large), give their actual estimated size.

- Give the approximate malignant potential of colonic adenomas based on their size, histology and dysplasia.

		(%)
○ Size	< 1 cm	1
	1-2 cm	10
	>2 cm	45
○ Histology	Tubular	5
	Tubulovillous Villous	25
	Villous	40
○ Dysplasia	Mild	5
	Moderate	20
	Severe	35
○ Site (colorectal cancer)	Cecum/Asc. Colon	25
	Transverse	15
	Descending	5
	Sigmoid	25
	Rectum	20

➢ Postulated Progression of Colonic Mucosa to Sporatic Adenoma

Normal crypt – Proliferative compartment at the base of the crypt

↓

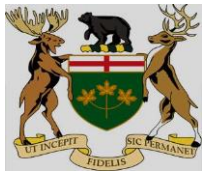
Aberrant crypt – Expansion of proliferative compartment to entire crypt

↓

Unicryptal adenoma – Monoclonal expansion

↓

Sporatic adenoma – Polyclonal expansion



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the name of the gene in the APC gene family which increases the risk of colon cancer (CRC) in Ashkenazi Jewish persons, and the genes which may be altered and increase the risk of CRC from the metabolism of nutrients and environmental agents.
  - In Ashkenazi Jewish persons
    - I 1307 K
  - Environmental risk
    - Methylene tetrahydrofolate reductase
    - N-acetyltransferase-1 and -2

- Give the predictive value of the findings if a distal polyp ('marker lesion") for the finding of a frequency of a proximal synchronous AAP (adenoma with advanced pathology).
  - ↑ with size of distal polyp
  - Varies with histopathology of distal polyp

Distal Colonic Lesion	Proximal AAP
- No polyp	3%
- Hyperplastic	3%
- Adenoma	1%
- Advanced adenoma (AA)	
Tubular > 1 cm	9%
Villous	12%
HGD	12%
Cancer (invasive)	25%

Note:

- Only 30% of proximal CRCs have a distal colonic marker lesion, and
- Only 50% of persons with proximal AAP have a distal marker

Adapted from: Itzkowitz SH, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/ Elsevier, Philadelphia, 2016, Table 126.7, page 2227.

- Give the possible use of all of this information about the predictive value of a distal lesion.
  - If you do sigmoidoscopy for CRC screening, you have an idea when you see a distal lesion, you must follow up with a colonoscopy.
  - But, because many proximal lesions do not have a distal marker (30%), you really should be arranging for your patient to have colonoscopy, regardless of what the distal colon shows.

- Give the cumulative risk over time of a 1 cm colonic polyp developing into CRC.

Time Interval (yr)	Cumulative Risk of Cancer at Polyp Site	Approximate Annual Rate
5	2.5%	0.5%
10	8%	0.8%
20	24%	1.2%

➢ Genetics

- Give the molecular pathways of tumour initiation and progression of CRC.

  - Tumour initiation
    - ↓ function of APC genes such as β-catenin, AXIN7 number, and of junction
    - Germline plus somatic mutation in FAP; 2 acquired somatic mutations in APC in sporatic adenomas from loss of function of both APC alleles
  - Tumour progression
    - ↑ K-Ras oncogene
      - The larger the adenoma, the greater the number of adenomas positive for K-Ras (small, 9%, large, 58%)
    - DCC
      - Small tubular/tubulovillous adenoma, 12% with foci of cancer, 73%

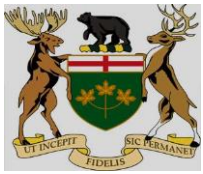
Abbreviation: DCC, deleted in colon cancer gene

  - Stability genes
    - MMR (DNA mismatch repair) gene
      - Germline mutations
        - hMLH1
        - hMSH2
        - hMSH6

- BER (base-excision repairs) gene
  - MUTYII (mutated BER gene; aka MYN)
  - MMR gene mutations load to MSI (microsatellite instability)
  - MSI in 15% sporatic and 55% of HNPCC CRC (colorectal cancers)

- Give biochemical changes that occur during the development of CRC.
  - ↑ CEA (carcinoembryonic antigen)
  - ↑ matrix metalloproteinases
    - MMP-1
    - MT1 – MMP
  - ↑ EGF increase angiogenesis and vasculization
  - ↑ selectins (on endothelium)
  - ↑ sialoglycoproteins (on tumour)

- Give the name of the gene in the APC gene family which increases the risk of colon cancer (CRC) in Ashkenazi Jewish persons, and the genes which may be altered and increase the risk of CRC from the metabolism of nutrients and environmental agents.
  - In Ashkenazi Jewish persons
    - I 1307 K
  - Environmental risk
    - Methylene tetrahydrofolate reductase
    - N-acetyltransferase-1 and -2



➢ Risk factors

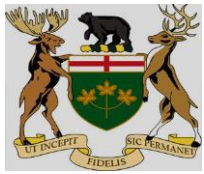
- Give factors which alter the **risk for development** of colonic adenomas or CRC.
    - ↑ risk
        - Lifestyle
            - ↑ fat diet (especially red meat)
            - Obesity (BMI > 100, waist circumference > 32-34 inches)
            - Alcohol
            - Smoking (cigarettes)
            - Low calcium intake
        - Medical conditions
            - Inflammatory bowel disease (IBD)
            - IBD + PSC
            - Ureterosigmoidostomy
                - Polyps and CRC at stoma
                - Adenomas and CRC at stoma
            - Acromegaly: pooled odds ratio
                - Adenomas, 2.4
                - CRC, 4.3
            - Infection
                - Streptococcus bovis bacteremia,
                - JC virus

- ↓ risk by increasing dietary intake
  - Carbohydrate
  - Fibre
  - Calcium
  - Folate
  - Fresh fruit and vegetables
  - Physical exercise
  - Chemopreventive compounds
    - NSAIDs, ASA, Coxibs
    - Calcium, 20% ↓ risk of adenomas
    - Selenium, 20% ↓ risk of CRC
    - HRT (hormone replacement therapy)
    - UDCA (ursodeoxycholic acid)
    - 5-ASA (in persons with inflammatory bowel disease)

Abbreviations: ASA, aspirin; CRC, colorectal cancer; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid

Screening and Surveillance for Non-polyposis Syndromes

- Terminology
  - Primary prevention
  - "identifying genetic, biological, and environmental factors that are etiologic or pathogenetic and subsequently altering their effects on tumour development" Secondary prevention



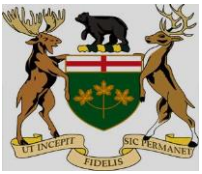
  - "….. identify existing preneoplastic and lesion and to treat them thoroughly and expeditiously" (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/ Elsevier, Philadelphia, 2016, page 2276).
- Case finding
  - The investigation of the patient with symptoms and/or signs suggestive of the diagnosis.
- Screening
  - The investigation of an asymptomatic person to find an early pathological lesion or condition.
- Surveillance
  - The investigation of a person at regular intervals after and index lesion has been discovered by screening or case finding.

- Give 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 UC
    - Dietary risk factors – low daily intake of fresh fruit, vegetables and fibre (possible); low intake of calcium and vitamin D; high intake of saturated fatty acids (especially red meat)

- Colonoscopic screening and surveillance
  - Persons who have more than 10 adenomas at one examination should be examined at a shorter (<3 yr) interval established by clinical judgment, 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 yr, except every 3 yr 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, and surveillance should be performed for these. This is discussed in a later section.

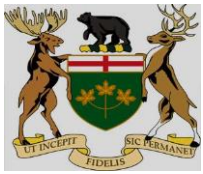
Source: Winawer, Sidney J. Screening and surveillance for colorectal cancer: review and rationale. *2009 ACG Annual Postgraduate Course:*21- 25.



- Improvement in survival from ↓ CRC
  - 10 yr global benefit LC > RC
  - Split dosing of preparation for colonoscopy provides better preparation (↑ cleanliness)
- Watch out for
  - ↓ FOBT CRC mortality ~18%
  - The performance characteristics (sensitivity and specificity) of FIT (fecal immunochemical test) is comparable to FOBT, without the need for dietary changes three days before FOBT, and with only, rather than 3 slides
  - CRC screening may be stopped at age 70 or 75, or at a time based on associated serious comorbidities and the life expectancy of the patient.
  - Persons of African heritage have a risk of CRC shifted to an earlier age than do Caucasians, and the 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 20% of women and 30% 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.
  - FDAs" (Flat & depressed adenomas)
    - Height < ½ of diameter
    - Aggressive biological behavior
      - ↓ K Ras and ADC mutations
      - Alternate neoplastic pathways
  - Lateral spreading tumour

- Sessile or flat
- Malignant potential is “significant”
  - LC HP (Hyperplastic polyp)
    TSA (traditional serrated adenoma)
  - RC SSA (Sessile serrated adenoma)
  - SSA/P (without/with dysphasia/cancer)
- CRC may develop in the interval between colonoscopiespolypectomies. These “**interval cancers**” develop in about 0.6% of persons screened, having polypectomy, and then followed with an appropriate surveillance program.
- While a single hyperplastic polyp normally does not have a malignant potential, followup is necessary if it is
  - Serrated
  - > 10 mm in size
  - Multiple hyperplastic polyps above the rectosigmoid area
- Newer endoscopy equipment such as high-definition, narrow band imaging, or chromoendoscopy (including FICS [fujinon intelligent chromoendoscopy system], and the Pentax-scan) may improve polyp detection and CRC mortality
- Persons with CRC associated with K-ras mutations do not respond as well to anti-EGFR therapy

Abbreviations: EGFR, epidermal growth factor receptor; FICS, fujinon intelligent chromoendoscopy system; FIT, fecal immunochemical test



Fecal Testing for Occult Blood

A variety of stool and structure-based tests of the colon are included as options for screening for CRC. In the process of providing your patient with informed consent with regards to their making a choice about these tests, it is necessary for you to know the sensitivity of these investigations.

- Give tests for screening for CRC, and their approximate sensitivities for CRC and AA (advanced adenomas) in average risk persons presenting for colonoscopy.

Test	Sensitivity % CRC	AA
❖ Stool-based		
○ Guaiac fecal occult		
– Standard	33-50	11
– "Sensitive"	50-75	20-25
○ FIT (fecal immunochemical test), 1-3 stool samples	60-85	20-50
○ DNA test, 1 stool sample	≥ 80	40
❖ Structure –based*		
○ CT colonography	Probably > 90	90
○ Colonoscopy (standard white light)	95	88-98**

* Flexible sigmoidoscopy is not reported here, because it demonstrates less than half of the colon, and its sensitivity will depend upon the distribution of CRC/AA.

** Sensitivities of 88% to 98% are reported

❖ Immunochemical FOBT (iFOBT)

Lesion	Sensitivity (%)
○ Cancer (overall)	~65
– Dukes' A	50
– Dukes' B	70
– Dukes' C/D	78
○ HGD	33
○ Adenoma ≥ 1 cm	20
○ Advanced neoplasia (overall)	27
– Proximal	16
– Distal	31

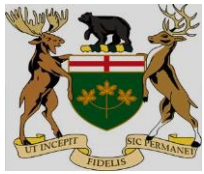
○ Test characteristics: Cancer

Fecal Hb Threshold	Sensitivity (%)	Specificity (%)
≥ 50 ng/mL	100	84
≥ 75 ng/mL	94	88
≥ 100 ng/mL	88	90

❖ Fecal DNA (fDNA) testing

○ Basis for fDNA testing
- 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



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the performance characteristics of FOBT and FIT for colonic adenomas and CRC.

❖ FOBT (fecal occult blood test, guaiac-based relying on the peroxidase reaction)

- Only adenomas > 1.5 cm bleed and thus FOBT sensitivity depends on the size of the lesions in the test group
- False negative for adenomas, 75%
- False positive (red meat, vegetables containing peroxidases [e.g., horseradish])
- PPV (positive predictive value): adenomas, ~30%; CRC, ~10%
- Annual FOBT (slide guaiac test for pseudoperoxidase activity of hemoglobin) results in 33% ↓ CRC mortality as compared with non-tested control group

❖ FIT (fecal immunochemical testing for human globin)

- Sensitivity (advanced adenomas), 25%
- Specificity (adenomas), 97% (93% for advanced adenomas)
- Fecal immunochemical tests (FIT) are preferred over guaiac-based fecal occult blood tests for CRC screening
- In a validation experiment performed at room temperature, conversion of test outcomes only occurred 10 days or longer after fecal sampling

From the following table, calculate the absolute risk (AR) of CRC in a 55 yr old patient whose father developed proven CRC at age 59, his 50 yr old brother had an adenomatous colonic polyp, and a grandmother and an aunt of unknown age had CRC (baseline absolute risk for 50 yr old, 6%).

Familial Setting	RR
○ One first-degree relative with CRC (overall)	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%)

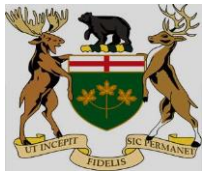
Printed with permission: Winawer SJ. *Best Pract Res Clin Gastroenterol* 2007; 21(6): pg. 1035.

- Give the recommended age of onset (yr) and interval (every "x" yr) for CRC screening for each of the following groups.

Group	Age	Interval
○ Average risk	50	10
○ Family history:		
– One first-degree relative (parent, sibling or child) with a CRC or 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 CRC or AP (adenomatous colonic polyp) at age > 60	40	10
– 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: 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

- Give 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 for Colonoscopy
• **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 yr after the initial polypectomy	▪ 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)



Risk Category	Age to Begin	Recommendation for Colonoscopy
○ Patients with > 10 adenomas on a single examination	– < 3 yr after the initial polypectomy	▪ Consider the possibility of an underlying familial syndrome.
○ Patients with sessile adenomas that are removed piecemeal	– 2 to 6 months to verify complete removal	▪ Once complete removal has been established by colonoscopy subsequent surveillance needs to be individualized based on the endoscopist's judgment. ▪ Completeness of removal should be based on both endoscopic and pathologic assessments.
• **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 yr after the resection or following the performance of the colonoscopy that was performed to clear the colon of synchronous disease.	▪ In the case of nonobstructing tumours, this can be done by pre-operative 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.

Risk Category	Age to Begin	Recommendation for Colonoscopy
○ Patient undergoing curative resection for colon or rectal cancer.		▪ This colonoscopy at 1 yr is in addition to the perioperative colonoscopy for synchronous tumours. ▪ If the examination performed at 1 yr is normal, then the interval before the next subsequent examination should be 3 yr. ▪ If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 yr. ▪ Following the examination at 1 yr, the intervals before subsequent examinations may be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy.

Risk Category	Age to Begin	Recommendation for Colonoscopy
• **Increased risk- patients with a family history**		
○ Either colorectal cancer or adenomatous polyps in a first-degree relative before age 60 yr or in 2 or more first-degree relatives at any age.	– Age 40 yr, or 10 yr before the youngest case in the immediate family.	▪ Colonoscopy very 5 yr.
○ 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 yr.	▪ 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 yr.	▪ Annual FSIG to determine if the individual is expressing the genetic abnormality and counselling to consider genetic testing. ▪ If the genetic test is positive, colectomy should be considered.

Risk Category	Age to Begin	Recommendation for Colonoscopy
○ Genetic or clinical diagnosis of HNPCC or individual at increased risk of HNPCC.	– Age 20 to 25 yr, or 10 yr before the youngest case in the immediate family.	▪ Colonoscopy every 1 to 2 yr and counselling 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.
○ Inflammatory bowel disease, chronic ulcerative colitis and Crohn colitis	– Cancer risk begins to be significant 8 yr after the onset of pancolitis or 12 to 15 yr after the onset of left-sided colitis (UC or CC).	▪ Colonoscopy with biopsies for dysplasia. ▪ Every 1 to 2 yr; these patients are best referred to a centre with experience in the surveillance and management of inflammatory bowel disease

Abbreviations: CC, Crohn 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

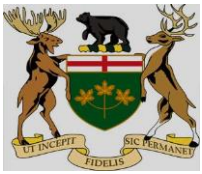
QUALITY ASSURANCE AND COLONOSCOPY

- Give ways to ↑ polyp detection rate from colonoscopy.
  - Access performance skills of endoscopist
    - Identify the adequacy of
    - Withdrawl time (> 7 min), and possibly retroflection of colonoscopy in rectum
    - Polyp (or adenomatous polyp) detection rate
    - Personal detection rate of adenomatous polyps on screening colonoscopy of average risk persons > 50 yr of age (males, 30%; females, 20%)
    - Rate of
      - Detection of CRC
      - Perforation
  - Better bowel cleansing / water instillation
  - Better patient sedation
  - Insertion
    - Cap-fit colonoscopy
    - Overtubes
  - Imaging
    - Wide-angle colonoscopy
    - 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
      - Narrowing band imaging (NBI) was introduced to overcome the limitations of white light endoscopy (WLE) for adenoma detection.
      - There is no difference in detection of polyps or adenomas with NBI and WLE.

        - There is no difference in miss rates of polyps or adenomas with NBI and WLE.
    - Chromoendoscopy
        - Dyes to stain the colonic mucosa
        - Sensitive and so can detect more dysplasia per (targeted) biopsy
        - Effective surveillance method
    - Electronic chromoendoscopy
        - Blue light for the excitation of tissue specific autofluorescence
        - Superior to conventional endoscopy for detecting dysplasia
    - Confocal laser microscopy
        - 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.

Source: *Gastroenterology and Hepatology* 2009; 6:672

- Give causes of focal white patches on the mucosa seen on colonoscopy.
    - Mucus
        - Easily washed away
    - Leukoplakia
        - Biopsy diagnosis
    - Pseudolipomatosis
        - Clear spaces in the mucosa and submucosal on biopsy
        - No individual cells seen in these spaces



Suggested Reading: suggested excellent tables to review the following topics:

- Endoscopic procedures for which antibiotic prophylaxis is recommended (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Table 40.1, page 654).
- Side effects of medications used for sedation, analgesia, and reversal (Vargo II. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Chapter 41, page 679-680).
- Risk factors for post-ERCP pancreatitis (Tenner S and Sternberg WM. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Box 58-5, page 978).

- Give the approximate risk of **serious complications** from endoscopic complications per 10^5 procedures.
  - EGD, 3-5
    - Removal of foreign bodies, 800
    - Malignant esophageal strictures, 2400
    - EUS-FNA
      - Infection (of pancreatic cyst), 1400
      - Pancreatitis,100
  - PEG, 150-400

- ERCP
  - Pancreatitis (including injection of pseudocyst), 200-2500
  - Bleeding (sphincterotomy), 100-200
  - Ascending cholangitis, 100
  - Acute cholangitis, 50
  - Perforation, 50
- DBE
  - Diagnostic, 100
  - Therapeutic, 400
- Capsule endoscopy, 100-200
- Sigmoidoscopy, 10
  - Balloon dilation of stricture, 1000
  - Placement of stents, 500

  - Perforation/PPES, 1/1000
  - Bleeding, 1/500
  - Polypectomy, 1/1000

  - Decompression for acute pseudo-obstruction, 200
  - Therapeutic (polypectomy), 200
  - Diagnostic, 30
- Colonoscopy
  - Perforation
    - Overall, 0.05 - 0.3%
    - Endoscopic ablation of angioectasias (R > L colon), 2.5%
    - Colonic decompression of Ogilvie syndrome (pseudo-obstruction), 20%

  - Bleeding
    - Overall, 0.1 - 0.6%
    - Polypectomy, 0.9%
  - Post-polypectomy electrocoagulation syndrome (PPES)
    - Abdominal pain, tenderness fever, WBC 1-5 d after polypectomy, 0.003% - 0.1%

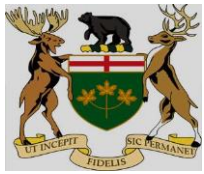
Abbreviations: DBE, double balloon enteroscopy; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; PEG, percutaneous endoscopic gastroscopy

Source: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2010, page 681-682.

- In the context of the percutaneous endoscopic placement of a double balloon feeding tube, give the meaning of "buried bumper syndrome'.
  - If the two balloons of the PEG feeding tube are applied too tightly together, the intragastric balloon may migrate into the wall of the stomach.

- Give the recommendations regarding the need to continue the use of aspirin or clopidogrel with endoscopic procedures with low or high risk of bleeding

Endoscopic Procedure	Continue Aspirin	Continue Clopidogrel
○ Low risk of bleeding		
– EGD and colonoscopy ± biopsy	Yes	Yes
– EUS without FNA	Yes	Yes
– Digestive stenting	Yes	No
– ERCP stent placement of papillary balloon dilation without endoscopic sphincterotomy	Yes	Yes
– Argon plasma coagulation of angiodysplasia	Yes	Yes
– Colonic polypectomy < 1 cm	Yes	No
– Dilation of digestive stenosis	Yes	No
– EUS with FNA of solid mass	Yes	No
○ High risk of bleeding		
– Esophageal variceal band ligation	Yes	No
– EMR, ESD	No	No
– Percutaneous endoscopic gastrostomy	Yes	NA
– Endoscopic sphincterotomy	Yes	No
– Ampullary resection	No	No
– Endoscopic sphincterotomy + large balloon papillary dilation	No	No
– EUS with FNA of cystic lesions	No	No
– Colonic polypectomy > 1 cm	Yes	No



Note: Some authorities suggest that the risk of stopping aspirin (ASA) in a patient with an indication for ASA-prophylaxis is higher than the risk of bleeding, and that the ASA should always be continued.

Abbreviations: EGD, esophagogastroduodenoscopy; EMP, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; NA not available

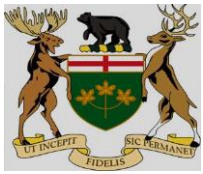
Printed with permission: Blero D, et al. Nat Rev Gastroenterol Hepatol. 2012;9(3):162-72

- Give the minimal set of quality indicators, auditable outcome measures and accepted standards in colonoscopy.

Quality Indicator	Outcome Measure	Standard
○ Bowel preparation	– Quality of bowel preparation	▪ ≥ 90% described as “excellent” or “adequate” preferably assessed with a validated bowel preparation scale
○ Cecal intubation	– Cecal intubation rate with photo-documentation of cecal landmarks	▪ ≥ 90% unadjusted (intention to scope) ▪ ≥ 90% in all colonoscopies and ≥ 95% in screening colonoscopies

Quality Indicator	Outcome Measure	Standard
○ Adenoma detection	– Adenoma detection rate (number of patients with a least 1 adenoma/total number of patients)	▪ ≥ 25 in men and ≥ 15 % in women during screening colonoscopies ▪ ≥ 20% during screening colonoscopy
○ Withdrawal time	– Time in minutes from cecal pole to anus	▪ ≥ 6 min inspection time in an intact colon
○ Polyp retrieval	– Polyp retrieval rate	▪ ≥ 90% of polypectomy specimens
○ Burden	– Gloucester comfort score	▪ Not established
○ Complications	– Incidence of perforation	▪ ≤ 1:1,000 colonoscopies (diagnostic or therapeutic) ▪ ≤ 1:500 colonoscopies with polypectomy
	– Incidence of post-polypectomy bleeding	▪ ≤ 1:100 colonoscopies with polypectomy

Printed with permission: Hazewinkel C and Dekker E. Nat Rev Gastro Hep 2011; 8: 554-564, Table 1



Pathology Alert

- Pseudoadenomatous epithelium
  - Ectopic benign epithelium below the muscularis mucosae (MM) may look like cancer (pseudoadenomatous epithelium), and has to be distinguished from invasion of mucosal adenocarcinoma through the MM.

Recurrence Rates of Adenomatous Polyps

- Give the post-polypectomy recommendations for surveillance colonoscopy.

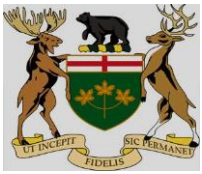
	Next Colonoscopy (yrs)	
❖ Non-serrated Lesions	10	No polyps
	5 – 10	1 – 2 TA (tubular adenoma) < 10 mm
	3	3 – 10 TA ≥ 1 TA > 10 mm ≥ 1 VA (villous adenoma)
	< 3	> 10 adenomas
	1	Adenoma plus HGD
❖ Serrated Lesions	10	Hyperplastic polyps (HPs) < 10 mm in rectosigmoid colon
	5	SSA < 10 mm (sessile serrated adenoma)
	3	SSA > 10 mm SSA plus dysplasia TSA
	1	SPS (serrated polyposis syndrome)

- 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)	
– Large sessile adenoma removed piecemeal	2-6 months to confirm complete removal
– Small distal hyperplastic polyps without adenomas	10 yrs
– Proximal colon hyperplastic polyps	Interval uncertain
– Sessile serrated adenomatous (SSA) polyp	Same as for adenoma

○ The index colonoscopy shows adenomatous polyp(s). The recurrence rates of adenomatous polyps or CRC are dependent on the number of index polyps, and the duration of follow up

# of Adenomas Removed at Index Colonoscopy	Types of Recurrent Lesion	Approximate Recurrence Rate at 10 yrs
1	Polyps	30%
> 1		70%
1	CRC	2%
> 1		10%



- In addition to number of polyps and duration of follow-up after the index colonoscopy, other features which ↑ cumulative risk of recurrence include:

Non-AAP	AAP
– Patient characteristics ▪ 60 yr ▪ CRC in a parent – Polyp ▪ Number ▪ Size ▪ Severe dysplasia ▪ Villous – Duration ▪ For 1 cm polyps, the cumulative risk of carcinoma (Ca) developing is approximately 1% per yr:	– Polyp characteristics ▪ > 1 cm ▪ Severe dysplasia ▪ Villous architecture – The risk of AAP recurrence depends on duration of follow up and the presence of three additional risk factors (ARF): ▪ ≥ 3 index adenomas ▪ > 60 yr ▪ A parent with CRC

Time Interval, Yr	Risk of Ca Developing
5	2.5%
10	8%
20	24%

  - For a polyp < 0.5 cm, it takes 2 to 3 yr to become 1 cm in size (~0.25 cm per yr)
  - Thus, the rate of growth of adenoma is slow (~0.25 cm per yr, before becoming the worrisome size of < 1 cm, and once 1 cm in size, the cumulative risk of the development of CRC is about 1% per yr.

- Give the approximate polyp recurrence rates.

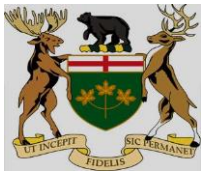
Time (yr) After Index Polypectomy	Usual AAP	ARF
3	4%	10%
6	8%	20%

Abbreviations: AAP, adenoma with advanced pathology; ARF, additional risk factors

- Give colonoscopic (gross) features which distinguish between an adenoma-like DALM.

	DALMs (flat dysplasia)	
Colonoscopic Features	Adenoma-Like	Non-Adenoma-Like
○ Shape	Sessile/ Pedunculated	Sessile
○ Borders		
– Circumscribed	Yes	No
– Clearly visible	Yes	No
○ Surface	Smooth	Irregular
○ Ulcer/necrosis	No	Yes
○ Stricture	No	Yes
○ Tethering of mucosa	No	Yes

* These may be referred to as areas of flat dysplasia



- Give the annual rates of conversion of colonic adenoma to carcinoma
  - Adenomas
    - Overall, 0.25%
    - > 1 cm, 3%
    - Villous components, 17%
    - Severe dysplasia, 37%
  - Mean doubling time of CRC, ~ 620 days

- Give the features of a malignant colonic polyp which suggest a favourable prognosis.

○	Differentiation	–	Well or moderately clear, or
	margin	–	> 2 mm margin
○	Invasion	–	Submucosa No
		–	Veins No
		–	Lymphatics No

Adapted from Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Table 126-8, page 2228.

➢ Efficacy and test performance characteristics

- The specificity of CTC for polyps 5-10 mm is 86-89%, and the NPV is 95-99%

Sensitivity	>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. *N Engl J Med*. 2008; 359(12):1207-17.

NON-HEREDITARY COLORECTAL POLYPS AND CANCERS

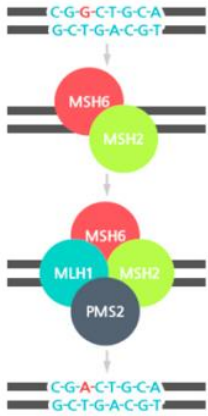
Zoya Bahreini and Alan Thomson

Lynch Syndrome (aka hereditary non-polyposis colorectal cancer [HNPCC])

- Demography
  - Most common form of hereditary colon cancer
    - 6% of CRCs
  - Autosomal dominant inheritance with high penetration
  - Colon cancer arises from discrete adenomas, in absence of polyposis

Definition Alert
- HNPCC is a familial/inherited causes of colorectal cancer, but it does not cause colonic polyposis

- Genetics
  - Microsatelite Instability (MSI) Impaired DNA Mismatch Repair (MMR)
    - Microsatelites = genomic regions in which short DNA sequences or a single nucleotide is repeated
  - During DNA replication, mutations occur is some microsatelites resulting in "instability"
  - These mismatched areas of DNA replication are usually repaired by mismatch-repair proteins (MMR)



Lynch Syndrome-MMR defects

- Germline mutations in genes responsible for repair of DNA mismatches → defective MMR proteins
- MMR genes affected in Lynch are
  - MLH1 (30%)
  - MSH2 (60%)
  - MSH 6 (7 – 10%)
  - PMS2 (< 5%)

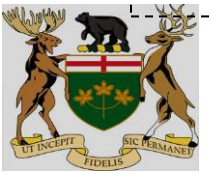
- Give the genes involved in the DNA mismatch repair in HNPCC.

Gene Implicated in HNPCC**	Frequency of Mutations in HNPCC Families
MSH2 (HNPCC1 [120435])	~60%
MLH1 (HNPCC2 [609310])	~30%
MSH6 (HNPCC5)	7 – 10%
PMS2 (HNPCC4)	< 5%

* OMIM name given in bracket ()

➢ Genetics
- Autosomal dominant, high penetrance
- Germline mutation in DNR MMR (mismatch repair) genes in 80%
- The 3 most common germline mutations in these DNA MMR genes are
  - Chromosomes 2
    - hMSH2 (40% to 50%)
- Chromosome 3
  - hMLH1 (20% to 30%)

MCQ Alert
- HNPCC/Lynch syndrome is a type of inherited CRC, but is no a polyposis syndrome.



- Give the 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 Kerato-xanthomas
○ MSH2	– Regions of MLH1, MSH2, and MSH6	▪ Endometrium	20-60%	▪ Café-au-lait spots
○ MSH6		▪ Stomach	11-19%	▪ Brain tumours
○ PMS2	– Large deletion analysis with Southern blot or MLPA[1] – MSI[2] and IHC[3] for the mismatch repair proteins – MLH1 methylation and BRAF testing to help differentiate sporadic MSI tumours from those due to Lynch syndrome	▪ Ovary ▪ Hepatobiliary tract ▪ Urinary tract infection ▪ Small bowel ▪ Brain/CNS ▪ Sebaceous carcinoma of the skin	9-12% 2-7% 4-5% 1-4% 1-3% 1%	▪ Hema-tological malignancies have been reported in individuals with biallelic mismatch repair mutations

[1]Microsatellite instability, [2]Immunohistochemistry, [3]Multiplex Ligation-dependent Probe Amplification

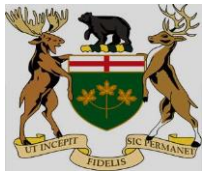
  - The Amsterdam and the Bethesda Criteria were developed to justify the screening for MMR gene mutations.
    - Increasingly, screening for MMR genes is being performed in all persons diagnosed with colorectal cancer (CRC).

- Clinical
  - Earlier onset than sporadic cancer (mean 45 yr old)
  - Proximal, right sided tumours (70% proximal to splenic flexure)
  - ↑ risk of synchronous CRC (CRC ≤ 6 mon before surgery) and
    - ↑ risk of metachronous (CRC > 6 mon after surgery)
  - ↑ risk of extracolonic tumours

		Life-time risk
– Non-GI	▪ CNS	10%
	▪ Skin	4%
	▪ Urinary tract	10%
	▪ Ovary	10%
	▪ Endometrium	50%
– Non-colon	▪ Small bowel	5%
	▪ Hepatobiliary	10%
	▪ Stomach	25%

- Give the clinical differences of CRC in HNPCC versus sporatic CRC.

Clinical Feature	Lynch Syndrome	Sporadic Colorectal Cancer
○ Mean age at diagnosis (yr)	45%	~70%
○ Multiple colon cancers	35%	~10%
○ Synchronous colon cancers	~20%	~5%
○ Metachronous colon cancers	~25%	1% - 5%

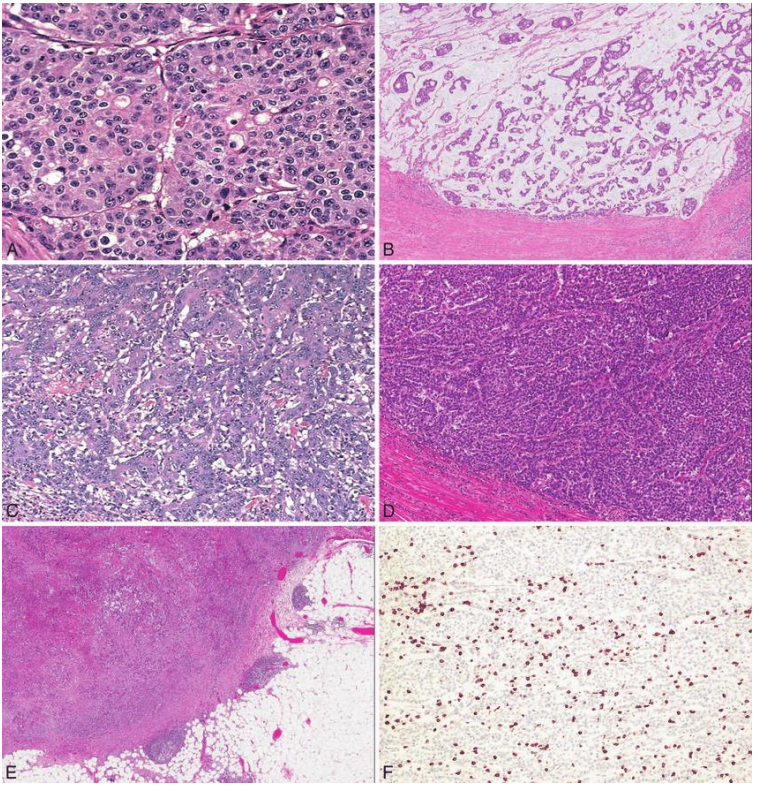


Clinical Feature	Lynch Syndrome	Sporadic Colorectal Cancer
○ Proximal location of the initial cancer	~70%	35%
○ ↑ risk of malignant tumours at other sites	Yes	No
○ Mucinous and poorly differentiated colon cancers	Common	Infrequent
○ Prognosis	Favourable	Variable

➢ Histopathology

- Give characteristic endoscopic and pathologic features of tumours that are highly suggestive of microsatellite instability (MSI) (Lynch syndrome).
  - Endoscopic
    - Multiple
    - Synchronous
    - Metachronous
    - Right-sided
  - Microscopic
    - Lymphocytes infiltrating the CRC tumour
    - Mucinous histology (“signet ring”)
    - Poor differentiation
    - Lack of “dirty” necrosis

Please see Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 122.1, page 2172; and 10th Edition, 2016, page 2270.



A: Microsatellite instability-high colorectal cancer.,
B: Medullary type, well circumscribed, with nested growth pattern, and large, uniform cells with vesicular nuclei and prominent nucleoli
C: Mucinous adenocarcinoma (.50% extracellular mucin) with occasional signet ring cells floating in mucin pools.
D: Prominent lymphocytic infiltration within and around the tumor
E: Medullary pattern and circumscribed/expansile pushing border
F: With prominent inflammatory reaction at the advancing edge of the tumor (Crohn-like reaction)

Source: Marginean EC and Melosky B. Arch Pathol Lab Med 2018; 142:1, 17-25.

- Lymphocytic infiltrate
  - As compared with sporadic colorectal cancer, HNPCC tumors are more often poorly differentiated
- Crohn-like reaction
  - Lymphoid nodules, including germinal centers, located at the periphery of infiltrating colorectal carcinomas)
- Mucinous within the tumour

➢ Clinical suspicion

❖ Amsterdam I criteria

- ≥ 3 relatives with histologically verified CRC
  - One must be a first degree relative of the other two.
  - ≥ 2 successive generations must be affected
  - ≥ 1 of the relatives with colorectal cancer must have received the diagnosis before the age of 50 yrs.
  - Familial adenomatous polyposis must have been excluded.

❖ Amsterdam II criteria

- ≥ 3 relatives must have a cancer associated with hereditary non-polyposis colorectal cancer (colorectal, endometrial, stomah, ovary, ureter or renal-pelvis, brain, small-bowel, hepatobiliary tract, or skin [sebaceous tumours]):

- ≥ 1 must be

Amsterdam II

- Specificity 98%
- Sensitivity 22%

- Revised Bethesda Guidelines for testing for hereditary non-polyposis colorectal cancer (Lynch syndrome) and microsatellite instability (MSI)
  - Sensitivity 82%, Specificity 77%

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 yr 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 yr
  - 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 yr
  - Individuals with colorectal cancer who have two 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-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

Printed with permission: Burt RW. *2007 AGA Institute Postgraduate Course:* pg. 237.

Please also see Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Box 127-3, page 2264.

- Sequence of testing for HNPCC
  - Diagnosis of CRC
  - Although multiple colonic tumours occur in HNPCC (~35%), only about 10% of persons with sporatic (non-HNPCC) CRC may have multiple polyps.
  - Although the mean average of development of CRC is younger in HNPCC than in sporatic tumours (4 versus 67 yr, respectively) in the individual patient it may be difficult to distinguish the two conditions.

- Give the cancer risk and the **screening recommendations** for Lynch syndrome (HNPCC) tumours.

Cancer	Cancer Risk	Screening Recommendations
○ Colon	80%	- Colonoscopy, q 1-2 yrs, 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 q 1-2 yrs, starting at age 25-30 yrs
○ Ovarian	9-12%	- Uncertain
○ Gastric	13-19%	- Upper GI endoscopy q 1-2 yrs, start at 30-35 yrs
○ Urinary tract	4-10%	- Ultrasound and urinalysis (urine cytology) q 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

Cancer	Cancer Risk	Screening Recommendations
○ 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.

- Give why HNPCC polyps might be missed.
  - HNPCC polyps may occur sporatically
  - The family may not have been carefully detailed (especially forgetting to use the Bethesda criteria and include high risk “Lynch” extraintestinal cancers).
  - The clinical suspicion of HNPCC may not be properly recorded on the pathology requisition.
  - Failure to diagnosis HNPCC has serious consequences for the patient and their family (not to mention the physician, who may be exposed to malpractice claims).
  - Sometimes the pathologist may consider that an adenomatous polyp is truly an HNPCC polyp from the histopathology.

(Please see Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 123.6, page 2206).

Tumours from individuals should be tested for MSI in the following situations

- Colorectal cancer diagnoses in a patient who is < 50 yr
- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours*, regadless of age.

"Colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome) tumours, sebaceous gland adenomas & keratoacanthomas in Mur-Torre syndrome, and carcinoma of the small bowel"

- Colorectal cancer with MSI-H histology* diagnosis in a patient who is < 60 yr.

"Presence of tumour-infiltrating jymphocytes, Crohn-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern.

- Colorectal cancer diagnosed ≥ 1 first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under age 50 yr.
- ≥ 2 first-degree relatives with an HNPCC-related tumour, regardless of age.

➢ Screening

- In individuals at risk for or affected with LS, screening for colorectal cancer by colonoscopy should be performed at least every 2 yr, beginning between ages 20 and 25 yr. Annual colonoscopy should be considered in confirmed mutation carriers (strong recommendation, moderate quality of evidence for screening and very low quality of evidence for annual surveillance and age of initiation).

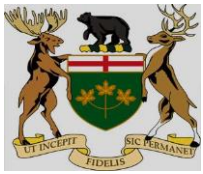
- Colectomy with ileorectal anastomosis (IRA) is the preferred treatment of patients affected with LS with colon cancer or colonic neoplasia not controllable by endoscopy. Segmental colectomy is an option in patients unsuitable for total colectomy if regular postoperative surveillance is conducted (conditional recommendation, moderate quality of evidence).
- Hysterectomy and bilateral salpingo-oopphorectomy should be offered to women who are known LS mutation carriers and who have finished childbearing, optimally at age 40-45 yr (conditional recommendation, low quality of evidence).
- Screening for endometrial cancer and ovarian cancer should be offered to women at risk for or affected with LS endometrial biopsy and transvaginal ultrasound annually, starting at age 30 to 35 yr before undergoing surgery or of surgery is deferred (consitional recommendation, very low quality of evidence).
- Screening for gastric and duodenal cancer can be considered in individuals at risk for or affected with LS by baseline esophagogastroduodenoscopy (EGD) with gastric biopsy at age 30-35 yrs, and treatment of H. pylori infection infection when found. Data for on going regular surveillance are limited, but ongoing surveillance every 3-5 yr may be considered if there is a family history of gastric or duodenal cancer (conditional recommendation, very low quality of evidence).
- Screening beyond population-based recommendations for cancers of the urinary tract, pancreas, prostrate, and breast is not recommended unless there is a family history of the specific cancers (conditional recommendation, low quality of evidence).

- Although data suggest that daily aspirin may decrease the risk of colorectal and extracolonic cancer in LS, currently the evidence is not sufficiently robust or mature to make a recommendation for its standard use (conditional recommendation, moderate quality of evidence).

Source: Syngal S, et al. Am J Gastroenterol 2015; 110(2): 223-62.

- Give the screening and management guidelines for Lynch syndrome (HNPCC).

Cancer	Screening	Age to Start	Treatment
• Annual screening			
○ Endometrial /Ovarian	Endometrial biopsy (for pre-menopausal women) and transvaginal ultrasound (preferably day 1-10 of cycle) for pre-menopausal women CA125	30-35 yrs (or 5-10 yrs before the earliest diagnosis in the family)	Consider prophylactic TAH/BSO after childbearing Consider oral contraceptives for premeno-pausal women.
○ Urinary tract	Pelvic and abdominal US Urinalysis with cytology	30-35 yr 30-35 yrs	



Cancer	Screening	Age to Start	Treatment
• Screening q 1-2 yr			
○ Colon	Colonoscopy	30-35 yrs 20-25 yrs (or 10 yrs before the earliest diagnosis in the family)	Consider colectomy if cancer or advanced adenoma is found.
○ Stomach	EGD	30-35 yrs	
○ Small bowel	Small bowel enteroclysis (CTE, MRE)	30-35 yr	
○ CNS	MRI	CNS symptoms	
○ Biliary tract, gallbladder	Liver function tests	30-35 yr	

Abbreviations: TAN/BSO, total abdominal hysterectomy, bilateral salpingo-oophorectomy; CNS, central nervous system; EGD, esophagogastroduodenoscopy

Printed with permission: Burt RW. *2007 AGA Institute Postgraduate Course.* pg. 240.

Muir-Torre Syndrome

- Extracolonic cancer in HNPCC is known as the Muir-Torre variant
- A rare subset of HNPCC associated genetically with
  - MSI
  - Loss of expression
    - hMLH1
    - hMSH2
- Associated cancers
  - Skin
    - Keratoacanthomas
    - Sebaceous adenomas
  - Carcinomas
    - Basal call
    - Squamous
- GI tract
  - Stomach
  - Small intestine
  - Biliary tree
- GU
  - Ovary
  - Uterus
  - Ureter
- CNS
  - Brain

Heritable Polyposis Syndromes

- Adenomatous polyposis syndromes
  - Familial adenomatous polyposis
  - Variants of familial adenomatous polyposis
    - Gardner syndrome
    - Turcot syndrome
    - Attenuated adenomatous polyposis coli
  - Familial tooth agenesis syndrome
  - Bloom syndrome
  - MUTYH polyposis (MYH polyposis)
- Hamartomatous polyposis syndromes (HPS)
  - Peutz-Jeghers syndrome
  - Juvenile polyposis
  - PTEN hamartomatous tumour syndrome
    - Cowden disease
    - Bannayan-Ruvalcaba-Riley syndrome
  - Rare HPS
    - Hereditary mixed polyposis syndrome
    - Intestinal ganglioneuromatosis and neurofibromatosis
    - Devon family syndrome
    - Basal cell nevus syndrome

Familial Adenomatous Polyposis

- Demography
  - Most common adenomatous polyposis syndrome
    - Prevalence $20/10^5$
  - AD inheritance, 80-100% penetrance
  - Represents ~1-5% of colorectal cancers

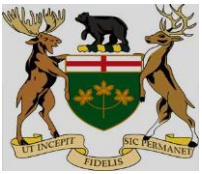
- Give the onset age of CRC in the phenotypes of FAP.

Phenotype	Age, yrs
Profuse	39
Intermediate	39-50
Attenuated (AFAP)	>50 (R colon)
MYH (MAP)	>60 (recessive)

MCQ Pearl

- Give the name of three attenuated syndromes of inherited CRC.
  - Attennuated AFP (AAFP)
  - APC gene mutationpathways
  - MuTYH (aka MYH gene)

- Genetics
  - 2-hit theory of cancer causation (germline [inherited] plus somatic [sporatic] mutation)
    - 1 mutated APC allele (chromosome 5) inherited as a germline mutation
  - 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)



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- It may be surprising to learn, but there are actually at least two attenuated adenomatous polyposis syndromes.

- Give the names, genetic mutations, and recommended frequency of surveillance colonoscopy in three **attenuated syndromes**.
  - AFAP (attenuated form of FAP)
    - < 100 adenomas, often in proximal colon
    - Some duodenal and gastric polyp associations as classic FAP
    - Loss of the 5' and 3' regions of FAP
    - CRC develops later than in FAP, ~5 yr rather than 32 yr
    - Surveillance colonoscopy of 2 yr
  - APC gene pathway mutations
    - B-catenin
    - Axin
  - MUTYH (aka MYH) gene
    - 15-100 colonic adenomas
    - Defective MUTYH gene causes G:C → T:A translocation
    - Autosomal recessive
    - ↑ risk of CRC with biallelic MUTYH mutations
    - Colonoscopic screening age 18 to 20 with surveillance of 2 yr
    - May be associated with osteomas and CHRPN (congenital hypertrophy of the retinal pigmental epithelium)

- Mutation of the tumour suppressor gene on the long arm of chromosome 5 q21 – q22 region
- MYH is a base-excision-repair gene on chromosome 1
- 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
  - Truncated germline mutation (stop codon) of first allele from affected parent causes APC mutation in all cells in the body
  - Loss of normal phosphorylation of B-catenin, with loss of inactivation of B-catenin, leading to instability of chromosomes, and their segregation
  - There may also be germline mutations of axin
  - Unaffected parent passes on somatic mutations in the mutations in the mutation cluster region near the centre of all APC gene or lost second allele

- Give 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 electrophoresis (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:
  - 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 syndrome): more commonly found with mutations in the distal portion of exon 15

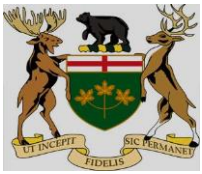
Abbreviations: CHRPE, congenital hypertrophy of the retinal pigment epithelium; DGGE, denaturing gradient gel electrophoresis; SSCP, single-strand conformational polymorphism

- Give the role of APC gene function, nuclear β-catenin, the Wat signal pathway, the LEF (lymphoid enhancer factor) / TCF (T-cell factor) family in the development of CRC.

- Normal
    - APC (tumour suppressor) gene
        - Association with E-cadherin → cell-cell adhesion
        - Binds β-catenin → ↑ phosphorylation
        - ↓ β-catenin - ↓ stimulation of Wnt-Tcf signal pathway
            - ↓ proliferation
            - ↑ apoptosis

- APC gene mutation
    - ↓ cell-cell adhesion
    - ↓ β-catenin phosphorylation
        - ↑ unphosphorylated β catenin complex with LEF/TCF
        - ↑ Wnt-Tcf
    - Target genes
        - ↑ proliferation
        - ↓ apoptosis

➢ Clinical
    - Classic FAP and its variants
        - Gardner syndrome
        - Turcot syndrome
        - Attenuated FAP (AFAP)
    - 100% will develop CRC by age 40 yr
    - Synchronous CRCs occur in about half of FAP patients.



- With AFAP (as compared with FAP)
  - Develop later
  - Fewer polyps (< 100)
  - Tend to be on the right side of the colon
  - CRC develops at a later age
  - 80% rather than 100% develop CRC
  - Screening must be done for gastric fundic gland polyps, periampullary polyps and for duodenal and cancer
  - Gardner syndrome is FAP plus extraintestinal lesions: CHRPE (congenital hypertrophy of the retinal epithelium, thyroid cancer, sebaceous cysts, supernumerary teeth, osteomas, fibromas, lipomas
- 10-500 adenomatous polyps, with 50% risk of CRC
- Even with recommended colonoscopic screening and surveillance, about a quarter already have CRC.

Extracolonic Periampullary Adenomas in FAP

- Stomach
  - A polyp in the fundic area of the stomach is a polyp in the fundus, and should not be called a fundic gland until the histopathology of the lesion proves this diagnosis of “fundic gland polyps”.
  - In FAP, when polyps are seen in the fundic area of the stomach
    - < 5% are adenomas
    - 95% are fundic gland polyps (FGP)
      - However at least a quarter of these FGPs already have epithelial dysplasia
- Small bowel FAP polyps
  - Jejunum, 40%
  - Ileum, 20%
  - Distinguished from lymphoid hyperplasia
  - Low risk of malignancy

- Duodenal FAP polyps/cancer
  - Occur in 60% to 90% of FAP patients
  - Usually periampullary region, and > half involve the ampulla of Vater
  - ~10% lifetime risk of duodenal cancer
  - ↑ risk of epithelial dysplasia is associated with
    - ↑ size
    - Site-associated duodenal polyposis
    - Association – Non-H. pylori antral gastritis
  - Surveillance with SV-EGD (side-viewing EGD, esophagogastroduodenoscopy).
  - Risk stratification for the development of duodenal cancer is based on the Spigelman classification.
  - Should begin at 2 yr of age, and then be followed by regular SV-EGD surveillance.

- Give the recommended interval of duodenoscopic screening (visualization and biopsy) of duodenal polyps in FAP, using the **Spigelman staging criteria.**

Polyp Characteristics	1	2	3
Polyp count	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Histologic type	Tubular	Tubulo-villous	Villous
Grade of intraepithelial neoplasia	Low-grade	Inter-mediate*	High-grade

- From the above, calculate the number of points (maximum 12)
  - From the number of points, determine the grade/stage, and the interval of EGD surveillance.

Points	Grade/Stage	Surveillance, yrs
0	0	5
1-4	I	3
5,6	II	
7,8	III	1
9-12	IV	≧ 6 mon

Grade	Surveillance Interval (yr)
0	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

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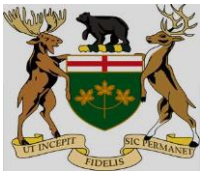
Turcot Syndrome

- Definition
  - "…. a syndrome of familial colonic [adenomatous] polyposis with primary tumours of the central nervous system" (Itzkowitz SN and Potack J. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, pg 2242).

The Turcot syndrome is considered to be variant of FAP, and as such has a mutation in the APC gene.

- Give the reason why the Turcot syndrome may be possibly misclassified, and instead should be considered either as a variant of HNPCC, or an overlap of both FAP and HNPCC.
  - In Turcot syndrome, the gene mutations are in FAP, or in DNA MMR, the same germline mutation seen in HNPCC.

- Give the difference in the CNS presentation of Turcot syndrome, depending upon which germline mutation is present.
  - Gene mutation in
    - APC medulloblastomas
    - DNA MMR glioblastoma multiforme tumours (familial tooth agenesis)



Gardner Syndrome (GS)

- A variant of FAP with numerous extraintestinal associations
- Extraintestinal findings

- Give the extraintestinal associations of the Gardner syndrome (GS) variant of FAP.
  - CNS
    - Medulloblastoma (Turcot syndrome)
  - Eye
    - CHRPE (congenital hypertrophy of the retinal pigmented epithelium)
    - Multiple in 63%
    - Bilateral in 87%
  - Teeth
    - Impacted teeth
    - Extra teeth
    - Supernumerary teeth
    - Familial tooth agenesis" is caused by mutation in APC pathway (AXIN2)
      - Both adenomatous and hyperplastic colonic polyps
  - Bone
    - Osteomas
      - Jaw (in 90% of GS)
      - Cysts
      - Skull
      - Long bones
    - Exostoses

- Soft tissue tumours (benign)
  - Desmoid tumours (Diffuse mesenteric fibromatosis)
  - Fibromas
  - Lipomas
    - $300/10^5$ person-yr
    - Treat with NSAIDs and tamoxifin chemotherapy, colectomy small bowel transplantation
    - May be a lethal association
- Mesentery
  - Mesenteric fibromatosis
- Endocrine tumours
  - Thyroid papillary tumour
  - Adrenal
- Skin
  - Desmoid tumours
  - Fibromas
  - Lipoma
  - Sebaceous cysts
  - Epidermoid (aka “inclusion”) cysts

Abbreviations: CHRPE, congenital hypertrophy of retinal pigmented epithelium (pigmented spots on the fundus of the eye)

CHRPE

Cute Quotes

"The presence of multiple [CHRPE] lesions appears to be a reliable marker for gene carriage in FAP" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2180; and page 2184; and 10th Edition, 2016, page 2242).

*Note: CHRPE is also seen in MUTYH.

Exam Alert

- The clinical examiner tells you that the patient has colonic polyps and hands you a fundoscope.
- She/he is expecting you to look for pigmented lesions in the ocular fundus, suggesting CHRPE in the Gardner variant of FAP.

MCQ Trick

- Remember: FAP in its classical form may be associated with dental abnormalities and osteomas of the jaw, without being considered to be a Gardner variant.
- Also remember, osteomas and CHRPH may occur in MUTYH.

Desmoid Tumour

SO YOU WANT TO BE A GASTROENTEROLOGIST – NERD

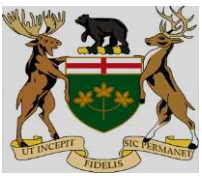
- The second most lethal complication of the Gardner variant of FAP is desmoid tumour (diffuse mesenteric fibromatosis).
- A strong family history of FAP ↑ risk of having desmoid tumours.
- Treatment may include an NSAID, tamoxifen, sulindac plus tamoxifen, progesterone; chemotherapy; resection, and even small bowel transplantation.

- Give the **Church staging system** for desmoid tumours in the Gardner variant of FAP.
  - Staging system for desmoid tumours in Gardner variant of FAP.

Findings	I	II	III	IV
– Symptoms	No	Mild	Moderate*	Severe
– Size, cm	<10	<10	10-20	> 20 (or rapidly growing)
– Growth	No	No	Slow	Rapid

*May be associated with symptoms of obstruction of the bowel or ureter

Adapted from: Itzkowitz SN and Potack J. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 126.13, page 2240.



➢ Treatment

- Give the clinical management of FAP (familial adenomatous polyposis)
- Genetic testing
  - Consider genetic testing between ages 10 to 12 yr.
  - Begin in first decade of life to determine who should be screened for hepatoblastoma.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Genetic testing in FAP is important because there may be skipped generations, and 20% of FAP patients may have a mutation.
- It is important in the screening of the family to know the genetic mutation in the index patient (performed on DNA from peripheral blood WBCs), and to better focus on which mutation to look for in the next-of-kin, thereby providing better genetic counselling.

- While all the family needs to be tested, if resources are a limiting factor, give the family groups that should be tested in FAP and MUTYH.
  - FAP autosomal dominant (1 in 2)
    - Parents and children
  - MUTYH autosomal recessive (1 in 4)
    - Siblings and spouse

- GI tract screening
  - Colon cancer risk > 90%
  - Sigmoidoscopy in gene carriers every 1 to 2 yr, beginning at age 10 yr, or in all at-risk persons if genetic testing is not done or not informative.
  - Colonoscopy every 2 yr beginning at age 20 in families with AFAP/AAPC, or sometimes earlier, depending on the age of polyp emergence in other family members

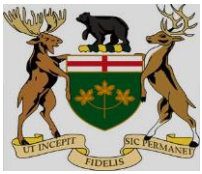
SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the postulated mechanism for the benefit of NSAIDs/ASA/Coxibs in the regressive of adenomatous polyps.
  - With adenomatous polyps → ↑ COX-2 expression
  - ↑ COX-2 → ↓ apoptosis
  - NSAIDs/ASA/Coxibs → ↓ COX-2
    - ↑ apoptosis
      - ↑ conversion of sphingomyelin to ceramide
    - ↑ arachidonic acid →
      - ↓ PPAR and gene
      - ↑ arachidonic acid

- Upper GI endoscopy
  - Upper GI tract (5-10% cancer risk for duodenal or peri-ampillary, 0.5% for gastric)
  - Begin when colon polyps emerge or by age 25 yr
  - Repeat every 1 to 3 yr, 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

- Give the recommended method, age to begin, interval of screening, and management of the person with FAP.

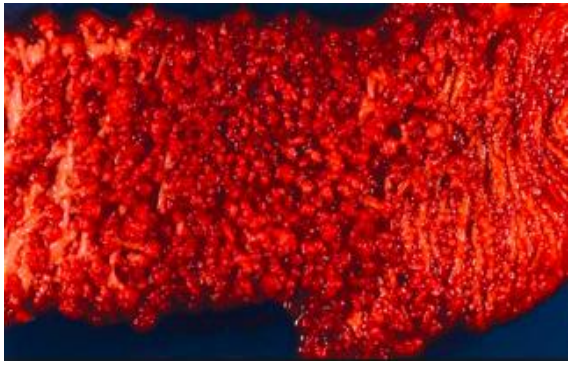
Screening Method	Age to Begin	Interval	Management
○ Colono-scopy or flexible sigmoido-scopy	– 10-12 yr, or late teens if attenuated FAP	▪ If polyps are detected, screen annually until colectomy	- Colectomy is recommended when polyps become too numerous to monitor safely, or if polyps are ≥1 cm or exhibit advanced histology. - Removal of the rectum should be based on polyp burden and family history.
○ Flexible sigmoido-scopy	– Within two yr after colectomy	▪ Every 6 months to 3 yr depending on polyp size and number	-Chemo-prevention with NSAIDs may be considered



Screening Method	Age to Begin	Interval	Management
○ EGD with end and side viewing instrument	– 20-25 yr or at the onset of colonic polyps	▪ 3 yrs if stage[1] 0, II ▪ 2 yrs if stage[1] III ▪ 6-12 monif stage[1] 4	- Chemo-prevention with NSAIDs is less effective for upper GI adenomas
○ Physical examination	– 10 to 12 yr	▪ Annually	
○ Physical exam, hepatic ultrasound, and alpha-fetoprotein	– 6 mon	▪ Every 6 mon 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

- Clinical
  - Progressive development of hundreds to thousands of adenomatous polyps
    - Tubular, Tubulovillous or Villous
    - Usually polyps start to develop at age 10-12 yr
  - CRC is inevitable, usually 10-15 yr after onset of polyposis but as early as 9 yr



  - Gastric polyps (30-100%)
    - Mostly non-neoplastic fundic gland polyps (FGP)
    - Gastric adenomas (5%)
    - Gastric cancer (0.5%)
  - Duodenal adenomas (60-90%)
    - Usually involve the periampullary region
    - Can cause biliary obstruction +/- pancreatitis
    - Duodenal cancer ~10% lifetime risk
    - Major cause of cancer death after prophylactic total colectomy
  - Jejunal adenomas (40%)
  - Ileal adenomas (20%)

Small bowel malignant transformation rare but possible

- Extra Intestinal Features
  - Jaw
    - Mandibular Osteomas
  - Teeth
    - Dental abnormalities
  - Thyroid Cancer
  - Congenital Hypertrophy of the retinal pigmented epithelium (CHRPE)
  - Desmoid tumors-diffuse
    - Mesenteric fibromatosis
  - GI
    - Obstruction
  - GU
    - External vascular obstruction

- Treatment
  - Total proctocolectomy preferred
  - If rectum spared, need frequent endoscopic and histopathological surveillance

Familial Adenomatous (FAP) / MUTYH-associated polyposis attenuated polyposis

- Individuals who have a personal history of > 10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumours (abdominal > peripheral), papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium ([CHRPE], epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes.
- Genetic testing of patients with suspected adenomatous polyposis syndromes should include APC and MUTYH gene mutation analysis.

- In individuals at risk for or affected with the classic AP syndromes, screening for colorectal cancer by annual colonoscopy or flexible sigmoidoscopy should be performed, beginning at puberty. In families with attenuated familial adenomatous polyposis (AFAP) or MAP, surveillance should be by colonoscopy (strong recommendation, moderate quality of evidence).
- Absolute indications for immediate colectomy in FAP, AFAP, and MAP include: documented or suspected cancer or signifi cant symptoms. Relative indications for surgery include the presence of multiple adenomas >6 mm, a significant increase in adenoma number, and inability to adequately survey the colon because of multiple diminutive polyps (strong recommendation, low quality of evidence).
- Screening for gastric and proximal small bowel tumors should be done using upper endoscopy including duodenoscopy starting at age 25–30 yr.
  - Surveillance should be repeated every 0.5–4 yr depending on Spigelman stage of duodenal polyposis: 0=4 yr; I=2–3 yr, II=1–3 yr, III=6–12 mon, and IV=surgical evaluation.
  - Examination of the stomach should include random sampling of fundic gland polyps.
  - Low-grade dysplasia is common in fundic gland polyps, and surgery should be reserved for high-grade dysplasia or cancer (strong recommendation, very low quality of evidence).
- Annual thyroid screening by ultrasound should be recommended to individuals affected with FAP, MAP, and attenuated polyposis (conditional recommendation, low quality of evidence).

- Biannual screening should be offered to affected infants until age 7 yr with α -fetoprotein and ultrasounds (conditional recommendation, very low quality of evidence).
- Postsurgical surveillance should include yrly endoscopy of rectum or ileal pouch, and examination of an ileostomy every 2 yr (strong recommendation, low quality level of evidence).

Source: Syngal S, et al. Am J Gastroenterol 2015; 110(2): 223-62.

Hamartomatous Polyposis Syndromes (HPS)

➢ Classification

- Give a classification of hamartomatous polyposis syndromes.
  - PJS (Peutz-Jegher syndrome)
  - JPS (Juvenile polyposis syndrome, aka familial juvenile polyposis)
  - PTEN tumour syndrome
    - Cowden disease
    - BRR (Bannayan-Ruvalcaba-Riley) syndrome
  - Neurofibromatosis (mutation in NF1 gene), and ganglioneuromatosis ↓ with MEN 2B)
  - Tuberous sclerosis
    - Hamartomas plus
      - CNS
        - Epilepsy
        - Mental challenge
      - Skin
        - Adenoma sebaceum

Note: JPS, when associated with multiple polyps, is a diagnosis of exclusion (e.g., exclude PJS, CS, BRR, NFTS)

Syndrome	Gene (% Chance of Finding a Mutation in Proband)	Lifetime Cancer Risk		Other Features
○ 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	▪ Muco-cutaneous pigmentation ▪ Histologically characteristic gastro-intestinal hamartomas, mostly small bowel, but in all areas ▪
○ 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[3] ▪ Digital clubbing ▪ Congenital defects

Syndrome	Gene (% Chance of Finding a Mutation in Proband)	Lifetime Cancer Risk		Other Features
○ CS	- PTEN (80-90%)	– Breast	25-50%	▪ Muco-cutaneous papules
		– Thyroid (especially follicular)	10%	▪ Macro-cephaly
		– Endometrium	5%	▪ Hamartomas of the gastrointestinal tract, thyroid, and breast
		– Kidney	↑	
		– Colon and upper GI tract	CRC may be ↑	▪ Lhermitte-Duclos disease

[1]Sex cord tumours with annular tubules; [2]Adenoma malignum

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Peutz-Jeghers Syndrome (PJS)

- Definition
  - Inherited mucocutanous pigmentation and GI harmatomatous polyposis
- Demography
  - Average age of diagnosis 23-26 yr

- Diagnosis (World Health Organization (WHO) diagnostic criteria for PJS: any one of the following):
  - ≥ 3 histologically characteristic PJS polyps
  - ≥ 1 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 PJS, plus characteristic and prominent mucocutaneous pigmentation

Clinical Pearl

- Give the way to distinguish freckles from the brown pigmentation of PJS.
  - These are the common sites of pigmentation in PJS
    - Nose*
    - Lips
    - Mouth (buccal mucosa)*
    - Hands
    - Feet
    - Perianal and genital regions
  - In PJS, freckles do not occur near the nostrils of the nose, or on the buccal mucosa of the mouth

- Genetics
  - 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 STK II (serine threonine kinase II, also called LKB I) gene on chromosome 19p13.3 (Serine-threonine kinase gene) on chromosome 19q)
- Autosomal dominant germline mutation in the STK II (LKB I) gene, with
  - Mutations seen in 90% of persons with PJS
  - There may be genetic heterogeneity
- 50% of mutations are inherited, and 50% are spontaneous, appearing de novo

- Give the gene mutation and lifetime cancer risk from affected organs in the Peutz-Jeghers syndrome (PJS, hamartomatous polyposis syndrome)**.**

Gene (% Chance of Finding a Mutation in Proband)	Lifetime cancer risk		Other features
STK11 (30-70%)	–Breast	54%	▪ Mucocutaneous pigmentation ▪ Histologically characteristic gastrointestinal hamartomas, mostly small bowel, but also in other areas
	–Colon/rectum	39%	
	–Pancreas	36%	
	–Stomach	29%	
	–Ovarian[1]	21%	
	–Small bowel	13%	
	–Lung	15%	
	–Uterine/cervix[2]	9%	
	–Testicle	Rare	

[1]Sex cord tumours with annular tubules; [2]Adenoma malignum

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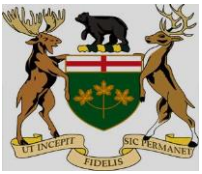
- Clinical
  - Clinical presentation age 10-20 yr from time of initial small bowel obstruction.
  - Polyps
    - Benign complications from the polyps (bleeding, obstruction and intussusceptions) predominate in the first three decades of life
  - Mucocutaneous pigmented macules
    - May be present at birth on buccal mucosa, lips, peroral region, fingertips or toes, hands or feet, perianal or genital area
    - 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
  - Pigmented
    - Face
    - Lips
    - Buccal mucosa
      - 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
  - Sex cord tumours
    - Men
      - Sertoli cell testicular tumour
    - Women
      - Ovary
  - Breast cancer



- Site of polyposis
  - Hamartomatous and adenomatous polyposis in stomach, small intestine, colon, and esophagus
    - Polyps most prominent in small bowel, causing
    - Small bowel obstruction and intussusception
    - Acute UGIB
      - Chronic fecal blood loss
  - Pancreatic cancer
  - Breast cancer
  - Lung airway polyps
  - GU
    - Ovarian sex chord tumors
    - Sertoli tumors of the testes

- Diagnosis
  - Individuals with perioral or buccal pigmentation and/or two or more histologically characteristic gastrointestinal hamartomatous polyp(s) or a family history of PJS should be evaluated for PJS.
  - Genetic evaluation of a patient with possible PJS should include testing for STK11 mutations.
  - Surveillance in affected or at-risk PJS patients should include monitoring for colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix, and testes cancers. Risk for lung cancer is increased, but no specific screening has been recommended. It would seem wise to consider annual chest radiograph or chest computed tomography (CT) in smokers (conditional recommendation, low quality of evidence).

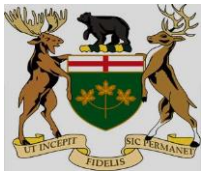
Source: Syngal S, et al. Am J Gastroenterol 2015; 110(2): 223-62.

- Screening

Site	Age to Begin	Interval (yrs)	Investigation
○ Colon	8, 18	3	– Colonoscopy
○ Stomach	8, 18	3	– Esophagogastro-duodenoscopy (EGD)
○ Small bowel	8, 18	3	– Video capsule endoscopy
○ Pancreas	30	1–2	– Magnetic resonance cholangiopancreato-graphy (MRCP) or endoscopic ultrasound (EUS)
○ Breast	13, 25	1	– Annual self-exam starting age 18; annual breast MRI, – Mammogram starting at age 25
○ Ovarian, Endometrium, SCTAT*	25	1	– Pelvic exam and pelvic – Transvaginal ultrasound
○ Cervix (adenoma malignum)	25	1	– Pap smear
○ Testicular (Sertoli cell tumour)	Birth to teenage yr	1	– Testicular exam, ultrasound if abnormalities palpated or if feminization occurs; 10 to 20% of benign Sertoli cell tumors become malignant
○ Lung	-	-	– Provide education about symptoms and smoking cessation

Abbreviation: SCTAT, sex cord tumor with annular tubules

*Almost all women develop SCTAT, but only 20% become malignant



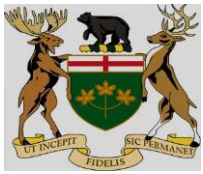
- Endoscopy
  - Cerebriform polyps on EGD
  - Smooth muscle arborization
  - Adenomatous changes occur in ~25% of PJS hamartomas, accounting for the development of adenocarcinomas
  - Cancer risk (hamartoma-carcinoma sequence) is 90% by age 65

- Pathology
  - 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%
  - 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

- 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 (hepato-blastoma)	<1	2-7	-
	– Colon	~100	~100	39
○ Non-GI	– CNS	<1 (medulo-blastoma)	1-3 (glio-blastoma)	-
	– Adrenal	2	-	-
	– Endometrium	<1	-	-
	– Ovary	-	20-60	9
	– Upper urinary tract	-	9-12	21
	– Skin	-	4-5	-
	– Breast	-		54
	– Lung	-	1	15
	– Testicle (Sertoli cell)	-		Rare

Adapted from: Burt RW. *AGA Institute Postgraduate Course book* 2007: pg. 235, 237 and 241.



Juvenile Polyposis Syndrome (JPS)

- Demography
  - The incidence of inherited JP is ~$1/10^5$
  - 20-60% have a family history, and the remainder appear de novo
  - 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.

- Genetics
  - Autosomal dominant
    - Germline mutations in MADH4 (SMAD4), a tumour suppressor gene (in ~18%)
    - Germline mutations of BMPR1A (bone morphogenetic protein receptor 1A) (in ~ 21%)
  - Sporatic (in ~ 66%)
  - At least a third of these will be found to have the autosomal dominantly inherited syndrome
  - Germline mutation in either the SMAD4 (MADH4) gene (in 35%) on chromosome 18q21.1 or in the BMPR1A (bone morphogenetic protein receptor 1A) gene (in 25%)
  - At least half of the affected families are found to have a disease from mutation of the SMAD4 gene
  - Half of the affected families have a disease causing mutation of the SMAD4 gene on chromosome 18
  - `Other genes may be involved (BMPRIA on chromosome 10)

- Distinguish from PJS and CS

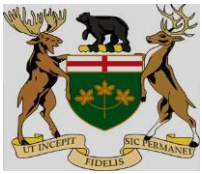
Syndrome	Gene	Chromosomes
– PJS	STK II	19p13.3
– JPS	SMAD4	18q21.1
– CS	BMPR1A	
	PTEN	10

Abbreviations: BMPR1A, bone morphogenetic protein receptor type 1A); CS, Cowden Syndrome; PTEN, phosphate and tensin homologue

❖ Familial JPS

➢ Clinical

- Colonic bleeding and anemia usually occur in the first decade of life
- Clinical management involves mainly screening for cancer prevention
- Empiric guidelines have been developed for organs in which cancer develops
- 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
- 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



- ❖ Non-familial JPS
  - Congenital defects have been noted with the non-familial but not the familial form of JPS.
    - Cardiac abnormalities
    - Cranial abnormalities
    - Cleft palate
    - Polydactyly
    - Bowel malrotations

Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, page 2244.

- ➢ Genetics

- Give the gene mutation and lifetime cancer risk from affected organs in the Juvenile Polyposis syndrome (JPS, hamartomatous polyposis syndrome)**.**

Gene (% chance of Finding a Mutation in proband)	Lifetime Cancer Risk		Other Features
○ SMAD4 (20%)	Colon	68%	- GI juvenile polyps
○ BMPR1A (20%)	Upper GI cancers including stomach, pancreas, and small bowel	21%	- Features of HHT* - Digital clubbing - Congenital defects

* HHT, Hereditary hemorrhagic telangiectasia

ENG is a very rare gene mutation in JPS

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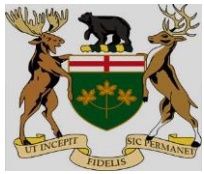
- Histopathology
  - The juvenile hamartomatous polyps demonstrate dilated cystic glands, columnar lining, abundant lamina propria which may contain an inflammatory infiltrate.
  - These juvenile polyps may be seen in JPS, CS, and BRRS or Gorlin syndrome.
  - The polyps are most commonly found in the 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.
  - Colorectal cancer (CRC) risk in JPS
    - 20% by age 25 yr
    - 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.
  - ↑ lamina propria



- Dilated cystic glands filled with mucus
  - Cowden disease (aka multiple hamartoma syndrome)
    - Autosomal dominant
    - Facial trichilemmomas around eyes, nose, mouth
    - Polyps in
      - Colon (hamartomas, ganglioneuromas
      - Esophagus (glycogenic acanthosis)
      - Stomach
  - Cancer
    - Breast
    - Uterus
    - Thyroid
    - **Not** in GI tract
  - BRR (Bannayan-Ruvalcaba-Riley) syndrome
    - Autosomal dominant
    - Macrocephaly
    - Delay in development
    - Pigment spots on penis
    - Thyroiditis
- Dilated cystic glands filled with mucus
  - GI
    - Meckel diverticulum
    - Malrotation of intestine
  - GU
    - Undescended testicle
    - Agenesis of one kidney
    - Bifid uterus and vagina

- CNS
  - Macrocephaly
  - Hydrocephalus
  - Heart
  - ASD (atrial septal defect)
  - C of A (coarctation of aorta)
  - T of F (tetralogy of Fallot)

Juvenile polyps are hamartomas, and usually are not be neoplastic. However, about 1/3 of JPS develop CRC, and a few even develop gastric cancer.

- Give a pathological explanation for this apparent contradiction.
  - JP and adenomatous polyps may occur in
    - The same person
    - The same polyp.

➢ Colon screening
  - Multiple juvenile polyps in colon (98%), stomach (14%), duodenum (2%), jejunum and ileum (7%)
  - This consists mainly of prevention of benign and malignant complications
  - Only empiric guidelines are available
  - Colonoscopy, beginning with symptoms or in early teens, if no symptoms occur. Interval determined by number of polyps but at least every 3 yr once begun.

Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, page 2244.

PTEN Hamartomatous Polyposis Syndrome (PHTS)

❖ **Cowden Syndrome** (CS)

➢ Definition

- Cowden syndrome is the presence of multiple facial trichilemmomas (the hallmark sign, most commonly around the mouth, nose and eyes), plus intestinal polyps and extraintestinal cancers.

➢ Demography

- CS occurs in < $1/10^5$

➢ Pathology

- A juvenile-like polyp which contains neural components is characteristic for CS

➢ Diagnosis

- Specific clinical diagnostic criteria have been suggested by the *International Cowden Consortium* for the diagnosis of CS.

- Pathognomonic criteria
  - 90% of affected persons have mucocutaneous papillomatous papiles (hamartomas), as well as hamartomas of the infundibulum of the hair follicles (trichilemmomas)
  - Mucocutaneous lesions
    - Trichilemmomas, facial
    - Acral keratosis
    - Papillomatous papules

- Skin
  - Café-au-lait spots
  - Vitiligo
  - Cysts, as well as squamous cell and basal cell carcinomas
  - Oral mucosal lesions
- Trichilemmomas
  - Cobblestone-like pattern in mouth from coalesced trichilemmomas in 40%
  - They develop a few yr 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
- Major criteria
  - Breast carcinoma
    - 75% of affected females have breast lesions, including fibrocystic disease and fibroadenomas
    - There is a ~40% incidence of breast carcinoma, with frequent bilateral occurrence, and a median age at diagnosis of 41 yrs
  - Thyroid carcinoma (non-medullary), especially follicular thyroid carcinoma
  - Macrocephaly (megalencephaly) (≥ 95th percentile)
  - Lhermitte-Duclos disease (LDD, cerebellar dysplastic gangliocytoma)

- Endometrial carcinoma
- Genitourinary abnormalities (44% of affected women)
  - Multiple uterine leiomyomas (fibroids) and/or bicornuate uterus

- Minor criteria
  - Other thyroid lesions (e.g., adenoma or multinodular goiter)
  - Mental retardation (IQ ≤ 75)
  - GI hamartomas
    - 40% have involvement of esophagus (glycogen acanthosis), stomach and colon (hamartomas)
  - Fibrocystic disease of the breast
  - Lipomas
  - Fibromas
  - GU tumour (eg: renal cell carcinoma, uterine fibroids or malformation

- Additional benign soft tissue and visceral tumours have been observed:
  - Hemangiomas
  - Lipomas
  - Lymphangiomas
  - Neurofibromas
  - Uterine Leiomyomas
  - Meningiomas

- Developmental or congenital abnormalities also occur:
  - Hypoplastic mandible
  - A prominent forehead
  - A high-arched palate

- 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

- Operational diagnosis in a person with mucocutaneous lesions alone if:
  - There are ≥ 6 facial papules, of which ≥ 3 must be trichilemmoma, or
  - Cutaneous facial papules and oral mucosal papillomatosis, or
  - Oral mucosal papillomatosis and acral keratoses, or
  - Palmoplantar keratosis ≥ 6
    - 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 diagnosed with CS
  - The pathognomonic criterion
  - Any one major criterion with or without minor criteria
  - Two minor criteria

- Genetics
  - Autosomal dominant
  - Mutations of the PTEN gene on chromosome 10
    - Seen in 85% of CS affected persons
  - Skin lesions (>90%; pathognomonic lesions)

- Give the gene mutation and lifetime cancer risk from affected organs in the CS**.**

Gene (% Chance of Finding a Mutation in Proband)	Lifetime Cancer Risk		Other Features
○ PTEN (80-90%)	- Breast	25-50%	- Mucocutaneous papules - Macrocephaly - Hamartomas of gastrointestinal tract, thyroid, and breast - Lhermitte-Duclos disease (LDD)**
	- Thyroid (especially follicular)	10%	
	- Endometrium - Kidney - Colon* and upper GI tract	↑	

*Cowden syndrome (CS) is **not** associated with an ↑ risk CRC

** Lhermittee-Duclos disease – Cerebellar dysplastic gangliocytoma

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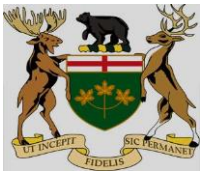
➢ Screening and surveillance

- Give the screening recommendations to detect early cancers associated with CS.

Cancer	Cancer Risk	Screening Recommendations
○ Colon	– About 17%	▪ No recommendations
○ Thyroid	– 3-10%	▪ Annual thyroid exam, starting in teens
○ Breast	– 25-50%	▪ Annual breast exam, starting at age 25 yrs; annual mammography, starting at age 30 yrs
○ Uterus/ovary	– Possible increase	▪ Uncertain

*Note: some authors suggest that there does not appear to be and ↑ risk of GI cancer.

Printed with permission: Zbuk KM, and Eng C. *Nat Clin Pract Gastroenterol Hepatol* 2007; 4(9): pg. 496.



- Give the surveillance recommendations for Cowden syndrome.

Women	Men
○ Training and education in breast self-exam (BSE) and monthly BSE starting at age 18 yr	– Annual comprehensive physical exam starting at age 18 yr or 5 yr 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
○ Semiannual clinical breast exam starting at age 25 yr or 5-10 yr earlier than earliest known breast cancer in the family	– Annual urinalysis; consider annual urine cytology and renal ultrasound, if family history of renal cancer
○ Annual mammography and breast MRI screening starting at age 30-35 yr or 5-10 yr earliest known breast cancer in the family (whichever is earlier)	– Baseline thyroid ultrasound at age 18 yr, and annual thereafter
○ Blinded endometrial aspiration biopsies annually for premenopausal women starting at age 35-40 yr, or 5 yr before earliest diagnosis of endometrial cancer in the family; annual endometrial ultrasound in postmenopausal women	– Education regarding the signs and symptoms of cancer
○ Discuss options for risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, extent of cancer risk, and reconstruction options	– Annual dermatologic exam
	– Advise about risk to relatives, and possibility of genetic testing for relatives

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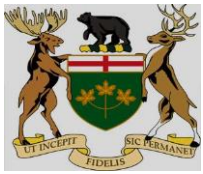
- The Bannayan-Ruvalcaba-Riley (BRR) syndrome, is now believed to be related to Cowden syndrome (CS).
  - CS and BBR are referred together as the PTEN hamartoma tumour syndromes (PHTS)
- BRR characteristics:
  - Macrocephaly
  - Lipomas
    - Pigmented macules on the glans penis
    - Other features of Cowden syndrome
- Intended poluposis syndrome, in addiction to CS and BRR syndrome, include
  - Colon
    - Multiple hamartomatous colonic polyps
    - Associated adenomatous tissue in 40% risk of CRC, 9%
  - Small bowel
    - Diffuse mucosal damage
    - SIBO (small intestinal bacterial overgrowth)
  - Stomach
    - ↑ risk of gastric cancer



❖ **Crohkhite – Canada Syndrome** (CCS)

- Give the clinical features which might make you suspect Cronkhite-Canada Syndrome (CCS).
  - Skin and hair changes
    - Alopecia
    - Dystrophic nails
  - Protein-losing enteropathy
  - No family history of similar condition (CCS is not inherited)
  - GI hamartomatous polyps (50%)
    - Colon
    - Small intestine
    - Stomach
  - No ↑ risk of CRC (colorectal cancer)

- Give the extracolonic manifestations of **Tuberous sclerosis**.
  - Skin
    - Angiofibromas
  - Brain
    - Epilepsy
    - Mental retardation
  - Heart
    - Cardiac rhabdomyomas
  - Bone
    - Bone cysts

- Kidney
  - Renal cysts
- Colon
  - Ganglioneuromas
  - Hamartomas

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- There are numerous types of inherited adenomatous and hamartomatous polyposis syndromes, as well as non-inherited colonic polyposis comprised of hamartomatous, hyperplastic, lymphomatous or lymphoid tissue (NLH, nodular lymphoid hyperplasia).
- One extremely rare inherited adenomatous polyposis syndrome associated with the risk of CRC is the **Bloom Syndrome**.

- Give the features of the Bloom syndrome.
  - Clinical inspection
    - Short stature
    - Red face / telangiectasia
  - Hematology
    - Leukemia
    - Lymphoma
  - Genitourinary
    - Male sterility
  - Gene mutation
    - BLM

COLORECTAL CANCER

Zoya Bahreini and Alan Thomson

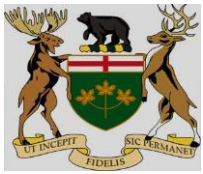
- Demography
  - The age-standardized incidence of CRC (colorectal cancer) in Canada is approximately $25/10^5$ persons per yr (27 for men, 21 for women) which means about 6% of the population will develop CRC in their lifetime.
  - Half CRCs are distal to the splenic flexus, but the proportion of right-sided tumours may be increasing.
  - Useful comparison: Approximate incidence of GI cancers (10^5/yr)

Yr of Age	<49	50-74	>75
Esophagus	<1	12	28
Stomach	<1	22	78
Colon	<1	150	400

Source: Canadian Cancer Surveillance, Health Canada

  - Lifetime risk of CRC 6%
  - Lifetime risk of dying form CRC 2.5%
  - Annual CRC mortality ↓ 33% for annual colonoscopy (2.5% → 1.6%, AR 0.8%↓)
  - Conversion rate (CR) to CRC
    - Adenoma, 30%
    - Synchronous risk 5%
    - Metachronous risk 5%

- Genetics
  - Pathways in the adenoma-CRC sequence:
    - Chromosomal instability (CIS)
    - Microsatellite instability (MIS), and
    - Epigenetic pathway
  - Hyperplastic polyps (HP) are the earliest colonic lesion in the genetic 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.
  - Epigenetic pathway, DNA methylation in the promoter region of genes leads to gene silencing, which is essentially equivalent to inactivating metastasis.
  - 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
  - Quantitative Systematic Reviews have shown that guaiac-based fecal occult blood testing (FOBT) reduce CRC mortality by ~15% on an intention-to-treat basis, and a 25% reduction when adjusted for screening attendance)



- Give examples of genetic changes associated with **sporatic** colorectal cancer (CRC).
    - There are multiple genes which are altered in at least some patients with CRC, and these gene mutations may become important at different stages in the development of CRC.
    - The gene mutations in CRC occur against a background of chromosomal instability (CIN).
    - CIN occurs in 80% of CRC
    - Candidate genes for CIN include genes responsible for
        - Mitotic spindle checkpoint
        - DNA damage checkpoint
        - Control of number of centrosomes
    - There are three important classes of these sporatic CRC-associated gene
        - ↑ proto-oncogenes (↑ activation)
        - ↓ tumour suppressor genes
        - MMR genes

❖ ↑ proto-oncogenes

- ↑ activation of proto-oncogenes
    - K-RAS
    - N-RAS
    - H-RAS
- Role in sporatic CRC
    - Activating point mutations (especially in K-RAS gene):
        - Adenomas < 1 cm 10%
          > 1 cm 58%
        - Carcinoma 47%

- Tumour suppressive genes
  - Loss of APC gene
    - Allelic losses at chromosome locations
      - 5q
      - 17p
      - 18q
  - Truncation of the APC protein
  - Loss of DCC (deleted in colon cancer)
  - Low of DPC4/SAMD4 (loss of activation of TGF-β receptors)
  - Loss of p53 tumour suppressor activity from deletion of chromosome 17p leads to loss of cells preventing damaged DNA from going from G1 to S phase of the cell cycle.
  - Loss of TP53 gene

- MMR (mismatch repair) genes (15%)
  - MSI (microsatellite instability)
    - Caused by mutations in
      - MMR genes
      - Epigenetic silencing mechanism
  - Alterations in hMLH, hPMS1, hPMS2, hMSH2, hMSH3, hMSH6
  - ↓ repair of mismatches in base pairs → MSI → DNA replication errors → tandem repeat DNA sequences
  - Seen in only 15% of sporatic CRC

❖ Non-MMR gene changes

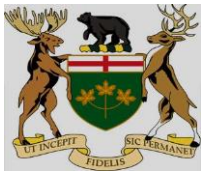
- CIMP (CPG island methylator phenotype)
  - Epigenetics is "…change in the genome that result in change expression or phenotype without a change in the sequence of DNA" (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, page 2212).
  - Hypermethylation of the hMLA, promotor, with inactivation of hMLH1.
  - Seen in 70% of sporatic MSI tumours.
  - Common pathway for the development of serrated adenomas.

❖ Other important gene mutations include

- RAS/RAF/MAPK pathway, with mutation in BRAF gene
- Expression pattern of micro RNAs

- Give examples of genetic changes associated with inherited CRC.
  - Familial Adenomatous Polyposis (FAP)
    - FAP – autosomal dominant inheritance of expression of gene changes
    - Only 80% penetrance of ARC gene – large protein, B-catenin pathway is important 2 hit hypothesis for FAP
    - Eye "CHRPE" congenital hypertrophy of the retinol pigment epithelium

- Attenuated FAP (AFAP)
- MUTYH-associated polyps (aka MYH-associated polyposis)
  - Suspect if patient has > 10 adenomatous polys
  - Germline mutation in MYH base excision repair gene
  - Occurs in APC region
  - 25% of AFAP with > 15 adenomas have MUTYH mutations
  - May be associated with breast cancer
  - Parents, siblings rarely affected
  - Recessive inheritance
- HNPCC
  - CRC in 50% - 80%
    - DNA mismatch
  - Younger age when CRC develops
  - Proximal colon
  - Glioblastoma (meduloblastomas in FAP)
  - Clinical criteria to suspect HNPCC
  - In family - Amsterdam criteria I, II
  - In individual - Bethesda
  - MSI-histology
    - Lymphocytes infiltrating tumour
    - Crohn-like lymphocytic reaction
    - Mucinous/signet ring appearance
    - Medullary growth pattern
  - MSI-Genetics
    - Test tumour for MSI (microsatellite instability) analysis, or IHC (immunohistochemistry) 90% of HNPCC tumours are positive



- Test patient for same gene abnormality as for the index patient (proband)
- Carrier with mutations need to be screened by colonoscopy

➢ Environmental risk factors

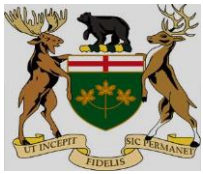
- Numerous environmental factors have been suggested to be associated with the development of adenomas, or their progression of CRC.
- Despite contrary popular views, dietary fibre supplementation, or the intake of antioxidants have failed to be beneficial when studied in properly designed prospective studies.

- Give factors for which there is adequate and appropriate human data to suggest a beneficial effect on reducing adenomas or CRC.

- Calcium
  - 5% ↓ recurrence of adenomas over 3 yr, with the small protective effect lasting for up to 5 yr after the calcium was stopped.
- NSAIDs/ ASA/ Coxibs
  - ASA
    - Relative risk among users, 0.68
    - ↓ adenoma, ~25%
    - ↓ advanced adenoma, ~ 40%
  - Sulindac
    - FAP
      - ↓ number of polyps by ~75% at 1 yr
      - ↓ diameter 35%

- Coxibs
  - FAP
    - ~30%
    - ↓ number in 3 yr of
      - New adenomas ~40%
      - Advanced adenomas ~60%
- DFMD (ornithrine decarboxylate inhibitor difluomethyornithine) plus sulindac
  - 70% ↓ new adenomas at 3 yrs
- Statins ~50% ↓ relative risk for CRC

- Streptococcus Bovis
  - Strep. Bovis bacteremia - gram positive cocci, Biotype I
  - Found in blood in 10% - 15% of normal persons, especially older males
  - When endocarditis occurs with S. bovis, there is usually no typical pre-existing conditions (e.g., artificial valves, IV drug use)
  - S. bovis – in fecal cultures
    - CRC 56% (control ~10%)
  - Scientific plausibility
    - CRC epithelial cells have receptors for S. bovis
  - S. bovis upregulates COX-2
    - Carcinogenic in rats
  - Recommendation and suggestion (R&S)
    - Colonoscopy for person with S. bovis in the blood (not if S. bovis is in stool)
    - Think of this issue as finding a source of the S. bovis bacteremia



- Give the **pharmacological** or nutritional agents which have been shown possibly to be effective chemoprevention to reduce the risk of development or redevelopment of colorectal adenomas/CRCs.
    - Drugs
        - ASA
        - NSAIDs +/- DFMD
        - Coxibs
        - 5-ASA in IBD
        - Hormone replacement therapy (HRT) in post menopausal women
        - Statins
    - 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 fibre
    - Exercise
    - Don’t forget – Stop smoking

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drug; DFMD, difluoromethylornithine

- Diagnostic imaging
  - The TNM staging system for colorectal cancer and published survival rates for different stages.

T – Primary tumour (T)

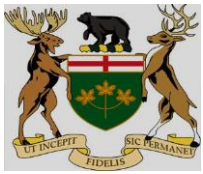
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into subserosa or into non-peritonealised pericolic 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-yr 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%

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➢ Treatment

- Adjuvant or Neoadjuvant Chemotherapy and/or Radiotherapy
  - Benefit
    - Stage III MR 33%
    - Colon Ca recurrence 42% ↓
  - Use
    - T3/4 rectal cancer (locally advanced)
    - After resection of liver/lung metastases
  - Before curative surgery – Neoadjuvant
  - After curative surgery – Adjuvant
  - The limitation to radiotherapy is its toxicity, but enhances of radiation therapy (e.g., capecitabine) may ↑ benefit without an ↑ toxicity
  - Studies also examining possible benefit of infusion of 5-FU, leucovorin plus oxaliplatin (combination called FOLFOX).

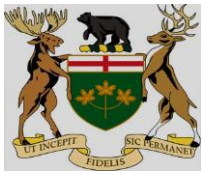
- Adjuvant therapy within 8 wks of resection for CRC
  - ↓ recurrence
  - ↑ survival
- 5-FU (5-fluorouracil) plus levamisole (levamisole increases tumour response rates from 12% for 5-FU to 23% for 5-FU + levamisole

Relative	Risk Reduction
– CRC	Overall
– Recurrence	Mortality

- Dukes C / Stage III 42%
  33%
  - 5-FU plus leucovorin > 5-FU plus levamisole in efficacy after curative surgery for CRC
  - 5-FU plus leucovorin plus oxaliplatin in Stage III
    - ↑ 3 yr disease-free survival
    - May also be small benefit in Stage II
  - For rectal CRC Duke B2 / Stage II (transmural extension) or Duke C / Stage III (positive lymph nodes)

5-yr Rates	Radiation	Radiation plus Chemotherapy
No recurrence	35	60
Survival	40	50

Adjuvant or neoadjuvant chemotherapy for Stage II or III resected CRC is often given as 5-FU plus leucovorin.



- Give the mechanism of action of 5-FU and leucovorin.
  - 5-FU – Binds to thymidylate synthetase → ↓ methylation of deoxyuridylic acid to thymidylic acid → ↓ DNA synthesis
  - Leucovorin – ↑ binding of 5-FU to thymidylate synthetase, thereby ↓ DNA synthesis (please see above)
- Surgery
  - Recommended: Total mesenteric excision for CRC
  - Surgical resection for liver metastases
    - 10% to 25% at presentation
    - Resection
      - < 5 metastases in liver
      - No extrahepatic metastases
      - No extensive liver involvement (< 70%)
  - Non-operable, metastatic CRC
    - Chemotherapy
    - Photoabalation
    - Stents, colorectal
- Give 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 (from stent placement)	1

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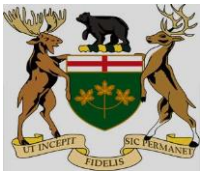
- Post-polypectomy colonoscopic surveillance
  - Risk of postoperative relapse of CRC
    - Stage II, 20% to 30%
    - Stage III, 50% to 80%
  - Surveillance must be continued.
  - Prior to resection for CRC, perform staging diagnostic imaging so that IOUS (intraoperative ultrasonography) does not need to be performed.

- Screening and surveillance
  - Miss rate of CRC on colonoscopy, 10%

- Use of EUS of rectum in CRC
  - Sessile polyp
  - Determine resectability of rectal CRC (surgeon needs 5 mm tumour-free margin)

- Post-surgical colonoscopic follow-up
  - Colonoscopy 0→1→3→5 yr
  - CT yrly for 3 yr follow-up 0→1→3→5 yr
  - CEA q 3 months for 3 yr
  - Adjuvant chemotherapy with 5-FU can ↑ serum CEA (false elevation of CEA)
  - “in patients whose tumour [CRC] recurs after hepatic resection, the liver is the initial site of recurrence in about 35% (Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2232; and about 75% of hepatic metastases appear within 2 yr after primary resection, 10th Edition, 2016, 2289).



- Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 yr.
  - 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 yr.
  - 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 yr
- 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 yr.

➢ Prognosis

The original Dukes staging system for CRC has been modified at least 6 times over the past 80 yr (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 123.9, page 2214), and has been largely replaced by the AJCC (American Joint Committee on Cancer), TNM (tumour-node-metastasis) staging of colorectal cancer (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Table 127-6, page 2272).

- Generally speaking, CRC of the left (distal) colon have a better prognosis than these of the right (proximal) colon, and CRC of the colon has a better prognosis than the rectum.

- Give the appropriate 5 yr survival rates for CRC base on the Duke Stage.

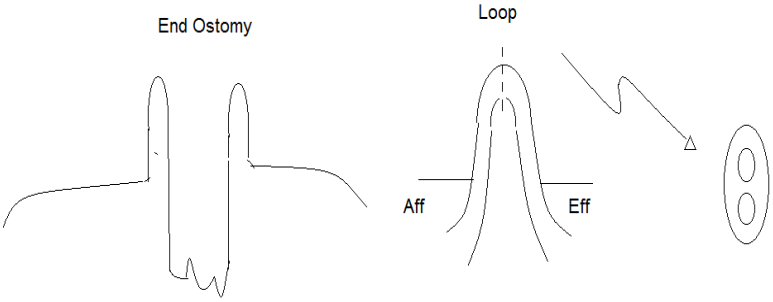
Dukes Stage		Approximate 5 yr Survival Rate
A	Limited to mucosa	
B1	Into muscularis propria (MP)	80
B2	Through MP	60
C	Regional node metastasis	40
C1	B1 plus regional node metastasis	
C2	B2 plus regional node metastasis	
C	1 to 3 nodes (N1)	50
	≥ 4 nodes (N2)	25
D	Distant metastases	0

Ostomies

- Definition
  - An ostomy is a hernia, a “protrusion of abdominal contents through a muscular defect”
- Indications
  - Acute inflammation, not safe for anastomosis
  - Protect an anastomosis downstream (prevent dehiscence; temporary diversion of fecal stream, giving distal anastomosis a chance to heal)
- Types

	Ileostomy	Colostomy
Protrusion	Yes	No
Size	Smaller	Larger
Smell	-	+++
Hernia	+	+++

Stroma, 2 openings – loop ostomy



- Placement site
  - Away from scars, umbilicus
  - Obesity
    - Away from “trough” of skin folds, and can be seen by patients to clean/change (mark prop)

➢ To fix ostomy hernia
- Move site of ostomy (recurrence rate of hernia is high, so move site)
- Repeated obstruction – big bulge

• Stomal output
- Ileostomy
  - 1-2 L/day (decreases over time)
- Colonostomy
  - Sigmoid, 200-250 mL/day
  - R. (right) colon, R. transverse- 0.5-1 L/day

➢ Types of ostomies
- Rectum vs anus
  - Ileorectal anastamosis – above the pelvic floor
  - Ileoanal anastamosis – below the pelvic floor
- Digital rectal examination (DRE) findings
  - Skin tag
  - Squamous cell tumour
  - Condyloma
  - Pseudopolyp (in lower rectum)

CANCER SCREENING IN PERSONS WITH A FAMILY HISTORY: GUIDELINE

Samuel Asfaha

Colorectal Cancer (CRC)

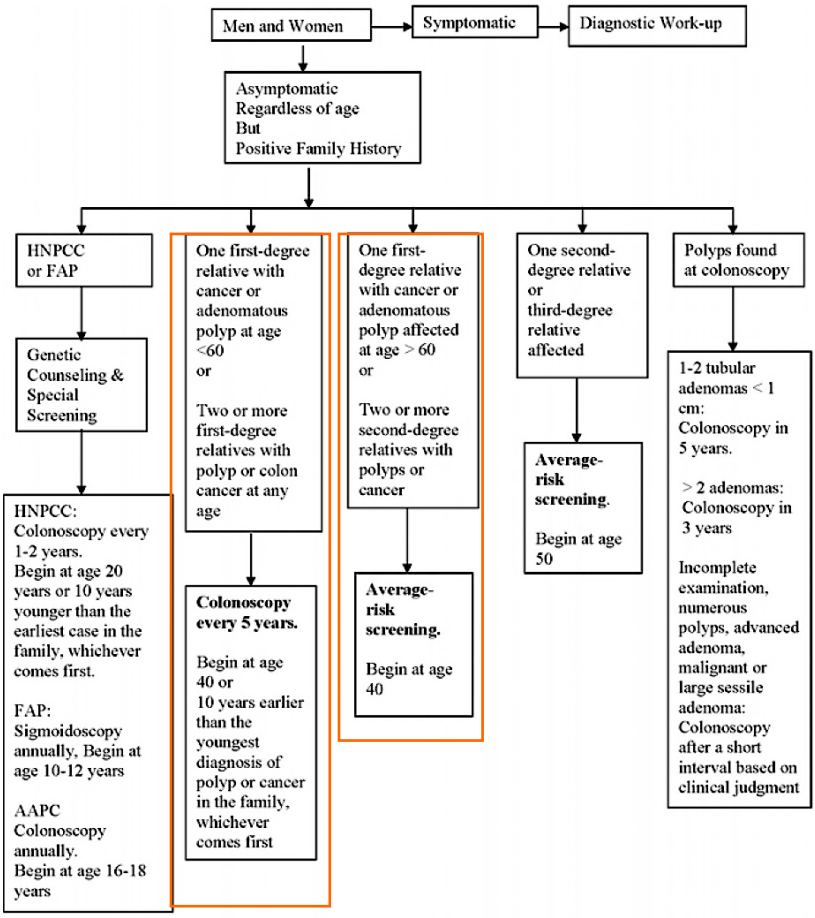
- Demography
  - Sporadic ~70%
  - Familial 25%
  - Genetic 5%
    - Polyposis
    - Non-polyposis
  - of CRC is CRC

Should screening begin at age 40 or 50 if you have a family history of CRC in a FDR?

CPG Recommendations

Organization	Family History	Recommendation
○ National Comprehensive Cancer Network (NCCN)	– 1 FDR with CRC at < 60 y or; ≥ 2 FDR with CRC at any age – 1 FDR with CRC at ≥ 60 yr – 1 SDR at < 50 yr – 1 FDR with advanced adenoma	▪ Start colonoscopy at 40 yr or 10 yr before earliest CRC (whichever is earlier); repeat q 5 yr ▪ Start colonoscopy at 50 yr or 10 yr before earliest CRC; repeat q 5-10 yr ▪ Start colonoscopy at 50 yr, repeat q 5-10 yr ▪ Start colonoscopy at 50 yr or at the age of adenoma (whicheveris earlier); repeat q 5-10 yr
○ Multisociety Task Force on CRC (AGA, ACS, and ACR, ASGE, etc)	– 1 FDR with CRC or adenoma at < 60 yr or ≥ 2 FDRs at any age – 1 FDR with CRC or denoma at ≥ 60 yr or ≥ 2 FDR at any age	▪ Start colonoscopy at 40 yr or 10 yr before earliest CRC (whichever is earlier); repeat every 5 yr ▪ Start screen at 40 yr (any modality); repeat as average risk
○ American College of Gastro-enterology (ACG)	– 1 FDR with CRC or advanced adenoma at < 60 yr or ≥ 2 FDRs with CRC or advanced adenoma – FDR with CRC or advanced adenoma at ≥ 60 yr	▪ Start colonoscopy at 40 yr or 10 yr before earliest CRC; repeat q 5 yr ▪ Start colonoscopy at 50 yr; repeat q 10 yr

Canadian CRC Guidelines



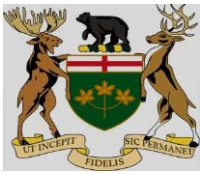
Source: Leddin D, et al. Can J Gastroenterol 2004; 18(2): 93-9.

- First degree relatives (1 FDR) with CRC / advanced adenoma
  - Screening
    - Begin CRC screening at age 40-50, or 10 yr younger than age of diagnosis of FDR
  - Surveillant
    - 5-10 yr screening intervals
    - Colonoscopy
    - If screening with FIT
      - 1-2 yr intervals
    - FIT second-line screening option
  - FDR
    - Important to document presence of advanced adenoma in a FDR with endoscopy or histology
  - Previous guidelines were based on risk of CRC in a 40 yr patient with a positive family history of CRC was equal to risk of CRC in a 50 yr old
    - This study may have overestimated risk due to inclusion of patients with unidentified hereditary CRC

- ≥ 2 FDRs with CRC / advanced adenoma
  - Screening
    - Colonoscopy in persons with ≥ 2 FDRs with CRC / advanced adenoma (recommended in individuals with 2 first-degree relatives [FDRs])
    - FIT is an alternative
    - Begin at age 40–50 yr or 10 yr younger than the age of FDR (whichever comes earlier)
  - Surveillance q 5 yr

- ❖ ≥ 1 SDR with CRC or advanced adenoma
  - Screening
    - ≥ 1 SDR
      - Non-advanced adenoma / polyp of unknown histology
      - Screened according to average risk guidelines
      - Commence screening at age 50 y

- ➢ Global Recommendations
  - Based on moderate-quality evidence, strongly recommend screening over no screening for all individuals with an FH of CRC or documented adenoma
  - Despite very-low quality evidence, colonoscopy recommended when 2 or more FDRs with CRC, because of the high-risk of life-threatening negative consequences of missed lesions



Summary of Recommendations for Screening for Colorectal Cancer in Individuals with a Family History According to Decreasing Level of Elevated Risk of Colorectal Cancer

	FH according to decreasing level of elevated risk of CRC →				
	High risk				Low risk
	2 or more FDRs with CRC	1 FDR with CRC	1 or more FDR with documented advanced adenoma	1 or more SDR with CRC	1 or more FDR with any non-advanced adenoma
○ Screening over no scoring	Yes	Yes	Yes	According to average-risk guidelines	According to average-risk guidelines
○ Preferred test	Colonoscopy	Colonoscopy	No recommendation for a preferred		
○ Age	40 yr or 10 yr younger than age of diagnosed FDR, whichever is earlier*	40-50 yr or 10 yr younger than age of diagnosis of FDR, whichever is ealier*	40-50 yr or 10 yr younger than age of diagnosis of earliest diagnosed FDR, whichever is earlier*	50 yr	
○ Interval	Colonoscopy: 5 yr	Colonoscopy: 5-10 yr FIT: 1-2 yr	Colonoscopy: 5-10 yr FIT: 1-2 yr	According to average-risk guidelines	

*The age of affected relative should be considered when making clinical decisions regarding screening

LIVER

CHANGING CONCEPTS OF COAGULOPATHY IN CIRRHOSIS

Zoya Bahreini

Cirrhosis: the epitome of the hemorrhagic coagulopathies

- Paradigm shift
  - PT prolongation NOT a good predictor of bleeding!
  - Hypothesis
    - Shortening of PT with FFP or PCC decreases the risk of bleeding in cirrhosis when PT values exceeded the upper limit of normal (ULN)
  - Studies
    - 30 patients with chronic liver disease undergoing biopsy
    - Effect of FFP, PCC or their combination on abnormal coagulation tests
    - PCC in combination with FFP normalized coagulation tests (PT, NT, KPTT)
    - PCC and FFP to be used to allow for liver biopsy to be performed safely in patients with severe coagulation defects

"Correction of abnormal coagulation in chronic liver disease by combined use of fresh-frozen plasma and prothrombin complex concentrates."

Mannucci PM, et al. Lancet 1976; 2: 542–5.

  - Conclusion
    - Indices of coagulation in the peripheral blood used in this study are unreliable guides of the risk of bleeding after liver biopsy and, hence, are of limited value in determining contraindications to this procedure.

- Additional support
  - 9212 liver biopsies
  - Identified risk factors for major bleeding
  - The only predictable risk factors for major bleeding were
    - Malignancy, age and number of passes to obtain liver biopsy
- Peripheral indices of coagulopathy NOT identified as risk factors

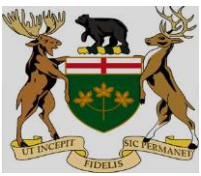
McGill DB, et al. Gastroenterology 1990; 99:1396–400.

- Conclusion
  - PT prolongation NOT a good predictor of bleeding!

PT prolongation NOT a good predictor of bleeding!

- "Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review" (Segal JB and Dzik WH. Transfusion 2005; 45: 1413–25).
  - Literature review of 1 trial and 24 observational studies
  - Bleeding rates in bronchoscopy, central vein cannulation, arteriography and liver biopsies
  - Insufficient evidence to conclude that abnormal test results predict bleeding
  - Similarly, skin bleeding time-index of a defective role of platelets in primary hemostasis- was found NOT to be a predictor of bleeding in cirrhosis

Mannucci PM, et al. Lancet 1976; 2: 542–5;
Boberg KM, et al. Thromb Haemost 1999; 81: 378–81.



- Explanation: Shifting the old paradigm
  - Prolongation of PT and INR not useful for coagulopathies of cirrhosis:
    - ↓ liver synthesis
    - ↓ procoagulant factors
    - Parallel ↓ synthesis of anticoagulant proteins (antithrombin, protein C, protein S)
    - Concept: Chronic liver disease causes an abnormal balance between the pro- and the anti-coagulant proteins.
  - New challenge: What peripheral blood test reflects the anticoagulation status of the patient with chronic liver failure?

Thrombin Generation Assay (TGA)

- Thrombin is a fundamental part of the clotting cascade
- Ability to generate thrombin correlates with risk of bleeding or thrombosis
- Degree of thrombin formation is influenced by both procoagulants and anticoagulants
- The newly developed Thrombin- Generation Assay may be a more suitable tool to assess coagulopathy
- Using TGA, plasma from patient with cirrhosis generated as much thrombin as those of healthy subjects!
- The ↓ procoagulant factors in patients with cirrhosis is compensated for by the ↓ anticoagulant factors → coagulation is “rebalanced” to normal due to concomitant deficiency of both coagulation drivers in cirrhosis

“Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests” (Tripodi A, et al. Hepatology 2005; 41: 553–8).

Back to platelets

- Platelets stick to site of vessel injury and aggregate to make thrombus
- Adhesion and aggregation of platelets dependent on von Willebrand factor (VWF)

- ↑↑↑ VWF in patients with cirrhosis
- ↑ adhesion of platelets to collagen surface
  → ↑↑↑ levels of VWF in cirrhosis
  → Induction of primary hemostasis
  → Compensate for thrombocytopenia of cirrhosis

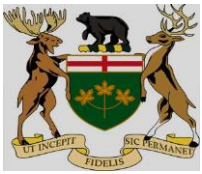
"Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity." (Lisman T, et al. Hepatology 2006; 44(1): 53-61)

- Cirrhosis is NOT an "auto-anticoagulated" state
- Cirrhosis is a procoagulant/thrombophilic condition
  - ↓ protein C and S
  - ↓ anti-thrombin levels
  - ↓ plasminogen
  - ↑↑↑ vWF/Factor VIII

  } ↑ thrombotic risk in cirrhosis

- Cirrhotic portal hypertension → ↓ flow in PV/DVL (edema) → ↑ thrombotic risk of all cirrhosis
- Portal Vein thrombosis seen in 10-20% of cirrhotics
  - Lower risk in Child's A, high risk in Child's B/C
- DVT/PE occurs in 5% of hospitalized patients with cirrhosis

Abbreviations: DVL, deep vein of the legs; PV, portal vein



- Question: IF there is ↑ risk of thrombosis in chronic liver disease, why is there also ↑ risk of bleeding?
  - Answer
    - Although hemostasis in cirrhosis is rebalanced, because of the relative deficit of procoagulants, anticoagulants, and platelets, it is not as stable as in healthy subjects and may therefore tip toward bleeding or thrombosis, depending on the prevailing circumstantial risk factors.

	Platelet-vessel wall interaction	Thrombin generation	Fibrin dissolution
– Pro-hemostatic drive	↑ VWF ↓ ADAMTD-13		↑ PAI ↓ plasminogen
– Anti-hemostatic drivers	↓ platelets	↓ XI, IX, X, VII, II, V, I	↑ tPA ↓ TAFI, anti-plasmin

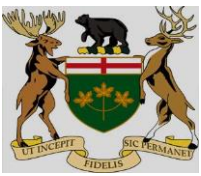
- Testing for coagulopathy
  - PT/INR-role in prognostication (severity of associated liver disease)
  - TGA-In vitro, research use
  - Thromboelastography (TEG)-measures viscoelastic properties of clotting blood

Thromboelastography (TEG)

- Mainly used in liver transplantation and cardiac surgeries to guide transfusion strategies
- Point of care test (30 min to complete)
- Does not necessarily correlate with PT/INR/ Platelet count (poor predictors of bleeding)

- Note
  - Pin remains motionless until clotting begins
  - The amplitude of the pin motion increases as the clot grows stronger, and the maximum valve for the clot strength is obtain
  - Amplitude decreases as fibrinolysis begins and the pin begins to slip
- R-reaction time
  - Time to initial fibrin formation
  - Reflects coagulation factor activity
- K-kinetics
  - Time to clot strength of 20mm (a angle-speed of clot formation)
  - Reflects level of fibrinogen activity
- MA-max amplitude
  - Strength of fibrin clot
  - Reflects level of platelets activity
- LY30
  - Amplitude at 30 min
  - Reflects degree of fibrinolysis

- Give factors which contribute to the **coagulation disorders** in cirrhosis.
  - ↓ synthesis of procoagulant factors
    - Vitamin K-dependent factors II, VII, IX, X
    - Factor V
    - Factor XI
  - Thrombocytopenia in cirrhosis
    - Hypersplenism
    - ↓ hepatic synthesis of thrombopoietin
    - Bone marrow toxicity
      - HCV infection
      - Alcohol
    - ↓ thrombin produced by platelets



- Dysfibrogenemia
  - Altered production of fibrolysis activators/inhibitors
  - Endotoximemia-associated activation of coagulation cascade
  - ↓ clearance of fibrinolytic proteins
  - ↑ D-dimer
  - ↑ fibrinogen degradation products
  - ↑ clot lysis time

Laboratory Alert

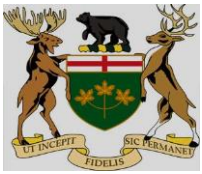
- An ↑ INR in the patient with cirrhosis, indicates ↓ hepatocyte function.
- In cirrhosis, the increase in INR predicts a bad prognosis, but the risk of spontaneous bleeding is not increased by ↑ INR.
- Because of the "coagulation imbalance" of pro- and anti-coagulation in factors, with the balance in favour of procoagulants persons with cirrhosis, they may need to be given anti-coagulation, such as in the perioperative period, or soon after a clinical significant DVT, PE, PVT, SVT

Abbreviations: DVT, deep vein thrombosis; HVT, hepatic vein thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis; SVT, splenic vein thrombosis

- Coagulation in chronic liver disease is a complex, balanced process
- PT/INR are not useful tests for measuring bleeding risk in these patients
- Correcting PT with FFP does not translate into clinically decreased risk of bleeding
- Increased risk of thrombosis exists even in the setting of apparent coagulopathy
- More information is needed about use clotting tests in cirrhosis

HEPATIC DISORDERS OF PREGNANCY

Mandark Gandhi



Hyperemesis Gravidarum

- Demography
  - Hyperemesis Gravidarum - 2% of pregnacies
    - Severe persistent vomiting
  - 4-5 wks gestational age (GA)
  - Improves by 14-16 wks
    - 20% persistence until delivery
- Causes/associations
  - Mother
    - Personal / family history
    - Multiple gestation
    - Gestational trophoblastic disease
    - Maternal H. pylori infection
  - Fetus
    - Female fetus
    - Fetal trisomy 21
    - Hydrops fetalis
- Clinical
  - Nausea – 60-70%
  - Vomiting - 40%
  - Ketouria + 5% decrease from pre-pregnancy weight
  - Fluid, electrolyte and acid-base disturbances
  - Nutrition deficiencies
  - Pyrosis
  - Hematemesis
  - Hypersalivation

- Pathophysiology
  - Hormonal changes
    - HCG
    - Estrogen
    - Thyroid
  - ↓ GI dysmotility
    - Estrogen may slow gastric transit time
  - H. pylori infection
    - Improvement after eradication
  - Psychosocial factors
  - Genetic predisposition
    - Familial clusters

- Laboratory
  - Hypokalemia
  - Hyponatremia
  - Ketouria
  - ↑ Aminotransferases/bilirubin
  - Hyperamylasemia
    - Triggered by excessive salivary gland production in response to vomiting

- Treatment
  - Eat multiple small meals
  - Avoid empty stomach
  - Avoid offensive odours
  - Anti-emetic and antireflux medications
    - Prochlorperazine, metoclopramide, pyridozine
    - Ondansetron if refractory
  - Intravenous fluids

Cholestasis of Pregnancy

- Demography
  - Incidence <1% - 27% of pregnancies
  - 3rd Trimester, rarely earlier
  - May be associated with HCV

- Clinical

- Mother
  - Pruritus
    - Worst in palms and soles
    - Most intense at night
  - Jaundice
    - 10-25%
  - Steatorrhea
    - Fat soluble vitamin deficiencies
  - Waxing and waning course
  - Complications
    - Gallstones
    - Cholecystitis
    - Pancreatitis

- Fetus
  - ↑ Fetal distress
  - Unexplained still birth

- Pathophysiology
  - Poorly understood
  - Genetics
    - Familial clustering
    - MDR3 gene mutations
  - Environmental factors
    - Geographic variation,
      - Low selenium and Vitamin D
  - Estrogen/progesterone, oral contraceptive pill
- Laboratory
  - ↑ Bile acid (>10umol/L confirms cholestasis)
  - Hyperbilirubinemia (mild)
  - ↑ ALP (mild), GGT normal or mild elevation
  - Rarely elevation in transaminases >1000
- Diagnostic imaging
  - Abdominal ultrasound – usually normal
- Histopathology
  - Liver biopsy is not usually needed, but if performed would show
    - Cholestasis without inflammation
    - Bile plugs in hepatocytes and canaliculi
      - Predominate in zone 3
    - Portal tracts unaffected

- Treatment (ACG Clinical Guidelines: Liver disease and pregnancy, 2016)
  - Delivery at 37 wks
    - To prevent ↑ risk of fetal complications. (strong recommendation, very low level evidence)
    - Need for premature delivery
  - Ursodeoxycholic acid (URSA; 10-15mg/kg)
    - Symptomatic improvement. (strong recommendation, moderate level of evidence)
  - Delivery improves symptoms and blood work
  - 60%-70% recurrence
    - OCP or pregnancies

Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP) **Syndrome**

- Demography
  - 12% of women with severe pre-eclampsia
    - 0.2-0.8% total pregnancies
- Pathophysiology
  - Unknown evidence in some populations for genetic component
- Types
  - Two major classifications systems
  - **Tennessee Classification**
    - MAHA with abnormal smear, ↓ haptoglobin, ↑ LDH
    - LDH >600 IU or 2xULN, and
      - AST >70 or 2 x ULN or bilirubin >1.2 mg/dL
    - Platelet count <100

- Incomplete HELLP syndrome = presence of only 1 or 2 of these abnormalities (may be less severe)

- **Mississippi Triple Class Classification**
  - Class I
    - Platelet nadir <= 50
  - Class II
    - Platelet nadir 50-100
  - Class II
    - Platelet nadir 100-150

- Clinical
  - Hypertension
  - Pain
    - Chest, epigastric, RUQ
  - Nausea/vomiting
  - Headache
  - Blurred vision
    - May be asymptomatic

- Laboratory
  - Blood work
    - Hemolysis, ↑ aminotransferase

- Diagnostic imaging
  - Abdominal ultrasound/CT
    - Indication
      - Severe abdominal pain or sudden ↓ BP
    - Findings
      - Hemorrhage

- Histopathology
  - Rarely needed for diagnosis
    - May cause parenchymal hemorrhage
  - If liver biopsy performed, then would show
    - Periportal hemorrhage
    - Intrasinusoidal fibrin deposition
    - Irregular areas of liver cell necrosis with mild reactive hepatitis

- Treatment (ACG Clinical Guidelines: Liver disease and pregnancy, 2016; SOGC, 2014)
  - Prompt delivery, especially after 34 wks (strong recommendation, very low-level evidence)
  - Consider transfusing to platelets 40-50 especially if c-section (conditional recommendation, very low level of evidence)
  - High risk of preeclamsia
    - Personal/family history preeclampsia
      - Chronic medical disease
      - Abnormal uterine artery Doppler before 24 wks GA
  - Low dose ASA 81 mg/d+ calcium (at least 1 g/d)
    - Women with low calcium intake in women and at high risk of preeclampsia (I-A)
  - ASA dose 75-162 mg/d (III-B) qHS (I-B)
    - Initiated after pregnancy diagnosed but before GA 16 wk (I-B)
    - Considered for continuation until delivery (I-C)

- Prophylactic doses of LMWH for those with previous placental complications (including preeclampsia)
  - ↓ recurrence of severe or early onset preeclampsia
  - ↓ preterm delivery and/or infants that are small for GA (I-B)

Acute Fatty Liver Disease of Pregnancy

- Demography
  - Presents late in pregnancy
    - Generally 34-37 wks GA
    - Could be as early as 19 wks
  - 1/6700 pregnancies
- Clinical
  - Nausea/vomitting
  - Abdominal pain
- Pathophysiology
  - Poorly understood
  - Association with inherited defects abnormal beta oxidation of fatty acids
- Diagnosis (Swansea Criteria)

  >=6 criteria
  - Clinical
    - Abdominal pain
    - Ascites or bright liver on hepatic US
    - Encephalopathy
    - Vomiting
    - Polydipsia/polyuria

- Laboratory
  - Leukocytosis >11
  - Coagulopathy (PT>14s or aPTT >34s)
  - Ammonia >47 umol/L
  - AST or ALT > 42 IU/L
  - Urate >340 umol/L
  - Hypoglycemia <4 mmol/L
  - Renal impairment Cr>150 umol/L
- Histopathology
  - Microvesicular steatosis on liver bx
- Non-Swansea features
  - Preeclampsia - 21-67% of cases
  - Malaise, anorexia

➢ Treatment (ACG Clinical Guidelines: Liver disease and pregnancy, 2016)

- Deliver promptly, expectant management is **not** appropriate (strong recommendation, very low level evidence)
- Women and children should have molecular testing for long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD; conditional recommendarion, moderate level of evidence)
- Offspring of mothers should be monitored carefully for manifestations of deficiency of long-chain 3-hydroxylacyl-CoA dehydrogenase including
  - Hypoketotic hypoglycemia and
  - Fatty liver (conditional recommendation, very low level of evidence)

- Prognosis
  - Mother
    - Survival in almost all cases with prompt diagnosis + delivery
    - Recurrence particularly in those with long chain 3-hydroxylacyl coenzyme A dehydrogenase deficiency
  - Fetus
    - Perinatal mortality rates < 7%

Viral Hepatitis During Pregnancy

- Hepatitis B
  - Mothers
    - May flare hepatitis post-partum
    - Not treated with interferon during pregnancy
  - Vertical transmission during delivery
    - 90% infants from mothers (E Ag +ve) -> chronic infection
    - 10% infants from mothers (E Ag –ve) -> chronic infection
  - Infants
    - Hep B immunoglobulin at birth
    - Hep B vaccine - first day of life, age 1 & 6 months
    - 1% treated infants -> chronic infection
  - Treatment (ACG Clinical Guidelines: Liver disease and pregnancy, 2016)
    - Active-passive immunoprophylaxis with to all infants born to HBV infected mothers (strong recommendation, low level evidence)
      - Hep B immunoglobulin + vaccine

- Women with HBV infection and high viral load (>10^6 log coppies/mL, 200,000 IU/mL) should be offered tenofovir or telbivudine in third trimester to ↓ perinatal transmission (strong recommendation, low level evidence)
- Avoid Elective C-Sections (Strong recommendation, very low level evidence)
- Women with chronic HBV infection
  - Encourage to breastfeed (strong recommendation, very low level evidence)

❖ Hepatitis C

- 1-2% women aged 20-39
- May be associated with
  - Gestational diabetes mellitus
  - Preterm delivery
  - Low birth weight
  - Cholestasis of pregnancy
- Vertical transmission uncommon
  - Unless maternal HCV RNA titres > 10^6 copies/mL (36% transmission)
  - HIV patients at risk
- Breastfeeding not a RF for transmission (eventhough HCV can be present in breast milk)
- Treatment (ACG Clinical Guidelines: Liver disease and pregnancy, 2016)
  - Invasive procedures (amniocentesis, invasive fetal monitoring) should be minimized to prevent vertical transmission (strong recommendation, very low-level evidence)
  - Avoid elective C-Section (strong recommendation, very low-level evidence)

- HCV therapy should not be offered to pregnant women either for treatment or to decrease vertical transmission (strong recommendation)

❖ Hepatitis E

- Virus
  - RNA virus, transmitted enterically
  - Vertical transmission from mother to fetus
- Source
  - Farmers – swine, chicken, cattle, sheep, & rats
  - Undercooked meat
- Clinical
  - Mother
    - Cause of fulminant hepatic failure (20% mortality)
  - Fetus
    - Intrauterine fetal death
- Prevention
  - Avoid endemic areas when pregnant

Suggested Reading

Tran T, et al. ACG clinical guideline: Liver disease and pregnancy. Am J Gastroenterol 2016; 111(2): 176 – 194.

Feldman M., Friedman L, and Brandt, L. Sleisenger and Fordtran's gastrointestinal and liver disease, Elsevier, Philadelphia; 2010: 650-63.

Lee R and Tran T. Approach to liver disease occurring during pregnancy. UptoDate 2017.

Lindor K and Lee R. Intrahepatic cholestasis of pregnancy. UptoDate 2017.

Lee R and Tram T. Acute fatty liver of pregnancy. UptoDate 2017.

HEPATITIS B VIRUS

Anouar Teriaky

- Demography
  - ~ 2 billion people worldwide have past or present infection with HBV
  - Worldwide there are about 250-400 million individuals who are chronic HBV carriers
  - Global prevalence of chronic HBV is 3.6% with
    - highest endemicity in Africa and Asia
  - Nearly 800,000 people die from HBV related complications each yr

Source: Ott et al. Vaccine 2012; 30: 2212-9; and Schweitzer et al. Lancet 2015; 386: 1546-55.

- 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 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

Please see: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Box 79-1page 1313.

- HBV progression

Acute HBV → chronic HBV:

- Neonate 90 asymptomatic enteric disease
- Children 50
- Adults 10 usually symptomatic, unless healthy carriers

Source: *Clin Liver Disease* 10; 14: 75-91; *Hepatology* 07; 45:1056-75

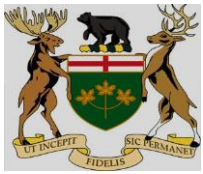
- Spontaneous HBeAg seroconversion, ~10%
- 5-yr cumulation risk of progression of HBeAg – positive chronic hepatitis B to cirrhosis, ~10%
- HBV-associated compensated cirrhosis progressing to decompensation, 16%
- 5-yr cumulative risk of developing HCC, 14%

➢ Modes of transmission

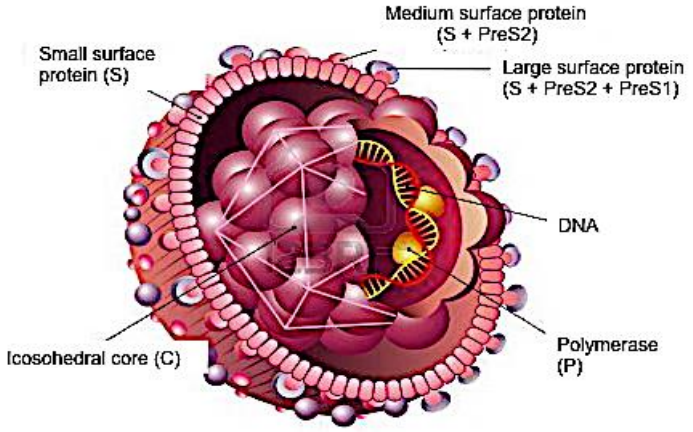
Transmission

- Perinatal
- Sexual
- Parenteral
  - Transfusion
  - Transplantation
- Percutaneous Inoculation
  - Injection Drug Users
  - Tattoos
  - Body Piercing
- Other
  - Nosocomial
  - Household articles
  - Skin and Mucous Membrane Breaks

Source: Sundaram et al. BMJ 2015; 351: h4263.



- Virology



Source: https://drug-dev.com/therapeutic-focus-applying-the-hiv-treatment-model-to-hepatitis-b-can-a-cocktail-provide-a-cure/

  - Genotype

Genotype	Geographic Distribution
A	Northwestern Europe, North America, Central Africa
B	Southeast Asia Including China, Japan and Taiwan
C	Southeast Asia
D	Southern Europe, Middle East, India
E	West Africa
F	Central and South America, American Natives, Polynesia
G	USA and France
H	Central and South America

Source: Boyer TD, et al. Zakim and Boyer's Hepatology: A Textbook of Liver Disease. 5th edition. Philadelphia: Saunders; 2006; Chapter 31: Hepatitis B.

➢ Pathogenesis

- Give the mode of transmission and the approximate lifetime risk of HBV infection in persons who reside in different geographical areas.

Geographical Area	Lifetime Risk HBV Infection	Mode of Transmission
○ NA, WE, SA, Au	< 20%	– Horizontal person-to person, young adults – Sexual
○ SE, EE, ME, IS fUSSR, NAFR	20% to 40%	– Infancy – Early childhood
○ SEA, CHINA, AFRICA	60% to 80%	– Perinatal – Horizontal, young children

Abbreviations: Au, Australia; EE, Eastern Europe; fUSSR, former USSR; IS, Indian Subcontinent; ME, Middle East; NAFR, Northern Africa; NA, North America; SEA, South East Asia; SA, South America; SE, Southern Europe; WE, Western Europe

➢ Molecular biology

- Give the **molecular biology** of HBV infection.
  - HBV is a DNA virus which goes through an RNA intermediate and requires an active viral reverse transcriptase/polymerase enzyme.
  - High daily point mutation rate, low replication fidelity
  - The 5 gene encodes HBsAg, a viral surface, envelop protein
  - Liver damage from HBV is immune-mediated (not a direct hepatocyte cytopathic effect of HBV).

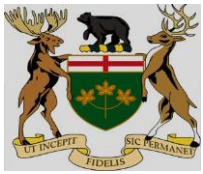
- Cellular immune response – innate and adaptive
- Viral clearance by CTLs (cytotoxic T lymphocytes)
- CD4+ T cells produce antiviral cytokines which reduce the production of neutralizing antibody.
- The core gene has
  - Precore region → HbeAg
  - Core region → core proteins
- HBV DNA polymerase reverse transcriptase pregenomic RNA into a negative-strand HBV DNA ("needed for encapsidation of viral RNA into a negative strand of viral DNA (reverse transcription) and conversion of this first HBV DNA strand into a second DNA strand of positive polarity (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, page 1314).
- The negative-strand HBV DNA is a template for the synthesis of a positive-strand.
- The positive strand is incorporated into the maturing nucleocapsid.
- The nucleocapsids are coated with the surface protein (HBsAg) in the ER.
- From the ER, the enveloped nucleocapsid bud off from the hepatocyte membrane, and enter the circulation.

Acute HBV Infection

- Most patients with acute HBV infection have a mild subclinical illness
- About a third develop clinical symptoms and signs of hepatitis
- The clinical incubation period of acute hepatitis B averages 2–3 mon
- Fulminant liver failure due to acute HBV occurs in less than 1% of cases

➢ Clinical

- Stages (based on serology)
  - Immune tolerant
    - Normal ALT level
    - Minimal or no inflammation or fibrosis
    - High levels of HBV DNA
    - HBeAg+
  - Immune reactive
    - May be high levels of HBV DNA, but HBeAg may cause an immune tolerant phase, with inflammation of the liver
    - ALT normal or near normal
  - When HBV is acquired early in life such as from vertical transmission, and in those who have a high-normal ALT, they may already have entered the immune clearance phase.
  - Liver biopsy "….can be a useful tool to distinguish persons in the immune clearance phase despite normal or near-normal ALT levels but with active liver disease from active liver disease". (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1294).

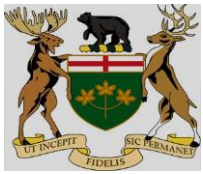


- Immune active
  - Liver inflammation and fibrosis
  - ↑ HBV DNA (lower than in immune tolerant)
  - HBeAg + or –
  - ↑ ALT
  - Active T cell response to virus
- Inactive
  - Normal ALT
  - Healing liver histology
  - Resolving liver fibrosis
  - Low or absent HBV DNA
  - Strong T cell response to virus
- Recovery
  - Lower risk of developing HCC
  - Loss of HBsAg

Adapted from: McMahon BJ, et al. Clin Gastro Hep 2012; 10: 218-219.

- Clinical presentations
  - Active hepatitis
    - Circulating HBsAg – anti-HBs complexes activate complement
    - HBsAg – anti-HBs complexes are deposited in wall of the blood vessels of the skin synovium
    - Serum sickness-like prodrome, with 1/3 of patients developing jaundice
    - Low levels of HBV may persist in the serum

- Fulminant hepatitis
  - Due to “massive immune-mediated lysis of infected hepatocytes”
  - Usual-onset
    - Within 4 wk of symptoms of HBV
  - May develop late-onset liver failure after several months of onset of HBV symptoms
  - Survival
    - Spontaneous, 20%
    - With liver transplantation, 50%
  - May be associated with “flares” (exacerbations of disease)
    - ↑ ALT (2x ULN)
    - IgM anti-HBe
    - Associated with histological disease progression
- Chronic active HBV carrier (active HBsAgcarrier)
  - HBV replication
    - PCR-based, +
    - Non-PCR-based testing, +
  - AST, ALT
    - Intermittent or persistent increases
  - Liver biopsy
    - Chronic hepatitis
- Chronic inactive HBV (inactive HBsAg carrier)
  - HBsAg positive for > 6 mon
  - 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)

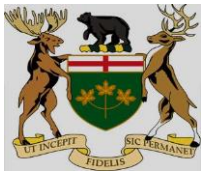


- Progression
  - Infection
    - Vertical, 95%
    - Horizontal, < 5%
  - HBV infection → carrier state, < 5%
  - Cirrhosis, 5 yr survival rate
    - Compensated, ~85%
    - Decompensated, ~15%
- Resolved hepatitis B
  - Previous known history of acute or chronic hepatitis B
  - HBsAg negative
  - HBeAg negative
  - HBcAb positive/HBsAb positive
  - Undetectable HBV-DNA
  - Normal ALT

Adapted from: Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62.

- Reactivation
  - A proportion of those with inactive carrier state undergo spontaneous or immunosuppression-mediated reactivation of replication of HBV DNA
  - ↑ HBV DNA in serum
  - ↑ ALT
  - Necroinflammation recurs
  - Seroconversion of $HBeAg^{+/-}$
  - During or after HBeAg seroconversion (anti-HBe → $HBeAg^{+}$), precore or core promoter mutants appear
  - Precore or core promoter mutants ↓ HBeAg production
  - Optimal time for treatment

- Immune clearance
  - ↓ HBV DNA
  - ↑ ALT
  - $HBeAg^+$
  - Hepatic necroinflammation (immune-mediated lysis of HBV-infected hepatocytes)
  - Optimal time for treatment
- Associations with HBV
  - Fibrosing cholestatic hepatitis
    - Reactivation of HBV from immunosuppressants ↑↑↑ HBsAg and HBeAg in liver tissue
  - Infection with other hepatotrophic viruses (A, C, D)
  - Extrahepatic manifestations
    - Fever, arthralgias (proximal interphalangeal pints), angioneurotic edema
    - Polyarteritis nodosa
    - HBV-associated renal disease
      - Cryoglobulinemia
      - Glomerulonephropathy
      - Immune-complex glomerulonephritis
      - Membranoproliferative glomerulonephritis
      - Membranous glomerulonephritis
      - Nephrotic syndrome
      - Renal failure



- Causes/ associations

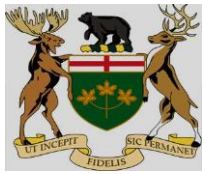
Causes/associations of acute flares in HBV

Cause	Comment
Spontaneous	Precipitating factors for antecedent viral replication unclear
Immunosuppressive therapy	Often observed suring withdrawal; requires pre-emptive antiviral therapy
Antiviral therapy	
– Interferon	Often during the second to third mon, may herald virologic response
– Lamivudine	
▪ On treatment	No more common than placebo
▪ YMDD mutant	Can have severe consequences in patients with advanced disease
▪ Withdrawal	Caused by rapid re-emergience of wild-type HBV; can have severe consequences in patients with advanced disease
HIV treatment	As above when using lamivudine; can also occur with immune reconstitution or secondary to antiretroviral drug hepatotoxicity
Genotypic variation	
– Precore and core promoter mutants	Fluctuations in ALT common with precore mutant
Superinfection with other hepatitis viruses	May be associated with suppression of HBV replication

Source: Zakim and Boyer's Hepatology. 5th Edition. Chapter 31: Hepatitis B.

- Laboratory
  - For patients not on treatment:
    - Follow up
      - q3-6 mon with liver enzymes, HBV serology and HBV DNA
      - can be increased to 6-12 mon for inactive carries stable for ≥1 yr
  - For patients on treatment:
    - Follow up
      - q3-6 mon with liver enzymes, HBV serology and HBV DNA
    - Typically monitored at 3 mon to confirm virologic response and can then increase interval

- Give 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
    - Absence cannot be taken as absence of viral replication (i.e., precore mutant, e.g., eAg negative)
  - Anti-HBe
    - Presence indicates seroconversion
    - Can also be found in active disease in patients with HBeAg negative chronic hepatitis. (not replicating – precore mutant)



- HBV-DNA
  - Detectable in serum
  - Measure of the level of viral replication. (infected; reflects risk of HCC)

Printed with permission: Balart LA. *2007 ACG Annual Postgraduate Course*: 198.

- 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 30-65 yr old are directly related to the likelihood of developing HCC 10 yr later

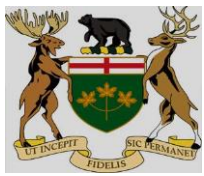
- Give the laboratory features which suggest each of the 5 stages of HBV.

Stage	HBeAg	HBV DNA	ALT/ AST	Progression to Fibrosis
○ Immune tolerant	+	↑↑	N/low	Very low
○ Immuno-reactive (HBeAg - positive necro-infllam-mation	+	↑	↑/ fluctua-ting	low
○ Inactive HBV carrier state	Negative (0 conversion to anti-HBe antibody)	< 2000 IU/mL Low/ undetectable	N	Low

Stage	HBeAg	HBV DNA	ALT/ AST	Progression to Fibrosis
○ After sero-conversion, or after yr of immune-reactive phase	Negative	↑/↓	↑/↓	High
○ HBs antigen negative	Negative	HBV DNA in liver but not detectable in blood	N	Low

- Give the clinical laboratory and histopathology characteristics of the **different stages** of chronic hepatitis B infection.

Features	Immune tolerant	Immune reactive	Low replicative stage	e- Ag negative reactivation
○ ALT	Normal	Elevated	Normal	Fluctuates (fluctuating 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/+ fibrosis	Inactive	Active/+ fibrosis
○ Course	No progression of disease for about 3-6 months	HBeAg sero-conversion with treatement	-	8-10% develops cirrhosis each yr, compared with 2-6% of HBeAg positive patients
○ Treatment	No	Yes	No	Yes



- Treatment
  - The goals of treatment are:
    - Suppression of HBV DNA
    - Loss of HBeAg in HBeAg positive patients
    - Loss of HBsAg
  - Treatment can reduce:
    - Liver related complications
    - HBV transmission

Chronic HBV

- Definition
  - Presence of ongoing HBsAg for greater than 6 mon

- Clinical
  - Many are asymptomatic or have nonspecific symptoms, such as
    - fatigue
    - mild right upper quadrant discomfort
  - Patients with cirrhosis may have stigmata of chronic liver disease

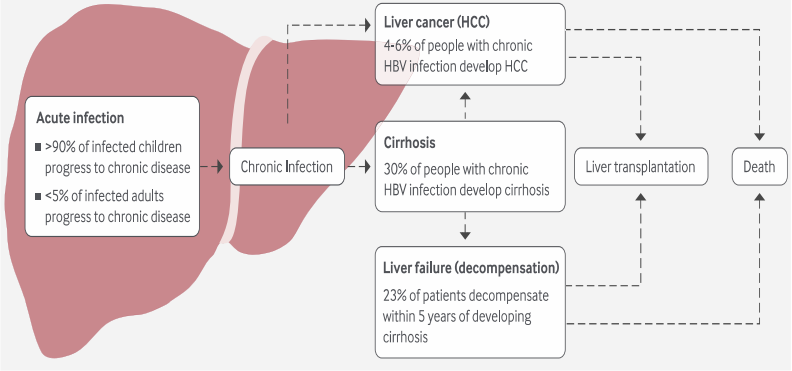
- Extrahepatic manifestations

System	Manifestation
Neurologic	Guillain-Barre syndrome Mononeuropathy multiplex Peripheral mononeuropathy Seizures
Cutaneous	Purpuric rash Pyoderma gangrenosum Porphyria cutanea tarda Lichen planus Erythema nodosum Dermatomyositis like syndrome

System	Manifestation
○ Renal	– Membranous GN – IgA nephropathy – Membranoproliferative GN
○ Hematologic	– Aplastic anemia
○ Rheumatologic	– Polyarteritis nodosa – Polymyalgia rheumatica – Cryoglobulinemia – Rheumatoid arthritis – Lupus
○ MSK	– Polymyositis – Myocarditis – Dermatomyositis

Source: Zakim and Boyer's Hepatology. 5th Edition. Chapter 31: Hepatitis B.

- Natural History



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- Initial evaluation

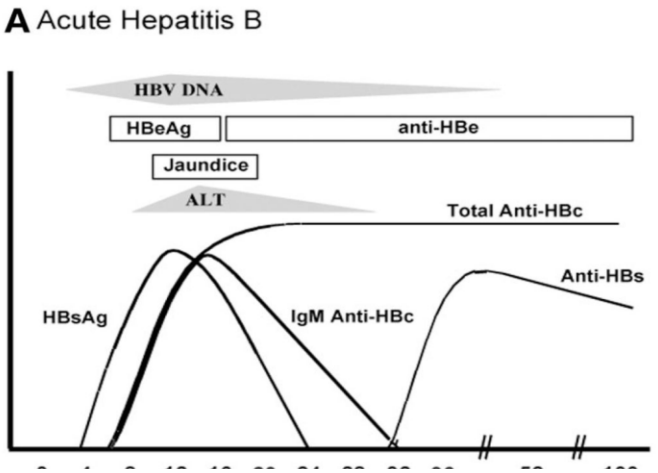
	History / Physical Examination	Routine Laboratory Tests	Serology / Virology	Imaging / Staging Studies
All patients	Symptoms/signs of cirrhosis Alcohol and metabolic risk factors Family history of HCC Vaccination status	CBC including platelet count, AST, ALT, total bilirubin, alkaline phosphatase, albumin, INR	HBeAg / anti-HBe HBV DNA quantitation Anti-HAV to determine need for vaccination	Abdomina ultrasound Vibration-controlled transient elastography or serum fibrosis panel (APRI, FIB-4, or FibroTest
Select patients		Tests to rule out other causes of chronic liver disease of elevated liver test(s) AFP, GGT	HBV genotype Anti-HDV Anti-HCV Anti-HIV in those who have not indergone one-time screening (ages 13-64)	Liver biopsy

Printed with permission: Terrault et al. Hepatology 2016; 63: 261-83.

- Laboratory
  - HBV serology

Variable	Description
HBsAg	– Acute or chronic HBV infection
HBeAg	– High level HBV replication and infectivity
Anti-HBc (IgM)	– Acute HBV infection
Anti-HBc (IgG)	– Recovered or chronic HBV infection
Anti-HBs	– Recovered HBV infection or vaccination
Anti-HBe	– Low level HBV replication and infectivity
HBV DNA	– Level of HBV replication

Source: Trepo et al. Lancet 2014; 384:2053-63.



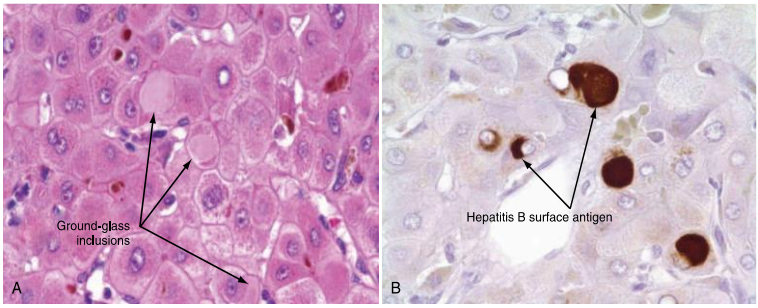
Source: Liang. Hepatology 2009; 49 (5 Suppl): S13-21.

- Self-testing
  - For each case, give your diagnostic interpretation of the serological finding

➢ Histopathology

- Give the hepatic histopathological features of HBV infection.
  - Ground-glass hepatocytes
    - HBsAg in the ER of infected hepatocytes
    - Cysteine in HBsAg stained by orcein, Victoria blue, aldehyde fuchsin indicates replication
    - HBV antigen in cytoplasm and hepatocyte nuclei
    - After treatment cytoplasmic core antigen disappears, but persistence of nuclear core antigen indicates presence of HBV cccDNA template

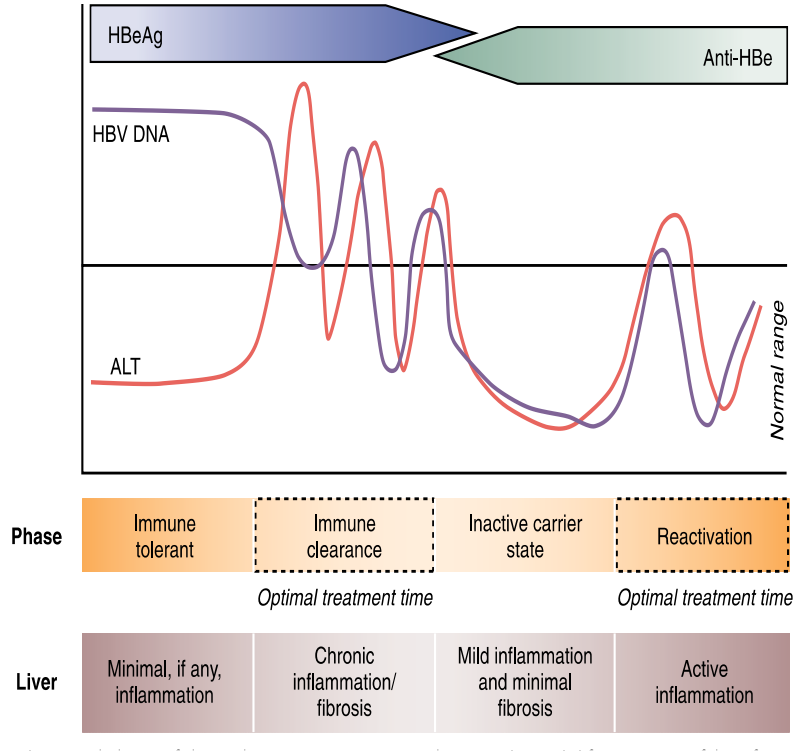
- Peripheral infiltration with mononuclear cells
- Interface hepatitis (disruption of hepatocytes of the limiting plate)
- Fibrous tissue extending from peripheral areas
- Septa mononuclear cells between fibrous extensions from portal tracts and hepatocyte parenchyma



Printed with permission: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th edition. Chapter 78.

- From liver biopsies from patients with chronic viral hepatitis, it is difficult without immunochemical staining, to differentiate between the various types of viruses; ground-glass appearing hepatocytes may suggest but does not prove the presence of HBV infection.

- Phrases of Chronic HBV infection
  - The old terminology



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➢ Treatment

- Give the importance of HBeAg status
  - Represents
    - ↑ viral replication
    - Active liver disease
    - Need for antiviral therapy

- Give the comparisons of HBeAg positive vs HBeAg negative HBV infection.

Comparisons	HBeAg Positive	HBeAg Negative
○ Epidemiology	– Most common type in North America	▪ ↑ incidence in Asia, Europe and other Mediterranean countries
○ Rate of progression to cirrhosis	– ↓ rate of progression to cirrhosis (10-20% /yr; immune tolerance)	▪ ↑ rate of progression to cirrhosis
○ 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

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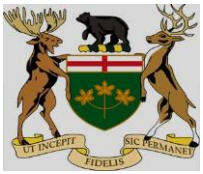
Adults who are HBeAg-positive usually have active HBV, whereas children who are HBeAg-positive do not.

- Give the explanation why $HBeAg^+$ in children is not usually associated with active hepatitis.
    - The secretion of HBeAg may be reduced by
        - Precore or core promoter mutations
        - Low levels of wild-type HBV

- Give goals of treatment of $HBeAg^+$ and $HBeAg^-$ HBV infection.
    - Loss of E-antigen (seroconversion, off treatment)
        - 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 yr after therapy has been completed)
    - Appearance of anti-HBe antibody
    - ↑ loss of HBsAgConversion to inactive status
    - Normalization in serum liver aminotransferase
    - ↓↓ detectable HBV DNA
        - Keep the HBV DNA levels as low as possible
            - ↑ immunological response to HBV
            - ↓ HLA class I antigen expression on surface of hepatocytes
            - ↑ CD8+ CTL activity



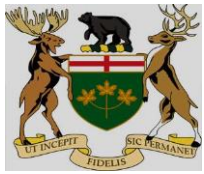
        - ↓ HBV ccc DNA (“the genomic template for viral transcription)
        - No drug resistance
        - Associated with seroconversion (HBeAg+ → HBeAg-)
            - Genotype A~ 50%
            - B, C, D ~ 25%
    - Does not completely eliminate HBV infection, since the HBV (a DNA virus) becomes integrated within the hepatocyte genome as, covalently closed circular (cccDNA)
- Improvement in liver hepatic necroinflammation
- Improve the patient’s quality of life
- Prevention of progression of the disease to cirrhosis, HCC, decompensation.
- ↓ risk of hepatocellular carcinoma (HCC)
- ↓ HBs Ag

➢ Indications

- Give the indications for initiation of HBV therapy.
    - ↑ HBV DNA (> 2000 IU/mL)
    - ↑ ALT (> ULN)
    - Liver biopsy
        - Moderate/severe necroinflammation, and/or
        - ≥ moderate fibrosis
    - When to start HBV therapy without liver biopsy
        - HBeAg-negative, ↑ ALT (2x ULN), HBV DNA > 2000 IU/mL; or
        - HBeAg-positive

- When to start HBV therapy with normal ALT but abnormal liver biopsy
  - ↑ HBV DNA, necroinflammation changes and fibrosis on a liver biopsy
  - Compensated cirrhosis, even if HBV DNA undetectable
  - Decompensated cirrhosis plus detectable HBV DNA
- Chronic HBV
  - $HBeAg^+$
    - 90% have HBV DNA > 105 copies/mL
  - $HBeAg^-$
    - Lower serum HBV DNA levels, especially if ALT is normal
    - Higher HBV DNA in $HBeAg^-$ with ↑ ALT
- Seroconversion ($HBeAg^+ \rightarrow HBeAg^-$, anti-HBe) usually associated with ↓ HBV DNA

- Give when anti-HBV therapy should be given for acute HBV.
  - Active HBV
    - HBeAg (+), HBV DNA >500,000 copies/mL (20,000 IU/ml), and elevated ALT > 2 X ULN
    - Variable degrees of fibrosis on liver biopsy
  - Pre-core mutations of HBV:
    - Includes patients with all features above, except eAg(-)
  - Inactive HBV:
    - 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)

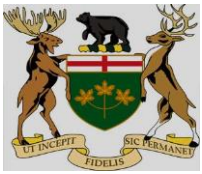


- HBV acute infection, when HBeAg lasts beyond 12 wks
  - HBV therapy may reduce the 5% risk of development of chronic HBV
- Fulminant HBV
  - INR > 1.5 plus clinically deep jaundice
  - Anti-HBV useful since patient may need a liver transplantation
- ↑ risk of progression (fibrosis progression, cirrhosis and HCC)
- Immune tolerant

- Give the pre-treatment **baseline evaluation** of the patient with HBV infection.
  - Revised normal ALT levels (30 IU/L for men, and 19 IU/L for women) should be used as criteria for treatment
  - Baseline evaluation should include HBV genotype, particularly if peginterferon therapy considered
  - Preferred first line treatment options: tenofovir or entecavir
    - Lamivudine not first-line choice secondary to high rate of resistance to Interferon alfa-2b
  - Liver biopsy should be considered for patients with normal ALT levels, especially if age >35-40 yr

- Give the **general management strategy** of the person with HBV.
  - PEG-IFN or NA monotherapy used for finite duration
    - PEG-IFN (in the absence of contraindications) for HBeAg- positive and -negative patients for 48 wk
  - Treatment strategies
    - NA monotherapy for long-term duration
  - Entecavir or tenofovir for 12 months after seroconversion in about 2/3 of those initially HBeAg-positive HBV patients
  - NA (continuously maintenance) for long-term duration
  - Entecavir or tenofovir monotherapy for
    - HBeAg-positive patients who failed to seroconvert or HBeAg-negative patients
    - All HBV cirrhosis
  - Monitoring and applying stopping rules

- Give the **potential management strategies** for HBV by on-treatment virologic response categories.
  - Virological response - HBV DNA < 2000 IU/mL at 0, 6 and 12 mon after the end of therapy
  - Sustained virological response - HBV DNA < 2000 IU/mL at 12 mon after the end of therapy
  - Virological break through
    - ↑ HBV DNA 1 $\log_{10}$ IU/mL compared to lowest previous level of HBV DNA on Rx
    - Characterized by ↑ ALT
    - Due to
      - Poor adherence to therapy, or
      - HBV resistance (due to therapy associated selection of HBV resistant variants)



Situation	Management
○ Primary treatment failure at wk 12	- If non-compliant, 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 wk 24	- Continue therapy with same drug; monitoring may be extended to 6-mon intervals
○ Partial virologic response at wk 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-mon intervals and continue beyond 48 wk - If drug has a delayed antiviral effect e.g., adefovir, repeat monitoring at 3-mon intervals and if response becomes complete at 48 wk, continue therapy; but if response remains partial or becomes inadequate at 48 wk, add a more potent drug
○ Inadequate virologic response at wk 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-mon intervals - Monitoring after 48 wk may be extended from 3 to 6 mon if response becomes complete

*patients with advanced disease should be monitored at 3-month intervals while on treatment, regardless of virologic response

- Give factors that are predictive of a viral response (VR) to treatment of HBV infection.
  - Patient
    - Immunocompetent
  - HBV
    - Adult-acquired infection
    - Low HBV-DNA level
      - ↑ response to interferon
      - HBV recurrence with liver transplantation
    - Absence of HDV or HIV co-infection
    - HBeAg +ve
  - Biopsy
    - Active liver disease—ALT > 5x upper limit of normal (ULN), active hepatitis on biopsy
  - Specific treatment algorithms
    - HBeAg+
    - HBeAg-

Adapted from: Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006;4(8):936-62.

- Give the recommendations regarding monitoring and stopping HBV treatment.

❖ PEG-IFN

- HBeAg-positive
  - On treatment
    - Every 6 and 12 mon: anti-HBe antibodies, serum HBV DNA, ALT, HBsAg at 12 mon
  - Off treatment
    - Every 12 mon: HBeAg, anti-HBe antibodies, serum HBV DNA, ALT, HBsAg

- HBeAG seroconversion (HBeAg-positive → negative
  - Test HBsAg every 12 mon (seroreversion)
- No HBeAg seroconversion (serum HBsAg > 20,000 IU/mL, or no ↓ HBsAg at 3 mon
  - Stop PEG-IFN

○ HBeAg-negative
- On treatment, at month 3 if ↓ HBV DNA ≥ 2 $\log_{10}$ IU/mL, and no ↓ HBsAg
  - Stop PEG-IFN (especially genotype D)

❖ NA (nuceos[t]ide)

○ On treatment every 6 months HBeAg, anti-HBe, HBV DNA, serum creatinine
- Measure HBsAg every 12 mon after HBe seroconversion
- Stop NA 12 mon after anti-HBe seroconversion, or
- Stop NA until loss of HBsAg (with or without antibodies to HBsAg), especially if there is severe fibrosis or cirrhosis.

• 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 wk 24

○ Development of antiviral drug resistance

Abbreviation: VR, viral response

Printed with permission: Keeffe EB. *2007 AGA Institute Postgraduate Course*: 75.

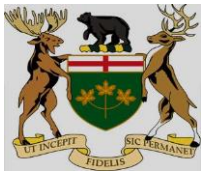
- If HBV DNA reappears during treatment of HBV, then resistance to the drug has likely occurred.
- In fulminant HBV, the HBsAg may have disappeared, but the diagnosis can be made by finding HBV DNA in serum.

Drug choices

- IFN (interferon)
  - PEG-IFN (pegylated IFN)
- Nucleosides
  - Lamivudine
  - Telbivudine
  - Emtricitabine
  - Entecavir
- Nucleotides
  - Adefovir
  - Tenofovir (disoproxil or alafenamide)

- 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 IU/mL	Normal	- No treatment - Monitor every 6-12 mon - Consider therapy in patients with known significant histological disease even if low-level replication



HBV DNA	ALT	Treatment Strategy
○ ≥20,000 IU/mL	Normal	- Low rate of HBeAg seroconversion for all treatments - Monitor every 3-12 mon - Younger patients often immune tolerant - Consider biopsy; particularly if older than age 35-40 yr; treat if significant disease. In the absence of a liver biopsy, observe for rise in ALT levels.
○ ≥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.

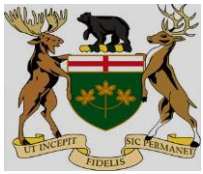
- HBV disease
  - “acute” > 20,000 HBV DNA IU/ml
  - “inactive” < 20,000 HBV DNA IU/ml

- 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 IU/mL	Normal	- No treatment: majority inactive HBsAg carriers - Monitor every 6-12 months
○ ≥2,000 IU/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 IU/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.

  - The dose of NAs (NTs and NSs) must be reduced if creatinine clearance < 50 mL/min.
  - All HBV positive patients must be screened for HIV before starting their HBV treatment with lamivudine, entercavir or tenofovir, since these drugs have activity against HIV and should not be used as more therapy for HBV for fear of causing HIV resistance.
    - PEG-IFN, adefovir and telbivudine are not active against HIV.



- PEG-IFN has advantages over nucleos(t)ide (NA) because of
  - The absence of resistance
  - The possibility of seroconversion (HBsAg-positive → negative) in about 25% of patients
  - The ~4% change of loss of HBsAg in persons who achieve and maintain undetectable HBV DNA (by sensitive testing).
  - IFN therapy responders enjoy a ~ 50% reduction in cirrhotic complications and 80% reduction in liver- related mortality.
- Overview of response rates in HBeAg positive and HBeAg negative patients with currently available antiviral drugs.

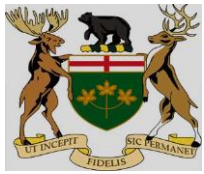
Antiviral Therapy	HBeAg Positive HBeAg Seroconversion		HBeAg Negative Undetectable HBV DNA	
	End of Therapy	Post Treatment	End of Therapy	Post Treatment
○ Interferon	35%	30%	60%	35%
○ Peginterferon	40%	35%	63%	19%
○ Lamivudine	19%	12%	65%	10%
○ Adefovir	12%	NA	51%	NA
○ Adefovir in lamivudine resistance	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

INTERFERON

- Give the advantages and disadvantages of interferon for the treatment of chronic HBV infection.

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

- Give the early and late adverse effects of interferon.
  - Early
    - Flu-like illness; headaches, nausea
    - Tenderness at site of infection
  - Late
    - General
      - ▪ Fatigue
      - ▪ Irritability Anxiety and depression
    - Eyes
      - ▪ ↑ retinopathy DM
      - ▪ Optic tract neuropathy
    - CNS
      - ▪ Neuropsychiatric issues
    - MSK
      - ▪ Muscle aches
    - Skin
      - ▪ Alopecia
      - ▪ Lichen planus worsens



- GI	▪ Weight loss ▪ Diarrhea ▪ Anorexia ▪ IBD worsens
- Endocrine	▪ Autoimmune autoantibodies ▪ Worsening thyroid disease ▪ Autoimmune diseases worsen
- Pregnancy class C	
- Bone marrow suppression	▪ Bacterial Infections

Abbreviations: CNS, central nervous system; DM, diabetes melitus; GI, gastroenterology; IBD, inflammatory bowel disease; MSK, musculoskeletal

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005: 547-563.

- Give **contraindications** to the use of IFN/PEG-IFN.
  - Decompensated HBV cirrhosis (↑ risk of bacteremia and ↑ decompensation)
  - Autoimmune disease
  - Uncontrolled severe depression/psychosis
  - Pregnancy
  - Renal transplant patients (↑ risk of rejection)

Nucleoside (NS) **/ nucleotide** (NT) **analogs (NA)**

- Competitive inhibitors of reverse transcriptase and DNA polymerase.
- Replace natural nucleoside during the synthesis of the first or second strand (or both) of HBV DNA.

- Give the advantages and disadvantages of nucleosides and nucleotide analogs for the treatment of chronic HBV infection.

Agent	Advantages	Disadvantages
○ Lamivudine	- Oral administration - Excellent tolerance - Use in ESLD - Use in adefovir failures	▪ Drug resistance: common (~20%/yr, and up to 70% with 4-5 yr 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 yr 1, 2% at yr 2, 7% at yr 3, 15% at yr 4, and 29% at yr 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 yr 1, 0.4% at yr 2 and 1.1% at yr 3), but common in patients with lamivudine resistance (6% at yr 1, 14% at yr 2, and 32% at yr 3)

Agent	Advantages	Disadvantages
○ Telbivudine	- Oral administration - Excellent tolerance - High potency in lowering HBV DNA levels	▪ Drug resistance: intermediate rates (5% at yr 1, and ~20% at yr 2 in HBeAg-positive patients, and ~10% in HBeAg-negative patients)
○ Tenofovir	- Oral administration - Excellent tolerance - No resistance - High potency in lowering HBV DNA levels - Used in entecavir, lamivudine, telbivudine failures	▪ May cause bone loss and renal toxicity

Abbreviation: ESLD, end-stage liver disease

Adapted from: Keeffe EB. *2007 AGA Institute Postgraduate Course*: 76; Bang KB et al. WJG 2014; 20(33): 11641-9.

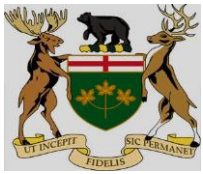
- **Lamivudine (LAM)**
  - High rate of viral mutation and viral resistance
- ~40% at 2 yr, 65% at 5 yr
- Higher rate of resistance with treatment of co-infection with treatment of co-infection with HIV.
- HBV viral suppression
  - LAM < adefovir (ADE) < enterocovir < telbivudine (TEL) < tenofovir (TEN)
- HBV resistance
  - TEN > THE > ENT > ADE
  - Rate of resistance
    - LAM 69% / 5 yrs
    - ADE 30% / 4 yrs
    - TEN rare

- Give pros and cons of Lamivudine versus interferon (IFN) for the treatment of HBV.

Favoring LAM	Favoring IFN
○ Needle phobia ○ HIV co-infection ○ Other immunosuppression (e.g., transplantation) ○ Patients with depression ○ Low WBC count ○ Low platelet count ○ Autoimmune disease ○ Decompensated cirrhosis ○ Vertical transmission ○ Cost concerns ○ Pregnancy, may be used ○ Has 70% resistance rate at 5 yr. 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 resistance with tenofovir	– Young Asian – Genotype A – Recent infection – AST > 100 – Low serum HBV-DNA – Active liver biopsy – eAg+ – Possibility of seroconversion (eAg+→eAb+) – Marginal benefit to baby – Contraindicated with depression, renal failure

Remember
- ○ No interferon during pregnancy

Adapted from: Grover PT, and Bain V. *First Principles of Gastroenterology* 2005:547-552.



- **Adefovir dipovoxil (ADE)**
  - Acyclic phosphate nucleotide analog of adenosine monophosphate
  - ↓ HBV polymerase and reverse transcriptase
- **Entercavir (ENT)**
  - Deoxyguanine nucleotide analog which selectively inhibits replication of HBV
  - ↓ priming of HBV DNA polymerase
  - ↓ synthesis of 192 nd strand of HBV DNA
  - Low rates of resistance (1.2% after 5 yr), and
  - 20% rate of eAg seroconversion after 48 wks
- Development of resistance is associated with flares.
- **Telebuvidine (TEL)**
  - L. nucleoside analog of thymidine

Treatment Alert

- Telbivudine is not effective in persons who have lamivudine resistance (telbivudine develops resistance mutations at the same site as for lamivudine)

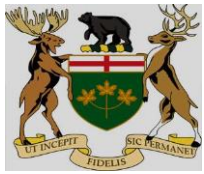
- **Tenofovir disoproxil fumarate (TDF)**
  - Chemically similar to adefovir mechanism of action similar to adefovir (a cyclic nucleotide inhibitor of HBV polymerase and reverse transcriptase
  - Resistance does not occur
  - The diagnosis of chronic HBV infection in an HIV patient is an indication to start tenofovir-based HAART
  - May cause bone loss and renal toxicity

- **Tenofovir alafenamide (TAF)**
  - Newer formulation of tenofovir
  - Prodrug of tenofovir which allows a lower dose to be used with similar antiviral activity
  - Less systemic exposure and thus decreased renal and bone toxicity

- Give the management of nucleoside and nucleotide resistance.
  - Nucleoside resistance
    - Lamivudine, telbivudine, entecavir → tenofovir or adefovir (nucleotide analogues)
    - Note: nephrogenic potential is adefovir > tenofovir
      - Tenofovir may actually improve renal function
  - Nucleotide resistance
    - Adefovir
      - Naïve → tenofovir or entecavir (preferred for ↑↑ HBV DNA levels)
      - Prior lamivudine resistance → tenofovir plus telbivudine or entecavir (nucleoside analogues)
    - Tenofovir
      - Naïve → lamivudine, telbivudine, entecavir
      - Prior lamivudine resistance→ entecavir

- 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



HBV DNA	Cirrhosis	Treatment Strategy
○ ≥2,000	Compensated	– Adefovir or entecavir are first-line options – Long-term treatment required, and combination therapy may be preferred
○ <200 or ≥200	Decompensated	– Combination with lamivudine, or possibly entecavir, plus adefovir preferred – Long-term treatment required, and combination therapy may be preferred – While patient is on wait list for liver transplantation

- 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.

Mutants and Mutations

- HBsAg mutants
  - Vaccine escape
    - In persons for whom HBIG does not prevent HBV, about half of these "escapes" are due to alterations in the "a" determinants of the HBsAg, leading to immune escape.
- Mutations in the Precore, Basal Core Promoter and Core Genes
  - More common in HBe-Ag-negative persons
  - Stop the synthesis of HbeAg
  - ↑ development of fulminant HBV
  - ↑ risk of HCC
  - ↓ response to interferon
- Mutations in HBV DNA polymerase
  - "HBV reverse transcriptase function of the polymerase gene is highly preserved

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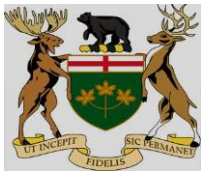
- Viral resistance may occur wks to months before a virologic breakthrough

- In the context of HBV, define "**virologic breakthrough**"
  - Virologic breakthrough
    - > 1 $\log_{10}$ (10-fold) increase in serum HBV DNA levels above the previous nadir

- Virologic rebound may follow virologic breakthrough; define "virologic rebound".
  - Virologic rebound HBV DNA > 10^5 (20,000 IU/mL)



Special Conditions in Treating HBV Infection

- **Chronic renal failure, dialysis and renal transplantation**
  - The dose of NAs (NTs and NSs) must be reduced if creatinine clearance < 50 mL/min.
  - Vaccinate HBV positive, renal impairment
    - NA dose reduction, except for tenofovir
    - Avoid PEG-IFN renal transplant patient (↑ risk of rejection)
    - Monitor creatinine clearance
    - Treat co-existing hypertension and diabetes mellitus
- **HIV co-infection**
  - All HBV positive patients must be screened for HIV before starting their HBV treatment with lamivudine, entercavir or tenofovir, since these drugs have activity against HIV and should not be used as more therapy for HBV for fear of causing HIV resistance.
  - PEG-IFN, adefovir and telbivudine are not active against HIV.
  - Tenofovir, emtricitabine or lamivudine, plus a third day which is active against HIV
- **HCV co-infection**
  - Treat HCV, monitor HBV DNA and treat HBV activation with NAs (activity of HBV is often suppressed in presence of HCV).

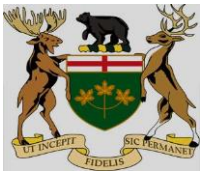
- **Post-LT** (liver transplantation)
  - Entecavir monotherapy prophylaxis, or
  - Tenofovir plus emtricitabine with or without HBIG (hepatitis B immunoglobulin), or
  - Lamivudine plus adefovir plus HBIG
- **Acute liver failure** (ALF) for severe acute HBV infection
  - Start entecavir or tenofovir
  - Assess for possible need for liver transplantation
  - Continue entecavir or tenofovir for at least
    - 3 mon after seroconversion of HBsAG (HBsAg → anti-HBs)
    - 12 mon after seroconversion of HbeAg (HBeAg → anti-HBe)
- The new

Natural history and assessment of patients with chronic HBV infection

↓ ↓

HBV markers
- HbsAg
- HBeAg / anti-HBe
- HBV DNA

Liver disease
- Biochemistry parameters: ALT
- Fibrosis markers: non-invasive markers of fibrosis (elastography or biomarkers) or liver biopsy in selected cases



	HBeAg Positive		HBeAg Negative	
	Chronic Infection	Chronic Hepatitis	Chronic Infection	Chronic Hepatitis
○ HBsAg	High	High/ Intermediate	Low	Intermediate
○ HBeAg	Positive	Positive	Negative	Negative
○ HBV DNA	$>10^7$ IU/mL	10^4-10^7 IU/mL	<2000 IU/mL	>2000 IU/mL
○ ALT	Normal	Elevated	Normal	Elevated
○ Liver disease	None/ minimal	Moderate/ severe	None	Moderate/ severe
○ Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

Source: EASL. J Hepatol 2017; 67: 370-98.

➢ Treatment

Guidelines recommendation on treatment initiation in patients with HBV

○ HBeAg Status

	Positive	Negative
AASLD (2009)	HBV DNA > 20,000 IU/mL and ALT > 2x upper limit of normal	HBV DNA > 20,000 IU/mL and ALT > upper limit of normal or stage 2 fibrosis
EASL (2017)	HBV DNA > 20,000 IU/mL with ALT > upper limit of normal or biopsy with moderate fibrosis or inflammation	HBV DNA > 20,000 IU/mL with ALT > upper limit of normal or biopsy with moderate fibrosis or inflammation

	Positive	Negative
APASL (2012)	HBV DNA > 20,000 IU/mL and ALT > 2x upper limit of normal	HBV DNA > 20,000 IU/mL and ALT > upper limit of normal or stage 2 fibrosis

- Cirrhosis

	Compensated	Decompensated
AASLD (2009)	HBV DNA > 20,000 IU/mL	All patients
EASL (2017)	All patients regardless of decompensation or HBV DNA level	All patients regardless of decompensation or HBV DNA level
APASL (2012)	HBV DNA > 20,000 IU/mL	All patients

Abbreviations: AASLD, American Association for Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian-Pacific Association for Study of the Liver; EASL, European Association for the Study of the Liver

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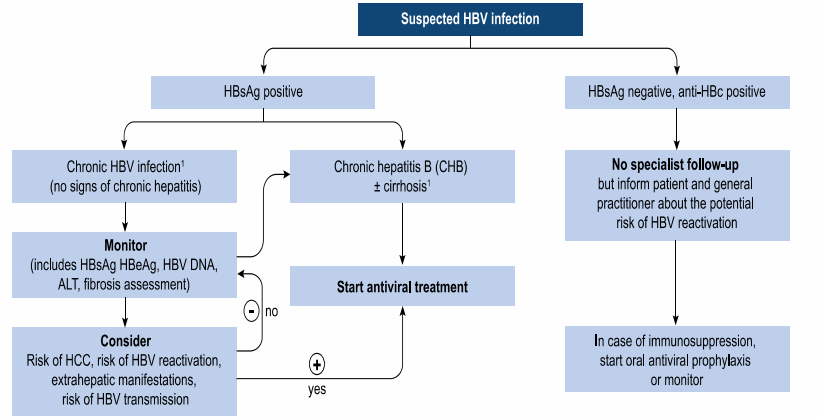

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- Options
  - Pegylated interferon
  - Nucleos(t)ide analogs:
    - Lamivudine
    - Adefovir
    - Telbivudine
    - Entecavir
    - Tenofovir

Drug	Dose	Mechanism of Action	Adverse Events
PEG-Interferon	180 ug sc q wk	Antiviral and immune-modulatory activity	- Influenza-like symptoms - Fatigue - Bone marrow suppression - Depression - Exacerbation or unmasking of autoimmune illnesses
Nucleos(t)ide Analogs: Lamivudine Adefovir Telbivudine Entecavir TEN TAF Emtricitabine	 100 mg po od 10 mg po od 600 mg po od 0.5 mg po od 300 mg po od 25 mg po od 200 mg po od	Competitive inhibitors of the viral reverse transcriptase and DNA polymerase	- Lactic acidosis - Pancreatitis - Risk of nephrotoxicity - Risk of myopathy and neuropathy - Risk of renal and bone toxicity

Abbreviations: TDF, Tenofovir disoproxil fumarate; TEN, Tenofovir alafenamide

Adapted from: Bhattacharya et al Clin Infect Dis 2010; 51: 1201-8.

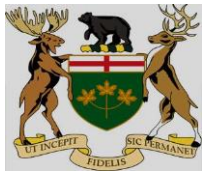
- Measurement of Response

Variable	Definition
– Biochemical response	▪ Normalization of ALT levels
– Serological response	▪ HBeAg loss and seroconversion to anti-Hbe in HBeAg+ patients ▪ HBsAg loss and development of anti-HBs in all patients
– Primary non-response	▪ <1 log10 IU/ml decrease in HBV DNA from baseline at 3 months of therapy with NA
– Virological response	▪ Undetectable HBV DNA usually evaluated every 3– 6 months during therapy with NA ▪ An HBV DNA concentration <2000 IU/ml in patients treated with PEG-IFN
– Partial virological response	▪ Decrease in HBV DNA of >1 log10 IU/ml, but detectable HBV DNA after ≥ 6 months therapy with NA
– Virological breakthrough	▪ Defined as an increase in HBV DNA level of >1 log10 IU/ml compared to the nadir HBV DNA on therapy with NA

Source: EASL. J Hepatol 2012; 57: 167-85.

- Comparison of NAs and interferon

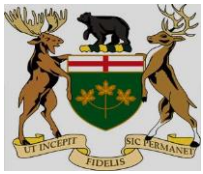
Advantages and disadvantages of pegylated interferon and oral nucleoside and nucleotide analogs as treatment for chronic HBV infection



Variable	Pegylated Interferon	Oral Agents
– Administration	▪ Subcutaneous injection	▪ Oral
– Tolerability	▪ Multiple side effects, dose reductions, discontinuations	▪ Well tolerated
– Monitoring	▪ Cytopenias, TSH, depression	▪ Serum creatinine for nucleotides
– Treatment duration	▪ Finite (48 wk)	▪ >1 yr in > 80% of patients
– Reduction in HBV DNA log (copies/mL)		
– - HBeAg-positive patients	4.5	3.5-6.9
– HBeAg-negative patients	4.1	3.9-5.2
– HBeAg seroconversion during therapy (%)	30	20
– HBeAg seroconversion with longer therapy (%)	NA	30 at 2 yr; 40-50 at 3-5 yr

Variation	Pegylated Interferon	Oral Agents
– Durability of HBV DNA suppression after treatment in HBeAg-negative patients (%)	13-18 at 3 yr	7 at 24 wk (lamivudine)
– Loss of HBeAg (%)		
▪ HBeAg-positve patients	3 at 1 yr	0-3 at 1-yr, 3-5 at 2 yr
▪ HBeAg-negative patients	4 at 1 yr, 8 at 3 yr after completion of 1 yr of therapy	≤ 1 at 1 yr, 5 at 4-5 yr (adefovir)
– Antiviral resistance (%)	None	Lamivudine, adefovir, and telbivudine: 0-30 at 1 yr and 3-40 at 2 yr; entecavir and tenofovir: 0 at 1 yr; entecavir: < 1 at 4 yr
– Cirrhosis		
▪ Decompensation	Contraindicated	Can be lifesaving
▪ Compensated	Not recommended	Shown to prevent decom-pensation

Source: Dienstag. NEJM 2008; 359: 1486-500.



- Treatment withdrawal
  - Withdrawal of nucleos(t)ide analogs can be considered 6-12 months after:
    - Anti-HBe seroconversion in patients who are HBeAg positive before they start treatment
    - After HBsAg loss in those who are HBeAg negative at the start of treatment

Guideline recommendations for management of antiviral resistance in patients with hepatitis B virus infection

Drug	AASLD (2009)	EASL (2012)
○ Lamivudine	Add adefovir or tenofovir	Switch to tenofovir if tenofovir not available
○ Telbivudine	Add adefovir, switch to emtricitabine	Switch to or add tenofovir
○ Adefovir	Add lamivudine; switch to or add entecavir; switch to or add tenofovir	Switch to entecavir or tenofovir if naïve to lamivudine; switch to tenofovir and add nucleoside analogue if has been exposed to lamivudine
○ Entecavir	Switch to tenofovir or tenofovir + emtricitabine	Switch to or add tenofovir

Abbreviations: AASLD, American Association for Study of Liver Diseases; EASL, European Association for the Liver

Source: Sundaram et al. BMJ 2015; 351: h4263.

Special Populations

❖ HBV in pregnancy

➢ Demography

- The risk of vertical transmission can be as high as 90% at birth in babies without vaccination

➢ Immunoprophylaxis

- Infants of all HBsAg-positive women should receive immunoprophylaxis
  - HBV vaccination
  - Hepatitis B immunoglobulin
- Pregnant women with immune-active HBV should receive treatment just as non-pregnant women

➢ Treatment

- HBV DNA for which antiviral therapy is routinely recommended in chronic carriers is >2 x 105 IU/mL
- The only antivirals studied in pregnant women are lamivudine, telbivudine, and tenofovir
- Antiviral therapy should be started at 28-32 wks of gestation
- In most studies antiviral therapy was discontinued at 0-3 mon postpartum
- With discontinuation, women should be monitored for ALT flares every 3-6 mon
- Continue breastfeeding
  - Breastfeeding is not contraindicated in chronic HBV carriers
  - Antivirals are minimally excreted in breast milk and are unlikely to cause significant toxicity
  - The unknown risk of low-level exposure to the infant should be discussed with mothers

- Delivery
  - C-section is not indicated as part of treatment as there is insufficient data to support benefit

Source: Terrault et al. Hepatology 2016; 63: 261-83.

❖ HBV and Healthcare Workers (HCW)

- Chronic carriers may require treatment even if they don't fulfill typical treatment indications to reduce direct transmission during procedures
- Antivirals should be started to reduce levels of HBV DNA to undetectable or at least to <2000 IU/ml before resuming exposure-prone procedures
- Frequently monitoring for compliance and efficacy in practicing healthcare workers is required

Source: Gunson et al. J Clin Virol 2003; 27: 213-30.

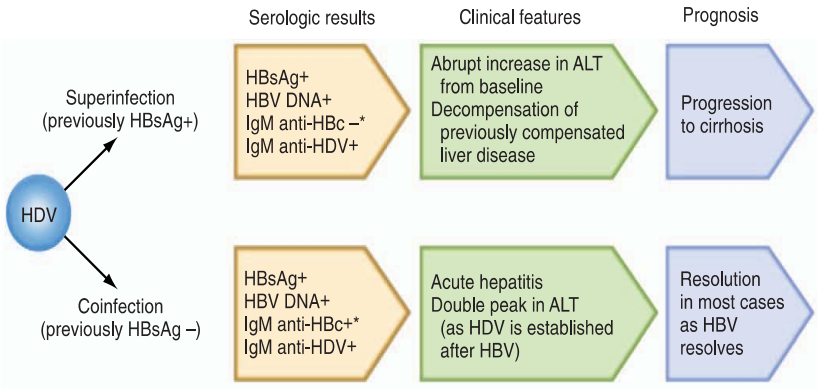
❖ HBV and HDV

➢ Demography

- HDV is a unique nuclear antigen dependent on HBV for complete virion assembly and secretion

➢ Virology

- The global burden of HDV infection is between 15 and 20 million with the highest prevalence in South America and the Mediterranean basin.
- Co-infection or superinfection typically manifests as self-limited acute hepatitis.
- Diagnosis can be made with anti-HDV (IgM and IgG) and HDV RNA
- Superinfection vs co-infection



Printed with permission: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th edition. Chapter 78: Hepatitis B and D.

- Treatment
  - The only therapeutic option available is pegylated-interferon alpha
  - The efficacy is related to the dose and duration of treatment which may need to be > 1 yr
  - About 25–40% of treated patients have a sustained response
  - NAs are not effective for treatment of HDV
  - Prevention of HDV can occur with vaccination for HBV in patients not infected with HBV

- HBV and HIV Co-infection
  - Chronic HBV and HIV co-infected patients are at increased risk of cirrhosis and HCC
  - Treatment of only HIV may lead to flares of hepatitis B due to immune reconstitution

- In patients not requiring HAART, therapy for HBV should be based on agents with no HIV activity
- In patients with CD4 counts <350/mm3, dual anti-HIV and anti-HBV agents should be used
- Co-infection accelerates the progression of liver disease and increases the risk of HCC
- HCV tends to be the predominant virus in co-infected patients with HBV DNA levels often being low or undetectable
- SVR rates for HCV tend to be similar in co-infected patients and only HCV infected patients
- HBV reactivation can occur in co-infected patients that are treated for HCV

Source: EASL. J Hepatol 2012; 57: 167-85.

❖ HBV Reactivation

- HBV persists in all infected patients, even in those with evidence of serological recovery
- There is a risk of viral reactivation in patients with HBV who receive immunosuppression
- Patients should be screened for hepatitis B with serology +/- DNA prior to immunosuppression
- Risk of reactivation is based on serologic status as well as the immunosuppressive therapy

Source: Terrault et al. Hepatology 2016; 63: 261-83.

- Clinical scenario
  - Cancer chemotherapy
  - Solid organ transplantation
  - Bone marrow or stem cell transplantation
  - Immunosuppressive therapy for benign conditions (e.g., rheumatoid arthritis, psoriasis, and inflammatory bowel disease)

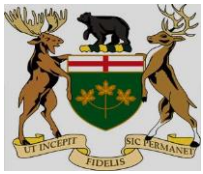
- Drugs associated with HBV reactivation
  - Corticosteroids
  - Conventional chemotherapeutic agents
  - Injectable or infused biological (e.g., anti-CD20, anti-tumor necrosis factor)

Source: Di Bisceglie et al. Hepatology 2015; 61: 703-11.

- Risk of reactivation

Therapy	HBsAg-positive	HBsAg-negative, anti-HBc-positive
○ Anti-CD20	Very high	Moderate
○ Hematopoiectic stem cell transplantation		
○ High-dose corticosteroids*	High	Low
○ Other cytokine inhibitors (e.g., anti-CD52)		
○ Combination cytoxic chemotherapy+ (without corticosteroids) ○ Anti-tumour necrosis factor ○ Anti-rejection therapy for solid organ transplant recipients	Moderate	Rare
○ Methotrexate ○ Azathioprine	Low	Rare
○ Androgen deprivation therapy ○ Estrogen and progesterone blockers	No known effect	No known effect

Source: Di Bisceglie et al. Hepatology 2015; 61: 703-11



- Treatment
  - HBsAg positive
    - Treat prior to chemotherapy, immunosuppressive therapy, HSCT, or solid organ transplantation
  - HBsAg negative, but anti-HBc positive patients receiving anti- CD20 therapies, HSCT, or solid organ transplantation
  - Antivirals which can be used include
    - Lamivudine
    - Entecavir
    - Tenofovir
  - Treatment should be continued for at least 6 months after therapy completed

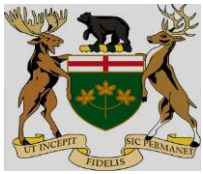
Source: Di Bisceglie AM, et al. Hepatology 2015; 61(2): 703-11.

- Occult HBV Infection
  - HBV DNA in the liver and absence of detectable HBsAg +/- presence of serum HBV DNA
  - HBV DNA levels are often less than 200 IU/mL
  - More common in patients with hepatitis C
  - Patients with negative HBsAg but with serum HBV DNA comparable to overt HBV
    - Classified as having false occult HBV
  - Patients with false occult HBV should be treated in the same manner as those with overt HBV infection

Source: Liang TJ. Hepatology 2009; 49 (5 Suppl): S13-21.

- Prevention (HBV vaccination)
  - Neutralizing antibody anti-HBs is produced against the “a” epitope of HBsAg by HBsAg-specific helper T cells, and by T cell-dependent B cells.
  - Protective levels of anti-HBs occur in > 90% of persons who are vaccinated with HBsAg.
  - Anti-HBc with mild disease
  - After HBV vaccination, subclinical HBV infection may occur, either because
    - Over time the titre of anti-HBs may have fallen to levels which are no longer protective (25% to 50% of vaccinated persons develop non-protective levels of anti-HBs over 5 to 10 yr)
    - Initial hyporesponders, with the development of low and non-protective concentrations of anti-HBS
      - Booster doses of vaccine are needed
  - In hemodialysis patients
    - In persons who are immunosuppressed
  - Some persons with low or no anti-HBS after vaccination appear to be protected
  - HBV anti-core^{+} can reactivate with Prednisone, azathioprine, anti-TNF therapy
  - Patients on infliximab are at risk for vaccine-preventable HBV.
  - Older age, lower albumin levels, and the presence of pancolitis are risk factors for the absence of protective antibodies against HBV.
  - A significant minority of previously vaccinated patients do not respond to an HBV booster, indicating that they are not at risk for HBV infection.

Source: Mosses J, et al. Am J Gastroenterol 2012; 107: 133-138.



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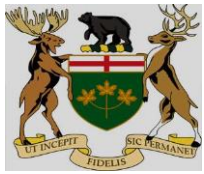
- Give causes of ground-glass hepatocytes.
  - Chronic HBV
  - DILI (drug-induced liver injury)
  - Fibrinogen storage disease
  - Glycogenesis, type IV

- Give 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 (MSM)
  - 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 persons with more than one partner
  - Staff and clients of institutions for developmentally disabled persons

SO YOU WANT TO BE A HEPATOLOGIST!

- Give reasons why a person immunized with HBs-Ag vaccine may not develop an adequate anti-HBs response.
  - Person
    - Very young, or old (> 50 yrs)
    - Obese
    - Smoking
    - Chronic liver disease
    - Immunosuppressed
      - Transplantation
      - Chemotherapy
      - Immunodeficient HIV positive
    - Co-infection
      - HIV
      - HCV
    - Administration of vaccine into buttock muscles
    - Genetic factors
      - HLA
    - Alleles DR3, DR7, DQ2
    - No HLA-A2
  - Vaccine -frozen
    - Wrong dose or timing of vaccine
  - Virus
    - Mutant HBV virus strains (HBV escapes mutants)



- 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

➢ Post-exposure prophylaxis for HBV

Vaccination Status of Exposed Persons	Prophylaxis
○ Not vaccinated	– HBIG 0.06 mL/kg x 1 dose, plus – HBV vaccination
○ Vacinated	
– Known responder	– No prophylaxis
– Known non-responder	– HBIG 0.06 mL/kg x 1 dose, plus – HBV vaccination or – HBIG 0.06 mL/kg x 2, time 0 and at 1 mon
○ Antibody response not known	– Test anti-HBs ▪ If > 10 mIU/L no treatment ▪ If < 10 mIU/L, HBIG x1 dose, plus vaccine booster

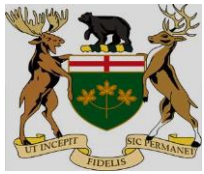
	HBsAg	HBcAb	Further action to victim
– Victim	-ve	+ve	None: Immune
– "Donor" (source)	+ve	-ve	Continue vaccine course
	-ve	-ve	None, or continue vaccine course if victim is at risk of further hepatitis B exposure

Adapted from: Sherlock S, and Dolley J. *Diseases of the Liver and Biliary System* (Eleventh Edition) 2002. pg. 285-303.

Please see *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, for the following additional information: Table 78.6, "High-Risk Groups for Whom Hepatitis B Virus (HBV) Vaccination Should be Considered", page 1308.

- Give the reason why it is important to distinguish between inactive HBV carrier state (stage III) from HBe-Ag negative chronic HBV infection.

	Prognosis	Risk of complications
○ Inactive HBV carrier	Good	Low
○ HBe-Ag negative CHB	Poor	High



Emerging Treatment

Treatment	Mechanism	Phase	Comments
○ Myrcludex-B	– Viral entry inhibitor	Ia	▪ Targets sodium taurocholate cotransporting polypeptide, a receptor for HBV entry
○ Bay 41-4109	– Viral nucleo-capsid inhibitor	I	▪ Part of heteroaryl-dihydropyrimidine family, which ↓ stability of viral capsid by misdirecting its assembly
○ GLS4	– Viral nucleo-capsid inhibitor	I	▪ Heteroaryldihydro-pyrimidine family
○ REP 9 AC	– HBsAg release inhibitor	Ib	▪ Blocks secretion of non-infectious subviral particles that may act as decoys to immune system; ▪ In combination with immune therapy may lead to HBsAg clearance
○ GS-9620	– Toll-like receptor 7 agonist	I	▪ Activation of toll-like receptor 7 induces innate immunity to inhibit HBV replication
○ DV-601	– Therapeutic vaccine	Ib	▪ Stimulates T and B cell antibody response against HBsAg comprises HBsAg HBcAg
○ Zinc finger proteins	– Block transcription cccDNA	Pre-clinical	
○ Disubstituted sulfonamides (CCC-0975 and CCC-0346)	– Reduce cccDNA levels	Pre-clinical	▪ Inhibit cccDNA production

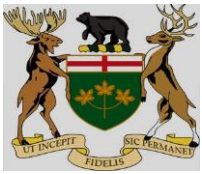
Abbreviations: cccDNA, covalently closed circular DNA; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen

Printed with permission: Sundaram et al. BMJ 2015; 351: h4263.

- Risk factors of cirrhosis and HCC

	Cirrhosis	HCC
○ Host	– >40 yr of age – Male sex – Immune compromised	– >40 yr of age – Male sex – Immune compromised – Positive family history – Born in sub-Sharan Africa
○ Viral disease	– High serum HBV DNA (>2,000 IU/mL) – Elevated ALT lelves – Prolonged time to HBeAg sroconversion – Development of HBeAg-negative CHB – Genotype C	– Presence of cirrhosis – High serum HBV DNA (>2,000 IU/mL) – Elevated ALT – Prolonged time to HBsAg seroconversion – Development of HBeAg-negative CHB – Genotype C
○ Environ-mental	– Concurrent viral infections (HCV, HIV, and HDV) – Heavy alcohol use – Metabolic syndrome (obesity, diabetes)	– Concurrent viral infections (HCV, HIV, and HDV) – Heavy alcohol use – Metabolic syndrome (obesity, diabetes) – Alfatoxin – Smoking

Printed with permission: Terrault et al. Hepatology 2016; 63: 261-83.



- Risk of HCC

HCC Surveillance

Cirrhosis	HCC Risk per yr
○ Hepatitis C	2-7%
○ Hepatitis B	3-5%
○ Gentic hemochromatosis	NA
○ Primary biliary cirrhosis	2-3%
○ Non-alcoholic steatohepatitis	NA
○ Alpha 1 antitrypsin deficiency	NA
○ Autoimmune hepatitis	NA
○ Hepatitis B carries without cirrhosis (HBV surface Ag+)	
– Asian males > 40 yr	0.4-0.6
– Asian females >50 yr	0.3-0.6
– Africans > 20 yr	NA
– Family history of HCC	NA

Source: El Serag et al. Ther Adv Gastroenterol 2011; 4: 5-10.

- Prevention
  - Pre-exposure
    - Vaccination
  - Post-exposure
    - HBV IVIG
  - All neonates*

- All chidren and adolescents not vaccinated at birthHigh-risk adults
  - Men who have sex with men (MSM)
  - People with multiple sexual partners (MSP)
  - Injection drug users
  - Patients on haemodialysis
  - Patients in institutions
  - Health-care workers (HCW) and public safety workers
  - Spouses, sexual partners, or household members of people who carry hepatitis B virus

*infants born to carrier mothers are also given hepatitis B immunoglobulin

Source: Trepo et al. Lancet 2014; 384:2053-63.

"The path to success is to take massive, determined action"

Tony Robbins

PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSING CHOLANGITIS

Anouar Teriaky

❖ **Primary Biliary Cholangitis** (PBC)

➢ Definition

- An autoimmune slowly progressive cholestatic liver disease characterized by
  - Biochemical cholestasis
  - Circulating anti-mitochondrial antibodies (AMA)
  - Characteristic liver biopsy findings

➢ Demography

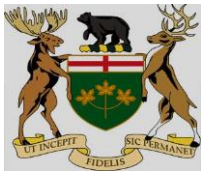
- Incidence ~$3/10^5$ person
  - Geographic variation, with a much higher prevalence in the North American and Northern Europe
- F>M 9:1
- Usually diagnosed between 30 and 65 yr of age

Source: Kim et al. Gastroenterology 2000; 119: 1631-6.

➢ Pathogenesis

- Give the pathoimmunology of primary biliary cholangitis (PBC).
  - Immune-mediated response to an unknown antigen (molecular mimicry)
  - Activation of CD4+ and CD8+ T lymphocytes, B cells, and NK cells
    - Aberrant polyclonal activation of B cells (↑ IgG, IgM)

- Breakdown of tolerance against mitochondrial antigens → production of autoantibodies against proteins on the inner membrane of mitochondria
  - AMA (anti-mitochondrial antibody, in 95% of PBC patients) directed against the E2 component of
    - PDC E2 (pyruvate dehydrogenase complex)
    - PDC E1a subunit of PDC
    - E3 BP subunit of PDC
    - BCO-ADC-E2 (branched-chain of 2-oxo-acid dehydrogenase complex)
- Molecular target is gene gp120 or nucleoprotein p62
  - Anti-gp 210 present in
    - AMA+PBC, 25%
    - Sensitivity AMA-PBC, 50%
    - Specificity, AMA+PBC, 99%, AMA-PBC, 25%
  - Gp 210 and p62 associated with poor prognosis
  - Gp 201 protein and AMA persist in serum after liver transplantation for PBC
- PDC-E2-specific CD4+ lymphocytes interact with duct cells in the small intrahepatic bile ducts
- This interaction of CD4+ and CD8+ T cells is facilitated by ICAM-1 (intracellular adhesion molecule 1)



- Clinical

Clinical Features	Prevalence	Mechanism
Fatigue	20-85%	– Manganese deposits in globus pallidum – ↑ inflammatory cytokines
Pruritus	20-75%	– Cholestasis – ↑ opiodergic tone
Jaundice	10-60%	– Cholestasis
Xanthomas	15-50%	– Hyper-cholesterolemia – Hyperlipidemia
Osteoporosis	35%	– Disturbances in bone remodeling (metabolic changes in PBC)
Dyslipidemia	>75%	– ↓ biliary secretion of cholesteroltoxic effects of unconjugated bilirubin

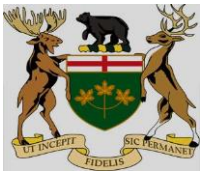
  - PDC-E2-specific CD4+ lymphocytes interact with duct cells in the small intrahepatic bile ducts
  - This interaction of CD4+ and CD8+ T cells is facilitated by ICAM-1 (intracellular adhesion molecule 1)
  - Natural History
    - AMA^+ 6 yr → ↑ AP, ↑ GGT 36-89%
    - Asymptomatic → 5-18 yr symptomatic
    - Median duration of survival
      - Asymptomatic ~16 yr
      - Symptomatic in 5-8 yr
  - Associated Autoimmune Diseases
    - Salivary glands
      - Sicca syndrome
    - Thyroid
      - Thyroid dysfunction

- GI
  - Celiac disease
  - Inflammatory bowel disease
- MSK
  - CREST
  - Raynaud phenomenon
  - Rheumatoid arthritis

- Pathogenesis
  - Genetics
    - Female gender
    - MHC, IL-12A, IL-12RB2 risk alleles
    - Innate immunity (IgM)
  - Environment
    - Bacterial mimics (e.g., Novosphingoblum aromaticivorans)
    - Xenobiotic chemicals
  - Immune response
    - Defective regulartory T cells
    - Production of AMAs
    - Autoreactive CD4/CD8 T cells to PDC-E2
  - Bile duct damage
    - Immune response, with bile duct apoptotic blebs and AMAs combined with macrophages

Souce: Younossi et al. Am J Gastroenterol 2018; epub

- Differential Diagnosis Cholestasis
  - Infection
    - Bacterial
    - Viral
    - Fungal
  - Immune
    - Sarcoidosis
    - Amyloidosis
    - PSC
    - IgG 4 cholangitis



- Infiltration
  - Bile duct malignancy
  - Lymphoma and solid organ malignancies
- Ischemic
  - Cardiac diseases
- Iatrogenic
  - Drug induced cholestasis
- Endocrine/biochemical
  - Gallstone
  - Endocrine disfunction
- Inherited/familial
  - Intrahepatic cholestasis of pregnancy
- Hepatic disease
  - Total parenteral nutrition
  - Viral hepatitis

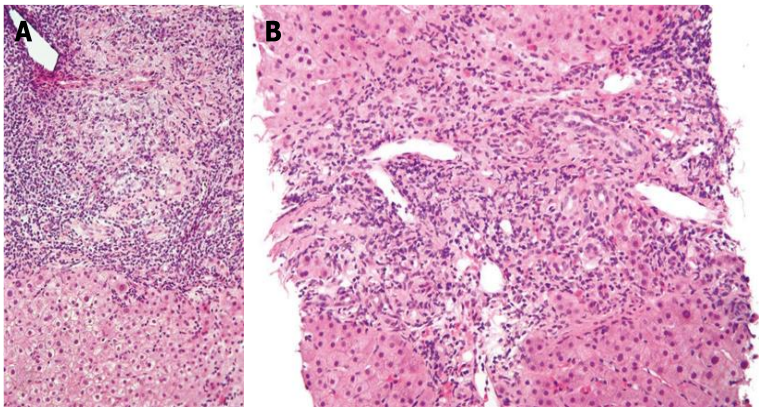
Source: Lindor et al. Hepatology 2009; 50: 292-308.

➢ Laboratory

❖ Autoantibodies

- Anti-mitochondrial antibody (AMA)
  - Most specific serological marker
  - Detected in > 90%
  - ANA ~70%
- AMA-negative PBC (40%)
  - Similar clinical/laboratory characteristics to AMA^+ - PBC
  - Liver biopsy necessary to diagnose PBC in AMA^- (seronegativity)
- AMA-negative PBC and classic PBC have similar clinical findings and laboratory characteristics
- Exclude other causes of cholestatic liver disease

➢ Histopathology



- Findings
  - Non-suppurative distractive cholangitis
  - Interlobular bile obstruction

Printed with permission: Purohit T. World J Hepatol 2015; 7: 926-41.

Ludwig Classification of Histopathology of PBC

Histologic Stage	Description
1	– Portal inflammation – Florid bile duct lesion
2	– ↑ size of periportal lesions – Interface hepatitis
3	– Distrotion of hepatic architecture – Fibrous septa
4	– Cirrhosis

- Diagnosis
  - The diagnosis of PBC is made provided ≥ 2 of the following criteria are satisfied:
    - ALP > 1.5x ULN for > 24 wk
    - AMA titer > 1:40
    - Compatible liver histology
      - Non-suppurative destructive cholangitis
      - Interlobular bile duct destruction

- Prognostic Models
  - 1 yr post-diagnosis values of ALP, bilirubin
    - Transplantation-free survival (Lammers et al. Gastroenterology 2014; 147: 133-49)
  - The Mayo Risk score (Dickson et al. Hepatology 1989; 10: 1-7)
    - Best and most widely used prognostic system
    - Incorporates age, serum bilirubin, albumin, prothrombin time, and degree of edema
    - This risk score is used to calculate expected patient survival for up to 7 yr of follow- up
    - Score of 7.8 is considered the optimal time for liver transplantation evaluation
  - Other score system (EASL. J Hepatol 2017; 67: 145-72)

	MRS	UK-PBC	Globe
Age	+	-	+
AP	-	+	+
Bilirubin	+	+	+
AST	-	+	
Albumin	+	+	+
Platelets	-	+	+
INR/PT	+		
Peripheral edema diuretics	+		

➢ Treatment

❖ Ursodeoxycholic acid (UDCA)

- Mechanisms of action
  - Protection of
    - Cholangiocytes from cytotoxicity of hydrophobic bile acids by modulating the composition
    - Hepatocytes against bile acid-induced apoptosis
  - ↑ biliary secretion of bile acids
- Recommended daily administered dose of 13-15 mg/kg per day
  - Symptoms
  - AP, GGT, IgM, HDL cholesterol
  - ↓ abnormal labs/histopathology
  - ↓ AMA
  - Ludwig histopathology grade
- Beneficial effect of UDCA on survival not shown

Goulis J, et al. Lancet 1999; 354: 1053-60.

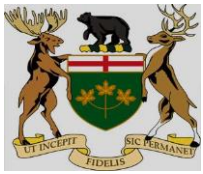
❖ Corticosteroids

- Prednisolone
  - Improved serum liver tests and histological features
  - Markedly worsened bone mineral density
  - Budesonide plus UDCA showed
    - Improvement in biochemical and histological parameters in early, but
    - No improvement in late stage disease

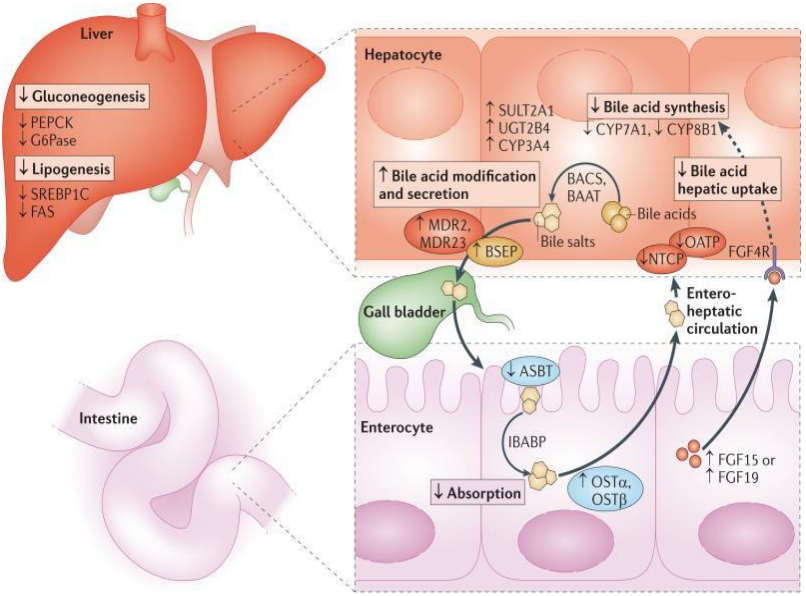
Angulo P et al. Hepatology 2000;31:318-23; Hempfling W et al. Hepatology 2003;38:196-202.

❖ UDCA and Fibrates

- ↓ AP, ↓ GGT, ↓ IgM



- Obetacholic acid

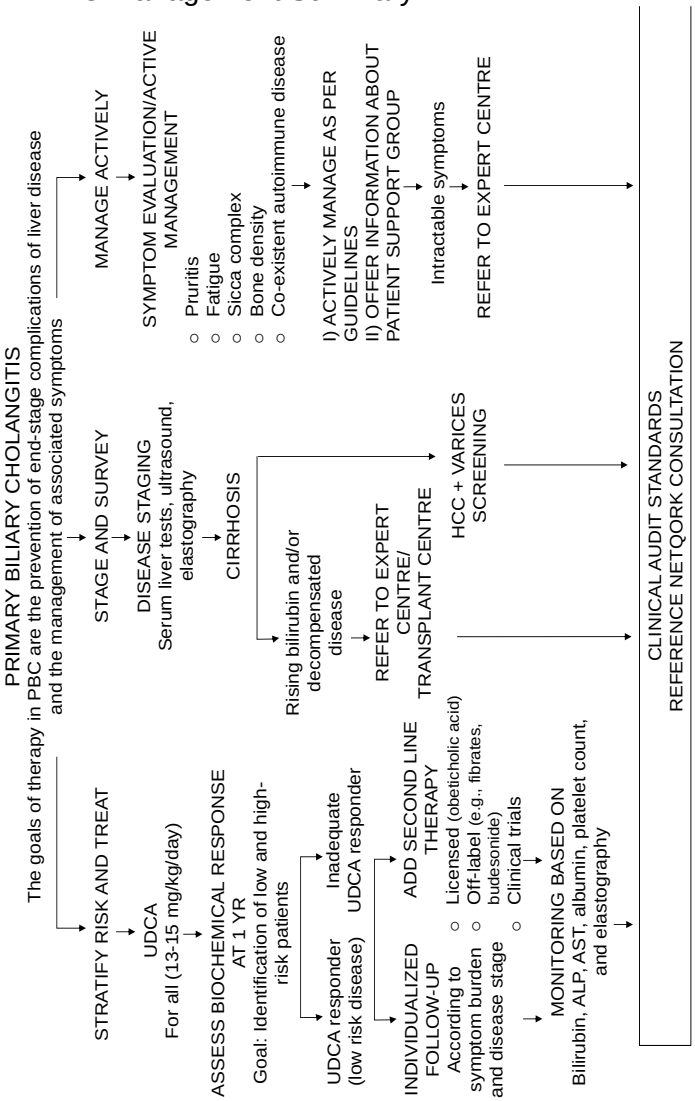


Printed with permission: Calkin AC and Tontonoz P. Nat Rev Mol Cell Biol 2012; 13: 213-24.

- Liver Transplantation
  - PBC is a common but decreasing indication for liver transplantation
  - Liver transplantation should be strongly considered in patients when:
    - Bilirubin approaches 103 umol/L
    - Mayo risk score is >7.8
    - MELD score is >12
  - Survival post-transplant rates
    - 1 yr > 90%
    - 5 yr 80-85%

Source: Goulis J et al. Lancet 1999;354:1053-60.

❖ PBC Management Summary



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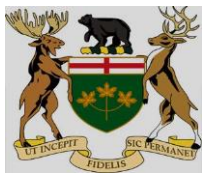


❖ **Primary Sclerosing Cholangitis** (PSC)

- Definition
  - A chronic cholestatic liver disease characterized by progressive inflammation, fibrosis, and stricturing of the bile ducts
- Demography
  - Incidence
    - $1/10^5$ person-yr
    - M>F 2:1
  - Prevalence 6-21/10^5
  - Median age at diagnosis
    - 40 yr

Source: Molodecky et al. Hepatology 2011:53: 1590-9.

- Clinical
  - Signs and Symptoms
    - Pruritus
    - Fatigue
    - Jaundice
    - RUQ Pain
    - Fever and Chills
    - Hepatomegaly
    - Splenomegaly
    - Osteopenic Bone Disease

- Natural History
  - 10-yr survival ~65%
  - Survival if symptomatic at the time of diagnosis
  - Median survival after diagnosis and without liver transplantation 10 to 12 yr

Boberg KM, et al. Hepatology 1996; 23: 1369-76.

➢ Complications

❖ Dominant Biliary Stricture

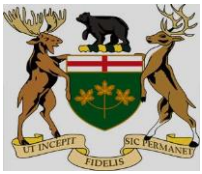
- A stenosis with a diameter of ≤1.5 mm in the common bile duct or of ≤1 mm in the hepatic duct
  - Patients can be symptomatic
- Occurs in ~50% of persons with PSC
- Should raise the suspicion of cholangiocarcinoma (CCA)
- Endoscopic or percutaneous therapeutic approaches are used for management
- Brush cytology and/or endoscopic biopsy with FISH should be obtained to help exclude malignancy

Source: Stiehl et al. J Hepatol 2002; 32: 151-56.

❖ Bacterial cholangitis

- Bacterial cholangitis can occur in patients with PSC and can be
  - Induced (ERCP) or
  - Spontaneous due to
    - Stones
    - Strictures
- Severe recurrent cholangitis may play a role in the progression of PSC
- Most patients respond to therapeutic drainage of the obstruction plus antibiotics
- Occasional patients with recurrent bacterial cholangitis may benefit from prophylactic long term antibiotics

Source: Chapman R, et al. Hepatology 2010; 51: 660-78.



- Cholangiocarcinoma (CCA)
  - Most common hepatobiliary malignancy in PSC
    - A cumulative lifetime risk of 10-15%
  - Up to 50% of CCA diagnosed within the first yr of diagnosis of PSC
  - CA 19-9 significantly higher in PSC patients with CCA than in those without
    - CA19-9 not adequate by itself for screen
      - CA 19-9 combined with cross-sectional liver imaging may be useful as a screening strategy

Source: Lazaridis KN and Gores GJ. Semin Liver Dis 2006; 26: 42-51.

- Gallbladder Cancer
  - Gallbladder mass lesions in PSC frequently represent adenocarcinomas independently of their size
  - The prevalence of gallbladder cancer among patients with PSC ~ 3-14%
  - Annual screening for gallbladder cancer using ultrasound is recommended
  - Cholecystectomy is recommended in PSC patients with a gallbladder mass even <1 cm

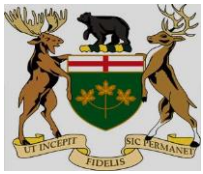
Source: Razumilava et al. Hepatology 2011; 54: 1842-52.

- ❖ UC plus PSC - ↑ risk of colorectal cancer (CRC)
  - ○ ↑ risk of CRC and dysplasia compared with patients with UC alone
    - – OR 4.79 (95% CI 3.58-6.41)
    - – Perform surveillance colonoscopy q 1-2 yr intervals from time of diagnosis of PSC
  - ○ CRC associated with PSC has a predilection for the proximal colon
  - ○ Patients with PSC who have CD plus Crohn colitis are surveyed similarly to patients with UC
  - ○ Persons with PSC without UC do not have ↑ risk of CRC
    - – Clinician must have low threshold to perform colonoscopy plus mucosal biopsies if there are colonic symptoms suggestive of onset of UC (if UC diagnosed in PSC) this would lead to annual colonoscopies plus biopsies to exclude dysplasia/cancer

- ➢ Laboratory
  - ○ Autoantibodies

Antibody	Prevalance
– Anti-neutrophil cytoplasmic antobody	50-80%
– Anti-nulcear antibody	7-77%
– Anti-smooth muscle antibody	13-20%
– Anti-endothelial cell antibody	35%
– Anti-cardiolipin antibody	4-66%
– Thyroperoxidase	7-16%
– Thyroglobulin	4%
– Rheumatoid Factor	15%

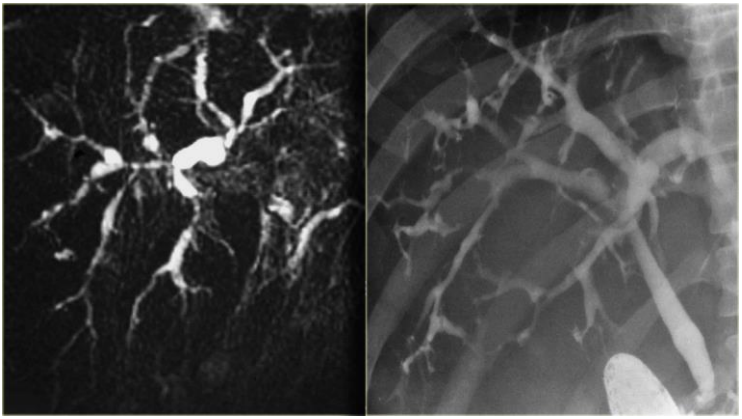
Source: Chapman R, et al. Hepatology 2010; 51: 660-78.



- Diagnosis
  - ↑ cholestatic serum markers
  - MRCP/ERCP
    - Characteristic bile duct changes with multifocal strictures and segmental dilatations
  - Causes of secondary sclerosing cholangitis / other cholestatic disorders are excluded
  - Small duct PSC
    - Clinical, biochemical and histological features of PSC
    - Normal cholangiogram
  - Better prognosis than classic PSC
    - May evolve into classic PSC

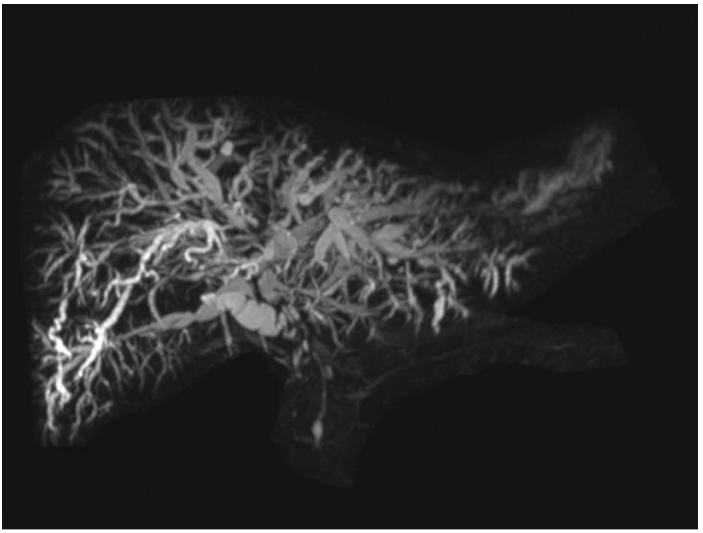
Source: Broome et al. J Hepatol 2002; 36: 586-9.

- Diagnotic imaging
  - MRCP
  - Cholangiogram



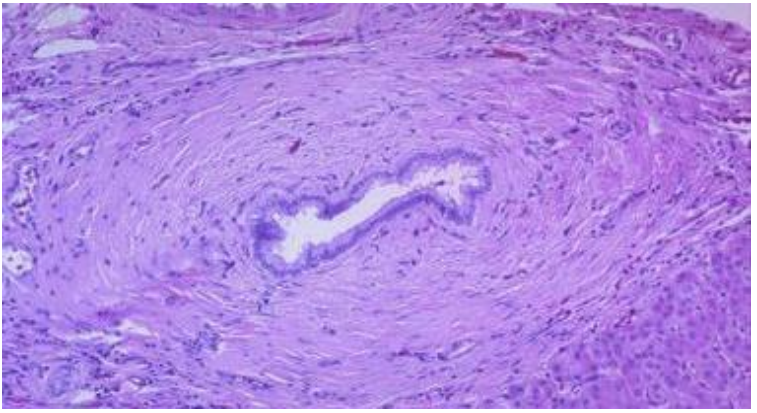
Source: www.radiologyassistant.nl

- MRCP



Printed with permission: Gossard AA and Gregory JG. Clin Liver Dis 2017; 21: 725-37.

- Histopathology



- “onion skin” appearance

Secondary Sclerosing Cholangitis

- Causes
  - AIDS cholangiopathy
  - Cholangiocarcinoma
  - Cholangitis
  - Choledocholithiasis
  - Diffuse Intrahepatic Metastasis
  - Eosinophilic Cholangitis
  - Hepatic Inflammatory Pseudotumor
  - IgG4-associated
  - Intra-arterial Chemotherapy
  - Ischemic Cholangitis
  - Mast Cell Cholangiopathy
  - Portal Hypertensive Biliopathy
  - Recurrent Pancreatitis
  - Histocytosis X
  - Recurrent Pyogenic Cholangitis
  - Surgical Biliary Trauma

PSC and IBD

- Associations
  - UC in PSC ~70%
  - PSC in UC ~5%
- A screening colonoscopy is necessary in all patients diagnosed with PSC

➢ Prognosis

- Mayo risk score includes
  - Patient
    - Age
    - History of variceal bleeding
  - Laboratory
    - ↑ bilirubin
    - ↓ albumin
    - ↑ AST, and.
  - Patients can be divided into the low, intermediate, and high-risk groups
  - Useful in assessing prognosis and determining timing for liver transplantation

➢ Treatment

❖ Ursodeoxycholic acid (UDCA)

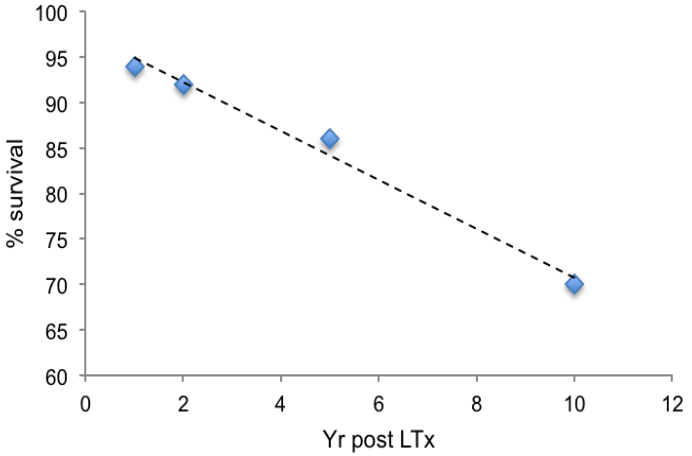
- Minimal benefit at 15 mg/kg/day
  - Some improvement biochemical abnormalities
  - No improvement in
    - Cinical symptoms
    - Survival benefit
    - Need for liver transplantation
- High doses of UDCA in PSC → poorer outcomes

Source: Shi et al. Hepatol Res 2009; 39: 865-73.

- Immunosupressive Therapy
  - No benefits
    - Anti-TNF (infliximab, etanercept, pentoxyfilline)
    - Azathioprine
    - Cyclosporine
    - Glucocorticoids
    - Methotrexate
    - Penicillamine
    - Tacrolimus

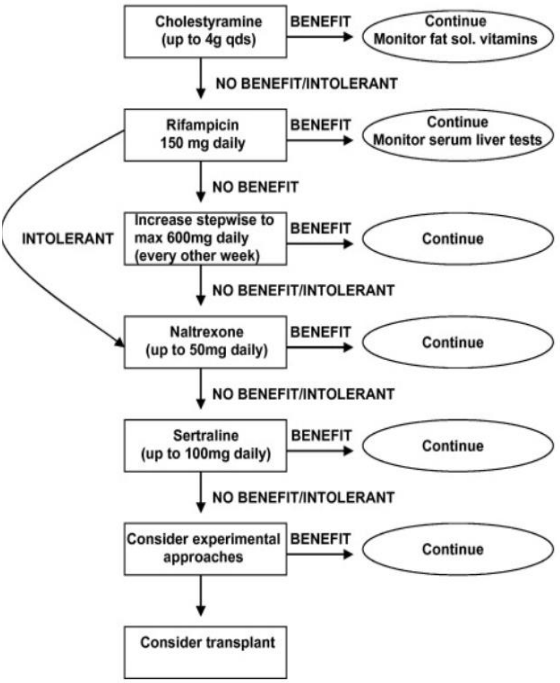
Source: Chapman et al. Hepatology 2010; 51: 660-78.

- Liver Transplantation (LTx)
  - Treatment of choice for patients with advanced liver disease due to PSC
    - Refer once MELD score ≥15
    - Also consider patients with
      - Recurrent cholangitis
      - CCA, or
      - Refractory pruritus



Adapted from: Dickson et al. Gastroenterology 1992; 103; 1893-901.

Symptomatic Treatment of Pruritis in PSC



Printed with permission: EASL. J Hepatol 2009; 51: 237-67.

Overlap Syndrome

- Some patients do not fit discretely into a specific subgroup or diagnostic category
- Controversy as to whether these overlap syndromes represent distinct entities
- These overlap syndromes include:
  - Autoimmune hepatitis (AIH)/PBC
  - Autoimmune hepatitis (AIH)/PSC

Variant Forms of AIH

	AIH+ PBC	AIH+ PSC	AIH+Cholestatic Features	Autoantibody-negative AIH
○ Clinical and laboratory features	- AIH features - AMA+	- AIH features - Ulcerative colitis - AMA- - Abnormal cholangiogram - Normal cholangiogram (small duct disease)	- ANA and/or SMA+ - AMA- - No ulcerative colitis - Normal cholangiogram	- AIH features - No auto-antibodies HLA-DR3 or DR4
○ Histology	- Cholangitis - Cholestasis	- Cholangitis - Cholestasis	- Cholangitis - Cholestasis	- Interface hepatitis
○ Treatment	- Prednisone if AP ≤ 2x ULN - Prednisone and UDCA if AP > 2x ULN and/or florid duct lesions	- Prednisone and UDCA	- Prednisone and/or UDCA depending on AP level and histologic features	- Conventional regimens for AIH

Source: Czaja AJ. Chapter 88. Sleisenger Fordtran. Gastrointestinal and Liver Disease. 9th edition

ALCOHOLIC HEPATITIS (AH) SCORING SYSTEMS

Matthew Cheah

- Demography
  - Alcoholic hepatitis (AH) occurs in persons who consume > 100 g/day for > 20 yr
  - 7% of AH patients are admitted to hospital, and
  - Of those with severe disease 40% die within 6 mon of clinical presentation

- Clinical/laboratory

- Maddrey Discriminant Function (DF)
  - DF = (4.6 x [prothrombin time (sec) - control prothrombin time (sec)]) + (serum bilirubin/17.1)
    - Approximate 28 day rate
      - DF > 32, 40%
      - Hepatic encephalopathy (HE) 50%
      - Hepatorenal syndrome (HRS) 75%

  - Alcoholic hepatitis score calculator
    - Age ☐ yr
    - Bilirubin ☐ µmol/L
    - INR ☐
    - Albumin ☐ g/L
    - Urea ☐ mmol/L
    - Creatinine ☐ µmol/L
    - Sodium ☐ mmol/L
    - White cell count ☐ $x10^9/L$
    - Hepatic encephalopathy ☐
    - Ascites ☐

Renal replacement twice in last wk ☐ Yes ☐ No

☐ I know my patient's prothombin time ☐ Seconds

☐ Estimate PT from INR

ISI: ☐

Reference PT: ☐ seconds

- AH Score for your patient
  - Maddrey Discriminant Function
    - Severe disease ≥ 32
    - 28 day mortality rate
  - Glasgow Alcoholic Hepatitis (GAH) Score
    - Severe disease ≥ 9 (benefit from treatment)
  - MELD (30 d mortality rate ≥ 12 yr
    - Severe disease ≥ 21
      - Option: Sn, 86%; Sp, 81%
  - Lille Score (predictor of steroid response after 7 days of therapy)
    - ≤ 0.16; complete responder
    - 0.16-0.56; partial responder
    - ≥ 0.56; null responder
  - ABIC Score (predicts 90 day mortality)
    - ≤ 6.71; low risk
    - 6.71-9.0; intermediate risk
    - ≥ 9.0; high risk

Abbreviations: HE, hepatic encephalopathy; HRS, hepatorenal syndrome; MELD, Model for End Stage Liver Disease; Sn, sensitivity; Sp, specificity;

- ❖ Lille Model
  - 3.19 - 0.101 x age (yr) + 0.147 x albumin (g/l) on day 0 + 0.0165 x change in bilirubin on day 7 (mmol/l) - 0.206 x renal insufficiency (rated as 0 if absent and 1 if present) - 0.0065 x bilirubin level on day 0 (in mmol/l) - 0.0096 x prothrombin time (in s).

- ❖ ABIC Score

Glasgow Alcoholic Hepatitis (GAH) Score in Adults and Adolescents

- [(age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine×0.3)+(INR×0.8)].
- Prediction of 90d survival

		Sensitivity	Specificity
– Low	6.7	100%	50%
– Medium			
– High	9.0	70%	33%

- Age
  - <50 yr old (1 point)
  - ≥ 50 yr old (2 points)
- WBC
  - $<15x10^9$/L (1 point)
  - ≥ $15x10^9$/L (2 points)
- Urea
  - < 14mg/dL (5 mmol/L) (1 point)
  - ≥ 14mg/dL (5 mmol/L) (2 points)
- INR
  - < 1.5 (1 point)
  - 1.5-2 (2 points)
  - >2 (3 points)

- Bilirubin
  - < 7.3 mg/dL (125 µmol/L) (1 point)
  - 7.3-14.6 mg/dL (125-250 µmol/L) (2 points)
  - > 14.6 mg/dL (250 µmol/L) (3 points)

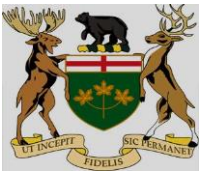
Total criteria point count ☐

- Patients with a score ≥ 9 may benefit from treatment with corticosteroids

AHHS for Prognostic Stratification of AH (2014)

	Points
Stage of fibrosis	
– No fibrosis or portal fibrosis	0
– Expansive fibrosis	0
– Bridging fibrosis or cirrhosis	+3
Billirubinostasis	
– No	0
– Hepatocellular only	0
– Canalicular or ducular	+1
– Canalicular or ductular plus hepatocellular	+2
PMN infiltration	
– No/Mild	+2
– Severe	0
Megamitochondria	
– No megamitochondria	+2
– Megamitochondria	0

Categories
0-3 Mild
4-5 Intermediate
6-9 Severe



- Treatment

- Management Principles:
  - Total abstinence from Alcohol
  - Hydration plus nutrition
  - Complications of concomitant cirrhosis
  - Definition of severe AH
    - Hepatic encephalopathy (HE)
    - Prolongation of PT (↑ INR)
    - ↑ bilirubin
    - Renal insufficiency (↑ Cr_s)
    - Severe patients >40% mortality
  - Pharmacological options
    - Glucocorticoids
    - Pentoxifylline
    - Discontinuation of NSBB previously prescribed for prophylaxis of esophageal variceal hemorrhage
    - NAC, GSCF, Oxandrolone
  - Use scoring system for severity of AH

BACTERIAL, PARASITIC AND FUNGAL LIVER INFECTIONS

Cassandra Townsend

- Mechanism
  - The liver serves as the initial site of filtration of absorbed intestinal contents
  - Can be affected by:
    - Viruses
    - Spread of bacterial or parasitic infection from outside the liver
    - Primary infection by spirochetal, protozoal, helminthic, or fungal organisms
    - Systemic effects of bacterial or granulomatous infections

❖ **Bacterial Infections**

- Gram positive and gram-negative bacteria
  - S. Aureus or GAS
    - Both of these organisms can be responsible for triggering Toxic Shock Syndrome (antigen causes T cell activation and massive cytokine release)
    - S Aureus risk factors: tampon use, surgical site infection
    - Typical findings include a scarlatiniform rash, mucosal hyperemia, hypotension, vomiting, and diarrhea
    - Liver involvement can range, but could include,
      - Transaminitis
      - Jaundice
      - Necrosis
    - Histology:
      - Microabscesses, granulomas
    - Diagnosis of microbe is confirmed by blood culture (nec fasc = clinical diagnosis)
    - Treatment
      - Necrotizing fasciitis – surgical intervention
      - Antibiotic – clinda in case of GAS, +/- IVIG (no definitive evidence according to IDSA guidelines)

- Clostridium perfringens
  - Mixed anaerobic infection
  - High mortality rate – hepatic involvement not predictive of mortality but poor prognosis in patients with cirrhosis
  - Clinical presentation:
    - Rapid development of local wound pain, abdominal pain, and diarrhea
    - Skin lesions become discolored and even bullous, and gas gangrene spreads rapidly
  - Liver involvement:
    - Jaundice
      - May develop in up to 20% of patients with gas gangrene and is predominantly a consequence of massive intravascular hemolysis caused by an exotoxin elaborated by the bacterium
    - Abscess
    - Gas in portal vein
  - Treatment
    - Surgical debridement with wide excision
    - Antibiotics – penicillin and clindamycin

- Actinomyces
  - Gram positive anaerobe (most commonly Actinomyces israelii)
  - Sites
    - Cervicofacial infection
    - GI involvement in 15-60%
    - Hepatic involvement in 15% - spread from other abdominal sites

  - Can get fistulization to pleural space or other surrounding tissues
- Clinical
  - Fever, abdominal pain, anorexia and weight loss
- Investigations
  - Anemia, leukocytosis, an elevated erythrocyte sedimentation rate, and an elevated serum alkaline phosphatase level
  - Radiographic findings are nonspecific; multiple abscesses may be seen in both lobes of the liver
- Diagnosis
  - Aspirate from abscess cavity or positive culture
- Treatment
  - Antibiotics (penicillin or tetracycline)
  - Abscess drainage as appropriate

- Listeria monocytogenes
  - Uncommon to involve the liver
  - Can develop abscess or acute granulomatosis hepatitis
  - Histologic features
    - Multiple abscesses
    - Granulomas
  - Risk factors
    - Immunosupression, diabetes, underlying liver disease (cirrhosis, hemochromatosis, chronic hepatitis)
  - Diagnosis
    - Positive blood culture or aspirate from abscess
  - Treatment
    - Ampicillin or penicillin plus gentamycin

- Shigella and Salmonella
  - Shigella
    - Cholestatic hepatitis in response to enteric infection
    - Histology: portal and periportal inflammation with PMLs, hepatic necrosis and cholestasis
  - Salmonella typhi
    - Elevated transaminases, elevated bilirubin
      - Mediated by bacterial endotoxin causing focal necrosis and periportal mononuclear infiltrate and Kupffer cell hyperplasia in the liver (similar to changes seen in gram negative sepsis)
      - Can have typhoid nodules – result of hypertrophy and proliferation of Kupffer cells
    - Complicated by cholecystitis and liver abscesses
    - Mortality rate approaches 20%, particularly with delayed treatment
    - Severe typhoid with acute liver failure
      - Jaundice and encephalopathy
      - Elevated ALP, AST>ALT, low PT, low platelets
    - Treatment
      - CTX, ciprofloxacin

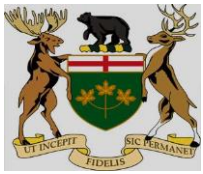
- Shigella and Salmonella
  - S. paratyphi A and B
    - Elevated transaminases
    - Rarely complicated by liver abscesses
    - Treatment
      - 3rd generation cephalosporin or fluoroquinolone

- Yersinia enterocolitica
  - Manifests as ileocolitis in children, terminal ileitis or mesenteric adenitis in adults
  - Can be complicated by:
    - Arthritis, cellulitis, erythema nodosm, septicemia
    - Risk factors for complicated disease
      - Diabetes, cirrhosis or hemochromatosis (growth is enhanced by iron)
  - Can present in subacute fashion with multiple abscesses diffusely in liver and spleen
  - Mortality – 50%
  - Treatment
    - Fuoroquinolones

- Gonococci
  - Disseminated gonococcal infection
    - Elevated ALP, AST
    - Unlikely to have jaundice
  - Fitz-Hugh-Curtis
    - Perihepatitis from direct pelvic spread of bacteria
    - Clinical
      - Sudden, sharp RUQ pain
      - Pelvic inflammatory disease
    - Diagnosis
      - Culture
    - Overall prognosis is unaffected by evidence of hepatitis
    - Treatment
      - Antibiotics (CTX), and also treat commonly associated chlamydial co-infection

- Legionella penumophilia
  - Fastidious gram-negative bacterium
  - Most often causes pneumonia, but can cause abnormal liver biochemistry
    - Transaminitis
    - ALP
    - Bili
  - Liver histology
    - Microvesicular steatosis and focal necrosis
    - Can occasionally see organisms
  - Diagnosis
    - Antibody in serum or sputum or antigen in urine
  - Treatment
    - Antibiotics (azithro or fluoroquinolone)

- Burkholderia pseudomallei (Melioidosis)
  - Gram negative bacterium found in soil and water
  - South East Asia
  - Clinical presentation
    - Ranges from asymptomatic infection to fulminant septicemia with involvement of lungs GI tract and liver
  - Histologic changes
    - Inflammatory infiltrates, multiple microabscesses, focal necrosis
    - Some liver abscesses may demonstrate honey combing appearance on CT
  - Treatment
    - Drain abscesses
    - Antibiotics: ceftriazone or meropenem, followed by a prolonged course of septra +/- doxycycline



- Brucella
  - Contracted from infected pigs, cattle, goats, and sheep (Brucella suis, Brucella abortus, Brucella melitensis, and Brucella ovis, respectively)
  - Clinical
    - Acute febrile illness
    - Hepatic abnormalities are seen in a majority of infected persons, and jaundice may be present in severe cases
  - Histology:
    - Multiple noncaseating hepatic granulomas
    - Less often, focal mononuclear infiltration of the portal tracts or lobules is
    - Rarely, hepatosplenic abscesses
  - Diagnosis
    - Isolation of the organism from a cultured specimen of liver tissue and is confirmed by serologic testing in combination with a history of exposure to animals
  - Treatment
    - Surgical drainage may be required for management of Brucella abscesses
    - The combination of streptomycin and doxycycline is the most effective antimicrobial therapy

- Coxiella burnetii (Q Fever)
  - Contracted by inhalation of animal dusts
  - Q fever syndrome
    - Relapsing fevers, headache, myalgias, malaise, pneumonitis, and culture-negative endocarditis
    - Liver involvement is common
      - Elevated ALP
      - Minimal elevations of AST or bilirubin

- Histology
  - Fibrin ring granulomas
- Diagnosis
  - Serologic testing for complement-fixing antibodies
- Treatment
  - Doxycycline

- Bartonella
  - Endemic to Colombia, Ecuador, and Peru
  - Gram-negative coccobacillus
  - Clinical
    - Acute febrile illness
    - Jaundice, hemolysis, hepatosplenomegaly, and lymphadenopathy.
    - Centrilobular necrosis of the liver and splenic infarction may occur
  - 40% of patients die of sepsis or hemolysis
  - Treatment
    - Chloramphenicol in combination with penicillin, clindamycin, or trimethoprim/sulfamethoxazole (prevents fatal complications)

- Bacillary Angiomatosis and AIDS
  - Primarily seen in patients with HIV or other immunodeficient states
  - Main causes
    - Bartonella henselae and Bartonella quintana
      - Gram negative bacilli
      - Can be associated with cat exposure

- Clinical
  - Multiple blood red papular skin lesions
  - Can affect liver, LN, pleura, bronchi, bones, brain, BM and spleen
  - Could have persistent bacteremia and sepsis
- Liver involvement
  - Transaminitis in absence of another explanation
  - Blood filled cysts (peliosis hepatitis)
- Histology
  - Inflammatory myxoid stroma containing clumps of bacilli and dilated capillaries surrounding the blood-filled peliotic cysts
- Diagnosis
  - PCR
- Treatment
  - Erythromycin +/- prolonged doxycycline for visceral infection

- Bacterial Sepsis and Jaundice
  - Jaundice may be seen in GN or GP bacterial sepsis
  - Mechanism
    - Exotoxins and endotoxin act directly or indirectly to inhibit transportation of bile acids and other organic anions across the hepatic sinusoidal and bile canalicular membranes, leading to hepatic cholestasis
  - Does not correlate with mortality
  - Liver biopsy does not show abnormality

- Chlamydia trachomatis
  - Fitz-Hugh-Curtis Syndrome
    - Similar to perihepatitis caused by chlamydial infection, with RUQ pain following urogenital infection such as PID
  - Diagnosis
    - Direct visualization at laproscopy or laparotomy
    - Diagnosis supported by demonstration of endometritis, salpingitis and microbiologic detection of C. trachomatis in the GU tract
  - Liver biochemistry
    - Generally normal
  - Treatment
    - Follow guidelines for C. trachomatis

- Rickettsiae
  - Rocky Mountain Spotted Fever
    - Multiorgan failure = high mortality
    - Clinical presentation
      - Severe vasculitis due to microbe-induced coagulopathy and jaundice
    - Hepatic involvement
      - Portal tract inflammation, portal vasculitis, and sinusoidal erythrophagocytosis
      - Little hepatic necrosis
    - Laboratory findings
      - Elevated transaminases, elevated ALP
      - Jaundice (bile ductular obstruction and hemolysis) increased mortality

- Ehrlichiae
  - Parasite to leukocytes
  - Infectious agents:
    - Human monocytic ehrlichiosis Ehrlichia chaffeensis and Ehrlichia canis
    - Human granulocytic erhichiosis Anaplasma phagocytophilum
  - Clinical
    - No rash
    - Elevated transaminases
    - Can have cholestasis, hepatosplenomegaly, liver failure
      - Liver injury is due to proliferation of organisms within hepatocytes and the provoked immune response
  - Histology
    - Focal necrosis, fibrin ring granulomas and cholestatic hepatitis
  - Mixed portal tract infiltrate and lymphoid sinusoidal infiltrate are usually seen
  - Treatment
    - Doxycycline

- Spirochetes
  - Leptospirosis
    - Contracted from infected feces or urine
    - Anicteric leptospirosis
      - 90% of cases
      - Biphasic illness
        - First phase: viral illness with fever, leptospiremia and conjunctival spread
        - Improves clinically, then second phase involves myalgias, nausea, vomiting, abdominal tenderness and aseptic meningitis
        - Elevated aminotransferase and bilirubin with hepatomegaly

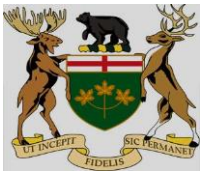
- Weil Syndrome
  - Severe icteric form of leptospirosis 5-10% of all cases
  - First phase: jaundice (can last for wks)
  - Second phase: fever, hepatic and renal manifestations, jaundice continues, transaminitis does not generally succeed 5x ULN
  - Acute tubular necrosis often develops and can lead to renal failure
  - Can get hemorrhagic complications from capillary injury caused by immune complexes
  - Histology non specific – altered mitochondria suggests toxin mediated injury
  - Rarely see spirochete in liver on autopsy, can be in kidney
  - Diagnosis
    - Clinical symptoms
    - Positive blood or urine culture
    - Serologic testing can also confirm diagnosis if cultures are negative
  - Treatment
    - Doxycycline (most effective in first several days)
    - Most patients recover with out residual organ impairment

- Syphilis (secondary)
  - Seen in up to 50% of patients
  - Clinical features:
    - Non-specific – anorexia, weight loss, fever malaise, sore throat
    - Maculopapular risk involving palms and soles
    - Jaundice, hepatomegaly and RUQ tenderness less common

- Laboratory
  - Elevated transaminases and bilirubin, particularly elevated ALP
  - Proteinuria
- Histology
  - Focal necrosis in periportal and centrilobular regions
  - Inflammatory infiltrate: neutrophils, plasma cells, lymphocytes, eosinophils and mast cells
  - Kupffer cell hyperplasia may be seen, bile duct injury rare
  - Granulomas
  - Spirochetes with sliver stain in 50% of patients
- Treatment
  - Penicillin
- Tertiary (Late) Syphilis
  - Hepatic lesions are common in late syphilis
  - Can have anorexia, weight loss, fatigue, fever or abdominal pain
  - Characteristic lesion = gumma (central necrosis, surrounding granulation tissue consisting of lymphoplasmacytic intiltration and endarteritis, can get scar tissue deposition giving the liver a lobulated appeatence (hepar lobatum)
  - If hepatic involvement is unrecongnized, can develop portal HTN with jaundice, ascites and gastroesophageal varices
  - Hepatic gummas may resolve after therapy with penicillin

- Lyme Disease
  - Causative agent
    - Borrelia burgdorferi
  - Liver involvement more common with disseminated disease, does not affect mortality
  - Clinical
    - Cardiac, dermatologic, neurologic and musculoskeletal involvement
    - Anorexia, nausea, vomiting, weight loss, RUQ pain and hepatomegaly within days to wks of onset of illness (tend to see elevated transaminases and LDH in patients with these symptoms)
    - Erythema migrans
  - Histology
    - Hepatocyte ballooning
    - Marked mitotic activity
    - Microvesicular fat, mixed sinusoidal infiltrate
    - Intraparenchymal
    - Sinusoidal spirochetes
  - Diagnosis
    - Serology
  - Treatment
    - Ceftriaxone

- TB and Mycobacteria
  - Granulomas are found in liver biopsy in 25% of people with pulmonary TB and 80% with extrapulmonary TB
  - TB granulomas – central caseation, AFB present, fewer granulomas with tendency to coalesce
    - Can also be seen following BCG vaccine, particularly if immunocompromised

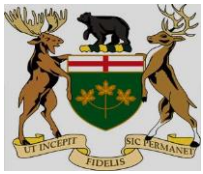


- Rarely get significant liver disease, occasional tender hepatomegaly
- Can get jaundice with elevated ALP in miliary infection
- Treatment
  - Regular TB treatment

❖ Parasitic Infections

- Protozoans
  - Liver Disease
    - Granulomatous hepatitis
      - Capillariasis
      - Fascioliasis
      - Schistosomiasis
      - Strongyloidiasis
      - Toxocariasis
    - Portal fibrosis
      - Schistosomiasis
    - Hepatic abscess or necrosis
      - Amebiasis
      - Toxoplasmosis
    - Cystic liver disease
      - Echinococcosis
    - Peliosis hepatis
      - Bacillary angiomatosis
  - Reticuloendothelial disease
    - Kupffer cell infection or hyperplasia
      - Babesiosis
      - Malaria
      - Toxoplasmosis
      - Visceral leishmaniasis
  - Biliary Tract Disease
    - Cholangitis
      - Clonorchiasis/ opisthorchiasis
      - Fascioliasis
    - Bialiary hyperplasia
      - Ascariasis
      - Clonorchiasis
      - Cryptosporidiosis
      - Fascioliasis
    - Cholangiocarcinoma
      - Clonorchiasis/ opisthorchiasis

- Malaria
  - Liver is affected in 2 stages
    - Pre-erythrocytic phase, then erythrocytic phase co-incides with clinical illness
  - Plasmodium vivax and Plasmodium ovale is associated with
    - Persistent exoerythrocytic stage, the hypnozoite
    - Persists in the liver
    - When activated can divide and mature into schizont forms
  - Plasmodium knowlesi has been identified as a fifth species capable of infecting humans and occasionally results in severe manifestations including jaundice, hepatic dysfunction, and acute kidney injury
  - Extent of hepatic injury varies with
    - Type of malarial species (most severe with P. falciparum)
    - Severity of infection
  - Unconjugated hyperbilirubinemia most commonly seen
    - As a result of hemolysis but
    - Could also be related to hepatic dysfunction
  - Laboratory
    - Elevated transaminase and 5'-nucleotidase level
    - May also see synthetic dysfunction
  - Histology
    - Acute malaria: Hepatic macrophage hypertrophy, large quantities of malarial pigment in Kupffer cells
    - Hepatocyte swelling and centrizonal necrosis may be seen
    - Reversible with treatment



- Clinical
  - Erythrocytic stage = associated with clinical illness
    - Symptoms and signs of acute infection develop with in 30 to 60 days following exposure
    - Fever, malaise, anorexia, nausea, vomiting, diarrhea, myalgias
    - Jaundice caused by hemolysis
  - Hepatic failure only seen with concomitant viral hepatitis or severe P falciparum infection
  - Tender hepatomegaly and splenomegaly
  - Cytopenias
- Diagnosis
  - Thick and thin smear
  - PCR to differentiate species
- Treatment
  - Depends on species and chloroquine resistance patterns
  - Atovaquone proguanil, or artemisinin derivatives
  - P vivax and ovale require primaquine (G6PD deficiency) or mefloquine to eliminate hypnozoites in liver

- Hyperreactive Malarial Splenomegaly
  - Repeated exposure in endemic areas may lead → over production of B lymphocytes → malarial antibody → ↑↑ levels of immune complexes that deposit into the liver (dense sinusoidal lymphocytosis)
  - Clinical features
    - Splenomegaly
    - ↑ antimalarial antibodies
    - Anemia
    - Variceal bleeding from portal hypertension

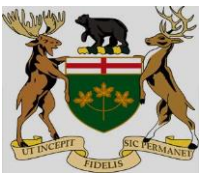
- Treatment
  - Lifelong malarial therapy

Disease (cause)	Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis
Malaria (Plasmodium falciparum, P.malariae, P.vivax, P.ovale, P.knowlesis)	Africa, Asia, South America	Blood transfusion, IV drug use	Sporozoite clearance by hepatocyte; exoerythrocytic replication in the liver	Tender hepatomaly, spenomegaly, rarely hepatic failure (P.falciparum)	Identification of the parasite on a blood smear

  - P. falciparum:
    - Chloroquine (chloroquine-sensitive),
    - Mefloquine, or
    - Quinine plus either
      - Doxycycline, or
      - Clindamycin; or
      - Pyrimethamine-sulfadoxine (Fansidar); or
    - Atovaquone/proquanil (chloroquine-resistant); or
    - An artesiminin
  - P.malariae
    - Chloroquine
  - P.vivax, P.ovale, P.knowlesi
    - Chloroquine plus primaquine (chloroquine-sensitive), or
    - Mefloquine and primaquine (chloroquine-resistant)

- Amebiasis (Entamoeba histolytica)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Worldwide, especially Africa, Asia, Mexico, South America	Poor sanitation, sexual exposure	Hematogenous spread and tissue invasion, abscess formation	Fever, RUQ pain, peritonitis elevated right hemidiaphragm, rupture	Cysts in stool, serology (e.g. ELISA CIE, IHA), hepatic imaging	Metronidazole 750 mg (oral or IV) 3 times daily x 7-10 d or tinidazole 2 g x 3 d, followed by iodoquinol 650 mg 3 times daily x 20 d or diloxanide furoate 500 mg 3 times daily x 10 d or aminosidine (paromomycin) 25-35 mg/kg/d in 3 divided doses x 7-10 d



- Babesiosis (Babesia spp.)

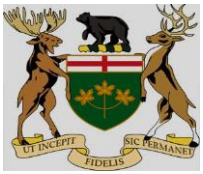
Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
United States	Exposure to deer tick	Hemolysis with multiorgan involvemnet	Fever, RUQ pain, peritonitis elevated right hemidiaphragm, rupture	Identification	Azithromycin 500 mg on day 1, then 250 mg daily and atovaquone 750 mg bid x 7-10 d or clindamycin 300-600 mg IV every 6 hr or 600 mg orally every 8 hr and quinine 650 mg every 8 hr x 7-10 d

  - Demography
    - Endemic to northeast and Midwest US
  - Clinical
    - Severe in immunocompromised patients
      - Pancytopenia in rare cases
      - Hepatic involvement reflects the severity of systemic illness, but generally not severe

- Visceral leishmaniasis (Leishmania donovani)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Eurasia, Central America, South America	Immuno-suppression (AIDS, organ transplantation)	Infection of RE cells	Fever, weight loss, hepato-splenomegaly, secondary bacterial infection, skin hyper-pigmentation kala-azar)	Amastigotes seen in the spleen, liver, or bone marrow	Pentavalent antimonial (stibogluconate sodium and meglumine antimoniate) 20 m/kg/d x 28 d; or liposomal amphotericin B (IV) 3 mg/kg/d on days 1-5, 14, and 21; or aminosidine (paromomycin) 16-20 mg/kg/d x 21 d; or pentamidine isethionate, 2-4 mg/kg/d for up to 15 d; or miltefosine 2.5 mg/kg/d x 28 d

- Demography
  - Consider in immigrants or returning travelers/military personnel from endemic areas
- Microbiology
  - Amastigotes ingested by the sand fly (Lutzomyia) and become flagellated promastigotes → phagocytosed by macrophages in the reticuloendothelial system → multiply
- Clinical
  - Incubation period of 2-6 mon prior to development of symptoms → ulcerated papular lesion at site of sandfly bite
- Histopathology
  - Organisms found in mononuclear phagocytes of the liver, spleen, bone marrow and lymph nodes
    - Proliferation of Kupffer cells can be seen with amastigotes detected within these cells (Leishman-Donovan bodies)
    - Noncaseating granulomas
    - Hepatocyte necrosis
    - Fibrosis with healing
- Diagnosis
  - Liver biopsy/spleen aspirate is less risky and essentially just as high yield (cultures take several wks
  - Serology supportive but not diagnostic
  - Skin test
    - Not helpful with visceral involvement
    - PCR for monitoring



- Toxoplasmosis (Toxoplasma gondii)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Worldwide	Congenital infection, immuno-suppression (AIDS, organ transplantation)	Replication in the liver leading to inflammation, necrosis	Fever, lymph-adenopathy, occasionally hepato-splenomegaly, atypical lymphocytosis	Serology (IF, ELISA), isolation of organism in the tissue	Pyrimethamine 100 mg loading dose followed by 25-50 mg/d; plus, sulfadiazine 2-4 g/day in 4 divided doses; or clindamycin 300 mg 4 times daily, plus folinic acid 10-25 mg daily for 2-4 wk

- Microbiology
  - Oocysts of T. gondii in soil, water, or contaminated meat → ingested and mature in the intestinal tract of humans → sporozoites
    - Penetrate the intestinal mucosa → become tachyzoites, → circulate systemically →invade many cell types
- Pathology
  - Hepatic involvement in severe, disseminated infection
- Clinical
  - Patients may be asymptomatic but can see atypical lymphocytes (usual feature of parasitic disease)
- Diagnosis
  - IgG/IgM antibody

❖ Nematodes (round worms)

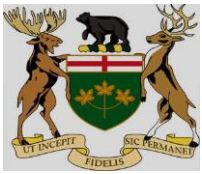
- Toxocariasis (Toxocara canis, T. cati)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Worldwide	Exposure to dogs or cats, especially for children < 5 yr	Migration of larvae to the liver (visceral larva migrans)	Granuloma formation with eosinophilia	Larvae in tissue, serology (ELISA)	Albendazole 10 mg/kg/d x5 d or mebendazole 100-200 mg twice daily x 5 d

➢ Microbiology
  - Acquired when embryos in the soil are ingested and hatch in the small intestine
  - Larvae then penetrate the intestinal wall and enter the portal venous circulation and reach the liver via the systemic circulation
  - When vessels narrow worms migrate into tissues provoke granuloma formation with eosinophils (liver, brain or eye most frequently)

➢ Clinical
  - Two main clinical syndromes
    - Visceral larva migrans – children with history of pica (findings of eosinophilic granulomas is specific)
    - Chronic cholestatic hepatitis and pyogenic liver abscesses, can have pulmonary and neurologic involvement
    - Occult infections with non-specific symptoms

➢ Diagnosis
  - Suspect in patients with history of PICA, dog/cat exposure or persistent eosinophilia
  - ELISA is supportive of diagnosis



- Laboratory
  - Stool studies (eggs are not produced in or remain in GI tract)

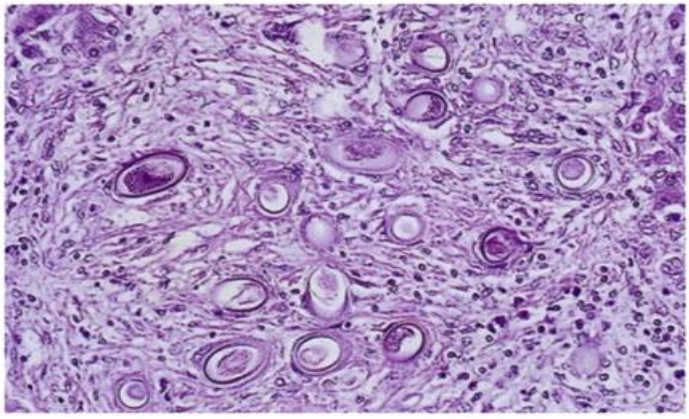
- Histopathology
  - Liver biopsy may be required to differentiate from hepatic capillariasis

- Hepatic capillariasis (Capillaria hepatica)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Worldwide	Exposure to rodents	Migration of larvae to the liver; inflammatory reaction to eggs	Acute, subacute hepatic, tender hepatomegaly, occasionally splenomegaly, eosinophilia	Adult worms or eggs in a liver biopsy specimen	Supportive; possibly dithiazine iodide, sodium stibogluconate, albendazole, or thiabendazole

- Microbiology
  - Acquired by ingesting contaminated food, soil or water with eggs
  - Larvae released in the cecum → penetrate intestinal mucosa → enter the portal venous circulation → lodge in the liver.
  - Four wks after infection, adult worms disintegrate → releasing eggs into the hepatic parenchyma → producing an intense inflammatory reaction with macrophages, eosinophils, and giant cells.
  - Resolution is accompanied by marked peri-egg fibrosis

Histology of hepatic capillariasis



- Granulomas surrounding eggs

Printed with permission: Burt AD, Portmann BC, Ferrell LD, editors. MacSween's pathology of the liver. 6th ed. London: Churchill Livingstone; 2012. p 436

- Laboratory
  - Increased WBC with eosinophilia, AST ALP bili elevations, anemia, pneumonitis on CXR

- Ascariasis (Ascaris lumbricoides)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Tropical climates	Ingestion of raw vegetable	Migration of larvae to the liver; invasion of the bile ducts by adult worms	Abdominal pain, fever, jaundice, biliary obstruction, granulomas	Ova or adult in stool or contrast study	Albendazole 400 mg x 1 dose; or mebendazole 100 mg twice daily x3 d; or pyrantel pamoate 11 mg/kg up to 1 g; or ivermectin 200 ug/kg x 1 dose

- Microbiology
  - Eggs hatch in the small intestine → larvae penetrate the mucosa → enter the portal circulation, and reach the liver, pulmonary artery, and lungs
  - Grow in the alveolar spaces, regurgitated and swallowed → mature adults in the intestine 2 to 3 mon after ingestion.
  - The cycle repeats itself (due to worm burden)
- Complications
  - Obstruction
  - Intussception/volvulus
  - Perforation
  - Appendicitis
  - Biliary calculi

- Strongyloidiasis (Strongyloides stercoralis)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Asia, Africa, South America, Southern Europe, USA	Immunosuppression (AIDS, chemotherapy, organ transplantation) predisposes to hyperinfection	Larval penetration from the intestine to the liver	Hepatomegaly, occasionally jaundice, larvae in the portal tract or lobule	Larvae in the stool or duodenal aspirate	Ivermectin 200 ug/kg/d x2 d; or albendazole 400 mg/d x 3 d

- Clinical
  - Acute infection
    - Pruritic eruption then followed by
      - Fever
      - Cough/wheeze
      - Abdominal pain
      - Jaundice
      - Diarrhea and eosinophilia

- In immunocompromised patients
  - Hyperinfection syndrome
  - Invasion of any organ (including liver, lung, brain)
  - Consider when patient is septic with multiple organisms seen
  - Liver involvement
    - Jaundice and cholestatic biochemical tests
    - Biopsy - periportal inflammation, eosinophilic granulomatous hepatitis, or both. Larvae may be observed in intrahepatic bile canaliculi, lymphatic vessels, and small branches of the portal vein

- Trichinosis (Trichinella spiralis)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Temperate climates	Ingestion of undercooked pork	Hematogenous dissemination to the liver	Occasionally jaundice, biliary obstruction, larvae in hepatic sinusoids	History, eosinophilia, fever, muscle biopsy	Glucocorticoids for allergic symptoms; albendazole 400 mg twice daily x 10-15 d; or mebendazole 200 mg/d x 10-15 d

➢ Microbiology

- Raw or undercooked pork bearing larvae → released in the small intestine → penetrate the mucosa → disseminate through the systemic circulation.
- Larvae can be found in the
  - Myocardium
  - Cerebrospinal fluid
  - Brain
  - Liver
  - Gallbladder
- The larvae then reenter the circulation and reach striated muscle, where they become encapsulated

- Clinical (when there is high worm burden)
  - Diarrhea
  - Fever / myalgias
  - Periorbital edema
  - Leukocytosis with marked eosinophilia
  - Hepatic complications associated with fatal cases
- Histopatholgy
  - Larvae seen invading hepatic sinusoids
  - Jaundice may result from biliary obstruction

❖ Trematodes (Flukes)

- Schistosomiasis (Schistosoma mansoni, S. japonicum)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Asia, Africa, South America, Caribbean	Travelers exposed to bodies of fresh water	Fibrogenic host immune response to eggs in the portal vein	*Acute*: esosinophilic infiltrate Chronic: hepato-splenomegaly, presinusoidal portal hypertension, granulomas	Ova in the stool, rectal or liver biopsy	Praziquantel 40-60 mg/kg in 2-3 divided doses x 1 d; or oxamniquine for S.mansoni (not readily available) Acute toxemic schistosomiasis: praziquantel 40-60 mg/kg in 2-3 divided doses x 1 d + glucocorticoids

- Microbiology
  - Schistosoma mansoni is found in the Western Hemisphere, Africa, and the Middle East
  - S. haematobium is found in Africa and the Middle East

- S. japonicum and S. mekongi are found in the Far East
- S. intercalatum is found in parts of central Africa.
  - The last 2 species are much less common than the other 3, and cause liver disease and colonic disease, respectively
- Skin penetration from freshwater source → Cercariae reach the pulmonary vessels within 24 hr → pass through the lungs → reach the liver, where they lodge, develop into adults, and mate.
- Adult worms then migrate to their ultimate destinations in the
  - Inferior mesenteric venules (S. mansoni)
  - Superior mesenteric venules (S. japonicum), or
  - Veins around the bladder (S. haematobium)
- Site of deposition correlates with clinical complications
- Eggs cause a granulomatous response

➢ Clinical Features

- Acute toxemic schistosomiasis
  - Consequence of the host immunologic response to mature worms and eggs
  - Occurs approximately 4 to 6 wks after exposure
  - Headache, fever, chills, cough, diarrhea, myalgias, arthralgias, tender hepatomegaly, and eosinophilia.
- Untreated acute schistosomiasis invariably progresses to chronic disease
  - Mesenteric infection → hepatic complications, including
    - Periportal fibrosis
    - Presinusoidal occlusion
    - Portal hypertension (result of the inflammatory reaction to eggs deposited in the liver)

- Development of periportal fibrosis appears to be related to production of TNF-α
- Lungs and central nervous system may be affected when eggs / adult worms pass through the liver into the systemic circulation (especially in S. japonicum infection)
  - Pulmonary hypertension / cor pulmonale may result
  - Portal hypertension becomes progressive →
    - Gastroesophageal varices
    - Splenomegaly
    - Ascites

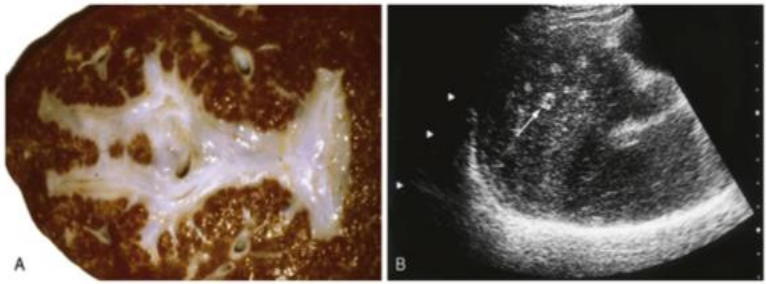
- ↑ susceptibility to
  - Salmonella infections
  - Hepatitis B / hepatitis C viral coinfection (may accelerate the progression of liver disease and development of hepatocellular carcinoma)
- African intestinal schistosomiasis
  - Pseudopolyps of the colon may develop →
    - Protein-losing colopathy and
    - Inflammatory mass in the descending colon

➢ Laboratory

- Anemia from
  - Recurrent luminal GI bleeding
  - Hypersplenism,
- Leukocytosis with eosinophilia
  - ↑ erythrocyte sedimentation rate (ESR)
  - ↑ serum IgE levels
- LEs generally are normal until the disease is at an advanced stage

- Diagnostic imaging
  - Ultrasound and liver biopsy may demonstrate clay pipestem fibrosis, but are not used in an acute infection (will not see eggs)
    - CT may show low-attenuation rings around main portal vein branches with marked enhancement with contrast

- Histopathology
  - Pipestem fibrosis



- Fascioliasis (Fasciola hepatica)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Worldwide	Cattle or sheep raising; ingestion of contaminated watercress	Migration of larvae through the liver; penetration of the bile ducts or surgery	*Acute*: fever, abdominal pain, jaundice, hemobilia *Chronic*: hepatomegaly	Ova in the stool, flukes in the bile ducts at ERC	Triclabendazole 10 mg/kg x 1 dose

- Microbiology
  - Eggs pass in the feces of infected mammals into fresh water → miracidia that penetrate snails → emerge as mobile cercariae → attach to aquatic plants such as watercress.

- Hosts become infected when they consume plants containing encysted metacercariae → bore into the intestinal wall → abdominal cavity → penetrate the hepatic capsule → settle in the bile ducts, where they attain maturity.
- Mature flukes release eggs → passed in the host's feces (complete the life cycle)

➢ Clinical

- Acute
  - Migration of young flukes through the liver
  - Urticaria with dermatographia
  - Non-specific GI symptoms
  - Enlarged tender liver
  - Eosinophilia
- Latent phase
  - Settling of flukes in bile ducts
    - Persistent eosinophilia
- Chronic obstructive phase
  - Intra-/extrahepatic bile duct inflammation plus hyperplasia (provoked by flukes)
  - Recurrent biliary pain, cholangitis, cholestasis and biliary obstruction
  - Cholestatic findings on liver biochemistry
- Long term can lead to
  - Bliary cirrhosis
  - Secondary sclerosing cholangitis
  - No definite link with malignancy

- Clonorchiasis and opisthorchiasis (Clonorchis sinensis, Opisthorchis viverrini, O. felineus)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Southeast Asia, China, Japan, Korea, Eastern Europe	Ingestion of raw fresh-water fish	Migration through the ampulla; egg deposition in the bile ducts	Biliary hyperplasia, obstruction, sclerosing cholangitis, stone, formulation, cholangio-carcinoma	Ova in the stool, flukes in the bile ducts at ERC or surgery	Praziquantel 74 mg/kg in 3 divided doses x 1 d

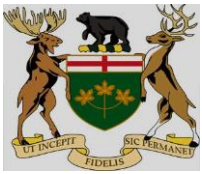
➢ Microbiology

- Eggs passed in the feces into fresh water → consumed by snails → hatch as free-swimming cercariae, which seek and penetrate fish/crayfish and encyst in skin or muscle as metacercariae. The mammalian host is infected when it consumes raw or undercooked fish. The metacercariae excyst in the small intestine and migrate into the ampulla of Vater and bile ducts → mature into adult flukes.
- Infection can be maintained for 2 decades or longer

❖ Cestodes

- Echinococcosis (Echinococcus granulosus, E. multilocularis)

Endemic Areas	Predisposing Factors	Pathophysiology	Manifestations	Diagnosis	Treatment
Worldwide	Cattle and sheep raising (E.granulosus)	Migration of larvae to the liver; encysment (hydatid cyst)	Tender hepatomegaly, fever, eosinophilia, cyst rupture, biliary obstruction	Serology (ELISA, IHA), hepatic imagine	Surgical resection or percutaneous drainage, Perioperative albendazole 400 mg twice daily continuing x 8 wk



- Microbiology
  - Humans eat vegetables contaminated by dog feces that contain embryonated eggs → eggs hatch in the small intestine → liberate oncospheres → penetrate the mucosa → migrate via vessels or lymphatics to distant sites.
  - The liver is the most common destination (70%), followed by the lungs (20%), kidney, spleen, brain, and bone.
  - In these organs, a hydatid cyst develops by vesiculation → produces thousands of protoscolices.
  - The cyst wall contains 3 layers
    - An outer adventitial layer (host-derived and can calcify) and intermediate acellular and inner germinal layers (worm-derived).
    - A protoscolex is produced asexually within small secondary cysts that develop from the inner layer → rupture of the hydatid cyst → viable protoscolices → set up daughter cysts in secondary sites.
  - The adult Echinococcus tapeworm consists of
    - A scolex (contains a rostellum with 20 to 50 hooklets and 4 suckers)
    - A neck
    - Ann immature, mature, and gravid proglottid
  - Dogs acquire the infection by consuming organs of sheep, cattle, or other livestock bearing the hydatid cyst.

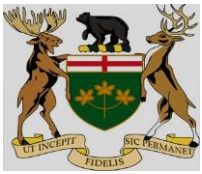
- Clinical
  - Most patients with hydatid cyst are asymptomatic
  - Cysts can rupture spontaneously if they grow large enough causing
    - Dyspnea/hemoptysis
    - Anaphylactic response
    - Rare complications include
      - Pancreatitis
      - Portal HTN
      - Budd Chiari syndrome
      - Rupture into pericardial sac

- Treatment
  - Surgical resection can be curative

❖ **Fungi**

- Candidiasis
  - May cause invasive systemic infection with hepatic involvement in severely immunocompromised patients (most often chemotherapy patients)
    - High mortality rate
    - Can get focal candiasis from colonization of GI tract
      - Local collections of candida collect in GI tract following onset of neutropenia and mucosal injury from high dose chemotherapy
      - Fungemia seeds the liver and can lead to formation of hepatic micro and macroabsceses

- Clinical
  - Fever, abdominal pain/distention, nausea, vomiting, diarrhea, tender hepatomegaly



- Laboratory
  - ↑ ALP
- Histopathology
  - Necrosis with hepatic microabscesses
  - Yeast of hyphae
- Diagnosis
  - PCR
- Treatment
  - IV amphotericin B, echinocandins, azoles

- Histoplasmosis

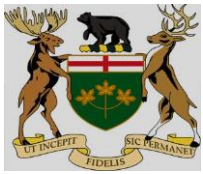
- Clinical
  - A respiratory illness that spreads to the liver
  - Disseminated form seen in immunocompromised patients
  - Fever, oropharyngeal ulcers, hepatomegaly, splenomegaly
- Laboratory
  - ↑ ALT/AST/ALP
  - Serology can be helpful in confirming diagnosis
- Histopathology
  - Liver biopsy showing organism (H and E stain)
  - Culture low yield

- Treatment
  - Amphotericin B, fluconazole or itraconazole

❖ Liver Abscesses

- Pyogenic Abscesses

- Predisposing conditions
  - Malignancy
  - Immunosuppression
  - Diabetes mellitus
  - Previous biliary surgery
  - Interventional endoscopy
- Microbiology
  - Most often polymicrobial
  - Frequently isolated organisms are
    - Escherichia coli
    - Klebsiella
    - Proteus
    - Pseudomonas
    - Streptococcus species (particularly the Streptococcus milleri group)
  - Most commonly identified anaerobic species are Bacteroides fragilis and Fusobacterium necrophorum
  - Pyogenic abscess associated with recurrent pyogenic cholangitis may be caused by Salmonella typhi
  - Fungal abscesses of the liver may occur in immunocompromised hosts, particularly those with a hematologic malignancy



- Pathogenesis
  - Infection may spread to the liver from the bile duct, along a penetrating vessel, or from an adjacent septic focus

- Clinical
  - May arise as a late complication of endoscopic sphincterotomy for bile duct stones or within 3 to 6 wks of a surgical biliary-intestinal anastomosis
  - Less common are complications of bacteremia
  - May be initial presentation of hepatocellular or gallbladder carcinoma
  - Fevers, RUQ pain, septic shock
  - Hepatomegaly, splenomegaly
  - Portal HTN if portal vein has been thrombosed

- Laboratory
  - Anemia
  - Leukocytosis
  - Elevated ALP / transaminitis
  - Blood culture may be positive

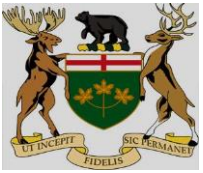
- Diagnostic imaging
  - US or CT
  - MRI helpful for looking at small abscesses
  - ERCP if biliary stones

- Histopathology
  - Plasma cell granuloma – benign lesion of proliferating fibrous tissue infiltrated by inflammatory cells

- Risk factors
  - Chronic inflammatory
  - Autoimmune disorders, particularly ascending cholangitis and PSC
  - Diabetes mellitus
  - Sjögren's syndrome
  - Gout
  - UC
  - Crohn disease
  - HIV
  - EBV
  - Acute myeloblastic leukemia.
- Treatment
  - Surgical resection
  - Antibiotics
  - Drainage

- Amebic Abscesses
  - Most common extraintestinal manifestation of amebiasis

- Risk factors
  - Travel to endemic area
  - Immunosupressed (HIV)
  - More common in males



- Clinical
  - Occurs following 2 wks of bloody diarrhea
  - Latency period following GI symptoms of yr is possible
  - RUQ pain, fever, malaise, myalgias, arthralgias, resp symptoms
  - Marked hepatomegaly, large or multiple abscesses
  - Jaundice is uncommon but signals a poor prognosis

- Diagnostic imaging
  - Commonly localized to the right hepatic lobe, close to the diaphragm

- Laboratory
  - Serologic tests include
    - ELISA
    - Indirect hemagglutination
    - Cellulose acetate precipitin
    - Counterimmunoelectrophoresis
    - Immunofluorescent antibody
    - Rapid latex agglutination tests
      - High sensitivity and specificity, but can get false negatives with in first 10 d of infection

➢ Treatment

- Metronidazole

Parameter	Pyogenic Liver Abscess	Amebic Liver Abscess
○ Number	– Often multiple	▪ Usually single
○ Location	– Either lobe of liver	▪ Usually right hepatic lobe, near the diaphagm
○ Presentation	– Subacute	▪ Acute
○ Jaundice	– Mild	▪ Moderate
○ Diagnosis	– US or CT ± aspiration	▪ US or CT and serology
○ Treatment	– Drainage (if technically feasible) + IV antibiotics	▪ Metronidazole, 750 mg 3 times daily for 7 d orally or IV; or tinidazole, 2 g orally for 3 d, followed by iodoquinol, 650 mg orally 3 times daily for 20 d; dilaxande furoate, 500 mg orally 3 times daily for 10 d; or aminosidine (paromomycin) 25-35 mg/kg/d orally in 3 divided doses for 7-10 d

GALLBLADDER

GALLSTONE DISEASES AND THEIR TREATMENT

May Alzahrani

- Risk Factors
  - Patient
    - Age: ↑with age
    - Gender: F to M 2:1
    - Race: Native American > Hispanic > Caucasians > Asian > African
    - Diet: Western diet
    - Pregnancy/Parity
    - Rapid Weight Loss
    - TPN
  - Lithogenic bile
  - Biliary Sludge
  - Lipid Abnormalities
  - Drugs
    - Estrogens
    - Octreotide
    - Ceftriaxone
  - Systemic Diseases:
    - Obesity
    - Insulin Resistance
    - DM
    - Diseases of the Ileum
    - SC injury

MCQ Trick!

- Not all drugs risk of cholelithiasis
  - Statin, Ascorbic acid and Coffee are protective against gallstone disease!

- Clinical and Laboratory Features in Biliary Tract Disease

	Biliary Pain	Acute Cholangitis	CDI	Cholangitis
○ May be asymptomatic pain				
– Epigastric	+		+	
– RUQ	+		+	
– Severe	+		+	
– Onset 15 min	+		+	
– Constant				
▪ 1-6 hr	+		+	
▪ 6 hr		+		
– Radiation (shoulder, back)		+		
– Previous attacks of biliary pain		75%		
○ Jaundice with pain			+	
○ Pain, jaundice, fever chills				70%
○ Pain, jaundice, fever, hypotension, ↓LOC				15%
○ Fever		+		+
○ Nausea/vomiting		++		

	Biliary Pain	Acute Cholangitis	CDL	Cholangitis
○ Tenderness RUQ	+			
○ Palpalok GB		33%		
○ Murphy sign		+		
○ Secondary bacterial infection		50%		+
○ WBC, bands		++		++
○ Bili, AP, Amylase	+	+	+	+
○ AST			+	
○ Recurrence*	70%			
○ Resolve spontaneously		50%		
○ Positive blood cultures predispose to cholangitis/ acute pancreatitis				+
○ Perforation				
– Local		10%		
– Free		1%		
○ Jaundice		20%		

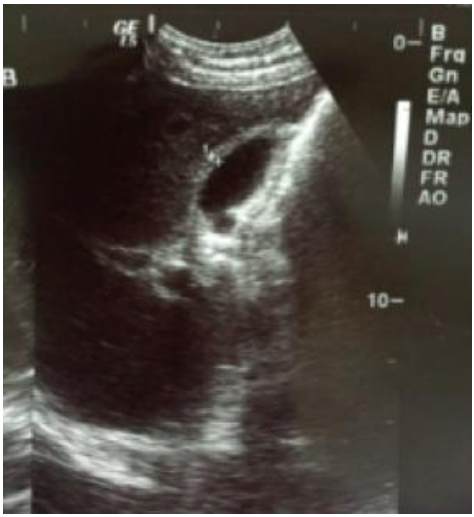
* in rendering 30% symptoms occur at 6% per yr, and complications at 1% to 2% per yr

Abbreviations: AP, alkaline phosphatase; Bili, bilirubin; Chol, Choledocholithiasis; GB, gallbladder; LOC, lovel of conscious-ness; RUQ, right upper quadrant; WBC, white blood cell

Cholelithiasis

- Diagnostic Imaging
- Abdominal Ultrasound (US)
  - Stones seen as mobile, dependent echogenic foci within the gallbladder lumen with acoustic shadowing and sludge appears as layering echogenic material without shadows
  - Sensitivity >95% for stones >2 mm
  - Specificity >95% for stones with acoustic shadows
  - Best single test for stones in the gallbladder
  - BD stones seen in 50%. It Can confirm, but not exclude, BD stones
  - Sonographic Murphy sign has a PPV of >90% in detecting acute cholecystitis when stones are seen
  - Pericholecystic fluid and wall thickening to >4 mm are nonspecific findings but suggestive of acute cholecystitis

Abbreviation: PPV, positive predictive value



Source: Koufakis T and Gabranis I. Case Reports in Hepatology, vol. 2016, Article ID 6080832, 3 pages, 2016.

- Endoscopic Ultrasound (EUS)
  - Highly accurate for excluding or confirming stones in the BD
    - Concordance of EUS with the ERCP diagnosis ≈95%; Specificity ≈97%
    - PPV ≈99%, NPP≈98%, accuracy ≈97%
  - With experienced operators, EUS can be used in lieu of ERCP to exclude BD stones, particularly when the clinical suspicion is low or intermediate
  - Considered for patients with low to moderate clinical probability of choledocholithiasis

- Oral cholecystography
  - Stones manifest as mobile filling defects in an opacified GB
  - Sensitivity and specificity > 90% when GB is opacified, but nonvisualization occurs in 25% of studies and can result from multiple causes other than stones
  - Opacification of the gallbladder indicates cystic duct patency
  - May be useful in the evaluation of acalculous gallbladder diseases such as cholesterolosis and adenomyomatosis

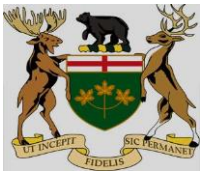
Abbreviation: BD, bile duct

- HIDA scan
  - Assesses patency of the CD
  - A normal scan shows radioactivity in the gallbladder, BD, and small bowel within 30-60 min

- A +ve result
  - Non-visualization of the gallbladder, with preserved hepatic excretion of radionuclide into the BD or small bowel
- Sn ≈95% & Sp ≈90%, with false-positive results seen in fasted critically ill patients
- With CCK stimulation, the gallbladder “ejection fraction” can be determined and may help evaluate patients with acalculous biliary pain
- A normal scan result virtually excludes acute cholecystitis

❖ ERCP

- The standard diagnostic test for stones in the BD, with sensitivity and specificity of ≈95%
- Use of ERCP to extract stones (or at least drain infected bile) is life-saving in severe cholangitis and reduces the need for BD exploration at the time of cholecystectomy
- Recommended for patients with a high clinical probability of choledocholithiasis
- When contrast agent flows retrograde into the gallbladder, stones appear as filling defects and can be detected with a sensitivity rate of ≈80%
  - US remains the mainstay for confirming cholelithiasis
- ERCP has therapeutic capabilities not available to MRCP.



- MRCP
  - A rapid, noninvasive, provides detailed bile duct and pancreatic duct images equal to those of ERCP
  - Sn ≈93% & Sp ≈94%, comparable with those for ERCP
  - Useful for examining nondilated ducts, particularly at the distal portion, which often is not well visualized by US
  - Adjacent structures such as the liver and pancreas can be examined at the same time
  - Recommended for patients with low to moderate clinical probability of choledocholithiasis

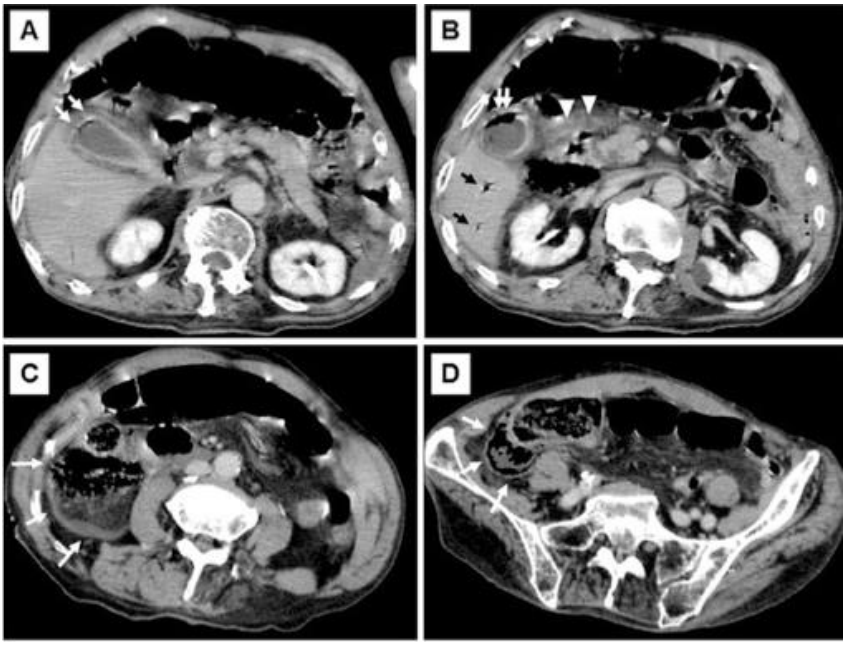
CT scan

- Not well suited for detecting uncomplicated stones but
  - Excellent for detecting complications such as abscess, perforation of gallbladder or BD, and pancreatitis

Emphysematous Cholecystitis

- Definition
  - Secondary infection of the GB wall with gas-forming organisms (Clostridium welchii, E.coli, and anaerobic streptococci)
- Demography
  - More common in older adult diabetic men; can occur without stones
  - High morbidity and mortality rates

- Clinical
  - Similar to severe acute cholecystitis
- Diagnostic imaging
  - Plain abdominal x-ray may show gas in the GB fossa
  - US and CT are sensitive for confirming gas



Abdominal CT findings

- A: CT shows a thickened wall and intramural air of the gallbladder, suggesting emphysematous cholecystitis (white arrows)

- B: Pneumobilia was detected in the intrahepatic bile duct (black arrows). The gallbladder contained air within the lumen (white arrows). Subserosal free air was detected in the hepatoduodenal ligament and around the pancreas head (white arrowheads)
- C: Massive pneumoretroperitoneum was observed behind the right-sided colon (white arrows)
- D: Pneumoretroperitoneum extended to the retroperitoneal space behind the ascending mesocolon, bordered by the cecum and iliopsoas muscle (white arrows)

Printed with permission: Yagi Y, et al. BMC Gastroenterology 2015;15:114.

- Treatment
  - IV antibiotics, including anaerobic coverage, and
  - Early cholecystectomy

Cholecystoenteric fistula

- Definition
  - Erosion of a stone through the GB wall into the adjacent bowel
- Clinical
  - Similar to those of acute cholecystitis, although sometimes a fistula may be clinically silent
  - The TI is the most common site of obstruction

- Diagnostic imaging
  - Plain abdominal x-ray may show gas in the biliary tree and/or a small bowel obstruction in gallstone ileus, as well as a stone in the RLQ if the stone is calcified.
  - Contrast upper GI series may demonstrate the fistula

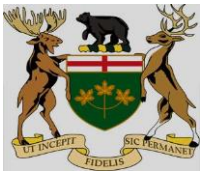
- Complications
  - Gallstone ileus
  - Gastric outlet obstruction (Bouveret's syndrome) may occur rarely.
  - A fistula from a solitary stone that passes may close spontaneously.

- Treatment
  - Cholecystectomy and bowel closure are curative
  - Gallstone ileus requires emergency laparotomy; the diagnosis is often delayed, with a resulting mortality rate of ≈20%

Mirizzi syndrome

- Definition
  - An impacted stone in the GB neck or cystic duct, with extrinsic compression of the common hepatic duct from accompanying inflammation or fistula

- Clinical
  - Jaundice and RUQ pain



- Diagnostic imaging
  - ERCP demonstrates
    - Dilated intrahepatic ducts
    - Extrinsic compression of the common hepatic duct
    - Possible fistula

- Treatment
  - Preoperative diagnosis is important to guide surgery and minimize the risk of BD injury

Porcelain gallbladder

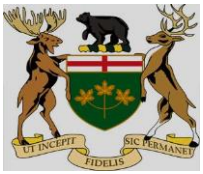
- Definition
  - Intramural calcification of the GB wall, usually in association with stones

- Clinical
  - No symptoms attributable to the calcified wall per se, but carcinoma of the gallbladder is a late complication in ≈20%

- Treatment
  - Prophylactic cholecystectomy is indicated to prevent carcinoma

Treatment of Gallstone Diseases

- UDCA
  - Oral dissolution with ursodeoxycholic acid +/-
  - Extracorporeal shock-wave (ECSW) lithotripsy for
    - Selection criteria similar to use of ursodiol (UDCA)
    - Small, radiolucent cholesterol gallstones in functional gallbladder
  - UDCA: 10 to 15 mg/kg of body weight per day
  - Selection criteria for oral bile acid dissolution therapy
    - Stages of gallstones disease
      - Symptomatic (biliary pain) without complications
    - Gallbladder function
      - Opcaification of gallbladder on oral cholecystography (patent cystic duct)
      - Normal result of stimulated cholescintigraphy (normal gallbladderemptying)
      - Normal result of functional US (normal gallbladder emptying after a test meal)
    - Stone characteristics
  - Successful dissolution
    - Followed by recurrence of gallstones in 30% to 50% of patients within 5 yr
    - Complete dissolution is achieved in 20% to 70% of patients.



- Treatment continued until stone dissolution is documented by 2 consecutive negative US at least 1 month apart.
  - Treatment should be stopped if
    - Patient does not tolerate the drug
    - Experiences a complication of gallstones during therapy
    - If the stones fail to dissolve after 6 months
    - Dissolve only partially after 6 months with lack of progression to complete dissolution by 2 yr.

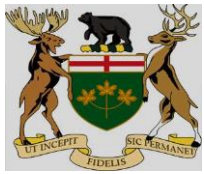
❖ Extracorporeal Shock-Wave Lithotripsy

- Multiple treatment sessions are often required to achieve sufficient pulverization
  - The energy of shock waves, number of shock waves per session, and number of sessions also influence the success rate.
- Ursodeoxycholic acid, is administered to dissolve stone fragments
- Success: free of stones at 6 mon 50% to 75%
  - Success (dissolution rates 12 mon)
    - Size < 16 mm
    - Few
    - Density < 84 Hounsfield units
- Adverse effects
  - Skin
    - Petechiae (~8%)
  - GU
    - Hematuria (~5%)
  - Liver
    - Hematoma (<1%)
  - Gallbladder
    - Cystic duct obstruction (~5%)
  - Pancreas (biliary) (<2%)

❖ Surgical

- Open Laparoscopic cholecystectomy

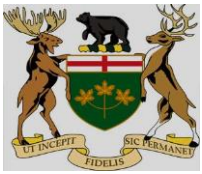
- Special consideration
  - Asymptomatic Gallstones
    - Indications for elective cholecystectomy in person with asymptomatic cholelithiasis
      - First Nations
      - Children
      - Heart and lung transplants
    - Prophylactic/preventive cholecystectomy not indicated in
      - Diabetes mellitus
      - Bariatric surgery
  - Acute Cholecystitis
    - Early (within days of presentation) cholecystectomy is preferable
      - ↓ mortality/morbidity
      - ↓ length of hospital stay
    - In high-risk patient with severe concurrent illnesses (such as liver, pulmonary, or heart failure)
      - Early initial cholecystostomy is preferable to cholecystectomy
  - Gallstone Pancreatitis
    - Early cholecystectomy for interstitial gallstone-induced pancreatitis
  - Gallstone Disease during Pregnancy
  - Indications
    - Acute cholecystitis
    - Gallstone pancreatitis
    - Pregnancy at risk
    - Mother's nutrition at risk
  - Safest timing (if possible)
    - T2 (second trimester)



PANCREAS

NEOPLASIA OF PANCREAS AND BILIARY TREE

Brian Yan



PANCREATIC CYSTS AND TUMOURS

➢ Causes/associations

- Give types of of cystic and cystic-appearing lesions of the pancreas.
  - Congenital true cysts
    - Cystic fibrosis
    - Dermoid cysts
    - Polycystic disease
    - Von Hippel-Lindau disease
  - Inflammatory
    - Abscess
    - Hydatid cyst
    - Pseudocysts
  - Angiomatous cysts
  - Cystic neoplasms
    - *Mucinous Neoplasms*
      - Mucinous Cystic Neoplasm (MCN) (aka macrocystic cystadenoma) and cystadenocarcinoma (MCAC)
      - Intraductal papillary mucinous neoplasm (IPMN) (aka mucinous ductal ectasia)
    - *Non-mucinous tumours*
      - Serous cystadenoma (SCN) (aka microcystic cystadenoma)
      - Papillary cystic tumour
      - Cystic cavitation of pancreatic adenocarcinoma or lymphoma
  - Acquired cysts
    - Central cavitary necrosis
    - Pseudocyst
    - Parasitic cyst

- Misdiagnosed nonpancreatic lesions
  - Choledochal cyst
  - Duodenal duplication cyst or diverticulum
  - Hypoechoic solid tumour
  - Lesser sac biloma
  - Lymphangioma
  - Mesenteric cyst
  - Splenic artery aneurysm
- Metastases, with cystic component

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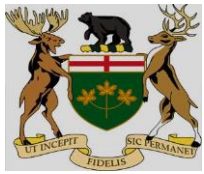
➢ Diagnosis

- Give the diagnostic features of types of pancreatic cysts.

Cyst Type	EUS Features	Fluid Appearance	Cytology
○ SCA	- Microcystic, honeycombed, 20% macrocystic	▪ Thin, clear, some-times bloody	▪ Cuboidal cells clear glycogen-positive cytoplasm
○ MCN	- Macrocystic	▪ Viscous, clear	▪ Mucin-rich fluid, columnar mucin-positive ovarian stroma cells, with variable atypia



Cyst Type	EUS Features	Fluid Appearance	Cytology
○ IPMN	- Duct dilation ▪ Main duct (MD – IPMN) ▪ Branch duct (BD – IPMN) ▪ Malignant potential MD >> BD – IPMN	▪ Viscous, clear	▪ Mucin-rich fluid, columnar mucin-positive cells, with variable atypia
○ PP	- Macrocystic, thick wall - Unilocular, internal debris	▪ Thin, dark, non-mucinous	▪ Inflammatory cells without evidence of mucin or epithelial cells
○ Pancreatic NET (cystic)	- Variable	▪ Variable, typically non-mucinous	▪ Small cells, scant cytoplasm, monomorphic nuclei
○ SPT	- Mixed solid and cystic	▪ Bloody	▪ Papillary structures, macrophages, myxoid stroma, monomorphic neoplastic cells
○ LEC	- Solid, hetero-geneous - Subtle posterior enhancement	▪ Thick and milky, gray or frothy	▪ Anucleated squamous cells, lymphocytes

Abbreviations: EUS: Endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm; LEC, lymphoepithelial cysts; MCN, mucinous cystic neoplasms; PD: Pancreatic duct; PET, pancreatic endocrine tumour; PP, pancreatic pseudocysts; SCA, serous cystadenoma; SPT, solid pseudopapillary tumours

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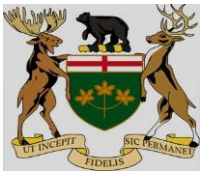
- Give a comparison of the viscosity, amylase, concentration, CEA and CA19-9 levels, and cytological findings in pancreatic serous cystadenoma, benign and malignant mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN) and pseudocyst (PC).

Parameter Analyzed	Serous Cyst-adenoma	MCN-Benign	MCN-Malignant	IPMN	PPC
○ Viscosity	↓	↑	↑	↑	↓
○ Amylase	↓	↓	↓	↑	↑
○ CEA	↓	↑	↑	↑	↓/↑
○ CA 19-9	↓	↓/↑	↑	?	↓

Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Table 60-7, page 1039.

- Give a comparison of pancreatic serous versus mucinous cystadenoma.

	Serous Cystadenoma	Mucinous Cystadenoma
○ Sex	- Female (2-3:1)	▪ Female (~100%)
○ Age	- 60s	▪ 60s
○ Ethanol abuse	- No association	▪ No association
○ Pancreatic history	- Yes (uncommon)	▪ Yes (uncommon)
○ Malignant potential	- No (rare)	▪ Yes



	SCA	MCA
○ Location	- Evenly distributed body/tail	▪ Body/tail
○ Locularity	- Multiple small	▪ Multilocular
○ Multilocular calcifications	- Central sunburst or stellate	▪ Peripheral, curvilinear

- Give a comparison of IPMN versus pancreatis pseudocyst.

	IPMN	Pseudocyst (PPC)
○ Sex	-Male (3-4:1)	▪ Male
○ Age	-60s	▪ Variable
○ Ethanol abuse	-No association	▪ Yes
○ Pancreatic history	-Yes uncommon	▪ Common
○ Malignant potential	-Yes	▪ No
○ Location	-Head	▪ Anywhere
○ Locularity	-Multilocular	▪ Unilocular
○ Calcifications	-No	▪ No, unless associated with chronic pancreatitis

Adapted from: Scheiman JM. *AGA Institute Postgraduate Course* 2006: pg. 586.

- The four major types of pancreatic cysts (SCA, MCN, IPMN, PC) are seen in patients in their 60s.
- The age of presentation of PC is variable.
- SCA and MCN are more common in women, IPMN and PC are more common in men.
- Malignant potential is
  - Higher in MCN and IPMN
  - Low in SCA and PC
- A history of pancreatitis is uncommon in SCA, MCN, and IPMN.

➢ Treatment

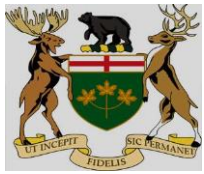
- Give the traditional therapeutic approach to the therapy of cystic lesions.

	Pseudocyst (PC)	Serous (SCA)*	Mucinous (MCN/IPMN)**	Malignant
○ Head	Drain	Monitor	Monitor	Resect
○ Body	Drain	Monitor	Monitor	Resect
○ Tail	Resect	Monitor	Monitor*	Resect

- Cyst fluid CEA < 3.1 ng/ml suggests non-mucinous, whereas CEA > 192 ng/ml suggest mucinous fluid

*Monitor all SCN unless causing symptoms;

**Monitor all MCN/IPMN unless has high risk features (associated mass/mural nodule, MPD >10mm, malignancy on cytology, or worrisome symptoms such as weight loss and jaundice)



Pancreatic Pseudocysts (PPC)

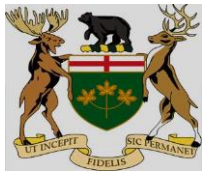
- Definitions
  - Pseudocyst
    - Non-epithelized fluid collection > 4 wk old as a consequence of
      - Trauma from disruption of pancreatic duct (PD)
      - Acute pancreatitis (AP)
      - Chronic pancreatitis (CP)
    - The acute pseudocyst may become chronic "….. as a sequelae of chronic pancreatitis and downstream pancreatic ductal obstruction with fibrotic strictures or stones" (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. *Saunders/Elsevier*, Philadelphia, 2010, page 1039).
  - Localized necrosis
    - Pancreatic tissue
    - Pancreatic plus peripancreatic fat necrosis

    → Causes a leak in the pancreatic duct → Cystic space filled with amylase-rich fluid
  - "…a [non-epithelialized] fluid collection that persists for 4 to weeks and becomes encapsulated by a wall of fibrous or granulation tissue (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 941).
  - Usually in adjacent to the pancreas, but occasionally seen in pelvis or chest

- Demography
  - May occur with
    - Acute or chronic pancreatitis
    - Infected or non-infected
    - Symptoms or no symptoms
  - Occur in ~25% of persons with chronic pancreatitis, particularity when alcoholic in origin
  - ↑serum amylase/lipase in ~50%
  - Complications occur in ~30%

- Give clinical, diagnostic imaging and laboratory features that distinguish pseudocysts from cystic neoplasms of the pancreas.

Feature	Pseudocyst	Cystic neoplasm
❖ Clinical		
○ Gender	- 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*		
- Septae	-	+
- Unilocular	+	+
- Multi-locular	-	+
- Solid component	-	+
- Calcification	+	+
- Mural wall nodules		
○ Communication between cyst and pancreatic duct on ERCP	- 70%	▪ Rare (except for IPMN)



Feature	Pseudocyst	Cystic neoplasm
❖ Cyst fluid		
○ Amylase	- ↑	▪ ↑
○ CEA, CA19-9	- ↓	▪ ↑
○ Cytology	- Inflammatory cells	▪ Glycogen ▪ Mucin-containing cells ▪ Malignant cells

Abbreviations: CEA, Carcinoembryonic antigen; CT, computed tomography; EUS, endoscopic ultrasound; US, ultrasonography

Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, Table 60-6, page 1039.

➢ Treatment

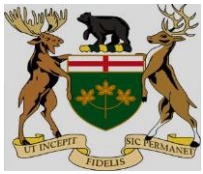
- Give indications for treatment of a person with a pancreatic pseudocyst.
  - Expansion of the pseudocyst producing
    - Abdominal pain
    - Duodenal or biliary obstruction
  - Pseudoaneurysm formation
  - Abscess formation
  - Fistula formation into adjacent viscera
  - Pancreatic ascites (tracking of pancreatic juice into the peritoneal cavity or pleural space)
  - Pleural effusion
  - Rupture
  - > 6 cm, 6 wks after episode of pancreatitis
  - Concern for malignant cystic lesion

Drainage

- Internal cystgastrostomy is preferred compared to percutaneous in almost all cases.
- Percutaneous drainage (PCD)
  - More prolonged drainage if connection with pancreatic duct
- Do a dynamic high-resolution CT after drainage to rule out pseudoaneurysm

Serous Cystadenoma (SCA)

- Laboratory
  - Cyst filled with clear, watery fluid (no mucin)
  - Potentially “dry tap” on EUS FNA
  - Cytology of fluid may show cuboidal cells with glycogen-rich cytoplasm.
- Diagnostic imaging
  - Body or tail of pancreas
  - May appear as conglomeration of many tiny cysts
  - Fibrous septa
  - Honeycomb appearance
  - Scar with stellate appearance
  - Stellate scar may be calcified
  - Central. “sunburst” calcification (on CT scan)
  - No communication with pancreatic duct
- Prognosis
  - Rarely malignant (3%)



Mucinous Cystic Neoplasm (MCN)

- Laboratory
  - Thick mucus material (or blood)
  - Fluid in cyst
    - ↑ CEA
    - ↓ amylase
  - Cytology shows
    - Columnar cells; ovarian stroma
    - Adenocarcinoma cells in Mucinous Cystadenocarcinoma (MCAC)

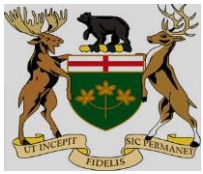
- Diagnostic imaging
  - May be benign, but all MCNs have malignant potential
  - Larger cysts (> 3cm) and/or mural nodules are more likely to be malignant than benign MCN.
  - Body or tail of pancreas
  - Thick wall
  - Occasional septa
  - No communication with pancreatic duct on ERCP/MRCP
  - Lesions are very rarely mutifocal, so once the single lesion is removed, surveillance is not necessary.

- Prognosis
  - MCNs with no high-risk features (associated mural nodule/mass or worrisome symptoms) tend to be slow growing, with 90% having no change in imaging after 3 years.

- 5-year survival rate after resection of tumour, 63% - 100%, depending on pathology of specimen (lower survival if invasive carcinoma is present)

Intraductal Papillary Mucinous Neoplasms (IPMN)

- Definition
  - "…. Papillary neoplasms within the main pancreatic duct showing mucin hypersecretion that often leads to duct dilation and chronic obstructive pancreatitis.
  - Thick (viscous) mucous with ↑ CEA, ↑ amylase
- Demography
  - Male: female ratio: 1-2.4
  - Mean age of diagnosis
    - 65 yrs
- Genetics
  - As compared with pancreatic adenocarcinoma
    - In IPMN there are more frequent molecular changes in SKT 11/LKB1 inactivation and PIK3CA mutation
    - Less frequent mutations in K-Ras and P53 tumour suppressor genes, P16 and DPC4
  - In IPMN, there is ↑ expression of
    - Fascin (an actin-bundling protein), methylated PPENK
    - Human telomerase reverse transcriptase
    - EUS fluid aspirate molecular analysis may demonstrate mutations in KRAS, GNAS, RNF43, TP53, p16/CDKN2a, and SMAD4. There may also be loss of heterozygosity in Chr 9, Chr 1q aneuploidy, and Chr 8p aneuploidy



- Types
  - Main Duct (MD-IPMN)
  - Side branch (SB-IPMN)
  - Main plus side branched (Mixed type IPMN)
- Clinical
  - Symptoms arise from mucin distending involved pancreatic duct; (may see mucus extruding from ampulla on ERCP)
  - 5-year survival rate after resection, > 75%
  - Main duct IPMN or branching chain IPMN > 3 cm are more likely to be malignant.
  - Main duct IPMNs are more likely to become malignant and to grow faster: ~65% develop HGD/cancer in 5 yrs, vs 15% for branched chain IPMNs
- Laboratory
  - ↑ serum bilirubin predicts ↑ risk of malignancy
  - ↑ CEA in 80-95% of IPMNs

- Give the significance of ↑ amylase concentration in the fluid aspirated from a pancreatic cyst.
  - Amylase in a gut aspirate only signifies that the cyst which contained the fluid was in communication with the pancreatic ductal system (either main duct or off of a side branch).

- Diagnostic imaging
  - MRI
  - CT
    - CT using pancreatic protocol (detects IPMN in 97% of cases)
  - MRCP
    - MRCP is superior to CT to demonstrate communication between ducts, and cyst morphology
    - MRCP with secretin (S-MRCP)
    - Breath-hold MRCP
  - EUS
  - ERCP
  - PET scanning sensitivity, 57-90%; specificity, 85-97%
  - Exclude pancreas divisium (MRCP, 100% accurate; CT; sensitivity 90%, specificity, 97%)

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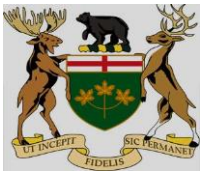
- Give “pathognomonic” findings which help to differentiate between the types of pancreatic cyst.
  - ERCP-mucus dripping from a fish mouthed ampulla of Vater → IPMN
  - CT-central, sunburst calcification → serous cystadenoma (SCA)



- Histopathology
  - Cytology
    - Columnar mucinous epithelial cells with variable atypia
  - Grape-like cluster of cysts, localized or diffuse dilation of main pancreatic duct, patulous ampulla of Vater (aka “fish mouth ampulla”)
  - Lesions of main or bronchial pancreatic ducts, with proliferation of the mucinous epithelium leading to ductal and cystic dilation
  - 20-30% of IPMNs are multifocal, arising from a field defect in the entire pancreas that can cause multiple primary neoplasms.
  - Range histologically from benign, low grade (LGD), high-grade dysplasia (HGD), carcinoma in situ (CIS), to invasive cancer (IC), with various grades of histology, probably being present with the same specimen
- Treatment
  - Surgical resection is the mainstay of therapy for high risk or malignant IPMN
  - Chemotherapy may be used as adjuvant therapy or for unresectable disease
  - Cyst ablation with ethanol +/- paclitaxel (a chemo-therapeutic agent which inhibits the disassembly of micro-tubules and induces apoptosis with complete resolution of cysts in 79%) may be reasonable for IPMNs with low risk of malignancy, but **only** under study protocols. Cyst ablation is more effective in MCN than IPMN. Those who may be suitable for ETOH ablation include:
    - No symptoms
    - < 3 cm size
    - Main duct < 6 mm
    - No mural nodules, thickness or septations

- Surgery
  - Fukuoka guidelines (2012) for resection
  - After surgical resection, 5 year survival is approximately 60% if there is invasive carcinoma, and 100% if no invasive carcinoma
  - Recurrences may occur in a median of 20 months, and 58% of these recurrences involve distal sites.

- Give the **Sendai Guidelines** for resection of IPMNs.
  - Symptomatic – All IPMNs (MD- and BD – IPMNs) with symptoms
  - Asymptomatic – All MD-IPMNs
    - BD-IPMNs > 3 cm
  - EUS – All IPMN with
    - Nodules
    - Thickening
  - CEA – > 192
  - Surveillance EUS, ERCP, MRCP (CT scan) – Enlargement on surveillance every 6-12 mon

Incidental Pancreatic Cysts

Asymptomatic Neoplastic Pancreatic Cysts which are Identified Incidentally by Diagnostic Imaging: AGA Guideline (2015)

Vege SS, et al. Gastroenterology 2015; 148: 819-822

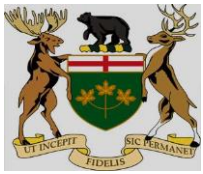
Please also see the Technical Review that accompanies these Guidelines: Scheiman JM, et al. Gastroenterology 2015: 148: 824-848.

- Demography
  - In person having an abdominal MRI for other reasons, unsuspected pancreatic cysts are seen in ~15% of patients
  - This increases to ~25% in persons > 70 yr
  - A pancreatic cyst for incidentally has a very low risk of being malignant
    - Mucinous invasive malignancy $10/10^5$
    - Pancreatic ductal carcinoma $17/10^5$

- Differential diagnosis for pancreatic cystic neoplasm

Type of Cyst	Key Characteristics
○ Mucinous cysts – Mucinous cystic neoplasm (MCN)	▪ 95% present in women, > 95% located in distal pancreas ▪ Median age of diagnosis: 45 to 48 years ▪ Pathognomonic finding: dense ovarian-like stroma and inner epithelium with tall, mucin-producing cells ▪ Imaging: thick-walled single cyst, septations, absence of duct communication ▪ EUS appearance: macrocystic, peripheral calcifications ▪ Malignancy rate 17.5%, slow progression

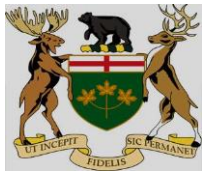
Type of Cyst	Key Characteristics
– Intraductal papillary mucinous neoplasm (IMPN)	
• Main-duct IPMN	▪ More frequent in males, common symptom is abdominal pain ▪ ~ 60% cases located in the head of pancreas ▪ Pathognomonic finding: bulging papilla extruding mucin on endoscopy ▪ Imaging: main pancreatic duct > 10 mm associated with increased malignant potential; additional findings include solid component, intraductal calcifications or atrophic pancreas ▪ EUS: dilated main pancreatic duct, intraductal solid components (mucin vs. papillary projections) ▪ Malignancy rate 30–60%
• Branch-duct IPMN	▪ Isolated side branch involvement with communication with main pancreatic duct ▪ Imaging: varied, isolated small cyst to numerous collections of cysts ▪ Malignancy rate: all considered pre-malignant with a malignancy rate of up to 17–25%



Type of Cst	Key Characteristics
• Mixed – Mucinous non-neoplastic cyst	▪ Imaging features of both main and branch-duct IPMNs ▪ No malignant potential.
○ Non-mucin producing cysts	▪ Serous cystic neoplasms (SCN) Predominantly affects women. Benign with < 1% risk of malignancy; rare case reports of malignant SCNs ▪ Can be associated with von Hippel-Lindau syndrome ▪ Pathognomonic finding: multicystic mass with central calcification ▪ EUS findings: micro and macrocystic features with a honeycomb appearance; cyst fluid with low CEA level < 5 ng/mL and low amylase; presence of cuboidal epithelium on FNA/FNB
○ Solid pseudopapillary neoplasm	▪ 80% present in women ▪ Imaging: large demarcated mass with mixed solid and cystic features ▪ EUS findings: FNA/B evidence of microadenoid structures and branching papillary clusters

Printed with permission: Phan J and Raman Muthusamy V. Curr Gastroenterol Rep 2018; 20(7):32.

- Guidelines
  - Post-surgery continued MRI surveillance q 2 yr
  - Only the AGA Guideline has "….pursued a systematic evaluation of the available evidence
  - The following points are new in these AGA guidelines
    - Surveillance
      - Cysts of any size should be followed by MRI q 2 yr
      - If cyst does not change after 5 yr of MRI q 2 yr, the surveillance is stopped
    - Surgery
      - Only in high-volume centres
      - Only if $\geq$ 2 high risk features on MRI, and confirmed on MRI, and confirmed on EUS
      - After surgery on cyst: no HGD / malignancy, no surveillance
  - The objective of these guidelines is to identify the asymptomatic incidentally identified pancreatic cysts which have an ↑ risk of high-grade dysplasia (HGD) or of invasive cancer
    - The PICO format was used, based upon
      - Population
      - Investigational/intervention being considered
      - Comparator
      - Outcome to be evaluated
    - The GRADE system was used
      - "….the Grading of Recommendations Assessment, Development and Evaluation"



- The PICO statement is described on a 4-point scale from high to very low
  - All the evidence related to incidental pancreatic cysts was rated as being very low (great uncertainty)

- Pathology
  - Risk of malignant transformation ~0.24% per yr
    - If there is no diagnostic imaging change for 5 yr
      - Even lower risk of cancer

- Suggested Diagnostic Imaging for ↑ risk of malignancy

	~ ↑ risk		
○ Size ≥ 3 cm	3x	If > 2 features present →	EUS plus FNA, to access possible HGD, malignancy – Sensitivity ~60% – Specificity ~90% – NPV, very high (close to 100%)
○ Solid components	8x		
○ Dilated pancreatic duct	Not known		

  - MRI q 2 yr for cyst of any size
  - Stop surveillance after 5 yr if no change

- If ≥ 2 high risk factors are present, surgery may be considered, and should be followed with MRI q 2 hr of HGD/malignancy found
- Stop if the patient is no longer a candidate for surgery

➢ Surgery

- Major morbidity ~30%
- Post-operative mortality ~2% (high-volume "pancreatic centre"; in non-high-volume centres, mortality ~6.6%
  - If no HGD/invasive centres. – none

❖ Suggestions of AGA Institute Guideline regarding Surveillance

- Before starting any pancreatic cyst surveillance program, patients should have a clear understanding of programmatic risk and benefits.
- Patients with pancreatic cysts < 3 cm without a solid component or a dilated pancreatic duct undergo MRI for surveillance in 1 year, and then every 2 year for a total of 5 years if there is no change in size or characteristics (conditional recommendation, very low-quality evidence).
- Pancreatic cysts with at least 2 high-risk features, such as size ≥ 3 cm, a dilated main pancreatic duct, or the presence of an associated solid component, should be examined with EUS-FNA (conditional recommendation, very low-quality evidence)

- Patients without concerning EUS-FNA results should undergo MRI surveillance after 1 year, and then every 2 year to ensure no change in risk of malignancy (conditional recommendation, very low-quality evidence).
- Significant changes in the characteristics of the cysts, including
  - Development of a solid component
  - Increasing size of the pancreatic duct
  - Diameter $\geq$ 3 cm are indications for EUS-FNA (conditional recommendation, very low-quality evidence)
- When to stop pancreatic cyst surveillance
  - Do not continue surveillance of pancreatic cysts if
    - There has been no significant change in the characteristics of the cyst after 5 years of surveillance
    - If the patient is no longer a surveillance candidate (conditional recommendation, very low quality)
- When to offer surgery
  - Patients with both a solid component and a dilated pancreatic duct and/or concerning features on EUS and FNA should undergo surgery to reduce the risk of mortality from carcinoma (conditional recommendation, very low-quality evidence)
  - If surgery is considered for a pancreatic cyst, patients are referred to a centre with demonstrated expertise in pancreatic surgery (strong recommendation, very low-quality evidence)

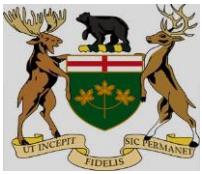
- Surveillance after surgery
  - Patients with invasive cancer or dysplasia in a cyst that has been surgically resected should undergo MRI surveillance of any remaining pancreas every 2 years (conditional recommendation, very low-quality evidence).
  - Do not do routine surveillance of pancreatic cysts
    - Without high-grade dysplasia
    - Malignancy at surgical resection (conditional recommendation, very low-quality evidence)

Pancreatic Ductal Adenomcarcinoma (PDCa)

- Demography
  - Incidence $10/10^5$
  - Prevalence
    - Because the mortality rate is so high, prevalence figures are meaningless
  - Only 10% are resectable/localized at the time of diagnosis
  - 1% endocrine

- Histopathology

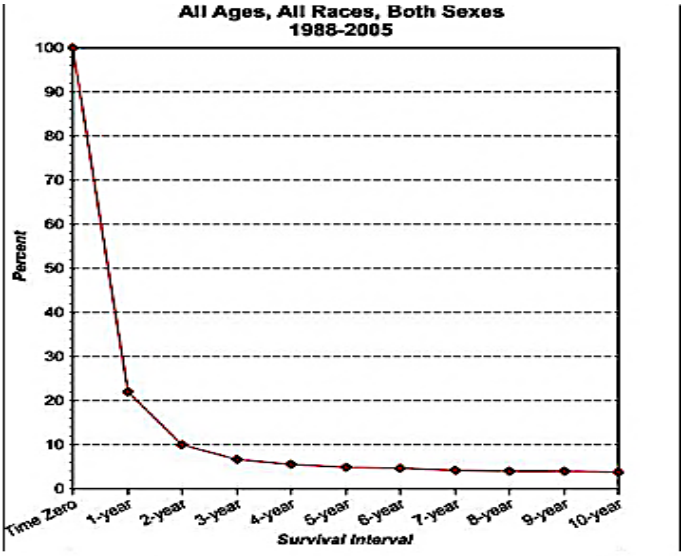
- Give the names of immunohistochemical markers which may be used to confirm that a tumour in the pancreas is mucus secreting and is not derived from acinar or neuroendocrine cells of the pancreas.
  - Markers for mucin
    - MUC_1, MUC_2, MUC_4
    - CEA (carcinoembryonic antigen)
    - CA 19-9, Ca 125
    - $DuPan_2$



- Markers for cytokeratins
  - 7, 8, 18, 19 (cytokeratin 7 is usually absent from pancreatic tumours arising from acinar or neuroendocrine cells).

Canadian Mortality Data

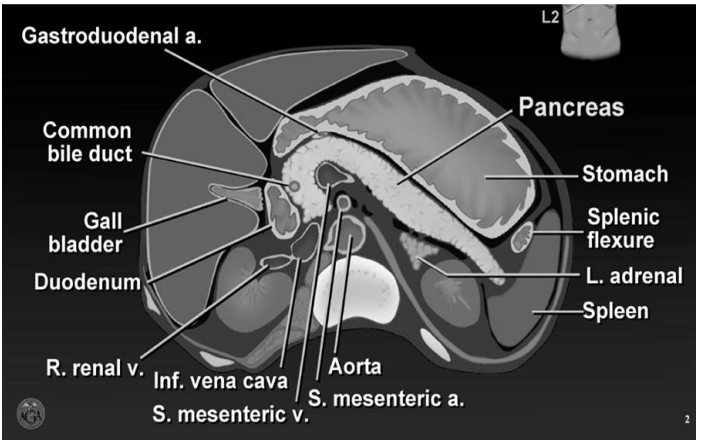
Background: Pancreatic Cancer



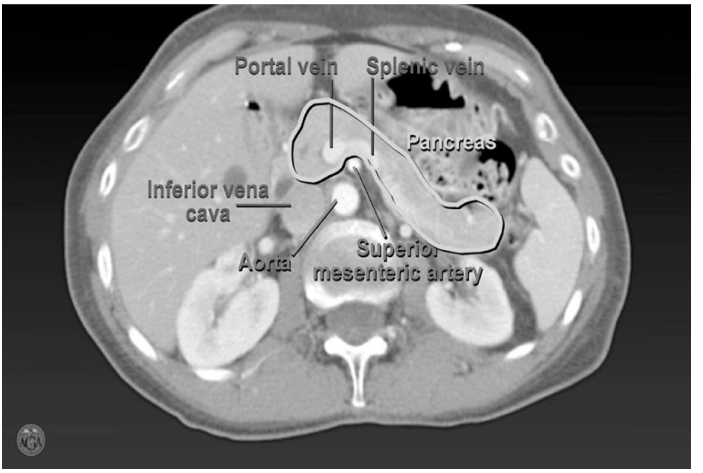
http://seer.cancer.gov/statfacts/html/pancreas.html

- Diagnostic Imaging

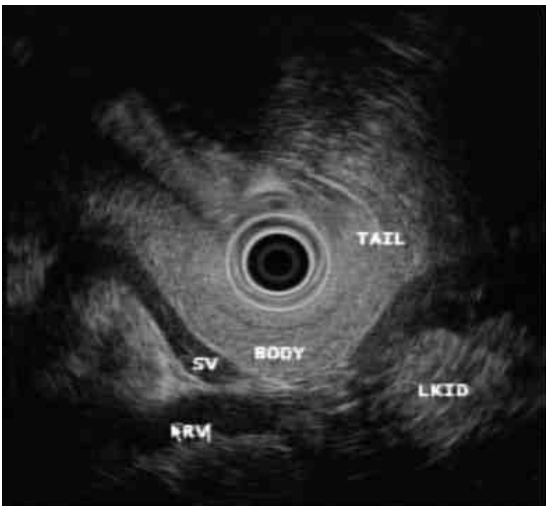
CT Scan: Normal



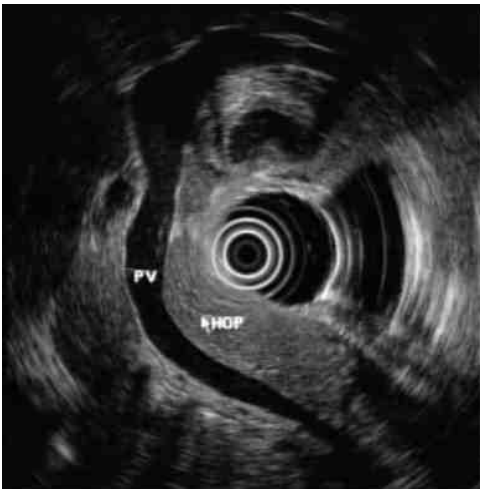
CT Scan: Normal



EUS: Normal

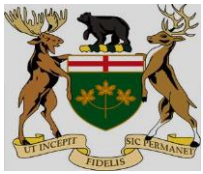


EUS: Normal



- Laboratory
  - ↑ **CA19-9** (tumour marker) occurs in
    - ~75% of persons with pancreatic adenocarcinoma
    - Some persons with biliary obstruction and cholangitis
  - The tumour marker CA 19-9 has a sensitivity of 86% and a specificity of 87% to diagnose PDCa.
  - CA19-9 may be falsely positive in the presence of jaundice or cholangitis.
    - The performance characteristics depend upon the value of the cut-off that is used
    - Post-operative CA 19-9 > 90 U/mL may not be as responsive to chemotherapy
    - A post-operative CA 19-9 falling from an ↑ pre-opt to a 6 mon survival time of 30 vs 15 mon
  - Because CA 19-9 is not suitable for screening, the diagnosis of PDCA is usually made by diagnostic imaging of the abdomen.

- Pathology
  - Most pancreatic carcinomas are from duct cells and may secrete mucin.
  - Site
    - Pancreas
      - 70% H (head of pancreas)
      - 15% B (body)
      - 15% T (tail)
    - Wall of duodenum
    - Ampullary of Vater
    - Distal bile duct (aka common bile duct)



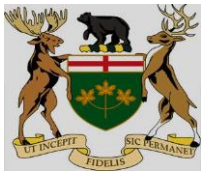
➢ Causes/associations

- Give genetic and non-genetic causes/associations of pancreatic duct cancer.
  - Familial

Number of First-Degree Relatives Affected	↑ Relative Risk
1	2.3x
2	6x
3	32x

  - Hereditary pancreatitis
    - Cationic trypsinogen (CT, PRSS-1)
    - CFTR
    - SPINK-1
  - Genetic abnormalities
    - Familial atypical mole and multiple melanoma
      - Germline p16 mutation
    - Hereditary breast cancer
      - Germline BRCA2 mutation
    - Oncogenes
      - K-Ras mutations (90%) and p53 (70%) mutations (occur early and indicate tumour induction by exogenous carcinogens)
    - TP53, APC4 (aka SMAD4) mutations (occur late)
    - EGF (epidermal growth factor) receptors
    - SONIC hedgehog product
    - Inactive tumour suppression gene (p59, p16 [DKN2A])
    - Familial pancreatic cancer
    - Familial ovarian and breast cancer

- Polyp syndromes
  - Familial adenomatous polyposis (FAP)
  - HNPCC (Lynch) mismatch MLH1, MSH2, BRCH2
  - Peutz-Jeghers syndrome (PJS)
  - Cowden syndrome (CS)
- Lifestyle
  - Smoking
    - ↑ risk 1.5 x
    - Interacts to further ↑ risk in
      - Alcoholism
      - $GSTT_1$
  - Alcohol
  - High-saturated fat (red meat) ↓ vegetable/vitamin diet
- Diet
  - ↓ intake of
    - Fresh fruits
    - Vegetables
    - Selenium
- Drugs
  - 7x ↑ risk after exposition to dichloro-diphenyltrichloroethane or deviates (e.g., ethylene)
- Metabolic
  - Chronic pancreatitis, especially when the pancreatitis is due to
    - Alcohol
    - Cystic fibrosis
    - Other forms of hereditary pancreatitis
    - Tropical pancreatitis
  - Diabetes mellitus
  - Partial gastrectomy



- Miscellaneous
  - Ataxia telangiectasia
  - Cystic fibrosis
  - Fanconi anemia
  - Familial adenomatous polyposis (FAP)
  - Neuroendocrine tumours (NET)

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): pg. 522.

- Give precursor lesions for PDCA.

Because the mortality rate for pancreatic ductal cancer (PDCA) is so high, it is important to recognize precursor lesions so that early diagnosis and possibly better survival will occur.

- PanIN – Pancreatic intraepithelial neoplasia
- MCN – Mucinous cystic neoplasms
- IPMN – Intraductal papillary mucinous neoplasms
- SPT – Solid pseudopapillary tumour
  - 20% risk of solid-pseudopapillary carcinoma
  - Abnormal expression of β-catenin and p120
  - ↓ expression of E-cadherin protein, or E-cadherin protein localized to cell nucleus
- Cystic islet cell tumour
- Serous cystadenomas may rarely (3%) be malignant (serous cystadenocarcinoma)

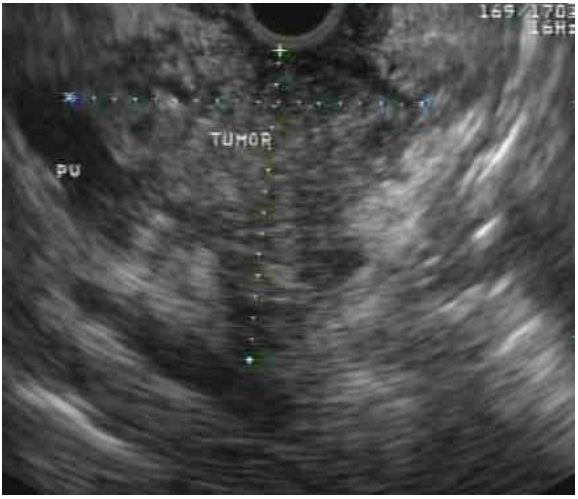
Note: Early events include K-Ras mutation and p16 loss, whereas late events include TP53 and APC4/SMAD4 loss.

- Diagnostic imaging

	Sensitivity	Specificity	Accuracy
○ Pancreatic Neoplasm			
– CEUS	~91%	~93%	~92%
– EUS +/- FNA	85-98%	67-91%	91-95%
– CT	77-86%	64-93%	66%
– MRI	85-99%	60-95%	79-81%
○ Lymphadenopathy			
– CEUS	60%	91%	88-100%
– EUS +/- FNA	68%	86%	75-81%
– CT	33%	75%	51-74%

Source: Mohamed RM and Yan B. World J Gastrointest Endosc 2010;2(7):237-43.

Referred for EUS and FNA

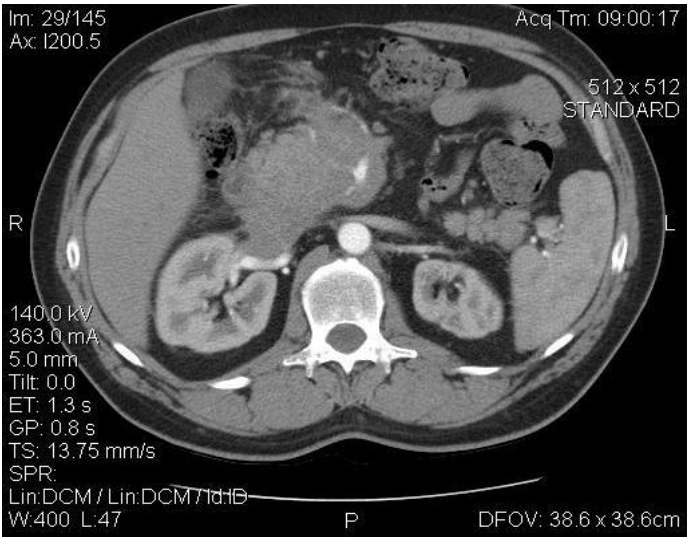


- Differential

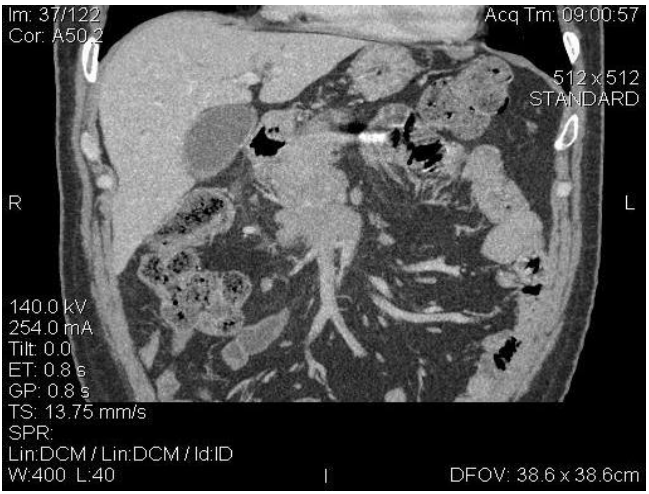
Not all cases are primary pancreatic duct adenocarcinoma

- Lymphoma
- Chronic pancreatitis, focal pancreatitis
- Autoimmune pancreatitis (AIP)
- Metastases

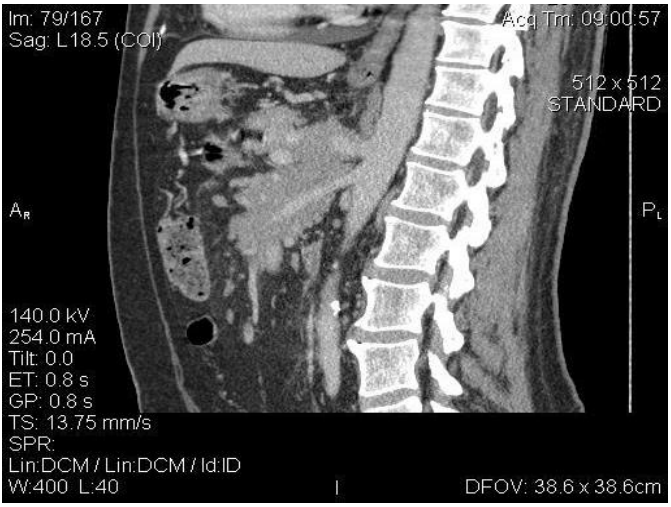
CT Scan of Pancreas



CT Scan of Pancreas



CT Scan of Pancreas



- Diagnostic imaging
  - Cystic neoplasms may mimic a pseudocyst, especially when there are nodules or internal septations.

- Give diagnostic imaging tests for PDCA.
  - Abdominal ultrasound
  - Helical CT pancreatic protocol
    - Direct signs
      - Dual-phase scanning after PO/IV contrast, with pancreatic arterial phase at 40 sec and portal venous phase at 70 sec after IV contrast agent is given.
      - Oral contrast, to distinguish between pancreas and duodenum
      - Hypoattenuating → adenocarcinoma
      - Hyperattenuating → neuroendocrine tumour (NET)
      - 10% are isoattenuating, so use indirect signs to distinguish PDCA from other tumours, e.g. NET
    - Indirect signs
      - Dilated PD, CBD, double duct (PD+CBD)
      - Mass effects
      - Pancreatic atrophy
      - Abnormal pancreatic contour
      - Gives 97% correct diagnosis of PDCA
      - 85% of persons predicted to have resectable disease by CT turn out to actually have unresectable disease

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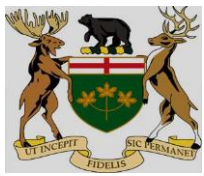
- Give the CT criteria for unresectable PDCA.
  - Distant metastases (does not include lymph nodes)
  - Encasement of celiac axis e.g., SMA or aorta
  - Occlusion of PV, SMV or VC

Abbreviations: PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; VC, vena cava

- MRI, MRA, MRV, MRCP
  - Magnetic resonance imaging
  - Gadolinium contrast used for MRA, MRV, MRCP
  - Image weighting
    - T_1 – MRI (solid)
    - T_2 – MRCP (fluid)
  - Use MRI to directly biopsy pancreatic mass
  - Staging sensitivity for PCDA
    - MRI 84%
    - CT 91%
- Positron emission tomography (PET) using radioactive fluorodeoxyglucose [FDG} F18)
  - Shows focal area of ↑ uptake of FDG in pancreas, and “hot spots” (↑ FDG uptake) of metastases in liver.
  - Performance characteristics: sensitivity of 95% to detect malignant pancreatic tumours.
  - Does not show details of anatomy of pancreas, so do CT or MRI.

Abbreviations: FDG, fluodeoxyglucose; MRA, magnetic resonance arterogram; MRCP, magnetic resonance cholangiopancreaticogram; MRV, magnetic resonance venogram; PDCA, pancreatic duct carcinoma



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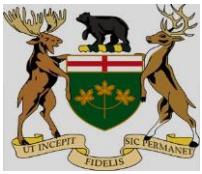
There are numerous good tests to diagnose and to stage PDCA. It is important to establish whether the patient is a surgical candidate for pancreatic resection, or if they are **non-resectable**.

- Give a non-endoscopic and non-diagnostic imaging test for non-resectability of PDCA.
    - Staging laparoscopy with peritoneal lavage and cytology yields data rendering a patient to be declared non-resectable, despite lack of this evidence on CT/MRI.
        - Staging laparoscopy, 25%
        - Peritoneal cytology, 10%

- A patient with a predicted resectable PDCa has a Whipple pancreaticoduodenectomy. The patient is hopeful for a 5-year mortality rate of 11% to 25%, and a median survival of 11 to 20 months. The patient asks, based on her/his case, what are the factors which predict that he/she will have a better outcome.
    - Outcome predictors forresectable PDCA
        - Size, < 3 cm
        - Margins, negative
        - Metastases (to lymph nodes), none
        - Blood loss during surgery, < 750 mL

- Endoscopy
  - ERCP (endoscopic retrograde cholangio-pancreatography)
    - Evaluation of recurrent pancreatitis (avoid in chronic pain syndromes)
    - Pancreatic duct disruptions or leaks
    - Symptomatic pancreatic pseudocysts
    - Drainage of pancreatic necrosis
    - Palliative stenting
  - EUS (endoscopic ultrasound)
    - Diagnostic procedure in acute and chronic pancreatitis
    - Consider before transmural drainage of pancreatic fluid collection/necrosis/pseudocyst
    - Pancreatic mass < 2 cm
      - Sensitivity
        - EUS 98%
        - CT 91%
    - Usually used to complement CT for staging
    - More sensitivity than CT to determine if there is vascular invasion
    - First line method for tissue acquisition (FNA, fine needle aspiration; FNB, fine needle core biopsy), and is preferable over percutaneous methods (CT or transabdominal ultrasound guided)
    - Useful for celiac plexus block/neuorlysis for palliation of pain
    - Types of EUS
      - Radial: 360^{o} perspective
      - Linear: (for sampling or injection)



- "EUS is superior to CT for detection of co-existent [pancreatic] malignancy [in a pseudocyst] particularly when the lesion is small" *Saunders/Elsevier*,
- EUS also has the substantial advantage of FNA.

- Contrast-enhanced harmonic EUS (CH-EUS)
  - Visualizes pancreatic parenchymal perfusion and the microvasculature
  - Determined hypo-enhancement pattern diagnosed ductal carcinoma with high sensitivity and specificity.
  - Superior to multi-detector-row computed tomography (MDCT) in distinguishing small ductal carcinomas from other tumours.
  - Combining CH-EUS with EUS-FNA improves the sensitivity with which EUS-FNA identifies ductal carcinomas.

Source: Kitano M et al. Am J Gastroenterol 2012; 107: 303-310.

EUS-FNA

- Chang et al. GIE 1997
  - N=44
  - EUS-FNA accuracy 95% for pancreatic lesions and 88% for lymph nodes
- Gress et al. Ann Intern Med 2001
  - 102 pts with suspected Panc Ca and negative CT guided bx or ERCP brushings
  - 57 positive cytology
  - 45 negative or inconclusive
    - 41 of 45 had no evidence of PDCA at 2 yr

EUS-FNA for Solid Pancreatic Masses

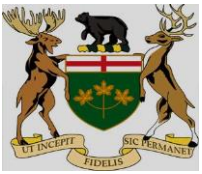
- 33 Studies 1997-2009
- 4984 pts
- Pooled Sen: 85%
- Pooled Spec: 98%
- PPV: 99%
- NPV: 65%
- + LR: 21
- - LR: 0.17

Hewitt MJ, et al. Gastrointest Endosc. 2012;75(2):319-31.

Errors in EUS-FNA

- Non-diagnostic rate 5-10%
  - Overall “real life” cross sectional multicenter academic (80%) and non academic diagnostic rate: 75-78%
- 1-5% false positives
  - Interpretative Error

Eloubeidi MA, et al. J Gastroenterol Hepatol. 2008; 23(4):567-70.
Savides, et al. Gastrointest Endosc 2007; 66(2):277-82.
Siddiqui, et al. Gastrointest Endosc 2011; 74(3):535-40.
Schwartz, et al. Gastrointest Endosc 2002; 56(6):868-72.
Eltoum, et al. Cytopathology 2007; 18(3):143-50.



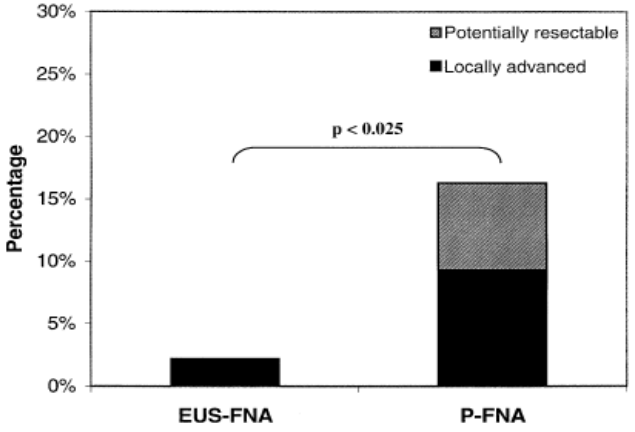
Risks of EUS-FNA in Pancreatic Cancer

Natural and frequency of major complications after EUS-guided FNA of solid pancreatic masses with their corresponding 95% CI

Nature of Complication	N (%) (N = 355)
○ Hospitalization	7 (1.97)
○ Total, all complications 25% (N = 9)	9 (2.54)
– Acute pancreatitis	3 (0.85)
– Severe abdominal pain	3 (0.85)
– Fever	2 (0.56)
– Oversedation-reversal medication	1 (0.28)
– Bleeding	0 (0)
– Perforation	0 (0)
– Death	0 (0)

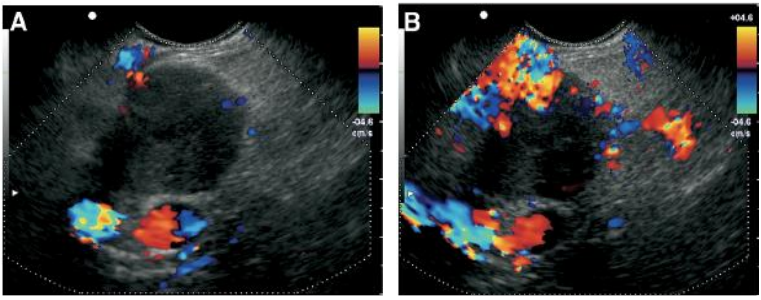
Adapted from: Eloubeidi MA, et al. J Gastroenterol Hepatol. 2008; 23(4):567-70.

○ Needle Tract Seeding



Adapted from: Micames C, et al. GIE 2003; 58(5): 690-5.

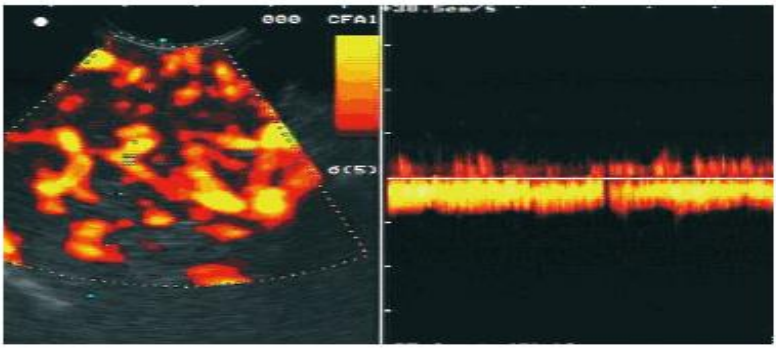
Contrast Enhanced EUS: Inflammation vs Malignancy



- CE-EDUS in patient with hypovascular ductal adenocarcinoma of the pancreas. (A) CDI and (B) contrast-enhanced Doppler ultrasound both revealed a hypovascular lesion

Printed with permission: Dietrich CF, et al. Clin Gastroenterol Hepatol 2008; 6(5):590-7.

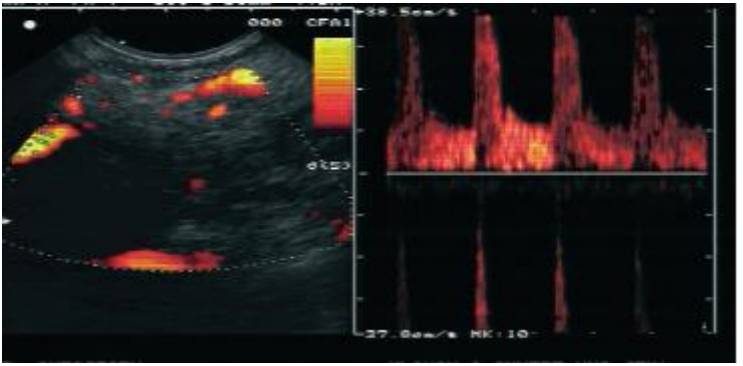
EUS: Chronic Pancreatitis



- Regular vascularization is shown with detection of venous vessels using contrast-enhanced power. Doplller scanning in combination with power Doppler

Printed with permission: Hocke M, et al. World J Gastroenterol. 2006 12(2): 246-250.

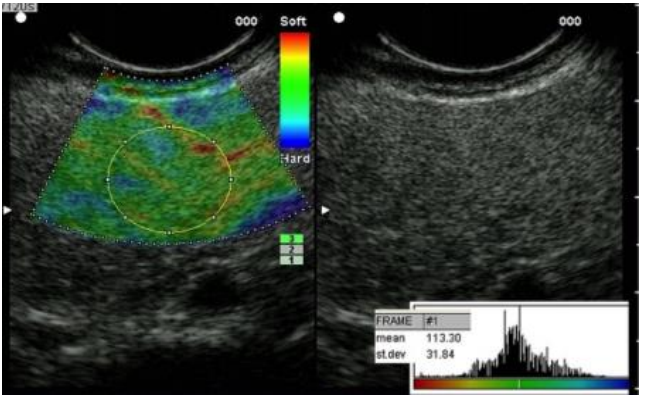
EUS: PDCA



- Irregular vascularization is shown with detection of only arterial and no venous vessels using contrast-enhanced power Doppler scanning in combination with pw-Doppler

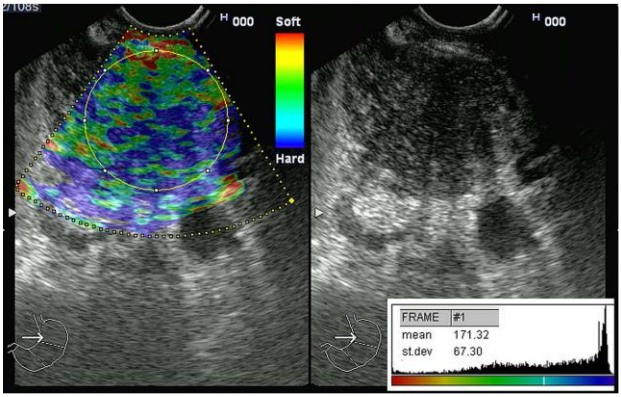
Printed with permission: Hocke M, et al. World J Gastroenterol. 2006 12(2): 246–250.

EUS Elastography (Normal)



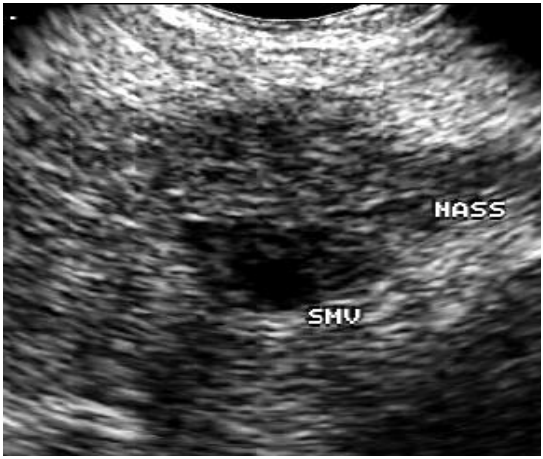
Printed with permission: Săftoiu A, et al. Gastrointest Endosc 2008; 68(6):1086-94.

EUS Elastography (Chronic Pancreatitis)



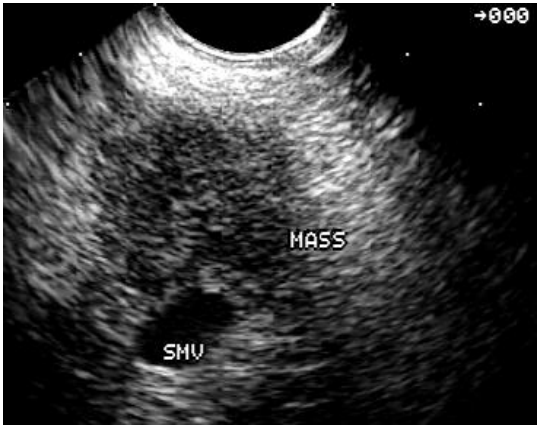
Printed with permission: Săftoiu A, et al. Gastrointest Endosc 2008; 68(6):1086-94.

SMV Invasion by Pancreatic Mass



Circumferential tumor invasion of the SMV

Courtesy of Dr. William Brugge Pentax



Tumor invasion of 180 degrees of SMV

Courtesy of Dr. William Brugge Pentax

Vascular Invasions

EUS Criteria (gold std: surgery)	Accuracy (%)
○ Irregular venous wall - Serrations along tumor surface - Distinct indentation of mass - Mass had direct contact with lumen	87
○ Loss of Interface - No evidence of line along tumor interface	78
○ Proximity of mass to venous wall - Adjacent < 3 mm - Remote: >3mm	73
○ Size (> 2.5cm)	39

Printed with permission: Brugge WR, et al. Gastrointest Endosc. 1996; 43 : 561-567.

EUS vs MDCT

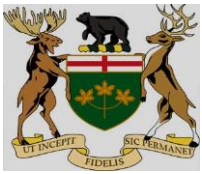
Comparison	EUS	CT
○ Sens for detecting mass	98	86
○ Determination of resectability	88	92

Adapted from: DeWitt J, et al. Ann Intern Med 2004;141(10): 753-63.

- Staging: AJCC 2018
  - T1: confined pancreas, <2cm
  - T2: confined pancreas, 2cm to <=4cm
  - T3: >4cm
  - T4: Tumor involves celiac, SMA, or common hepatic artery regardless of size
  - EUS Accuracy
    - T staging: 78 - 84%
    - N staging: 64 – 92%

- Treatment
  - Current Standard of Care
    - Surgery
    - Chemotherapy
    - Radiation

- Surgery
  - Best chance for cure
  - 10-15% resectable at diagnosis
    - 75% ultimately recur +/- mets
    - Lymph nodes positive in 75-80%
  - At best, 25% 5 yr survival
  - Operative mortality 5%



Surgical Survival: London

- Mean Overall Survival
  - R0: 45 mon (95% CI 35-55 mon)
  - Non- R0: 16 mon 995% CI 13-21 mon)
- Mean Disease-Free Survival
  - R0: 20 mon (95% CI 14-26 mon)

Courtesy of Dr. Ken Leslie

- Prognosis
  - Overall 5 yr Survival 10% (7-25%)
  - Median Survival 18 – 20 mon
  - Size
    - <2cm 20% - 40%
    - >3cm 1%

    5 yr Survival:
  - Differentiation
    - Well 50%
    - Poor 10%

    5 yr survival:
  - Node Status
    - Negative 4.5 yr
    - Positive 11 mon

    Median Survival
  - Margins
    - R0 16.9 mon
    - R1/R2 7 – 12 mon

    Median Survival:

- London 5 yr Surgical Experience

Total N	122
Gender M:F	65 (53%): 57(46.7%)
Age (mean+/-SD)	65.6 yr (+/- 9.3 yr)
CT Analysis	83 (68%)
Operation	77 (63.1%) Whipple 45 (36.9%) bypass
R0 Resection	46/77 (59.7%)

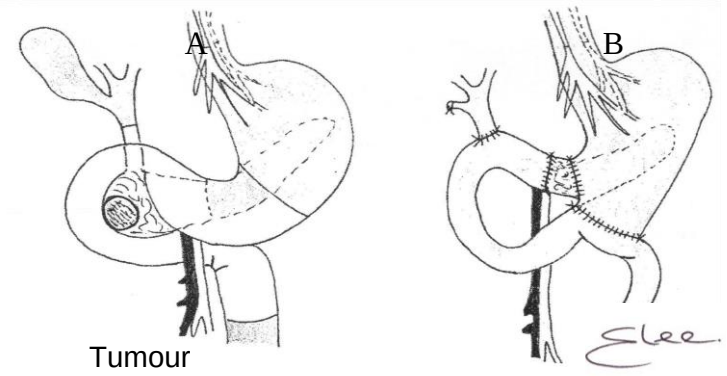
Courtesy of Dr. Ken Leslie

➢ Treatment

❖ Surgery (for resectable lesion)

- Give factors which usually preclude surgery for pancreatic cancer (i.e., patient is not a surgical candidate).
  - Metastases
  - Ascites
  - Mental caking
  - Vascular involvement
  - Degree of involvement of circumference of vessel reflects likelihood of vessel invasion

- Give a description and a picture of the **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 performed.

B.
- Gastrointestinal continuity is restored by performing a pancreaticojejunostomy, a choledochojejunostomy, and a gastrojejunostomy.

Adapted from: Reber HA and Way LW: 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.

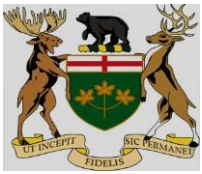
- Important Prognostic Features
  - Size < 2 cm
  - Well Differentiated
  - Node Negative
  - R0 resection

- ❖ Chemoradiation Therapy
  - Chemotherapy agents
    - Gemcitabine / 5-FU
      - 2 months longer survival
      - Palliation for fit patients (pain control)
    - 5-FU, irinotecan, oxaliplatin (FOLFIRINOX)
      - For patients with unresectable PDCa, Median overall survival of 11m vs 6.8m for gemcitabine
  - Radiation
    - Palliation
    - Focal radiation – sterotactic or tomographic radiotherapy

Adapted from: Conroy, T et al. N Engl J Med 2011; 364(19): 1817-25

- ❖ Pain control
  - Celiac plexus neurolysis (CPN) (CP block [CPB])
    - EUS or CT directed
    - Block = bupivacaine +/- lidocaine and steroid (triamcinolone)
    - Neuorlysis = bupicaine +/- lidocaine and 99-100% ethanol

- Give immediate complications of CPN/CPB (celiac plexus neurolysis (CPN) / celiac plexus block (CPB).
  - Postural hypotension
  - 2 wk worsening of pain, before pain/quality of life improve (CPN, not for CPB)
  - Diarrhea (2%) for 48 hr post CPN (celiac plexus neurolysis) / CPB (celiac plexus block)



- Lethargy
- Rare complictions (reported almost exclusively with CT guided approach)
  - Infection
  - Bowel perforation
  - Intra-abdominal hemorrhage
  - Fistula formation
  - Gastroparesis
  - Paraparesis, lower extremity paraesthesia, epidural anesthesia
  - Chronic diarrhea
  - Anterior spinal artery syndrome
  - Aortic dissection or pseudoaneurysm
  - Pleural effusion
  - Pneumothorax
  - Hematuria
  - Shoulder/Chest pleuritic pain

Non-Adenomatous Masses of the Pancreas

➢ Types

- Give types of non-adenomatous acinar or ductal masses of the pancreas.
  - Lymphoma
    - High index of suspicion
    - Flow cytometry needed
    - Round
    - Discrete
    - More hypoattenuating
    - Large size but does not cause CBD or MPD obstruction

- NET (neuroendocrine tumour)
  - Non-Functioning
  - Functioning
    - Gastrinoma
    - Glucagonoma
    - Insulinoma
    - VIPomas
    - Somatostatinoma
- Pancreatitis
  - AIP (autoimmune pancreatitis)
  - Chronic pancreatitis
- Ectopic spleen/splenule
- Serous Cystadenoma
- TB (tuberculosis)

Pancreatic Neuroendocrine Tumours (NET)

- Non-functioning
  - > 50% are malignant
  - Usually in pancreatic head
  - Often large
  - Have worse survival compared to functioning pancreatic neuroendocrine tumours
  - Resect all sporadic tumours, or if > 2 – 2.5 cm in MEN I

- Functioning (hormone secreted by tumour)

Gastrinoma

- Incidence 1 per year/10^6 population
- Malignant ~ 66%
- 20% are MEN I associated
- > 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

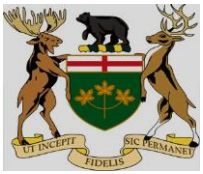
- 1 per year/10^6 population
- Benign in ~90%
- Solitary in 95%
- <2 cm in 85-90%
- 4% are MEN I
- In MEN I patients insulinomas are multiple in 90%
- Clinical features
  - Neuroglycopenia (90%)
    - Amnesia or coma (47%)
    - Confusion (80%)
    - Visual changes (59%)
    - Convulsions (17%)
    - Altered consciousness (38%)
  - Sympathetic overdrive (60-70%)
    - Weakness (56%)
    - Sweating (69%)
    - Tremors (24%)
    - Palpitations (12%)
    - Hyperphagia (14%)
  - Obesity (<50%)

Glucagonoma

- Demography
  - Occur in 10-15% of patients
  - Frequently multiple (>30%)
  - Tumours >3 cm are aggressive (metastases)
- Clinical
  - Migratory necrolytic erythema (70-90%)
  - Weight loss (80%)
  - Diarrhea (25%)
  - Thromboembolism (15%-25%)
  - Glossitis, chelitis (15%-40%)
  - Psychiatric symptoms (0%-17%)
- Laboratory
  - Glucose intolerance (40%-90%)
  - Normochromic, normocytic anemia (35%-90%)
  - Hypoaminoacidemia (80%)

Adapted from: Metz DC and Jensen RT. *Gastroenterology* 2008; 135: 1469-92.

- Treatment
  - 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



VIPoma

- Definition
  - Neuroendocrine tumour, usually (> 80%) of the pancreatic tail, secreting ↑ PNM-27 (vasoactive intestinal peptide)

- Pathophysiology
  - ↑ PHM-27 in VIPoma NET tumour
  - PHM-27 shares a common precursor with VIP2
  - When ↑ PHM-27 → VIP-like actions → ↑ activity of adenylate cyclase → ↑ cAMP
    → ↑ Cl^- secretion (diarrhea)
    → Secondary hyperaldosteronism

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the pathophysiology of the flushing, bone disease and hyperglycemia which occur in VIPoma.
  - Flushing - Vasodilation
  - Bone disease - ↑ osteolysis of bone
  - Hyperglycemia - Glycogenolytic effect of VIP

- Clinical
  - ↑ VIP → WDHA syndrome
    - Watery diarrhea
    - Hypokalemia → renal and heart failure
    - Achlorhydra

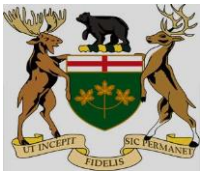
➢ Laboratory

Serum VIP levels are increased with VIPoma, especially when the patient is having diarrhea (levels may fluctuate).

- Give other causes of chronic diarrhea which may also be associated with ↑ VIP, but without an associated secreting pancreatic endocrine tumour.
    - Laxative abuse
    - Short bowel syndrome (surgical resection of a portion of the small bowel)
    - Radiation enteritis

➢ Pathology
    - Single large tumour
    - ~ 75% in tail of pancreas
    - High rate of metastases

➢ Treatment
    - Octreotide (benefit does not always reflect changes in blood levels of VIP)
        - Caution alert: do not use in pregnancy (risk of uterine ischemia)
    - Surgical resection of VIPoma



Somatostatinoma

- Clinical

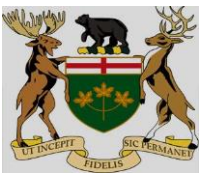
	Somatostatinoma	
	Pancreatic	Intestinal
○ Diabetes mellitus	95	20
○ Gallbladder disease	94	40
○ Steatorrhea	85	10
○ Hypochlorhydria	85	15
○ Diarrhea	75	25
○ Weight loss	50	35

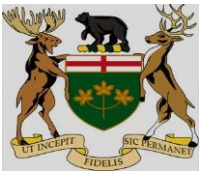
- Treatment
  - Local
    - Liver resection
    - Chemoembolization
    - Radiofrequency ablation
  - Systemic
    - Somatostatin analogues (e.g., octreotide)
    - Somatostatin receptor radionuclide therapy
    - MIBG radionuclide therapy
    - Chemotherapy, especially for poorly differentiated tumours
      - Chemotherapeutic agent may be bound to carrier target tumour

Printed with permission: Alexakis N, and Neoptolemos JP. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): 199.

INDEX

Note: Page number followed by f and t indicates figures and tables, respectively.





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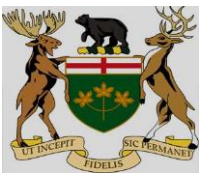

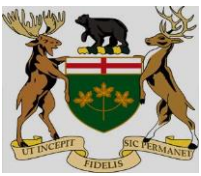

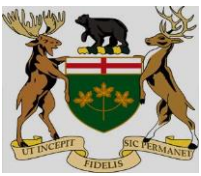

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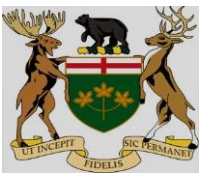

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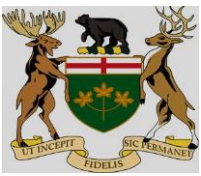

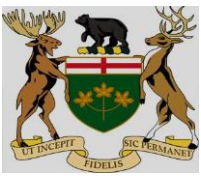

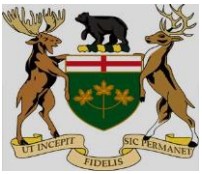

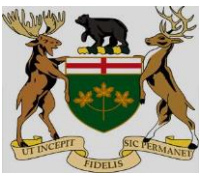

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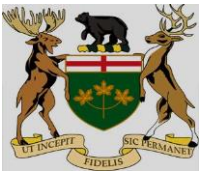

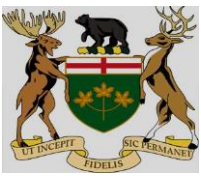

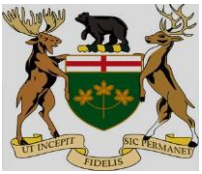

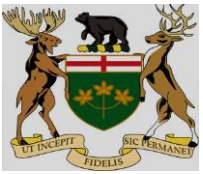

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