MEDICAL MINI REVIEW SERIES IN GASTROENTEROLOGY AND HEPATOLOGY

Efficient Refresher for the Busy Clinical Gastroenterologist

Volume 3

Edited by

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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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Dr. Alan Thomson has been President of the Canadian Association of Gastroenterology, a member of the Bockus Society, two-term Governor for Western Canada for the American College of Gastroenterology, winner of the prestigious University Cup in 2001, a recipient of the Gold Medal in Medicine of the Royal College of Physicians and Surgeons (Canada), Chief Royal College examiner in Gastroenterology, Director of the Division of Gastroenterology, three-time Teacher of the Year at the University of Alberta, Award for Excellence in Mentoring Graduate Students and Postdoctoral Fellows, and awarded Distinguished University Professor. Dr. Thomson is a Distinguished Emeritus University Professor, University of Alberta, and is currently an Adjunct Professor at Western University.

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DEDICATION

This book and its chapters is dedicated to the patients for whom we care and our families who support us.

Alan Thomson

For Shannon and our children who keep my mind on the important things in life.

Nilesh Chande

TABLE OF CONTENTS

ESOPHAGUS

Overview of Esophageal Disorders

Alan Thomson

CONGENITAL ABNORMALITIES

Esophageal Atresia and Tracheoesophageal (TE) Fistula

- Definition
  - Congenital abnormalities of failure of the foregut to divide at week 4 of embryonic development into trachea and esophagus
- Demography
  - ~ $20/10^5$
  - Present in children
- Causes / associations
  - Trisomies partial 13, 18, 21
  - Anal atresia
  - Renal agenesis
  - Vertebral abnormalities
  - Cardiac anomalies
  - Limb defects
- Clinical
  - Feeding difficulties
    - Regurgitation
    - Salvation
    - Drooling
  - Respiratory symptoms
    - Aspiration
    - Cyanosis
    - Pneumonia

- Diagnostic imaging

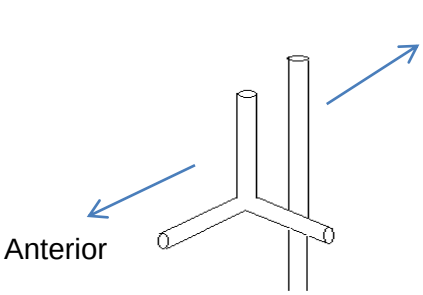
		Atresia	TE fistula
○ Chest X-ray	– Air in esophagus	√	√
	– Air in stomach	No	√
○ Upper GI barium swallowing	– Barium in esophagus	√	√
	– Barium in stomach	No	√
	– Fistula between tracheal and esophagus	No	√

- Differential
  - Congenital esophageal stenosis
  - Pyloric stenosis
- Treatment
  - Surgical correction
  - Treat any associated malnutrition or complication (e.g., pneumonia)
- Prognosis
  - Excellent, unless associated with other congenital abnormalities, e.g. trisomies

Duplications and Cysts

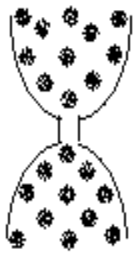
- Definition
  - Congenital abnormalities of failure of normal development of esophagus at weeks 5 to 8.

- Demography
  - 12 / 10^5 autopsies
  - Lower 1/3 of esophagus



- Clinical
  - May be asymptomatic
  - Feeding difficulties
  - Respiratory symptoms

- Diagnostic imaging
  - Barium swallow
    - Esophageal
      - Filling defect in lumen of lower 1/3 of esophagus
    - Neuroenteric
      - Vertebral abnormal abnormalities
      - Hour glass shape
    - Bronchogenic cysts
      - Mass extending into anterior mediastinum



Posterior mediastinum

Vertebral canal

- Differential
  - Diverticula
    - Acquired
    - Communicated with esophageal lumen
    - Lined by squamous mucosa → erosions, ulceration

- Histopathology
  - Intramural
    - Intact muscle layers
  - Intact muscle layers
  - Non-communicating with lumen
  - Average size, 5 cm
  - Mucosa duplication
    - Squamous
    - Cuboidal
    - Celiated
  - Neuroenteric
  - Gastric or intestinal mucosa
  - Bronchogenic
    - Contain cartilage

Esophageal Heterotopia

- Demography

	Heterotrophic gastric mucosa in esophagus	Heterotrophic sebaceous glands in esophagus
Incidence		
– Endoscopy	4%	4%
– Autopsy	70%	-

- Clinical
  - Dysplasia
  - Dyspepsia
- Pathology
  - Site
    - Proximal esophagus (aka inlet patch)
  - Colour
    - Pink round patches
    - Yellow bumps
    - Rare
- Differential diagnosis
  - Barrett esophagus (distal)
  - Glycogenic acanthosis (whitish)

Acquired Esophageal Diverticula

- Definition
  - Acquired outpouching of all layers of esophagus
- Demography
  - Zenker diverticulum is commonest acquired esophageal diverticulum (70%)
  - Incidence ~ 50 / 10^5
  - M > F
  - > age 70 yr

		Zenker	Mid esophageal (traction)	Epiphrenic
➢ Pathology				
	○ Site	– Proximal (Killian triangle)	At bifurcation of trachea	Distal 10 cm
	○ Etiology	– ↑ UESP	Mediastinal	Hiatus
	○ Mucosa	– May become inflamed or ulcerated		
	○ Muscle	– May be thickened		
	○ Cancer	– Rare (0.3%)		
➢ Clinical		○ Asymptomatic ○ Regurgitation ○ Dysphagia ○ Mass in neck	Usually asymptomatic	Symptoms of GERD

Abbreviation: UESP: upper esophageal pressure

➢ Differential

- ○ Pseudodiverticula
  - Do not contain all layers of esophagus (lack muscle of their on)
  - Dilations of submucosal glands
  - Single or multiple
  - Multiple pseudodiverticula called DEIP (diffuse esophageal intramural pseudodiverticulosis)

Abbreviations: GERD, gastroesophageal reflux disease; uESP, upper esophageal sphincter pressure

- Treatment
  - Myotomy
    - Endoscopic
  - Surgical resection
    - Surgical

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the anatomical boundaries of Killian triangle at the junction of the pharynx and esophagus.

Esophageal Webs and Rings

- Definition
  - Acquired mucosal fold indenting lumen of esophagus

	Web	Ring
Demography		
Incidence	~ 7%	~ 7%
	When symptomatic, F > 40 yr	F = M
	F > 40 yr	F = M
Clinical		
Asymptomatic dysphagia	✓	✓
Association	Plummer-Vinson syndrome	GERD

	Web	Ring
➢ Pathology		
○ Colour	Pale pink	Pale pink
○ Circumference of lumen	Partial	Complete
○ Site		Lower esophagus when associated with GERD (then called Schatzki ring)
○ Mucosa		
- Proximal side	Squamous	Squamous
- Distal side	Squamous	Columnar
○ Muscle thickening	No	Sometimes
➢ Diagnostic imaging		
○ Thin filling defect	✓	✓
○ Notch	✓	✓
○ Curvilinear shadows	✓	✓
○ Hiatus hernia	No	✓
➢ Endoscopy		
○ Pale mucosa	No	✓
○ Erosions, ulceration	✓	✓

Abbreviation: GERD, gastric esophageal reflux disease

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the alternate name to the Plummer Vinson Syndrome (English).
  - Patterson-Kelly Syndrome (Irish)
- Give the clinical features which make up this syndrome.
  - Web of upper esophagus
  - Iron deficiency
  - Glossitis
  - Cheilosis

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

- Definition
  - Increased frequency and duration of regurgitation if usually acidic contents into esophagus, sometimes causing pathological changes, and sometimes causing both.
- Demography
  - 30% of adult population each year suffers from symptoms suggestive of GERD (dyspepsia)
  - Of persons with dyspepsia, ~40% will have endoscopic / pathological changes.
- Pathophysiology
  - ↓ LESP (lower esophageal sphincter [basal] pressure
  - ↑ TLESPR (transient lower esophageal sphincter pressure relaxation)

- Clinical
  - May be asymptomatic
  - Heartburn
  - Regurgitation
  - ENT / pulmonary symptoms
  - ↑ risk of Barrett mucosa and esophageal adenocarcinoma (ECA)

- Endoscopy
  - Spectrum of
    - Normal
    - Redness
    - Erosions
    - Ulcers
    - Stricture
    - Barrett esophagus (Barrett epithelium)
    - ECa

- Histopathology
  - Early reactive changes
    - Basal cell hyperplasia (> 15% of thickness of epithelium)
    - Elongation of papillae (> 60% of thickness of epithelium)
  - Inflammatory infiltration
    - Lymphocytes
      - Intraepithelial T cells

  - Eosinophils
    - Lower esophagus; < 20
    - Upper portion of mucosa
    - Clumps
- Edema, congestion, haemorrhage
- Erosion, ulceration
- Granulation tissue
- Submucosal fibrosis → stricture
- Barrett mucosa
- Adenocarcinoma

- Diagnosis
  - Symptoms
  - Endoscopy / biopsy
  - Esophageal pH studies
  - Diagnostic imaging
    - Reflux
    - Associated condition
    - Complications

- Differential
  - Infectious and toxic causes of esophagitis
  - Other causes of dyspepsia e.g.
    - Peptic ulcer disease (gastric ulcer [GU], duodenal ulcer [DU])
    - H. pylori / NSAID gastritis
    - Function abnormalies
  - Immune
    - Eosinophilic esophagitis

- Treatment
  - Manage associated conditions and complications
  - Lifestyle changes
  - Reduction of gastric acid (H2-receptor antagonists, proton pump inhibitors

BARRETT ESOPHAGUS (BE)

- Definition
  - Velvety salmon-pink tongues of mucosa of the lower esophagus seen to extend proximally from the gastroesophageal junction Z line, associated on mucosal biopsy with intestinal metaplasia comprised of goblet cells, with or without interspersed gastric parietal cells (please see below for controversy) (American College of Gastroenterology [ACG], 2008)

- Demography
  - In Japan, United Kingdom and most other parts of Europe, Barrett esophagus (BE) is an endoscopic diagnosis, and the biopsy finding of intestinal metaplasia is not required
  - Because of the variation in the accepted definition of BE (abnormal endoscopy with or without biopsy-demonstrated intestinal metaplasia), the epidemiology is uncertain with or without biopsy-demonstrated intestinal metaplasia), the epidemiology is uncertain
  - Prevalence 5% - 8% of persons in GERD (gastroesophageal reflux disease) risk of development of esophageal adenocarcinoma ~ 1/1000.

- Highest risk group-Caucasian males > 50 yrs with > 10 yr history of moderately-severe GERD symptoms ≥ 3 times per week

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the reason why the European definition of Barrett epithelium is not plausible.
  - The major importance of BE is "…. Its status as a condition that predisposes to the development of esophageal adenocarcinoma (Iacobuzio-Donahue and E. Mont gomery, 2012 page 41).
  - Not all mucosa that looks like BE is BE, so a mucosal biopsy is necessary before alarming the patient and embarking on a program of frequent endoscopies with biopsies

➢ Pathogenesis
  - GER (gastroesophageal reflux) causes ulceration of mucosa → less of mucosal squamous epithelium → re-epithelialization with columnar epithelium (metaplasia) → multi-layered squamous and columnar epithelium → columnar BE.

➢ Clinical
  - Asymptomatic
  - Usual GERD symptoms of heartburn, regurgitation
  - ↓ heartburn with development of BE
  - May develop symptoms of esophageal adenocarcinoma

- Endoscopy
  - No endoscopic (white light) difference in metaplasia versus dysplasia

- Histopathology
  - Columnar epithelium containing goblet cells
  - Architecture (lower power): glands
    - ↑ number
    - Δ shape
      - Crowding of normal-appearing glands
      - Cribriform
      - Containing necrotic debris
      - Lamina propria abundant between glands
  - Cells (high power)
    - Normal ratio of nuclei / cytoplasm
    - Nuclei, basal zone nuclear
      - ↑ size (mild)
      - Atypia (mild)
      - Smooth membranes
      - Few nucleoli, with smooth outline
      - Normal polarity
    - Few mitoses

  - Immunohistochemistry (from Gastrointestinal and Liver Pathology, C. A. Iacobuzio-Donahue and E. Montgomery, 2012, page 43.
    - CK 17, CDX2
    - MUC2, variable MUCSAO, MUC6
    - DAS1
    - Racemase

SO YOU WANT TO BE A GI PATHOLOGIST!

The presence of goblet cells in the metaplastic columnar epithelium of Barrett esophagus (BE) can be highlighted by staining esophageal endoscopic biopsies with acidic (pH 2.5) Alcain blue. Name 2 additional cell types in the biopsies which may also stain with this dye, and thereby reduces the specificity of establishing BE in the manner.

- Esophageal submucosal glands
- Gastric foveolar cells (incomplete metaplasia)
- Any columnar mucosa

SO YOU WANT TO BE A GI PATHOLOGIST!

- Give an explanation of the terms “normal nuclear polarity, and in the context of Barrett epithelium (BE), give its importance.

  - Normal nuclear polarity: nuclei are
    - Perpendicular to basement membrane
    - Parallel to each other
  - Loss of nuclear polarity, just like crowding of abnormal glands, is a sign of dysplasia

Dysplasia in BE

Pathology	Indefinite metaplasia (IND)	Low grade (LGD)	High grade (HGD)
○ Progression to cancer*	1% - 18%	7% - 18%	16% - 60%
○ Mucosal columnar cells			
– Surface	Globlet cells		
– Deep**	Globlet cells		
– Crowding	No	+	++
– Abrupt transition (normal to abnormal)	No	Yes	↓↓↓ intervening LP
– Gastric foveolar cells	+/-		
– Maturation	Slight		None
○ N/C	↑		
○ Nuclear	Basal cell		
– Size	↑	↑↑	↑↑↑
– Chromatin	↑	↑↑	↑↑↑
– Stratification	↑	↑↑	↑↑↑ (may show small monolayer of hyperchromatic rather than stratified nuclei)
– Smooth membrane	+	+/-	Irregular
– Nucleoli	Small smooth outline		

Pathology	Indefinite metaplasia (IND)	Low grade (LGD)	High grade (HGD)
○ Glands			
– Atypical	Very mild +	++	+++
– Size	↑	↑↑	↑↑↑ (may extend to surface)
– Δ shape	+	↑↑	↑↑↑
– Budding	+	□□	+++
– Crowding	+	++	+++
– Lamina propria	+++	++	+ / 0
– Clumps	0	+	+++ Regular clumps, with ↑↑ chromatin ↓↓ nucleoli, or Irregular clumps, with ↑↑ chromatin and irregular nucleoli
○ Loss of			
– Nuclear polarity	+	++	+++
– Mitoses	0/+	++	+++

Abbreviations: LP, lamina propria; N/C, nuclear / cytoplasmic size

*Progression of metaplasia but no dysplasia to cancer, 0% - 4%

**When changes occur just in blood cells, known as basal crypt dysplasia

Note: not all pathologists use the term “indefinite dysplasia”

- Explanation
  - Small glands in a monolayer of hyperchromatic / rather than stratified nuclei, called non-adenomatous dysplasia

	Intramucosal (Stage T1a) Carcinoma
Lamina propria	
– Thickness	↑ / 0
– Effacement	+
Syncytial	
– Growth pattern	+
Microglands arranged	
– Back-to-back	+
Small cells mixed with	
– Small clusters of cells	+
Submucosa	
– Invasion	+
– Desmoplasia	-

- Special studies
  - Barrett esophagus
    - CK7, CK20, CDX2, MUC1, MUC2, MUC5AC, MUC6
    - DAS-1
  - Predictive of progression in non-dysplastic BE
    - Promotor
    - Methylation of some genes
  - Dysplasia
    - P53 mutation and deletion, Ki-67

- Additional terms

Name	Mucosal esophageal biopsies	Endoscopic tongues	Goblet cells	Inflam-mation
Carditis	Any gastric type	-	0	+
Barrett mucosa	Goblet cell containing	+	+	-
Goblet cells at the cardia	Goblet cell containing	-	+	-

Note: goblet-cell containing mucosa from esophageal mucosal biopsy, with no endoscopic tongues, is either ‘goblet cells at the cardia, or “carditis”, depending upon the presence of any gastric-type mucosa; carditis is associated with inflammation

ESOPHAGITIS

- Inflammatory / immune
  - Eosinophillic > 20 eosinophils per high power field in biopsy taken from mid esophageal body
- Infection
  - Candidiasis
    - Yeast
    - Pseudohyphae
    - Severe acute inflammation
  - HSV
    - Multinucleated giant cells
    - Nuclear molding
    - Chromatin marginated

- CMV
  - Large infected cells of submucosal capillaries
  - Intranuclear / - cytoplasmic viral inclusion

- Drugs / toxins
  - "pills"
    - Granulation tissue
    - Ulcers
  - Radiation
    - Cytomegaly
    - Nuclei pale
    - Cytoplasm vacuolated
    - Vessels hyaline
    - Parakeratosis
    - Acanthosis
  - Chemotherapy
    - Nuclei
      - Hyperchromatism
      - Mitosis

Eosinophilic Esophagitis (EoE)

- Definition
  - Ideopathic but likely immune condition causing inflammatory infiltration of eosinophils into mucosa of all portions of esophagus, and not responding to a therapeutic trial of PPI.
  - Note: EOE represents the patient who has dyspepsia / dysphagia plus ↑ eosinophils in the esophageal mucosal biopsies, and who has failed a course of proton pump inhibitors.

- Demography
  - Frequent in children and young adults
  - M > F

- Endoscopy
  - Spectrum of normal
    - Abnormal
    - Furrows
    - Rings (trachealization)
    - Microabscesses
    - Strictures
- Histopathology
  - Inflammatory infiltration with
    - Eosinophils
      - > 20 / hpf
    - Mast cells
      - Proximal > distal esophageal
  - Reactive changes
    - Basal cell hyperplasia
    - Elongation of papillae
    - Congestion, haemorrhage
  - Multiple stricture
- Special tests
  - ↑ T lymphocytes
  - ↑ IL-5
  - ↑ TNF-α
  - ↑ IgE
- Clinical
  - GERD-like symptoms
  - Frequent presentation with
    - Solid food bolus dysphagia
    - Atophy / allergic symptoms

- Differential
  - Other causes of esophagitis / dyspepsia
  - PPI-responsive eosinophilic esophagitis (PPI-REE)
  - Eosinophilic gastroenteritis
  - Systemic causes of eosinophilia
- Treatment
  - PPI (proton pump inhibitor), if non-responsive, then
  - Topical corticosteroids
  - Elimination diet
  - Dilation of symptomatic strictures

Pill Esophagitis

- Definition
  - Inflammation of the esophagus from medication, resulting in non-specific symptoms, as well as changes on endoscopy and histopathology
- Demography
  - $4 / 10^5$ per year
  - F > M
  - Older persons
- Etiology
  - Adherence of pills to esophageal mucosa and causing local damage

- Endoscopy
  - Discrete erosion / ulcer
  - Usually at the level of the arch of the aorta
  - Note: because of usual older age of patient, ensure lesion is not a cancer
- Histopathology
  - Prominent granulation tissue
  - Pills may be seen
  - Non-specific changes of esophagitis
- Clinical
  - Heartburn
  - Dysphagia
  - Non-specific
    - Bloating
    - Nausea
  - Positive history of medication use
- Treatment
  - Discontinue offending medication, and prescribe a substitute
  - Short course of mixture of antacid and local anaesthetic for rapid pain relief
  - 4 wk course of standard dose of PPI, ½ hr before breakfast, to relieve associated ulceration

Infectious Esophagitis

- Definition
  - Inflammation of the esophagus caused by infection, usually C. albicans, Herpes simplex virus type 1 (HSV), or cytomegalovirus (CMV)

- Demography
  - Usually seen in immunocompromised persons of any age
  - HSV may be seen in young immunocompetent persons

- Clinical
  - Odynophagia
  - Mouth lesions
  - Immunosuppressive (not always for HSV)

	Candida species	HSV	CMV
❖ Gross / endoscopy	○ White plaques ○ Do not wash away ○ Localized or diffuse	– Multiple ulcers – Halo – Varying sizes	▪ Single discrest large ulcers ▪ Distal esophagus ▪ Yellow exudate
❖ Histo-pathology	○ Yeast / pseudo-hyphae in mucosa ○ Necrotic debris ○ Inflammation	– Multi-nucleated giant cells – Cowden B type cells – Nuclei ▪ Molding ▪ Intranuclear inclusion – Chromatin-marginated	▪ Large cells ▪ Submusal capillary ▪ Viral inclusions in – Nuclei: Red owl's eye inclusion – Cytoplasma: blue, basophilic inclusion

- Special statins
  - PAS (periodic acid-Schiff)
  - GMS (Gomori Methenamine silver)
  - Papanicolaou stain for cytology for Candida species
- Treatment
  - Ketoconazole, or
  - Fluconazole po / IV
  - Acyclovir
  - Ganciclovir, or cidofovir

Esophageal Caustic Injury

- Definition
  - Injury to esophagus as a result of accidental or suicidal intake of alkali or acids.
- Demography
  - Children – Accidental
  - Adults – Suicidal (in 60%)
  - $1 / 10^5$
- Clinical
  - Dynophagia and dysphagia
  - May be burns in mouth
  - May also involve stomach
    - Perforation
    - Mediastinitis
    - Peritonitis

- Endoscopy
  - Do not due to acute setting because of risk of perforation from third degree lesions of transmural inflammation and necrosis
- Histopathology
  - Erosion / diffuse ulceration
  - Acute / chronic inflammation
  - Stricture
  - Coagulative necrosis
  - Mucosal cast, extruded in severe cases
- Diagnostic imaging
  - Chest X-ray
    - Mediastinitis / free air chest
    - Pneumothorax
    - Subcutaneous emphysema
    - Free air in abdomen
  - Barium swallow (not in acute setting)
    - Early
      - Stricture
      - Fistula
    - Late
      - Cancer
- Treatment
  - Avoid studies or endoscopy early
  - Supportive and symptomatic
  - Early
    - Surgery for perforation of esophagus or
  - Late dilation of stricture
    - Feeding tubes

Chemo' / Radiotherapy Esophagitis

- Definition
  - Injury to esophagus caused chemotherapy, radiotherapy, or both
- Demography
  - Older persons
  - Combination of both chemo- and radiotherapy worse than either alone
  - Radiotherapy of esophagus, lung, mediastinum
- Causes
  - > 6000 rads → damage usually irreversible
- Clinical
  - Dysphagia
  - Odynophagia
- Endoscopy
  - Confluent ulcers
- Histopathology
  - Cell size / shape
    - Large, bizarre-appearing epithelial and stromal cells
  - Nuclei
    - Large
    - Multiple
    - Vacules in cytoplasm with radiation
    - Hyperchromat nuclei chemotherapy
  - Blood vessels
    - Hyaline
  - Acanthosis
  - Parakeratosis

- Special stains to rule out HSV, CMV (PAS, periodic acid-Schiff; GMS, Gomori methenamine silver
  - Note of caution
    - If esophageal cancer may be on the differential, look for
      - ↑ nuclear / cytoplasm (N / C) ratio
      - ↑ mitosis
      - ↑ nuclear chromatin

➢ Treatment
  - Supportive and symptomatic care
  - Dilation for symptomatic esophageal stricture

ESOPHAGEAL TEARS AND PERFORATION

➢ Causes

o Iatrogenic (~50%)	– Endoscopy with / without dilation – Bougie / balloon dilation for benign / malignant stricture
o Trauma (~35%)	– Penetrating or blunt – Ingested foreign bodies
o Spontaneous	– Overindulgence of ▪ Food (includes Mallory-Weiss tears) – Hyperemesis gravidarum – Sudden heavy lifting

- Clinical
  - Chest pain
  - Vomiting
  - Upper GI bleeding (Mallory-Weiss tear)
- Diagnostic imaging
  - Chest X-ray
    - Subcutaneous emphysema
    - Pleural effusion
    - Pneumomediastinum
  - Barium swallow
    - Visualize site of perforation (in 90%)
    - Of no use in diagnose tear of esophagus
- Pathology
  - Perforations and tears usually in lower 1/3 of esophagus
  - Perforation size usually 1-2 cm
  - Site of perforation not well seen on endoscopy (EGD)
  - Clue for site of perforation on EGD is presence of hematoma
  - Tear appears on endoscopy as longitudinal red line across the Z line
- Treatment
  - Tear-endoscopic hemastatic therapy
  - Perforation (depending on size and cause)
    - Endoscopic clipping
    - IV fluids and antibiotics
    - Surgical repair

TUMORS OF THE ESOPHAGUS

- Fibrovascular polyps
  - Mucosa-covered fibrovascular lesion with fatty tissue
  - There may be degenerative atypia in the fatty tissue
- Liposarcoma
- Adenocarcinoma
- Squamous cell carcinoma
  - Squamous differentiation
  - Keratinization
  - Spindle cells
  - IHC+ CK 5/6, p63
- Melanomas
  - IHC
    - S-100, HMB 45, MART, MITF, melama (melanoma-specific)
- Sarcoma
  - Closely packed large cells in submucosa with small / pyknotic nuclei occasional nucleoli, and squamous “pseudoepithelism hyperplasia of overlying mucosa
- Granular cell tumor
  - IHC positive
    - S-100
    - Calretinin
    - Inhibitor α
    - Myelin basic protein (MBP)
    - Nestin
    - CD68 / Kpl

- Rhabdomyoma
  - Markers positive for
    - Skeletal muscle
    - All muscle markers
    - TFE3-positive
- Alveolar Soft Part Sarcoma (ASPS)
  - Markers
    - Alveolar pattern
    - Nucleolus in mast cell
    - PAS-positive rhomboid shape
    - TFE3-positve
  - Not usually a diagnostic problem
- Squamous papilloma
  - Polypoid squamous mucosa with fibrovascular core and coating

Esophageal Fibrovascular Polyp (and Liposarcoma)

- Definition
  - Large pedunculated, sausage-shaped benign tumor of submucosa of cervical esophagus comprise of fibrous and adipose tissue with prominent vasculature
- Demography
  - $< 1 / 10^5$
  - M > F
- Pathology
  - Very rarely associated with secondary squamous cell carcinoma of esophagus

- Clinical
  - Esophageal and respiratory symptoms
  - Pedunculated; sausage-shaped tumor may
    - Regurgitate into mouth, or large (~ 15 cm)
    - Cause asyphyxiation

- Differential
  - Liposarcoma
    - Nuclei
    - May see lipoblasts
    - Immunohistochemistry (IHC)
    - Positive staining for nuclear MDM2

- Treatment
  - Polypectomy
    - Endoscopy
    - Surgery

Esophageal Squamous Papilloma

- Definition
  - Small, asymptomatic nodules of distal esophagus comprised of proliferated squamous mucosa

- Demography
  - ~ $1 / 10^5$
  - More common in Caucasian women > 40 yr

- Clinical
  - Usually an incidental finding on endoscopy
  - May be associated with HPV-related laryngeal papillomatosis

- Non-larynx associated lesion usually not HPV-positive (< 10%)
- May be associated with synchronous or metachronous cancers of mouth or respiratory tract

Esophageal Adenocarcinoma (ECA)

- Definition
  - A carcinoma in the esophagus which shows glandular differentiation
- Demography
  - $5/10^5$ per yr in USA
  - Caucasian M >> F
  - > 60 yr
- Clinical
  - Long-term GERD symptoms may be present
  - Dysphagia, weight loss
- Association
  - Obesity (↑ BMI)
- Endoscopy
  - Usually in lower 1/3 of esophagus
  - May be typical changes of Barrett esophagus (BE) plus esophageal luminal mass

- Histopathology
  - Malignant cells with
    - Glandular differentiation
      - Ducts, or
      - Mucin production
    - Pattern
      - Papillary
      - Tubular
      - Signet-ring cells
    - Desmoplasia (HGD [high grade dysplasia] does not show desmoplasia

- Special studies (molecular genetic changes)
  - Deletion
    - p53 (with mutation)
    - p16
    - Rb
    - APC
  - Over expression
    - EGFR
    - TGF-α
    - Clonal DNA aneuploidy

Note: These genetic studies may be helpful to distinguish poorly differentiated adenocarcinoma from spindle cell tumors

  - Staging
    - T1 invades lamina propria or submucosal
    - T2 invades muscularis mucosae

- Prognosis
  - Presentation with
    - Low-grade lesions
    - High-grade lesions
    - Overall 5 yr survival rate

Squamous Cell Carcinoma (SCCA)

- Definition
  - Carcinoma in the esophagus which shows squamous differentiation, usually with keratinization
- Demography
  - Incidence 5 / 10^5 per yr in USA
  - M >> F
  - African Americans
  - > 60 yr
- Endoscopy
  - Middle to upper esophageal mass
  - Polypoid appearance in esophageal squamous cell tumors with histopathology showing a prominent spindle cell appearance
- Histopathology
  - Squamous mucosa
  - Keratinization
  - At edge of invasive tumor
    - High grade dysplasia, or
    - Intraepithelial neoplasia

- May have a spindle cell appearance
- Special stains
  - Epithelial markers e.g. CK5/6, p63, and other keratins
  - Deletion
    - p53 (with mutations)
    - Rb p16
  - Over expression
    - EGFR (epidermal growth factor receptor)
    - ILGFR-1 (insulin-like growth factor receptor-1)

- Clinical
  - Dysphagia, weight loss
  - Inherited
    - Tylosis
  - Drugs / toxins
    - Tobacco
    - Lye ingestion
    - Alcohol
      - Asians with ↓ ALDH (aldehyde dehydrogenase) activity due to a polymorphism
  - Nutrition
    - Hot beverages
  - Esophagus
    - Head / neck cancers
    - Deprivation
    - Achalasia
    - Diverticulum
    - Plummer-Vinson syndrome

SO YOU WANT TO BE A GI PATHOLOGIST!

The incidence of squamous cell cancer of the esophagus is about 5 / 10^5 per year. A very rare condition is tylosis (non-epidermolytic palmoplantar keratoderma). The importance of this condition is that 95% of persons with tylosis have esophageal squamous cell cancer by age 70 years.

- Give the genetics changes in tylosis.
  - Autosomal dominant
  - Genetic abnormality at chromosome 17q25

- Treatment
  - Chemo' / radiotherapy
  - Resection

- Prognosis
  - 5 yr survival rate, 5% - 10%

Esophageal Granular Cell Tumor

- Definition
  - A tumor in the esophagus which show differentiation of the nerve sheath, plus H/E (hematoxylin and eosin) staining shows a granular cytoplasm.

- Demography
  - Often associated with tumor of tongue
  - F >> M
  - African Americans

- Clinical
  - Usually asymptomatic (incidental finding)
- Endoscopy
  - Distal esophagus
  - 5% are multifocal
  - Almost always benign
- Histopathology
  - Overlying mucosa shows 3 squamous hyperplasia (aka ‘pseudoepithiomatous” hyperplasia)
  - Clear margin, no capsule
  - Cells
    - Large
    - Dose together
    - Cytoplasm, full of amphophilic granules
  - Mostly in submucosa
  - Nuclei
    - Small Pyknotic
    - A few nucleoli
  - Special studies (positively staining granular cells)
    - S-100 protein
    - Calretinin
    - Inhibin-α
    - Myelenin basic protein
    - CD68 / Kp1
    - TFE3

Esophageal Melanoma

- Demography
  - Very rare (about 300 cases reported worldwide)
  - M > F
  - 60 yrs
- Endoscopic
  - Polypoid
  - May bulge into lumen
  - Black pigment in 85%
- Histopathology
  - Spindle – Epitheloid-shaped
  - Pigment may be apparent
  - Nuclei – Prominent nucleoli
    – Pseudo-inclusions

Immunohistochemistry (IHC) of Esophageal Tumors

IHC	Barrett epithelium	Adeno-carcinoma	Squamous carcinoma	Granular cell tumor	ASPS	Melanoma
CK7	+	+				
DAS7	+					
Racemase	+					
p53	+					
Ki-67	+					

IHC	Barrett epithelium	Adeno-carcinoma	Squamous carcinoma	Granular cell tumor	ASPS	Melanoma
Variable						
– CDX2	+	+				
– MUC2	+					
– MUC 5AC	+	+				
– MUC6	+	+				
CK 5/6			+			
p63			+			
S-100 protein				+		
Keratins				+		
Calretinin				+		
Inhibin alpha				+		
Myelin basic protein				+		
Nestin				+		
CD68				+		
kp1				+		
TFE3				+	+	
HMB45						+
MART						+
MITF						+
Melana						+

Abbreviations: ASPS, alveolar soft part sarcoma

ESOPHAGEAL MOTILITY DISORDERS (EMD)

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

- Types
  - Esophageal motility disorders may be primary or secondary to (associated with) another disease process.

- Classification

A simple classification of esophageal motility disorders (EMD)

Primary EMD	Secondary EMD	Manometric variants
○ Achalasia (three subtypes)	– Pseudoachalasia	▪ Hypertensive peristalsis
○ Diffuse esophageal spasm	– Chaga disease	▪ Hypertensive LES
○ Nutcracker	– Scleroderma esophagus	▪ Ineffective esophageal motility
○ Absent peristalsis	– Parkinson disease	
○ Gastroesophageal reflux disease (GERD)	– Infiltrative disorders	

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

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

- Manometry
  - Esophageal intraluminal pH testing is now being incorporated into EMIIT (esophageal multichannel intraluminal impedence testing).

- Standard manometry
  - Normal: Normal velocity, <8 cm/s in > 90% of swallows; normal peristaltic amplitude; (≥7 peristaltic contractions with an intact wave progression [amplitude >30 mmHg])
  - ↑/↓ LES tone
    - Hypotensive: 10 s mean <10 mm Hg, with normal peristaltic function
    - Hypertensive: 10 s mean >35 mm Hg, with normal peristaltic function and EGJ relaxation
  - Aperistalsis: Absent or simultaneous contractions (<30 mmHg)
  - Ineffective esophageal motility (IEM): ≥3 peristaltic contractions with failure of wave progression due to an ineffective distal contraction amplitude (< 30 mmHg) or failed peristalsis over a segment of the distal esophagus
  - Nutcracker (hypertensive) esophagus: average peristaltic amplitude >180 mmHg over pressure sensors 3 and 8 cm above LES
  - Distal esophageal spasm (DES): contractile velocity >8 cm/s mmHg over pressure sensors 3 and 8 cm above LES in ≥2 swallows
  - Isolated hypertensive LES: basal LES pressure greater than 45 mmHg (mid-respiratory pressure)
  - Achalasia: abnormal LES relaxation; absent or simultaneous contractions

- Atypical disorders of LES relaxation: abnormal LES relaxation, with some normal simultaneous or peristalsis.
- A video barium examination may be normal even when UES manometry is abnormal
- It is useful to perform provocative testing (intraesophageal acid infusion, balloon distention, edrophonium injection) to attempt to reproduce the patient's symptoms in the setting of NCCP (non cardiac chest pain)
- Combined multichannel intraluminal impedence (MII) and pH testing detects impedence data at 3, 5, 7, 9 and 15 and 17 cm above the LES, and 5 cm above the LES

Abbreviations: DES, distal or diffuse esophageal spasm; DSRS, distal 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.

- High resolution
  - Testing conditions for ambulatory manometry are less well standardized as compared with stationary manometry.
  - HRM (high resolution manometry) allows for topographic plotting of esophageal pressures in a test called HREPT (high-resolution esophageal pressure topography).

- 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.

➢ Diagnostic criteria for esophageal motility, 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
    - Normal elevation of intra-bolus pressure at <8 cm/s to <30 mm Hg in > 90% of swallows
    - Mean distal contractile index (DCI) <5000 mm Hg·s·cm**

- Peristaltic dysfunction
    - Mild: 3-6 swallows with failed peristalsis or a >2 cm defect in the 30 mm Hg isobaric contour of the distal esophageal peristalsis (15 mm Hg in proximal-mid esophagus)

- Severe: ≥ 7 swallows with either failed peristalsis or a >2 cm defect in the 30 mm Hg isobaric contour of distal esophageal peristalsis (15 mm Hg in proximal-mid esophagus)
- Aperistalsis: Contractile pressure <30 mm Hg throughout mid-distal esophagus in all swallows (*Scleroderma* pattern: aperistalsis with LES pressure <10 mm Hg)

- Hypertensive dysfunction
  - Peristaltic velocity <8 cm/s in >80% of swallows
  - Mean distal contractile index (DCI) >5000 mm Hg·s·cm**
    - *Hypertensive peristalsis*: mean DCI >5000-8000 mm Hg·s·cm
    - *Segmental hypertensive peristalsis*: hypertensive contraction restricted to mid- or distal esophagus or LOS after-contraction: mean DCI 5000-8000 mm Hg·s·cm
    - Hypertensive peristalsis ± repetitive or prolonged contraction: DCI >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.
    - 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 a relatively common heterogeneous condition encountered in normal controls, dysphagic patients, and patients with reflux disease.
- 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

Achalasia

- Demography
  - Achalasia is rare (< 10 / 10^5), and is usually thought of in the context of its dysmotility. The gender ratio is M = F, although M > F in spastic esophageal disorders.

- Definition
  - Primary achalasia is associated with loss of ganglion cells in the myenteric plexus of the esophagus.
  - Complete absence of peristalsis (One peristaltic contraction rules out achalasia)

- In order to make the diagnosis of achalasia, there must be standard manometric or HREPT evidence of
  - Loss of relaxation of LES (lower esophageal sphincter), plus
  - Loss of peristalsis in distal esophagus (GBA)
  - There may also be ↑LES pressure (not required for diagnosis)
- Impaired deglutative EGJ relaxation and/or opening
- Elevation of intra-esophageal bolus pressure due to resistance to flow at EGJ
- *Classic*
  - Aperistalsis with no identifiable contractile activity
- *Vigorous*:
  - with persistent contractile activity (spasm) or gross elevation of intra-esophageal bolus pressure, with or without esophageal shortening
- *Variant*
  - with preserved peristalsis in the distal esophagus in ≥20% swallows

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

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

➢ Histopathology

- Give the pathological changes in the dilated portion of the esophagus in achalasia.
  - Ganglionitis (chronic inflammation of the ganglion cells)
  - Loss of myenteric plexus
  - Wallerian degeneration

- Lewy bodies
- Muscle layer may be hypertrophic
- In megaesophagus, esophageal wall may be thin
- If there is associated stasis esophagitis, then associated
  - Erosion
  - Ulceration
  - Fibrous stricture
- Risk of development of squamous cell esophageal cancer

➢ Types

- Distal segment, impaired esophagogastric junction (EGJ) relaxation
  - Classic achalasia (Type I)
  - Achalasia with esophageal compression (Type II)
  - ≥ 20% test swallows with esophageal compression (Type III)

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

	Type I	Type II	Type III
○ Peristalsis			
– Absent peristalsis	+		
– Compartmentalized pressurization		+	
– Spastic contraction			+
○ Response to treatment			
– Heller myotomy	67	100%	0
– Pneumatic dilation	38	73%	9
– Botulinim toxin	0	86%	22

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

➢ Causes

- Give causes of secondary (**pseudoachalasia**) achalasia.

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

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

- Cancer (Non-GI; Paraneoplastic syndrome)
  - Lung carcinoma (non-small cell)
  - Metastatic prostate carcinoma
  - Metastatic renal cell carcinoma
  - Breast adenocarcinoma
  - Leiomyoma
  - Lymphoma
  - Reticulum cell sarcoma
  - Lymphangioma
  - Mesothelioma

- Motility abnormalities
  - Parkinson disease
  - Achalasia with associated Hirchsprung disease
  - Hereditary hollow visceral myopathy
  - Familial achalasia
  - Fundoplication
- Surgical
  - Post-fundoplication
  - Post-vagotomy
- Miscellaneous
  - Allgrove syndrome (AAA syndrome) – (Alacidygia; Addisons; Achalasia)
  - Hereditary cerebellar ataxia
  - Autoimmune polyglandular syndrome type II
  - MEN IIb (Sipple's Syndrome)

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

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Achalasia is rare, and an even rarer condition is achalasia secondary to a tumor (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.

- High-resolution manometry (HRM) allows for better definition of esophageal motility disorders, including achalasia.
- Using HRM achalasia has been classified into three subtypes: type I (classic achalasia), type II (esophageal compression), and type III (spastic achalasia).
- Response to achalasia treatment appears to vary by subtypes.
- There is some variability in distinguishing between type I and type II achalasia.
- Thus, clarification of the criteria for type I and type II achalasia might improve the reliability of the classification.

Source: Hernandez et al. Am J Gastroenterol 2012; 107:

Useful background: Radiographic and manometric diagnosis of achalasia

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

➢ Treatment

- Smooth muscle relaxation (relaxants taken 15 to 30 min before meals)
  - Nitrates
  - Calcium channel blockers
    - Nifedipine
  - Botulinum toxin injection into the area of LES
    - Inhibits the acetylcholine-releasing excitatory neurons inervating the smooth muscle of the LES (lower esophageal sphincter), which thereby lowers the LES pressure.
- Smooth muscle damage
  - Esophageal dilation
    - Bougie
    - Forceful balloon dilation (tears some of the smooth muscle fibres)
    - Success rates

Months	%
6	74%
12	68 to 90%
24	86%
≥ 36	58%

- Post-procedure
- Perforation 2 to 4%
- Heartburn 45%
- May require repeated dilations if dilation approaches fail, there may be risk of complications from subsequent surgical myotomy
  - Especially if patient < 40 years
  - 25% to 50% within 5 years

- 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 proceeded 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%

  - ○ Surgical myotomy (Heller myotomy, thoracic, or abdominal approach)
    - Success rate higher (70% to 90%), and recurrence rate lower at 10 years, 70% to 85%; 20-30 years, 65% to 75% lower than forceful pneumatic dilation

  - 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%
- The 5 year likelihood of being asymptomatic after laparoscopic myotomy for achalasia is 87%.
- Laparoscopic myotomy

- Give the preoperative 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
  - Endoscopy (POEM, peroral endoscopic myotomy [a form of NOTES: natural orifice transluminal endoscopic surgery])
    - Peroral endoscopic myotomy (POEM) has been demonstrated to be a highly effective treatment resulting in a more than 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

❖ 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		
- Minor	▪ Headache, hypotension (30%)	- Rash - Transient chest pain (20%)
- Major	▪ NR	- NR
○ Advantage	▪ Rapidly initiated, well accepted	- Low morbidity - Modest response durability - Well accepted
○ Disadvantage	▪ Inconvenient side effects ▪ Tachyphylaxis ▪ Poor effect on esophageal emptying	- Repeat injection often required within 1 yr - Fibroinflammatory reaction at LES

❖ Endoscopic and 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 - Echinique-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
○ 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 Esophageal Spasm (DES)**, Nutcracker Esophagus** (Hypertensive Esophagus)**, and Hypertensive LES**

- Treatment of DES, nutcracker esophagus and hypertensive LES
  - Generally small and less than ideal studies
  - 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
  - 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

Source: 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 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!

Why? Because the device may become trapped in the pseudodiverticulum.

- 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)
    - Artificial hygiene
  - Esophagus
    - SSc associated loss of LES and 1% 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
  - Octreotide
  - TPN (total parenteral nutrition) / HPN (home parenteral nutrition)
  - PEE / PEJ (percutaneous endoscopically-placed gastrostomy or jejunostomy feeding tube)

- Small intestine
  - SIBO (small intestinal bacterial overgrowth)
    - Slow small intestinal transit in SSc from ↓ MMCs (migrating motor complexes) leads 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
    - Probiotics
  - Pneumatosis cystoides intestinalis, pneumoperitoneum
    - ↓ dietary intake of gas-forming malabsorbed carbohydrates
    - Antibiotics (SIBO)
    - O_2 therapy / Hyperbaric O_2
- Colon
  - Constipation
  - Fecal incontinence
  - Wide-mouthed colonic diverticula
- Liver
  - PBC (primary biliary cirrhosis)

Gastroesophageal Reflux disease

Mansour Alghanem

Background

- Definition
  - GERD
    - Reflux of gastric contents into the esophagus sufficient to cause symptoms or esophageal injury/complications
  - NERD (non-erosive reflux disease)
    - Patients with GERD symptoms, but normal endoscopy off medications (still have to prove *acid* reflux – i.e. pH study)
  - Only 30-40% of patients with GERD have esophagitis (i.e. approximate prevalence of 5-7%) - the rest are NERD

- Demography
  - Incidence
    - $500 / 10^5$
  - Prevalence
    - 10% – 20% of adult population

- Pathophysiology
  - Imbalance between Protective factors (anti-reflux barriers and acid clearance) and aggressive factors (Gastric acidity ,Volume and Duodenal contents)
  - Anti Reflux Barriers:
    - Lower esophageal Sphincter(LES)
      - 10-30 mm Hg
    - Diaphragm
      - 5-10 mmHg
    - Angle of His
      - Oblique angle at which the entrance of esophagus into the stomach is formed.

Modulators of Lower Esophageal Sphincter Pressure

	INCREASE LES PRESSURE	DECREASE LES PRESSURE
○ Hormones / peptides	– Gastrin – Motilin – Substance P	▪ Secretin ▪ Cholecystokinin ▪ Somatostatin ▪ VIP
○ Neural agents	– α-Arenergic agonists – β-Arenergic antagonists – Cholinergic agonists	▪ α-Arenergic antagonists ▪ β-Arenergic agonists ▪ Cholinergic antagonists
○ Foods	– Protein	▪ Fat ▪ Chocolate ▪ Peppermint
○ Other factors	– Histamine – Antacids – Metoclopramide – Domperidone – Cisapride – Prostaglandin F2α – Baclofen	▪ Theophylline ▪ Prostaglandin E2 and I2 ▪ Serotonin ▪ Meperidine ▪ Morphine ▪ Dopamine ▪ Calcium channel blockers ▪ Diazepam ▪ Barbiturates

Lower Esophageal Sphincter (LES)

- It is not just the basal (at rest) pressure of the LES that is important
- The transient LES relaxations play a major role in the pathogenesis of reflux events
- Transient lower esophageal sphincter relaxations (tLESR) is the most important mechanism leading to GERD.
  - Occur independent of swallowing
  - Not accompanied by peristalsis (i.e. volume clearance)
  - Typically long (>10 seconds)
  - Triggered by proximal stomach distention

- Other contributing mechanisms include hypotensive LES
- Acid clearance
  - Volume clearance (through peristalsis and gravity)
  - Acid clearance (neutralization of acid by saliva and esophageal gland secretion)
- Tissue Resistance
  - Pre-epithelial (mucous layer on mucosa),
  - Epithelial (multi-cell layered mucosa with intact tight junctions, intracellular buffering of acid),
  - Post-epithelial (adequate blood flow to mucosa to maintain buffering)
- Aggressive factors
  - Gastric factors (gastric pH <4 – which is the injurious level, delayed gastric emptying)
  - Duodenal factors (bile causes damage in the presence of acid and pepsin)
    - Conjugated BA with acid and pepsin = damage
    - Deconjugated BA with trypsin = damage!

➢ Clinical

- Esophageal Symptoms
  - Heartburn—retrosternal burning discomfort
  - Regurgitation—effortless return of gastric contents into the pharynx without nausea, retching, or abdominal contractions
  - Waterbrash (hypersalivation)
  - Belching
  - Non-cardiac chest pain
  - Dysphagia

- Extra-esophageal Symptoms
  - Nonallergic asthma
  - Hoarseness
  - Pharyngitis
  - Tracheal stenosis
  - Globus
  - Dental erosions

➢ Diagnosis

"Clinical tests help us determine if the patient's symptoms are related to the GE reflux of acid"

- Clinical tests
  - Therapeutic trial
    - A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric medical therapy with a PPI is recommended in this setting.

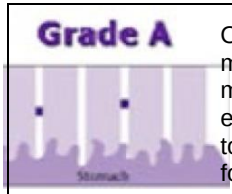
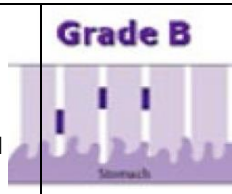
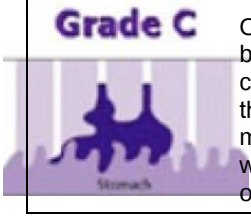
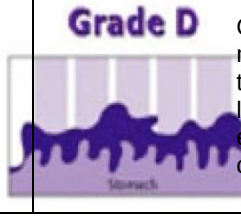
Symptoms	Treatment	Sens (%)	Spec (%)
Heartburn and regurgitation	Omperazole BID for 1 wk	80 %	56%
Noncardiac Chest pain	Omperazole BID for 2 wks	75%	85%
Extraesophageal	PPI BID for 12 wks		

  - Symptom association indices
    - Please see section on physiological (functional) studies, esophageal pH / PI studies

- Endoscopy (EGD)
  - Structure an “endoscopic and diagnostic imaging as well as biopsy studies help us determine if the patients symptoms are associated with damage to the esophagus”
  - First line testing in presence of alarm symptoms (e.g. dysphagia, chest pain, involuntary weight loss, anemia, GIB, persistent vomiting, breathing difficulties
  - Refractory GERD despite optimal PPI treatment (to evaluate for other causes of GERD e.g. EoE)
  - Diagnosis of complications i.e. Barrett’s esophagus, stricture)
  - Endoscopy has a high specificity (90%) but low sensitivity (50%); normal endoscopy does not rule out GERD (i.e. NERD)

Abbreviations: EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; NERD, normal endoscopy reflux disease

The LA Classification system for the endoscopic assessment of reflux esophagitis

 One (or more) mucosal break, ≤ 5 mm, that does not extend between the tops of two mucosal folds	 One (or more) mucosal break > 5 mm long that does not extend between the tops of two mucosal folds
 One or more mucosa break that is continuous between the tops of ≥ 2 mucosal folds, but which involves < 75% of circumference	 One (or more) mucosal break that involves at least 75% of the esophageal circumference

Ambulatory Esophageal pH Study

- Indications:
  - Patients with NERD who are being considered for surgery
  - Patients with medically or surgically refractory GERD
    - Patients being considered for surgery or those with persistent or recurrent symptoms after surgery should have testing OFF medications
    - Patients with medically refractory symptoms should have pH testing ON medications to define 2 populations:
      - Those with (escalate therapy) and those without (chose another therapy) continued abnormal acid exposure times
  - Patients with atypical symptoms like NCCP
  - Extra-esophageal manifestations (hoarseness, laryngitis, asthma, cough)
- Performed with either a telemetry capsule (usually 48 hr) or transnasal catheter (24 hr)
- Excellent sensitivity (77–100%) and specificity (85–100%) in patients with erosive esophagitis
- Results may be reported as the Demeester score includes:
  - % Total time pH < 4 (normal < 4%)
  - % Upright time pH < 4
  - % Supine time pH < 4
  - Total number of reflux episodes (normal < 50 in 24 hr)
  - Number of episodes > 5 mins (normal < 4 in 24 hr)
  - Longest duration of an episode (normal is < 10 min)
    - An abnormal Demeester score is > 22
- Combination with Manometry is required prior to anti-reflux surgery to r/o Motility disorders.

- Symptoms correlation either using symptom index (SI) and symptom association probability (SAP) can aid in determining the decision for management.
- Positive correlation indicates the need for therapeutic intervention. If negative correlation, the Symptoms attributed to non-reflux etiology.

Bernstein Test

- Infuse 0.1 N HCl and saline into the esophagus to determine if the HCl quickly reproduces the patient's usual GERD symptoms.
- Positive results with acid infusion but NOT with saline infusion.
- Sensitivity and specificity for typical GERD symptoms, but not for atypical symptoms

➢ Treatment

- Life style Modifications:
  - Do not eat within 3 hours of sleeping
  - Weight loss*
  - Raise the head of the patient's bed*
  - Do not lie flat after eating
  - Stop smoking (↓ saliva)
  - Decrease EtOH intake
  - Avoid chocolate and peppermint
  - Avoid irritating food, e.g. spices, orange juice, tomato sauce
  - Avoid tight fitting clothes
  - Avoid high fat meals that may delay gastric emptying

* Evidence based

Note: Although many of these recommendations are not evidence-based, individual patients may find some of these maneuvers to be helpful

- Pharmacotherapy
  - Proton Pump inhibitors (PPIs)
    - Mechanism of Action is irreversibly complex with the H+-K+-ATPase pump
    - An adequate course of therapy is 4-8 weeks; daily PPI therapy is generally adequate
    - BID standard dose PPI therapy may be used for patients who have
      - Severe symptoms despite standard once-daily PPI therapy
      - Severe esophagitis or stricture as it may hasten healing
      - NCCP
      - Extraesophageal manifestations of GERD
      - Not all guidelines support the use of bid dosing; use on a patient-by-patient basis
    - PPIs are 50% more effective for GERD and 20% for NERD compared to H2RA
    - Treatment of erosive esophagitis for 8 weeks has healing rates between 75% and 95% for PPI; H2RAs have healing rates of 60%
    - Among all PPIs, esomeprazoloe has ↑ healing rate of 3-6%
    - Unknown clinical significance
    - May be superior for severe esophagitis (LA grade C/D)
    - All of the PPIs with the exception of omeprazolesodium and dexlansoprazole, should be administered 30 – 60 min before meals to assure maximal efficacy.

- Side effects:
  - Nausea, diarrhea, headaches, abdominal pain, flatulence and rash in a minority of patients
  - Vitamin B12 deficiency
  - Osteoporosis and fractures
    - Calcium is better absorbed in an acidic environment
    - Case control studies have shown an increased risk of hip fracture with prolonged (>1 year) PPI use – OR 1.5-2.5
  - Nosocomial pneumonia
  - C. Difficile
    - Dial S et al. JAMA 2005 – Case-control study – OR 2.9
    - Leonard J et al. AJG 2007 – Systematic Review – OR - 2
  - Fundic Gland Polyposis, atrophic gastritis

- H2 blockers
  - Blocks the histamine-induced stimulation of the parietal cells.
  - Higher mucosal healing compared to placebo 50%, but much less than PPI.
  - Adjunctive role to PPI with controlling nocturnal acid breakthrough (NAB; nighttime periods of gastric pH < 4 for >1 h on bid PPI)
  - Limitation due to potential tachyphylaxis of pH control occurring after a month of therapy

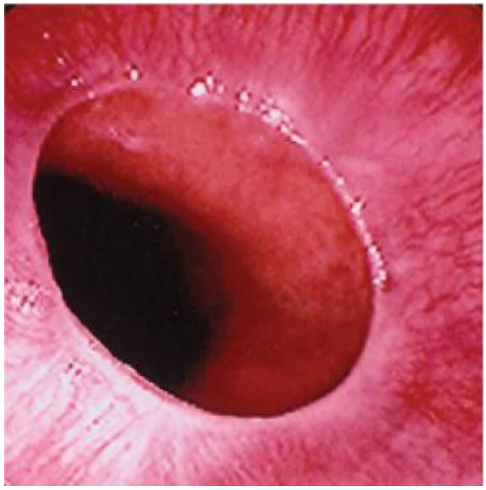
- Other Treatments
  - Prokinetics
    - ↑ LESP, ↑ esophageal peristalsis and ↑ gastric emptying.
    - Limited role due to CNS and CVS side effects.

- Baclofen
  - GABA(b)
    - ↓ tLESR → ↓ reflux episodes
  - Data on benefit in refractory cases, but lacks longterm efficacy and safety data.

Abbreviation: tLESR, transient lower esophageal relaxation

- Surgery
  - Indications
    - Generally not recommended in patients who do not respond to PPI therapy.
    - Regurgitation-dominant reflux symptoms
    - Dissatisfaction with the need for long-term PPI
    - Poor compliance with medical therapy
    - Presence of a large hiatus hernia
    - Recurrent peptic strictures in a young patient
    - Lung transplant with GERD with aspiration
  - Options:
    - Nissen fundoplication (laproscopic vs Open)
    - Complete vs. partial Fundoplication
    - Gastric Bypass
    - Endoscopic approach:
      - Radiofrequency application to increase LES reflux barrier
      - Endoscopic sewing devices
      - Injection of a non-resorbable polymer into LES area
    - Sphincter Augmentation (Linx Device)
  - Post-surgery
    - 10% have solid food dysphagia
    - 2-3% have permanent symptoms
    - 7-10% have gas, bloating, diarrhea, nausea, early satiety
    - Efficacy within 3-5 years 52% of patients back on antireflux medications

- Complications
  - Peptic stricture:
    - Caucasians
    - Older patients with longer duration of untreated symptoms
    - Abnormal esophageal motility.
    - True peptic strictures occur at the squamocolumnar junction (except for inlet patch)
    - Management with EGD +dilatation + PPIs
    - Maintenance with PPI indefinitely (improve dysphagia, decrease frequency of dilatations and/or increase the interval between dilatations)
  - Schatzki Rings
    - Linked to GERD
    - Often asymtpomatic but may cause dysphagia.
    - Dilatation is the mainstay of treatment
    - PPI ↓ recurrence



Schatzki Rings

Barrett Esophagus (BE)

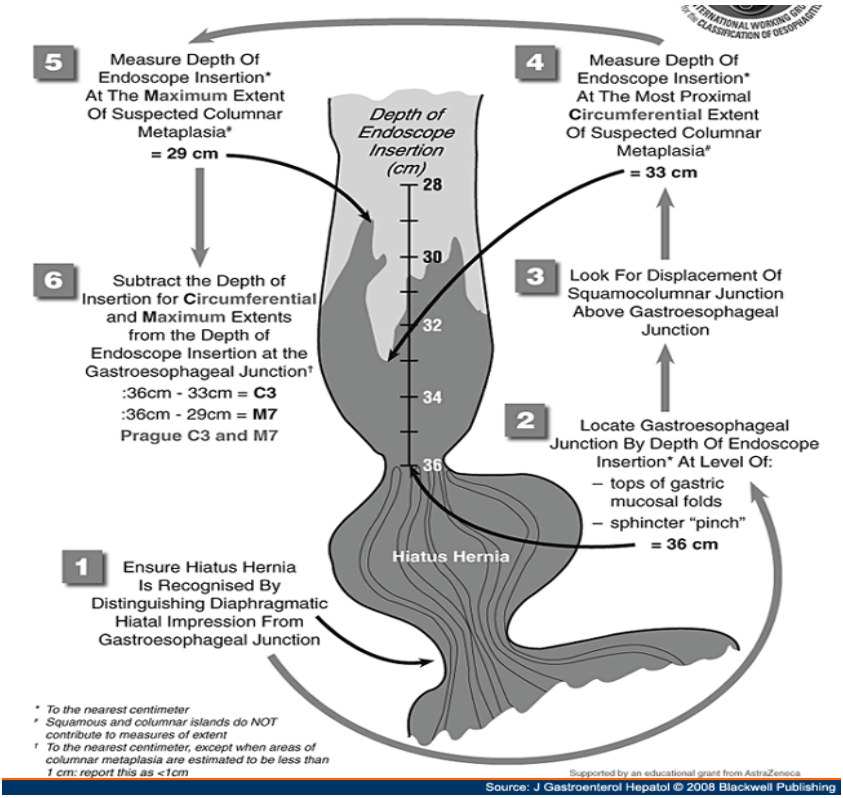
- Histopathology
  - Intestinal metaplastic replacement of squamous epithelium at the GE junction with specialized columnar epithelium (columnar cells goblet cells)

- Endoscopy
  - Salmon-pink coloured tongues of mucosa rising from GE junction into esophagus
  - Length
    - LSBE: > 3cm
    - SSBE: < 3 cm
    - Ultra short: at the Z line

- Risk factors
  - Typical profile:overweight middle-aged Caucasian male with severe, frequent (≥ 3 episodes of GERD / wk), amd for 10 yr
    - OR = 7.7 in patients with recurrent reflux vs. 43.5 in those with long-standing (> 20 yrs), frequent, severe symptoms

- Screening
  - Not recommended for guidelines recommends
  - Progression if GERD to BE ~ 10% progression of Barrett metaplasia to dysplasia ~ 1 per 1000 patient years
  - Limitations of screening for BE:
    - Discordance between reflux symptoms and presence of BE / adenocarcinoma
    - ↓ mortality
    - Exposure to invasive procedures

- Diagnosis
  - Red (columnar) mucosa in the esophagus; variable length
    - Described by the Prague classification
  - **C**: length of the circumferential section
  - **M**: length of the any circumferential section plus the length of any tongues
  - Biopsies demonstrate intestinal metaplasia
    - Biopsies of all mucosal abnormalities (ulcer, nodule, plaque)
    - Four quadrant (jumbo) biopsies at 1 – 2 cm intervals



- Imaging options in BE.
  - Visibility of abnormal areas to be able to target esophageal mucosal biopsies narrow band imaging
  - Confocal microscopy
  - Autofluorescence imaging - blue light to detect fluorescence from cellular components – dysplasia not as intense as normal tissue and appear dark red

- Treatment
  - Intestinal metaplasia
    - Ensure biopsies taken by Seatle profile, and after healing of any associated esophagitis
    - Confirm absence of dysplasia with 2 expert pathologists
    - Repeat EGD within one year to document absence of dysplasia.
    - Repeat EGD q 3 yrs
    - PPI for GERD symptoms
  - Low-grade Dysplasia
    - Confirm by 2 expert GI pathologists
    - Options surveillance or definitive treatment
    - Repeat EGD within 6 months to document absence of high grade dysplasia.
    - Surveillance with EGD annually until dysplasia is not present on 2 consecutive endoscopies
    - Endoscopic mucosal resection (EMR) or ablation (ASGE guidelines)
  - High-grade displasia
    - 2 pathologists with expertise should review the biopsy

- Surgery (esophagectomy)
  - Standard of care but high morbidity and mortality
  - Endoscopic resection:
    - EMR
    - Best for raised lesions
  - Endoscopic ablations:
    - RFA, PDT,Cryotherapy,APC
    - Best for flat lesions

Abbreviations: APC, argon plasma coagulopathy; PDT, photodynamic therapy; RFA, radiofrequency ablation

Endoscopic ablation

- Radiofrequency ablation (RFA) of the esophageal mucosa
- SHAM RCT for LGD and HGD (Shaheen NEJM 2009)
  - For HGD at 12 months, % with no dysplasia – 81% for RFA vs. 19% for SHAM ablation
  - Progression to cancer – 1% for RFA vs. 9% for SHAM
  - Much lower complications than PDT (1-5%)
- Photodynamic therapy
  - 5-aminolevulinic acid porporfimer sodium as photosensitizing agent
  - Effective to eliminate HGD (77% over 5 years) as well as early EAC
  - AEs
    - Photosensitivity 70%
    - Esophageal stricture 36%

- Cryotherapy:
  - Apply cold nitrogen or CO2 gas to BE
  - Tissue frozen for 40 sec
  - ~85% eradication of HGD dysplasia; but 3% had BE buried in submucosa
- Endoscopic mucosal resection (EMR)
  - Indicated in
    - Shorter segment dysplastic BE
    - Nodular dysplasia
    - Superficial (T1a) EAC
    - Esophageal squamous cell carcinoma (ESC)
    - Bleeding strictures and perforation
    - EMR 5 year survival rates ~ 95%
  - Disadvantages
    - High rates of residual or recurrent BE need ongoing surveillance or concurrent ablative therapy.

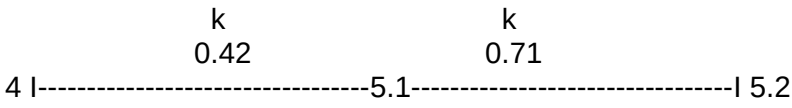
Tumors of the Esophagus

David Yik

- Give the Vienna Classification of esophageal neoplasia based on the internationally accepted histopathologic evaluation of endoscopic mucosal biopsies.

Category		Histopathology
1	–	No dysplasia
2	–	Indefinite for dysplasia
3	–	Low-grade dysplasia / adenoma (aka high-grade intraepithelial neoplasia)
4	–	High-grade dysplasia / adenoma (aka high-grade intraepithelial neoplasia, non-invasive carcinoma, non-invasive epithelial neoplasia suspicious for invasive carcinoma)
5	–	Invasive epithelial neoplasia Intramucosal carcinoma (5.1) Submucosal carcinoma (5.2)

Note: there is high inter-observer variability (as reflected by low kappa [k] statistic) distinguishing category 4 from 5.1, and 5.1 from 5.2



Classification of esophageal tumors

Epithelial Tumors	Non-epithelial Tumors
Malignant ○ Adenocarcinoma ○ Adenocarcinoma of GEJ ○ Malignant melanoma ○ Small cell carcinoma Squamous cell carcinoma ○ Verrucous carcinoma	**Malignant** – GIST – Lymphoma – Metastatic carcinoma – Sarcoma, including malignant
Benign ○ Adenoma ○ Inflammatory fibroid polyp ○ Squamous papilloma	**Benign** – Fibrovascular tumor – GIST – Granular cell tumor – Hamartoma – Hemangioma – Leiomyoma – Lipoma

- Give causes of multiple filling defects in the esophagus seen on barium swallow.
  - Foreign body
    - Effervescent granules
  - Infection
    - Candidiasis
  - Tumour
    - Squamous cell cancer
    - Candidiasis
    - Papillomatosis
  - Blood vessels
    - Varices

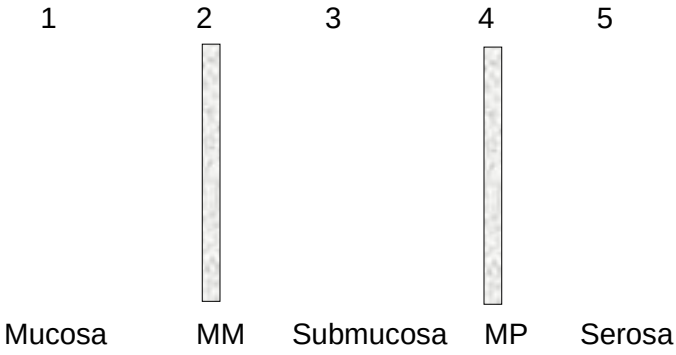
Endoscopic Ultrasound (EUS)

- Advantages
  - Endosonography allows distinction between intramural and extramural lesions by examination to a depth of ~20 mm (gut wall is about 4 mm thick)
  - Allows localization of intramural lesion to a specific layer of intestinal wall.
  - Provides the means to obtain tissue for pathological examination by way of FNA (fine needle aspiration) or trucut biopsy for cytological examination.
  - Miniprobes may be passed through the working channel of a standard EGD, and provide more detail, but only for flat lesions or lesions < 1 cm.
  - Describe the EUS image
    - Size
    - Vascularity
    - Echogenicity
      - Hyperechoic
        - Bright
        - Intensity of similar to or greater than that layers
          - 1 mucosa (superficial)
          - 3 submucosa
          - 5 serosa
      - Hypoechoic
        - Dark
        - Intensity similar to or lower than that of layers
          - 2 LP (lamina propria)
          - 4 M (muscularis propria)
      - Anechoic
        - Black, no internal echo
        - Intensity of water
        - Acoustic enhancement (a brighter echo behind a black fluid filled cyst, vessel or gallbladder
      - Light, hyperechoic

➢ Pathology

- Give the histological counterpast of the 5 layers of the wall of the GI tract seen on EUS (endoscopic ultrasound).

	Histology	Colour	EUS layer
○ Epithelial layer			
– Superficial	Mucosa	W white (hyperechoic)	1
– Deep	M. mucosa		2
		B black (hypoechoic)	
	Submucosal	W white	3
	M. propria	B black	4
	Serosa	W white	5



▪ Dark, hypoechoic

Abbreviation: MM, muscularis mucosa; MP, muscularis propria

– Overall accuracy of layer and location of tumor ~80%

- Localization of tumor by EUS may suggest its pathology
  - (light) hyperechoic (1,3,5)
    - Usually a
      - Lipoma (especially when in Layer 3)
      - Duplication cysts in layer 3
  - (dark) hypoechoic (2,4)
    - Usually a
      - GIST (especially in 4)
      - Leiomyoma (especially in layer 4)
      - Cyst, filled with mucin, debris
      - Carcinoids (usually layer 2)
      - Aberrant pancreas
      - Pancreatic pseudocysts
  - Note: esophageal varices (EV) are seen in layers 2, 4
  - Anechoic
    - Black
    - Often associated with acoustic enhancement
    - Misclassifications in ~50% of hyoechoic tumor

- Give the EUS layers and the tumors which are most common in each layer.

EUS layer	Tumor
1	Lipoma
2	GIST ECL (granular cell) Duplication cyst
3	Lipoma ECL (granular cell)
4	GIST Leiomyoma Glomus Schwannoma

Lipoma	1, 3
GIST	2, 4
EV	2, 4

- Give ways to increase the depth of an EGD biopsy (e.g. for a submucosal lesion).

  - EGD - tunnel biopsy (take a second biopsy from an initial biopsy site)
  - EMR - unroof the mucosa, biopsy submucosal tissue
  - EUS - FNA, or trucut biopsy
  - Overall accuracy for determining malignant GIST
    - EUS 78%
    - EUS + FNA 91%
    - EUS + FNA + KL-67 ~100%
  - ESD - endoscopic submucosal dissection, including use of IT (insulated tip) knife for en bloc dissection

➢ Heterogeneous appearance of lesion on EUS

  - Especially when large and in esophagus – likely
    - Leiomyosarcoma
    - Lieomyoblastoma
  - May be due to associated
    - Liquefaction necrosis
    - Hyaline degeneration
    - Connective tissue
    - Cystic generation

➢ EUS features

- Suggestive of malignant tumor
  - Irregular Extraluminal margins
  - Cystic space (heterogeneous)
  - Associated large lymph nodes

# of above findings	Sensitivity	Specificity	PPV
1	91%	88%	93%
2	-	-	100%

Abbreviation: PPV, positive predictive value

- Benign tumor
  - Regular margins
  - Homogeneous
  - Size ≤ 3 cm
  - If all 3 above signs present , ~99% likelihood the GIST is benign
  - Note: GISTs > 1 cm have the potential to be malignant, so even if A > 1 cm GIST looks benign on EUS, perform annual EUS surveillance for change in size, or development of malignant EUS features

- Esophageal varices on EUS
  - Anechoic
  - Layers 2 and 3
  - Distinguish from esophageal duplication cyst, using Doppler colour ultrasound

SO YOU WANT TO BE AN ENDOULTRASONOGRAPHER!

On EUS of the esophagus, a duplication cyst (DC) is anechoic, homogeneous, has regular margins, and is usually seen in EUS layer 3.

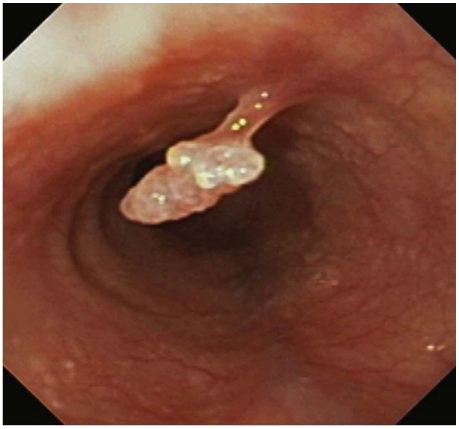
- Give the name of a much more common anechoic lesion than DC seen on EUS of the esophagus, and name the diagnostic imaging test which helps to distinguish between these two lesions.
    - Esophageal varices are also anechoic and are seen in layers 2 and 3 on EUS
    - Dopper colour ultrasound will show flow in varices, but not in a duplication cyst.

- Give the clinical circumstance when EUS may be falsely negative for demonstrating esophageal varices (EV).
    - Small EV may be compressed and made obscure by the EUS endoscope, or by the balloon o the transducer.

Duplication cysts (DC) are usually in the submucosal (EUS layer 3), and are anechoic, homogeneous and have regular margins.

- Give the complications of a DC which may make it difficult on EUS or on CT scan to distinguish a duplication cyst from a solid malignancy.
    - A DC is, as the name implies, a cyst. However, it may become solid if
    - It undergoes malignant degeneration, and becomes solid.
    - It may become with debris, and appear to be solid.

Benign epithelial tumors



Squamous papilloma of esophagus

Squamous papilloma

- Usually small, pink/white, sessile or polypoid benign tumors
- Histologically composed of finger-like projections of lamina propria covered by hyperplastic squamous epithelium
- GERD and HPV may be associated

- Adenoma
  - True adenomatous polyps arise in areas of Barrett epithelium (very rare)
  - Considered dysplastic with malignant potential → standard snare or mucosectomy techniques usually curative

- Inflammatory fibroid polyp
  - Often related to chronic GERD (gastroesophageal reflux disease)
  - Usually in distal esophagus at GEJ (gastroesophageal junction)
  - Endoscopic resection usually indicated to establish diagnosis, also curative

Fibrovascular Polyp

- Clinical
  - Presentations
    - Dysphagia
    - Globus
    - Asphyxiation
      - 2 cm (risk of tracheal obstruction → asphyxiation)
- Treatment
  - Surgical resection
    - Penetrating vessel
  - Endoscopic polyectomy
    - No penetrating vessel: < 2 cm

- Is the patient crazy – “Dr. Bob, I cough up a piece of tissue that disappears back into my mouth”.
  - No, the patient is not making this up. This is likely a long fibrovascular polyp of the upper esophagus, near the cricoid.

A patient with dyspepsia has nodules in the esophagus. There is no esophagitis, no cobblestoning of the mucosa, and no whitish exudate.

- Give the name of the likely diagnosis, and describe the histopathology.
  - Large squamous cells
  - Cytoplasm of these large squamous cells contains glycogen

Clinical curiosities: Cobblestoning of

- Buccal mucosa
  - Cowden syndrome
- Tongue
  - Crohn disease

Malignant Epithelial Tumors of Esophagus

Esophageal Carcinoma (ECA)

- Demography
  - In the USA, for 2012:
    - 17,460 new cases of esophageal cancer diagnosed (13,950 men ; 3510 women)
    - 3-4 times as common in men
    - Lifetime risk: 1 in 125 for men; 1 in 400 for women
    - Esophageal CA rates in Iran, northern China, India, southern Africa are 10-100 times greater than in the US. 90% are SCCA ("*Asian esophageal cancer belt*")
    - US/Canada considered low risk
  - 1960s: >90% of esophageal CA was SCCA
  - In Western countries, adenocarcinoma now of higher incidence

➢ Clinical

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

➢ Classification

PRE-OPERATIVE CLASSIFICATIONS

- **Ultrasound** (US TNM) classification for esophageal cancers

uT1 – Tumour invading the mucosa and the submucosa

uT2 – Tumour invading the mucosa without going beyond

uT3 – Tumour invading the tunica adventitia (or the serous membrane)

uT4 – Tumour invading the adjacent structures

uN0 – No lymph node invasion

uN1 – Lymph nodes invaded around tumour; round, same echogenicity as the tumour

uN2 – Lymph nodes invaded distant from the tumour (5 cm above or below the upper or lower pole of the tumour)

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

ctT1 – Non-visibility or mass <10 mm in diameter

ctT2 – Mass 10-30 mm in diameter

ctT3 – Mass >30 mm in diameter with no sign of invasion t mediastinal structures

ctT4 – Idem + sign of spread to mediastinal structures

- Lymph nodes (N)*

ctN0 – No detectable adenopathy

ctN1 – Regional adenopathy (mediastinal and/or perigastric)

- Distant metastases

ctM0 – No distant metastasis

ctM1 – Presence of distant metastases (including celiac and cervical adenopathies)

- Definition of US and CT stages

US or CT stages	– I TI N0 M0
	– IIa T2 N0 M0; T3 N0 M0
	– Iib T1 T2 N1 M0

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

POST-OPERATIVE CLASSIFICATIONS:

- TNM classification

T-Primary tumour

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

- N-Regional adenopathy

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

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

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Staging esophageal cancer

- Important for planning stage-specific therapy
- Associated with prognosis:
  - SEER data from 2005, one-year survival
    - Local disease – 68%
    - Regional disease – 54%
    - Metastatic disease – 28%

Tis – Carcinoma in situ/ high grade dysplasia

T1 – Invades lamina propria, muscularis mucosae, or submucosal

T2 – Invades muscularis propria

T3 – Invades adventitia

T4 – Invades adjacent structures

N0 – No regional lymph node metastasis

N1 – Metastasis in 1-2 regional lymph nodes

N2 – Metastasis in 3-6 regional lymph nodes

N3 – Metastasis in 7 or more regional lymph nodes

G1 – Well differentiated

G2 – Moderately differentiated

G3 – Poorly differentiated

G4 – Undifferentiated

Risk factors

- Squamous cell carcinoma (SCCA)
  - Most important etiologic risk factors estimated by a study determining the population attributable risk which accounted for 90% of esophageal SCCA in US
    - History of smoking
    - Alcohol consumption
    - Diet low in fruits and vegetable
  - Other dietary factors:
    - N-nitroso compounds
    - Chewing of areca/betel nuts
    - High temperature drink/food
    - Red meat consumption
    - Low selenium and zinc intake
  - Underlying esophageal disease
    - Achalasia
    - Caustic strictures
  - Atrophic gastritis
  - Tylosis – ASGE suggests screening begin at 30 yr of age
  - Other SCCA of aerodigestive tract
  - Bisphosphonates – Uncertain, but FDA recommends against using in patients with Barrett epithelium
  - Family history

- Adenocarcinoma (AdCA)
  - Most important risk factors which accounts for 80% of AdCA in US
    - Smoking
    - BMI higher than lowest quartile
    - GERD
    - Diet low in fruits and vegetable
  - Helicobacter pylori (HP)
    - Absence of HP may be a risk factor for distal esophageal AdCA
    - HP may be a risk factor for gastric cardia AdCA, which can be difficult to distinguish from distal esophageal CA
  - Family history

Esophageal adenocarcinoma and GERD

- >50% of cases of adenocarcinoma have no GERD symptoms
- Reflux symptoms significantly associated with adenocarcinoma of esophagus (OR 7.7), gastric cardia (OR 2.0)
  - Risk greatest with long-standing symptoms (20y > 10y > 5y)
  - Weekly symptoms increase risk 5-fold
  - Daily symptoms increase risk 7-fold
- Barrett esophagus increases risk of esophageal cancer at least 30x
  - Absolute risk still low (~0.12% per year , lower than previously thought)
- Conditions which predispose to GERD may be risk factors for AdCA, eg. Obesity ↑ BMI)

- Risk factor differences between esophageal SCCA and ECA
  - Gender and ethnicity
    - ECA more prevalent in Caucasian males (6:1 M:F)
    - SCCA incidence highest in blacks, Asians; sex ratio comparable for all ethnicities
  - Alcohol is likely NOT a risk factor for adenocarcinoma, and risk may be decreased significantly by wine consumption (not liquor or beer)
  - Obesity associated with ECA, not SCCA

- Give risk factors for esophageal squamous cancer (SCCA) and for adenocarcinoma (ECA).

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

  - Previous head and neck squamous cell carcinoma
  - Radiation therapy
  - Lye ingestion

- Plummer-Vinson (Paterson-Kelly) syndrome
- Achalasia
- Nutritional deficiencies– riboflavin, niacin; high-starch diet without fruits and vegetables
- Nitrosamines; “bush teas” (diterpene phorbol esters)
- Gluten sensitive enteropathy (GSE)
- Tylosis palmaris

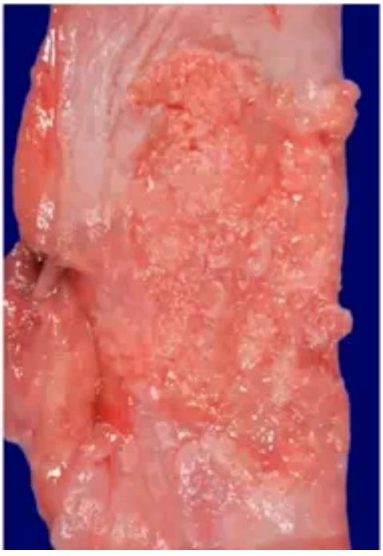
Abbreviations: BE, Barrett epithelium; GERD, gastroesophageal reflux disease

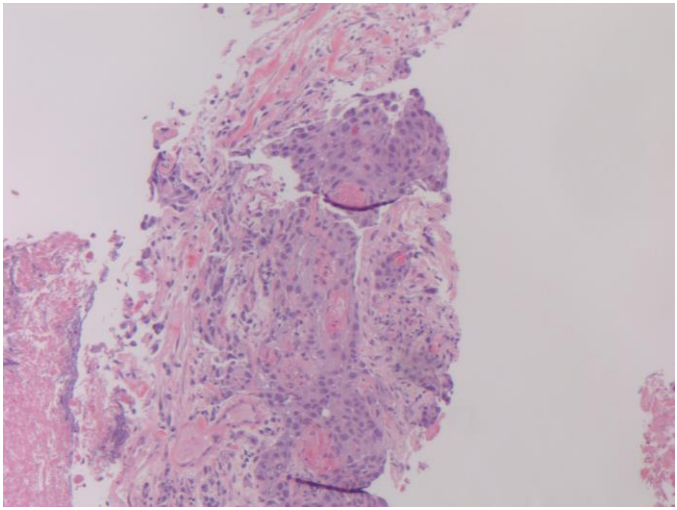
- Clinical features
  - Adenocarcinoma much more common in distal esophagus
  - Dysphagia
    - Usually occurs with luminal diameter of <13 mm
  - Chronic GI blood loss common, overt GI bleeding uncommon
  - Tracheobronchial fistulae uncommon, late presentation

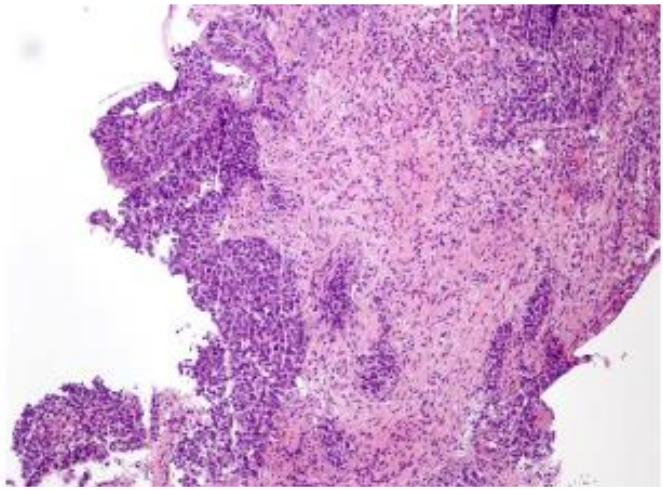
- Pathology
  - Esophageal SCCA develops from dysplastic precursor lesions
  - Dysplasia = “intraepithelial neoplasia” (WHO terminology)
  - Low-grade dysplasia
    - Often involves the basal layer of epithelium only

- High-grade dysplasia
  - Usually involves entire epithelial layer
  - May extend into ducts of esophageal glands
- Architectural changes
  - Disorganization
  - Loss of polarity
  - Overlapping nuclei
- Cytologic changes
  - Coarse chromatin
  - ↑ nuclear:cytoplasm ratio
  - Nuclear hyperchromasia
  - Nuclear polymorphism
  - Mitotic figures

Esophageal SCCA

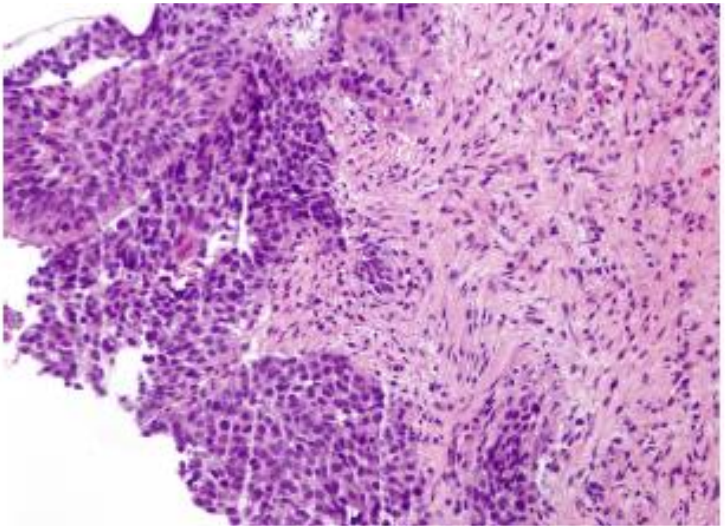






Kindly provided by Dr. Aducio Thiesen, University of Alberta

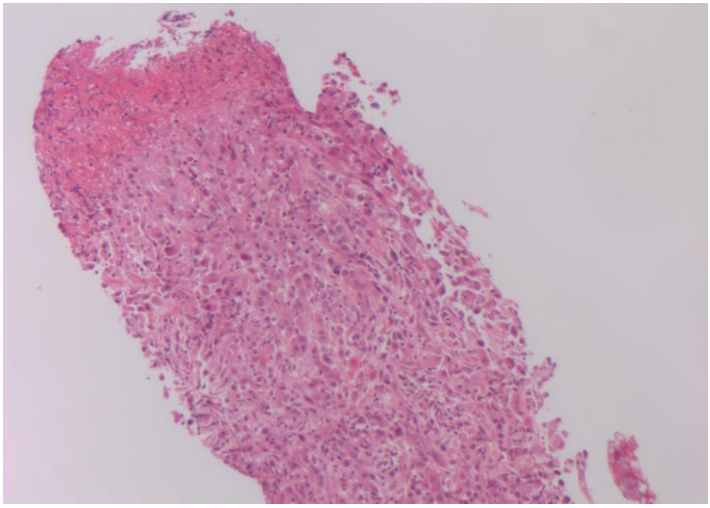
- (1) Abrupt transition between normal (left) and dysplastic (right) epithelium.
- (2) Enlarged, irregular, hyperchromatic nuclei with loss of maturation.

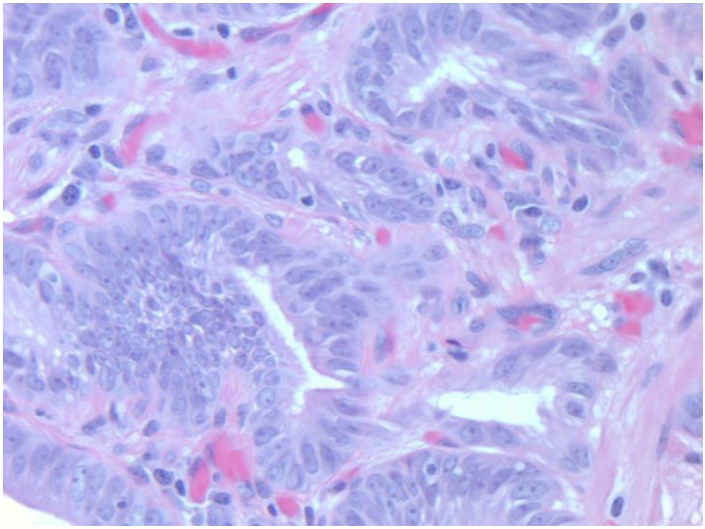


Kindly provided by Dr. Aducio Thiesen, University of Alberta

- Pathology –Adenocarcinoma
  - Arises from ectopic gastric-type epithelium which is glandular
    - Almost all secondary to Barrett changes distal third of esophagus
    - Extremely rarely from foci of gastric heterotopia in cervical esophagus (inlet patch)
  - Dysplasia described as low vs. high grade, similar changes as in SCCA
  - “Indefinite for dysplasia” often used when true dysplasia cannot be differentiated from reactive changes from esophageal inflammation
    - Immunohistochemical markers may help differentiate (PCNA, Ki67, cyclin D1); also immunostaining for AMACR

Esophageal Adenocarcinoma





Anatomic stage / Prognostic groups

Squamous Cell Carcinoma

Stage	T	N	M	Grade	Tumor locations**
Stage 0	Tis (HGD)	N0	M0	1, X	Any
Stage IA	T1	N0	M0	1, X	Any
Stage IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
Stage IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
Stage IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
Stage IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
Stage IIIB	T3	N2	M0	Any	Any
Stage IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IV	Any	Any	M1	Any	Any

Adenocarcinoma

Stage	T	N	M	Grade
Stage 0	Tis (HGD)	N0	M0	1, X
Stage IA	T1	N0	M0	1-2, X
Stage IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
Stage IIA	T2	N0	M0	3
Stage IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
Stage IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
Stage IIIB	T3	N2	M0	Any
Stage IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
Stage IV	Any	Any	M1	Any

NCCN 2012 Guidelines

Staging esophageal cancer – 2012 NCCN Guidelines

**all recommendations are category 2A

- History and physical, CBC and chemistry profile
- Upper GI endoscopy and biopsy
  - Large forceps, 6-8 biopsies
- PET evaluation preferred if no evidence of M1 disease (and PET/CT preferred over PET)
- Bronchoscopy
  - If tumor at or above carina, no M1 disease
  - Can be useful for biopsy and brush cytology in locally advanced nonmetastic tumors at or above level of carina
- Laparoscopy (optional) if no evidence of M1 disease, tumor is at EGJ
  - Controversial
  - Sometimes performed to detect occult intraperitoneal mets to limit aggressive treatment in pts with advanced disease (EUS and PET are insensitive for this)
  - Perhaps more accurate for regional lymph nodes than EUS or CT alone,
  - No data exists comparing against EUS + CT or EUS + PET
- [HER2-neu testing if metastatic adenoCA suspected; assign Siewert category; smoking cessation, counseling, pharmacotherapy]
- CT chest/abdomen/pelvis (as indicated), with oral / IV contrast
  - Detects metastases in
    - Lung
    - Liver
    - Periaortic lymph nodes

- Poor accuracy for detecting T stage
- Insensitive for detection of celiac lymph nodes
- (MRI offers no significant advantage over CT)

- EUS (endoscopic ultrasound)
  - Best modality for T staging if no evidence of M1 disease
  - High resolution images of periesophageal tissues
    - Celiac trunk
    - Left lobe of liver
    - Left adrenal gland
    - Thoracic and abdominal aorta, others)
  - Permits FNA (fine needle /aspiration) of lymph nodes

EUS layer	Histologic layer
1st layer Hyperechoic	Superficial mucosa
2nd layer Hypoechoic	Deep mucosa/ lamina propria
3rd layer Hyperechoic	Submucosa
4th layer Hypoechoic	Muscularis propria
5th layer Hyperechoic	Adventitia

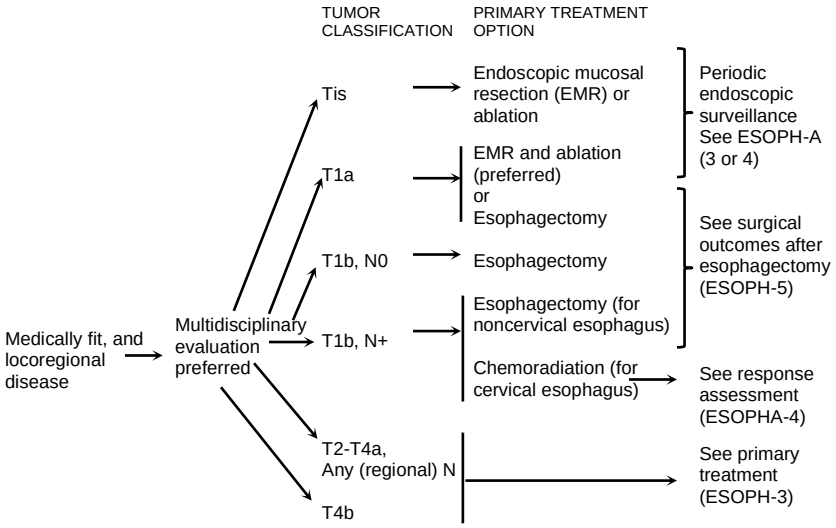
- PET scan (Fluroine 18-fluoro-deoxyglucose [FDG] positron emission tomography)
  - More sensitive than EUS or CT for distant metastases
  - Poor spatial resolution of PET scanning alone may be improved by integrated PET/CT scanning

Esophageal cancer – Treatment

- Stage IV / metastatic disease – palliation (may include chemotherapy)
- For medically fit patient, locoregional disease:

- Give **palliative treatments** for the care of the patient with esophageal carcinoma.
  - Non-endoscopic techniques
    - Surgery
    - Radiation therapy
      - External beam radiotherapy
      - Intraluminal radiotherapy (brachytherapy)
    - Chemotherapy
  - Endoscopic techniques
    - Laser therapy
      - Thermal (Nd:YAG)
      - Photodynamic therapy
    - Dilation
    - Electrocoagulation (BICAP probe)
    - Chemical injection therapy
    - Stent placement
  - Nutritional support
    - Nasoenteric feeding tube
    - Percutaneous endoscopic gastrostomy (PEG)

Printed with permission: Siersema PD. *Nat Clin Pract Gastroenterol Hepatol* 2008;5(3): pg.143.

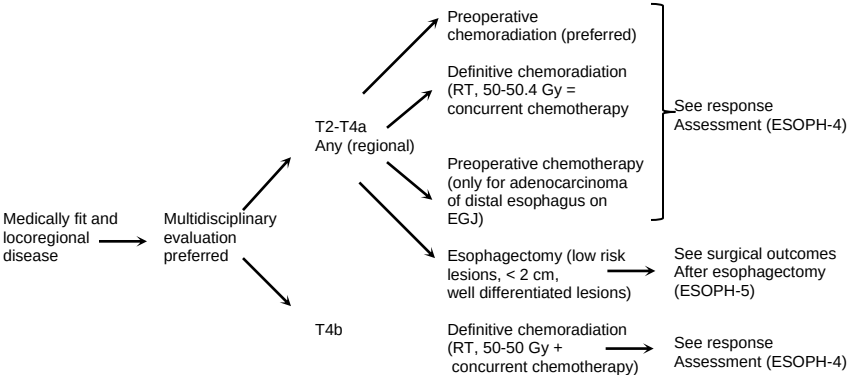


NCCN 2012 Guidelines

Endoscopic ablative therapies

- Photodynamic therapy (PDT)
- Radiofrequency ablation (RFA)
- Cryoablation
- Argon plasma coagulation (APC)
- Laser therapy

- For medically fit, locoregional disease T2 or greater:



NCCN 2012 Guidelines

Esophageal cancer – Post-treatment surveillance

- Endoscopy ≥ 5-6 weeks post pre-operative therapy, with biopsy and brushings
  - Preop chemo-radiation reduces accuracy of EUS staging and of biopsies to diagnose residual disease
  - PET/CT may be emerging as preferred for restaging
- Patients who have had EMR for Tis or T1a disease should have surveillance endoscopy q3m for one year, then annually
  - Biopsies should be taken of the neo-squamous mucosa even in the absence of visible abnormality
  - 4-quadrant biopsies should be taken if Barrett's is suspected
  - Ablation of residual or recurrent dysplasia is recommended
  - Ablation of non-dysplastic Barrett's is not recommended

NCCN 2012 Guidelines

Screening and Surveillance

- Screening for esophageal SCCA cannot be recommended in North America given the low incidence
- Screening for Barrett epithelium (BE) in the general population cannot be recommended at this time; in selected high risk populations, decisions must be individualized (ACG 2008 Guideline)
- Challenges to screening for BE:
  - Inability to predict who will have BE
  - Lack of evidence-based criteria
  - Invasiveness and expense of endoscopy
  - 44% of patients with BE lack GERD symptoms

Surveillance of BE

Dysplasia	Documentation	Follow-up
○ None	– Two EGDs with biopsy within 1 yr	▪ Endoscopy every 3 yrs
○ Low grade	– Highest grade on repeat EGD* with biopsies within 6 mon – Expert pathologist confirmation	▪ 1 yr internak until no dysplasia x2
○ High grade	– Mucosal irregularity – Repeat EGD with biopsies to rule out EAC* within 3 months – Expert pathologist confirmation	▪ ER* ▪ Continued 3 mon surveillance or intervention based on results and patient

* EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy, ER, endoscopic resection;

ACG 2008 Guideline

Other malignant epithelial tumors of esophagus

- Small cell carcinoma
  - 1-4% of all esophageal neoplasms
  - Esophagus is most common site of extrapulmonary small cell
  - Early metastasis common (periesophageal and mediastinal LNs, liver) – 10% one-year survival
  - Surgical resection if no metastatic disease
- Malignant melanoma
  - 0.1% of all esophageal neoplasms
  - Early metastasis common
    - Lymph nodes
    - Liver
    - Lung
  - Very poor prognosis

BENIGN NON-EPITHELIAL TUMORS

Gastrointestinal Stromal Tumors (GIST)

- Pathology
  - Mutational activation of genes
    - KIT
    - PDGFRA
    - DC117
  - Site
    - Stomach ~70%
    - Small bowel ~25%
    - Colon / rectum 5%

- Malignant potential
  - All GISTs > 10 m
- Immunohistochemical (IHC) studies

- Give how to distinguish GIST from leiomyomas (LM) and leiomyosarcomas (LMS).

IHC antibody	GIST	LM / LMS
C-kit (CD117)	+	-
Smooth muscle actin	-	+
Desmin	-	+

Note: EUS / FNA rather than IHC will differentiate between leiomyoma and leiomyosarcomas

- Diagnosis
  - EUS plus FNA

- Laboratory
  - C-kit (a stem cell factor receptor) (~99%)
    - CD34 (a hematopoietic cell progenitor cell antigen) (70%)
    - Smooth muscle actin (20% to 30%)
    - S 100 protein (marker of neural differentiation)

- Treatment
  - Medical
    - TK (tyrosine kinase) inhibitors, e.g. imatimib, used as adjuvant or no adjuvant therapy (before surgical resection)\
      - GISTs ≥ 3 cm
      - ↓ GIST recurrence is post-op yr 1

- Surgical
  - Segmental resection for ≥ 2 cm; leaving the tumor pseudocapsule intact
  - Obtain negative tumor resection margins
  - Laroscopic resection if possible

- Types of GIST of esophagus
  - Leiomyomas
    - Commonest stromal tumor
      - Endogastric (grow into the lumen)
      - Mid- or lower- third of esophagus
    - Perform at least annual EUS for small tumors
  - Polypoid leiomyomas < 2 cm endoscopic snare resection

- Treatment
  - Surgical resection
    - Symptoms
    - > 1 cm
    - Structural changes from previous EUSs
    - Open en bloc esophagectomy for
      - Tumor ≥ 2 cm
      - Involvement of GE junction
  - Leiomyosarcomas
    - May require partial or total esophagectomy
  - GCTs granular cell tumors, aka schwannomas submucosal, hypoechoic on EUS, layer 243, 5-100 protein positive on IHC

- Postsurgical follow-up (suggested, but not evidence-based)
  - GIST
    - Clinical (history & physical)
      - Every 3 month to 6 month for 5 years, then every yr
    - CT scan
      - Every 3 months to 6 months for 3 years to 5 years, then every year

- Leiomyosarcoma
  - Clinical & CT
    - Every 3 months to 6 months for 2 years to 3 years, then every year
    - Consider regular imaging of the chest
  - If margins of resected leiomyosarcoma are positive, perform follow-up as above, only more intense long-term:
    - Every 3 months to 6 months for 2 years to 3 years
    - Then every 6 months for 2 years, then every year

Granular Cell Tumor

- Often in esophagus (mid- and lower- third)
- EUS layer 2 or 3
- Hypoechoic on EUS
- Homogeneous
- Usually benign unless > 4 cm
- IHC (immunohistochemistry) – S -100 protein positive

Duplication Cysts

- Usually in proximal small intestine
- May or may not communicate with the lumen
- Epithelium
  - Squamous
  - Columnar, or
  - Ciliated
- Contain mucoid fluid
- Usually benign

Fibrovascular Polyp

- Most commonly in the upper third of the esophagus, near the cricopharyngeus muscle
- EUS-assisted endoscopic snare resection can be considered for small polyps
- Surgery for large symptomatic polyps

Lipoma

- EGD/C
  - Single indentation of mucosa
  - Yellowish
  - Smooth
  - Easily indented (“pillow” sign, aka “cushion” sign; sensitivity o 40%, specificity of 99%)
- Easily tented (mucosa can be piled away from submucosal growth by gently tugging on mucosa biopsy forcep; known as “tenting” sign)
- EUS
  - Layer 1,3*,5 (hyperechoic – light)

Neuroendocrine (Carcinoid) tumor (NET)

- EGD / C commonest sites (in USA)
  - Appendix
  - Rectum

    } usually are single

  - Ileum
  - Stomach

    } often are multiple

- EUS
  - Usually layer 2
  - Hypoechoic
  - Homogeneous

Malignant non-epithelial tumors

- Lymphoma
  - Primary lymphoma of esophagus is very rare, except in the setting of AIDS
  - More commonly affects esophagus via external compression from involved mediastinal lymph nodes
- Metastatic carcinoma
  - Unusual, two most common sites of origin are
    - Melanoma
    - Breast
  - EUS-guided FNA useful to confirm diagnosis

Esophageal Cancer

Yacoub Alawadh

- Demography
  - Incidence rates vary internationally by nearly 16-fold
  - The highest rates found in Southern and Eastern Africa and Eastern Asia
  - The lowest rates in Western and Middle Africa and Central America in both males and females
  - Incidence vary for the two major histologic types of esophageal cancer
  - Highest-risk area
    - Northern Iran through the central Asian republics to North-Central China
    - 90 percent of cases are SCCA
    - Poor nutritional status, low intake of fruits and vegetables, and drinking beverages at high temperatures
  - Low-risk areas
    - Such as the United States and several Western countries,
    - Smoking and excessive alcohol consumption account for about 90 percent of the total cases of esophageal SCCA

Cancer statistics, 2014. Siegel R, Ma J, Zou Z, Jemal A CA Cancer J Clin. 2014;64(1):9.

  - Incidence rates for adenocarcinoma of the esophagus have been increasing in several Western countries, in part due to increases in known risk factors such as
    - Overweight
    - Obesity.

- In contrast, rates for SCCA have been steadily decreasing in these same countries because of long-term reductions in
  - Tobacco use and
  - Alcohol consumption

➢ Etiologic

- Squamous cell carcinoma (SCCA)
  - Demographic and socioeconomic factors
    - Lower socioeconomic status was associated with esophageal SCCA
  - Smoking and alcohol
  - Dietary factors
    - Foods containing N-nitroso compounds eg pickled vegetables
  - Underlying esophageal disease
    - Eg. achalasia and caustic strictures
  - Tylosis
    - Hyperkeratosis of the palms of the hands and soles of the feet
  - Bisphosphonates
  - Upper aerodigestive tract cancer
    - Association between a current or past history of SCCA of the head and neck
  - Celiac disease

Pottern LM, Morris LE, Blot WJ, Ziegler RG, Fraumeni JF Jr. Esophageal cancer among black men in Washington, D.C. I. Alcohol, tobacco, and other risk factors. J Natl Cancer Inst 1981;67(4):777.

Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr, Doll R. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997;337(24):170.

Lu SH, Montesano R, Zhang MS, Feng L, Luo FJ, Chui SX, Umbenhauer D, Saffhill R, Rajewsky MF. Relevance of N-nitrosamines to esophageal cancer in China. J Cell Physiol Suppl 1986;4:51.

- Adenocarcinoma
  - GERD
  - Smoking
  - Obesity
    - Indirect risk factor for both esophageal adenocarcinoma and Barrett's esophagus because it increases the risk of GERD

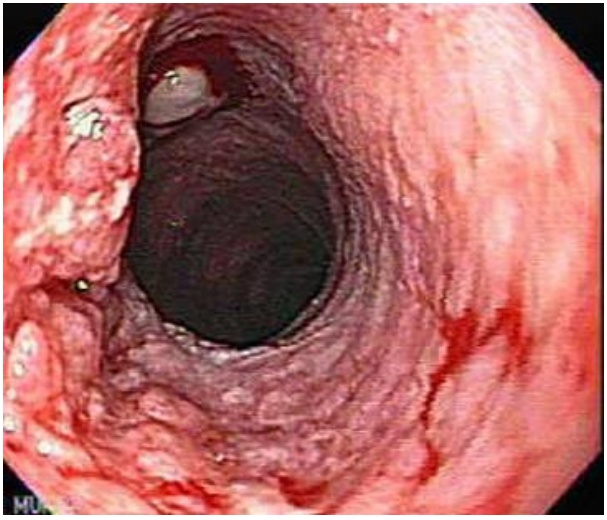
Bytzer P, Christensen PB, Damkier P, Vinding K, Seersholm N. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. Am J Gastroenterol. 1999;94(1):86.

Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010;102(17):1344.

Lagergren J, Bergström R, Nyrén O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med. 1999;130(11):883.

➢ Pathology

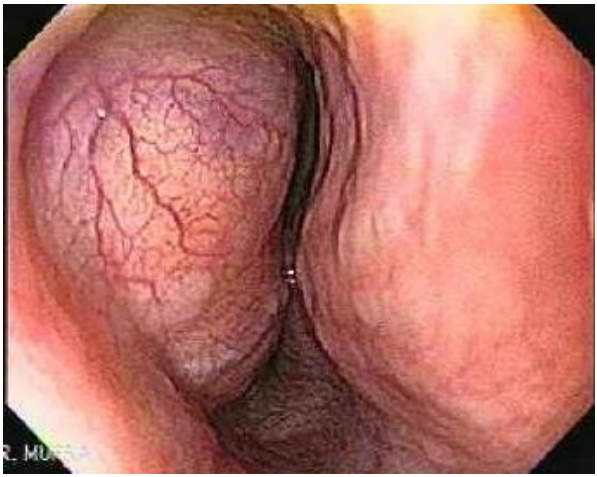
- Gross endoscopy

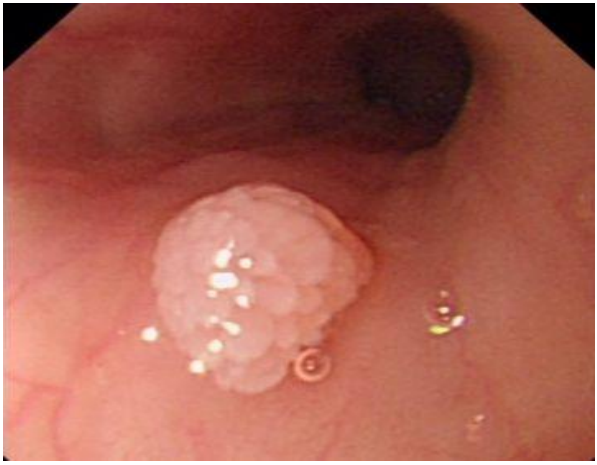


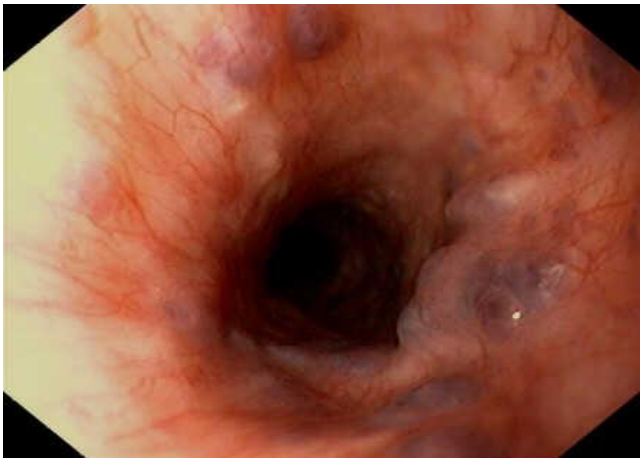
➢ Differential diagnosis of esophageal mass

- Epithelial tumors
  - Malignant
    - SCCA
    - Adenoca.GEJ
  - Benign
    - Squamous papilloma
    - Inflammatory fibroid polyp
- Non epithelial tumors
  - Malignant
    - GIST/sarcoma
    - Lymphoma

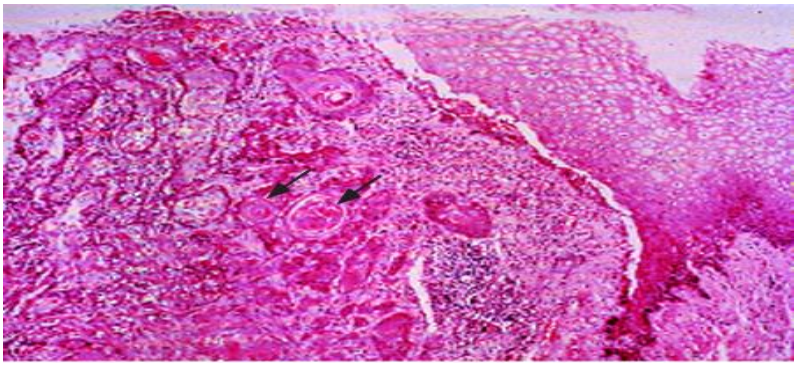
- Benign
  - GIST
  - Fibrovascular tumor
  - Leiomyoma
  - Granular cell tumor
  - Hemangioma



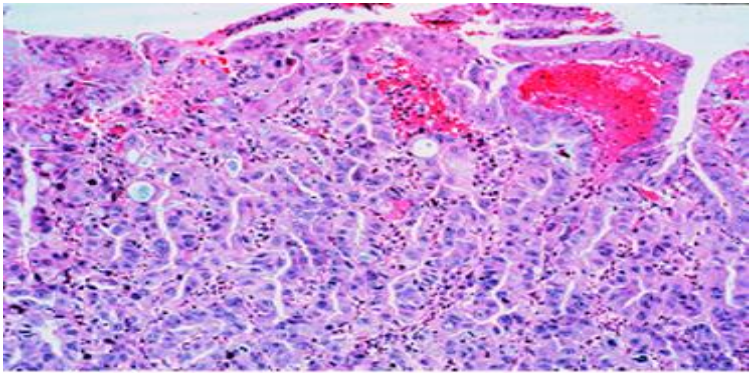




- Histopathology



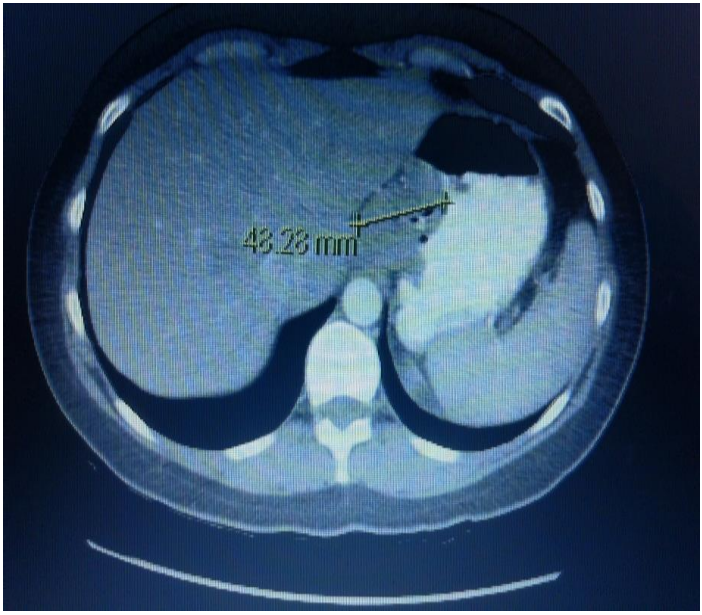
Squamous Cell Carcinoma

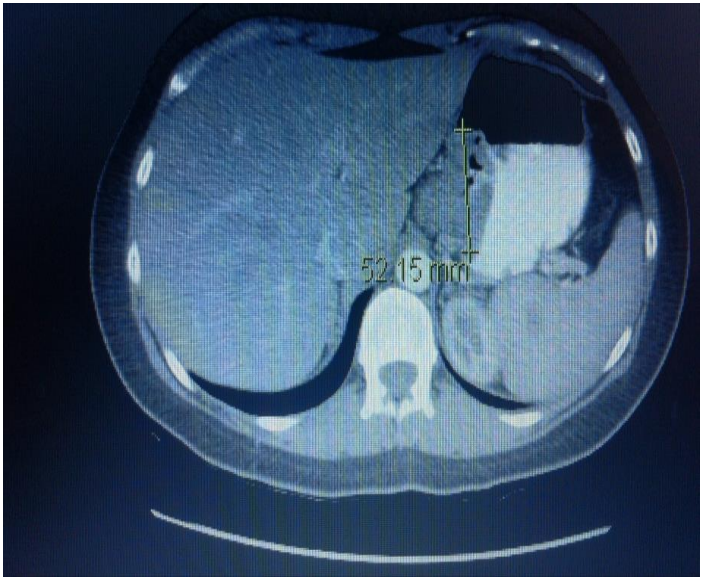


Adenocarcinoma

- Clinical features
  - Adenocarcinoma and SCCA have similar clinical presentations
  - Progressive solid food dysphagia
  - Weight loss.
  - Retrosternal discomfort
  - Aspiration pneumonia is infrequent. Hoarseness may occur if the recurrent laryngeal nerve is invaded.
  - Iron deficiency anemia
  - Tracheobronchial fistulas are a late complication
    - Present with intractable coughing or frequent pneumonias
  - Acute UGIB is rare
    - As a result of tumor erosion into the aorta or pulmonary or bronchial arteries.

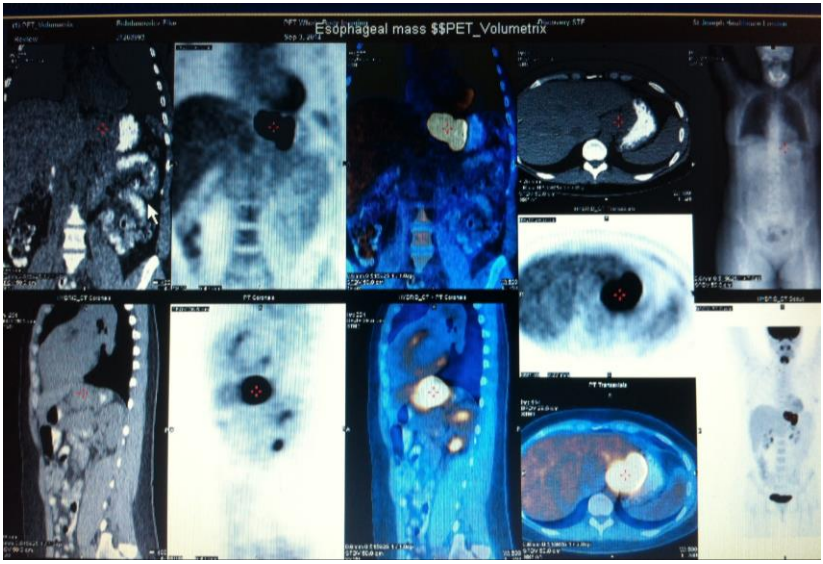
- Diagnostic imaging
  - CT Chest/Abd (with IV and oral contrast)
    - Evaluate for the presence of metastatic disease
    - Large ulcerated irregular mass identified in the distal esophagus at the level of GE junction with extension into the proximal portion of the stomach (4.2x5.2x4.8)
    - No mediastinal or paraeophageal lymphadenopathy
    - No evidence of enlarged gastrohepatic lymph nodes or hepatic mets
    - No pericardial effusion and the aorta and central pulm arteries are unremarkable





- EUS
  - Most accurate technique for locoregional staging of invasive esophageal cancer with an overall accuracy for (T) and (N) staging of 80 to 90 %
  - Allows assessment of both perigastric and mediastinal lymph nodes,

- PET/CT
  - Detect metastatic disease in patients who are otherwise believed to be surgical candidates
  - Restaging after initial induction therapy
  - Hypermetabolism distal esophageal mass extending to the distal portion of the stomach consistant with primary esophageal Ca
  - No focal hypermetabolism is seen to suggest local or distant metastasis



- Rigid bronchoscopy
  - For patients with supracarinal primary tumors, including those involving the middle third of the esophagus

- CT or magnetic resonance imaging (MRI) of the brain
  - For patients who have symptoms referable to the central nervous system

- Treatment

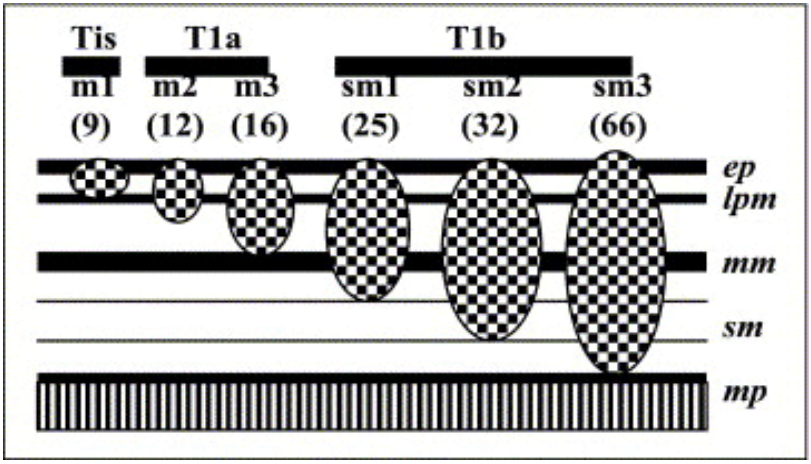
- Stage (AJCC Stage Grouping)
  - Early esophageal cancers
    - Tis or T1 (STAGE 0,1)
  - Locally advanced cancer
  - Locally advanced unresectable cancer
    - T4,M1a,M1b (ie STAGE III,IV)

- Options
  - Endoscopic Therapy
  - Surgical Therapy
  - Radiation Therapy and Chemotherapy
  - Endoscopic Palliative Therapy
    - Dilatation and SEMS
    - Ablative
      - Laser therapy
      - PDT
      - APC
      - Cytotoxic Injection therapy

Early Esophageal Ca (limited to the mucosa or submucosa, T1)

- Two major treatment options for early esophageal cancer
  - Surgical esophagectomy
  - Endoscopic resection
    - EMR
    - ESD (endoscopic submucosal dissection)
- Depth of tumor invasion into the wall of the esophagus is an important factor in selecting treatment

Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57(9):1200.



- M1, M2 and well-differentiated M3 tumors without lymphovascular invasion
  - Esophagectomy, or
  - Endoscopic mucosal resection (EMR)
- Fit patients with submucosal (T1b) cancer
  - Esophagectomy (better than EMR)
- Superficial esophageal cancer ineligible for endoscopic therapy (because of
  - Presence of varices,
  - Previous perforation,
  - Severe cervical spine disease
  - RT and/or chemoradiotherapy
- T1N0 esophageal or EGJ adenocarcinoma is less clear
  - Benefit of preoperative chemoradiotherapy

Locally Advanced Resectable Cancer

- Surgical resection
  - Total esophagectomy with cervical esophagogastrostomy plus a partial gastrectomy
  - Ivor-Lewis procedure, with a thoracic esophagogastrostomy. (laparotomy with a right thoracotomy)
- The indications for an esophagectomy as the initial therapeutic approach to the patient with an esophageal cancer include:
  - Clinical T1N0M0 lesions
  - Clinical T2N0M0 lesions
- The indications for induction therapy first, followed by an esophagectomy include:
  - Full-thickness (T3 or T4) involvement of the esophagus with/without nodal disease
  - Patients with esophageal cancer invasion of local structures (pericardium, pleura, and/or diaphragm only) that can be resected en bloc, without evidence of metastatic disease to other organs (eg, liver, colon).
- Esophagectomy post-adjuvant therapy — Patients who tolerate their induction well and have a response by CT scan, radiographic evaluation, and endoscopy are generally candidates for a surgical resection four to six weeks following completion of the chemotherapy or chemoradiotherapy

Locally Advanced, Unresectable Esophageal SCCA or Adenocarcinoma

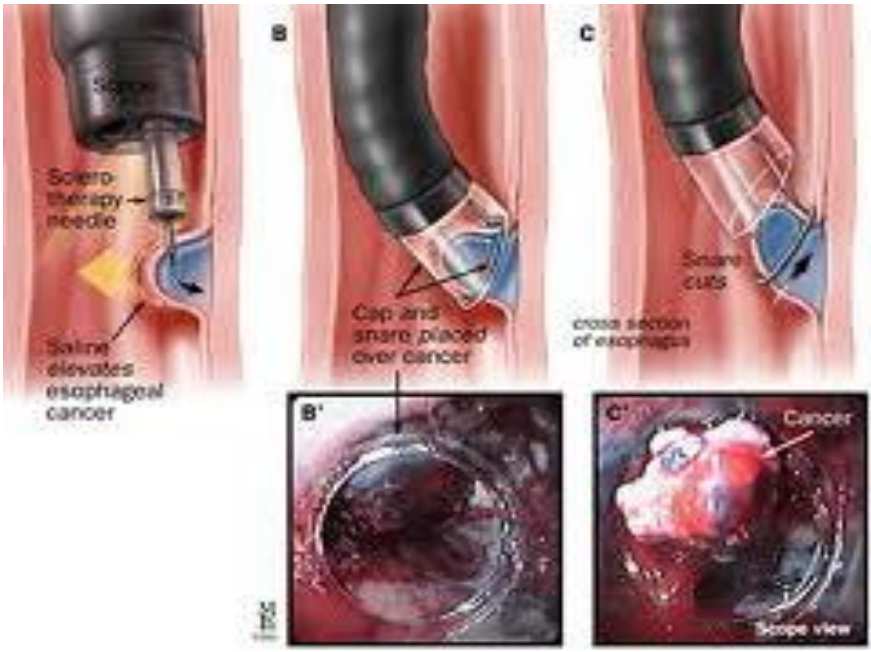
- Distant metastases
- Unresectable primary disease (ie T4b)
  - Thoracic or abdominal esophagus
    - Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc
  - Cervical esophageal tumors
    - Infiltration into the prevertebral fascia or posterior larynx,
- Incurable in the majority of patients.
- Goal of treatment is improvement in quality of life
- Concurrent chemoradiotherapy rather than radiation therapy (RT)
- Palliation
  - Restoring and/or maintaining the ability to swallow and sustaining adequate nutrition
- May be appropriate in the following setting
  - Failure to achieve adequate palliation of dysphagia with initial therapy
  - Recurrent dysphagia due to locoregional failure
  - Recurrent dysphagia due to benign strictures in patients who are successfully treated with RT
  - Patients are poor candidates for either chemotherapy or RT
- Options
  - Placement of a prosthetic self-expanding metal stent (SEMS)
    - For patients with a malignant stricture and/or fistula

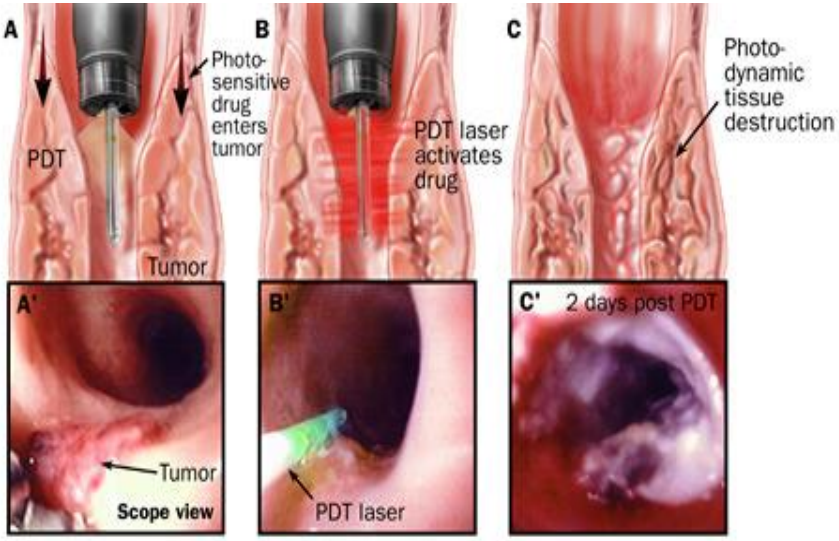
- Dilation
  - Esophageal dilatation with either through-the-scope balloon or wire
  - guided polyvinyl bougies can provide temporary relief of dysphagia.
  - Most malignant strictures can be safely dilated to 16 or 17 mm in
  - several sessions
  - Repeat dilatation is usually required every three to four weeks

Boyce HW Jr. Palliation of Dysphagia of Esophageal Cancer by Endoscopic Lumen Restoration Techniques. Cancer Control. 1999;6(1):73.

- Ablative
  - Laser therapy
  - Endoscopic injection therapies
  - Endoscopic mucosal resection (EMR)
    - EMR are available for patients with
      - Early stage tumors
      - Too ill to undergo surgery or who refuse surgery
    - Technique: Involves lifting of the mucosa by submucosal injection of saline and endoscopic suction into an overtube in which a snare is fitted, with subsequent snare removal of the tumor
  - Photodynamic therapy (PDT)
    - A tissue ablative technique, uses a photosensitizing agent in combination with endoscopic low power laser exposure.
    - Only one photosensitizing agent, Porfimer sodium (Photofrin, Lederle Parenterals, Carolina, PR), is currently available in the United States.

- Porfimer sodium is a hematoporphyrin derivative, which is approved for the palliation of esophageal cancer.
- PDT with porfimer sodium is thought to have a direct toxic effect on malignant cells via the production of singlet oxygen, which damages the microvasculature of the tumor and renders it ischemic

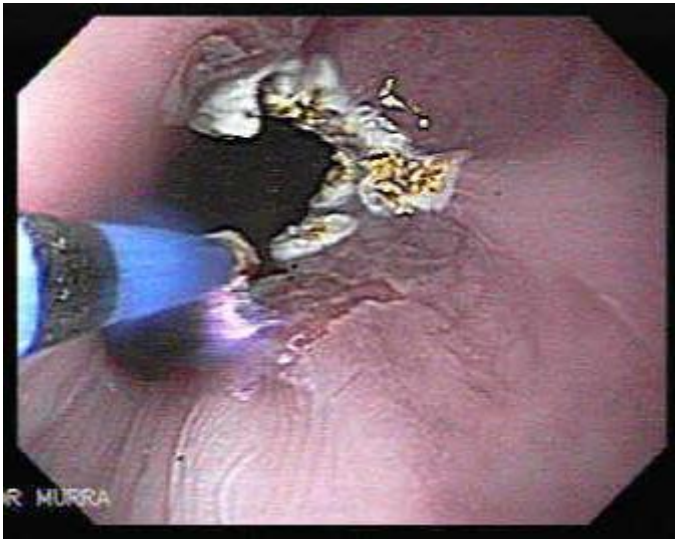




- APC
  - Control slow hemorrhage from friable tumor masses
  - Treating tumor in-growth in esophageal stents

Eickhoff A, Jakobs R, Schilling D, et al. Prospective nonrandomized comparison of two modes of argon beamer (APC) tumor desobstruction: effectiveness of the new pulsed APC versus forced APC. Endoscopy. 2007;39(7):637.

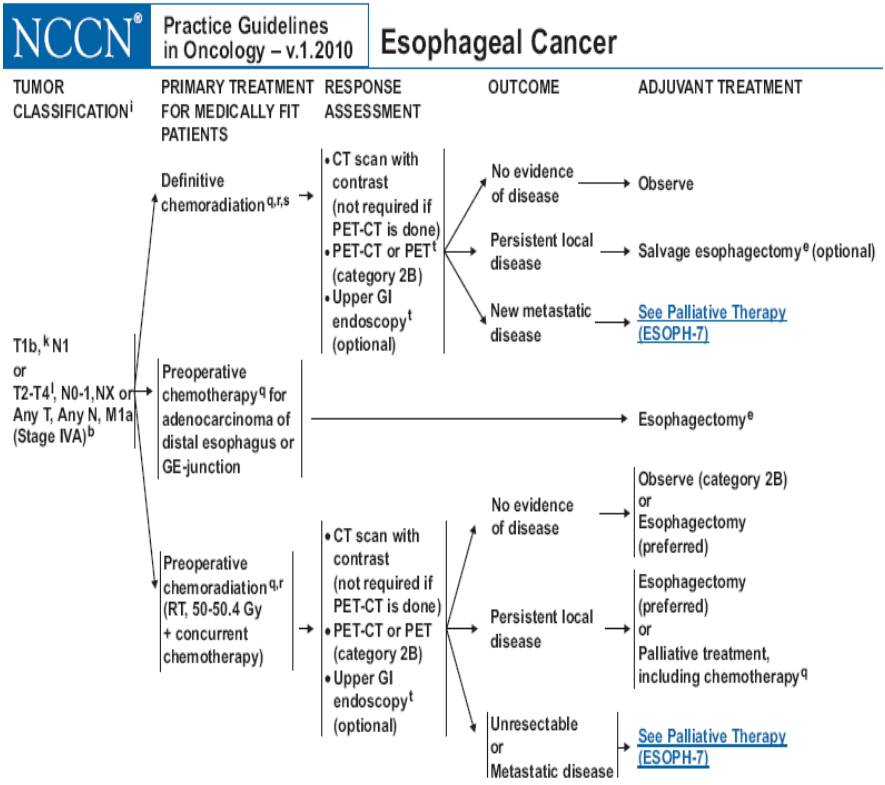
Rupinski M, Zagorowicz E, Regula J, et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). Am J Gastroenterol. 2011;106(9):1612.



- Brachytherapy
  - Treatment of a localized area of the esophagus to high radiation doses, with relative sparing of surrounding structures.
  - It should be considered an alternative to stent placement for palliation of dysphagia, particularly when the extent of extraluminal disease is limited and long-term palliation is likely.
  - Although stenting has the advantage of palliating dysphagia immediately, the palliative effect of brachytherapy is frequently more durable
  - Its use should be restricted to patients with a short life expectancy (less than six months).
  - For patients who are expected to live less than three months, short-term palliation of swallowing may be better achieved with endoscopic stent placement.

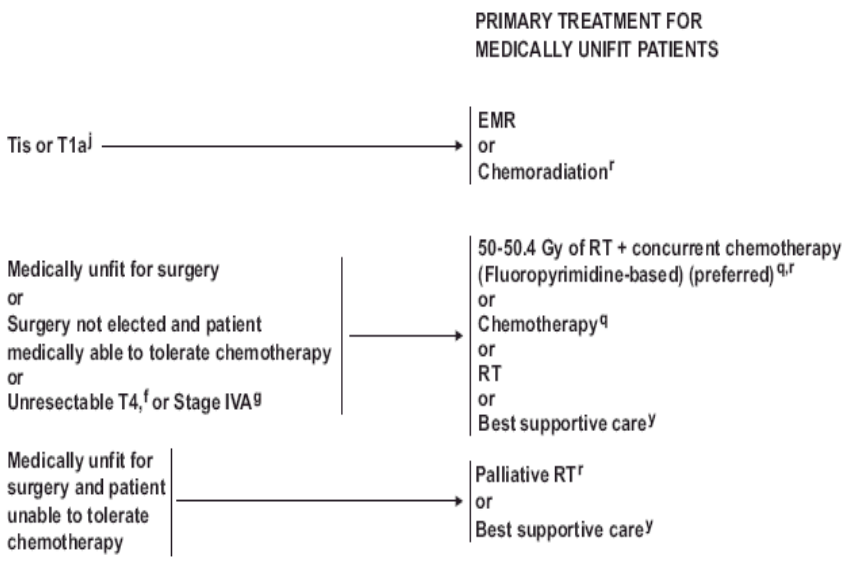
- Brachytherapy should be used with extreme caution in the setting of a local recurrence after prior chemoradiotherapy because of the risk of fistula formation.
- Brachytherapy alone can provide successful long-term palliation of dysphagia in patients with unresectable and/or advanced esophageal cancer

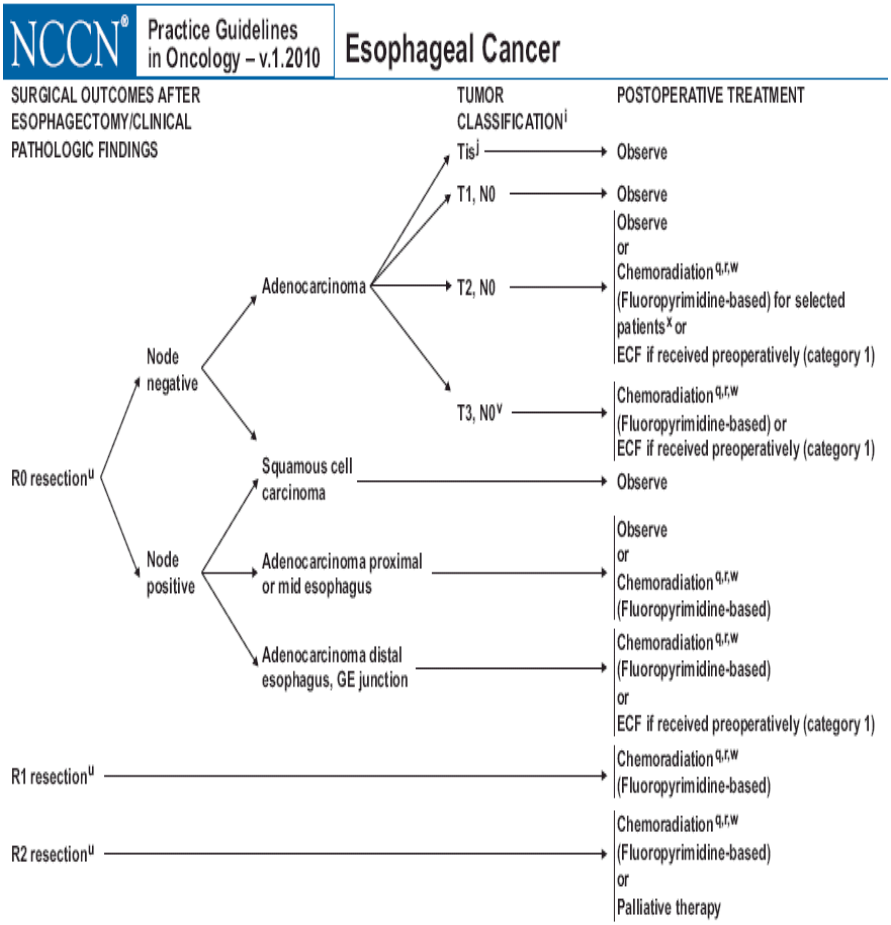
➢ Practice Algorithm



NCCN® Practice Guidelines in Oncology – v.1.2010

Esophageal Cancer




NCCN
Practice Guidelines in Oncology – v.1.2010
Esophageal Cancer
SURGICAL OUTCOMES AFTER ESOPHAGECTOMY/CLINICAL PATHOLOGIC FINDINGS
TUMOR CLASSIFICATION[i]
POSTOPERATIVE TREATMENT
R0 resection[u]
Node negative
Adenocarcinoma
Tis[j]
Observe
T1, N0
Observe
T2, N0
Observe or Chemoradiation[q,r,w] (Fluoropyrimidine-based) for selected patients[x] or ECF if received preoperatively (category 1)
T3, N0[v]
Chemoradiation[q,r,w] (Fluoropyrimidine-based) or ECF if received preoperatively (category 1)
Squamous cell carcinoma
Observe
Node positive
Adenocarcinoma proximal or mid esophagus
Observe or Chemoradiation[q,r,w] (Fluoropyrimidine-based)
Adenocarcinoma distal esophagus, GE junction
Chemoradiation[q,r,w] (Fluoropyrimidine-based) or ECF if received preoperatively (category 1)
R1 resection[u]
Chemoradiation[q,r,w] (Fluoropyrimidine-based)
R2 resection[u]
Chemoradiation[q,r,w] (Fluoropyrimidine-based) or Palliative therapy

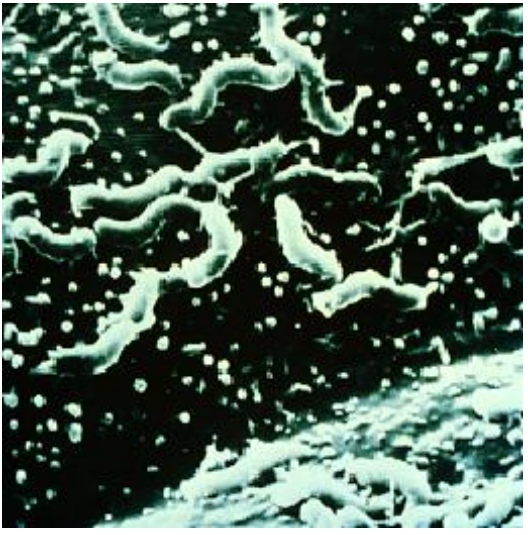
STOMACH

Helicobacter Pylori

Dan Segal

H PYLORI

- *H. pylori* is a spiral shaped, micro-aerophilic, gram negative bacterium measuring approximately 3.5 microns in length and 0.5 microns in width
- In 1982, Marshall and Warren identified and subsequently cultured the gastric bacterium, *Campylobacter pyloridis*, later reclassified as *Helicobacter pylori* (*H. pylori*)
- Slow growing
- Spiral shaped
- Catalase +
- Oxidase +
- Urease +



- Demography

  - 50 % of world infected
  - Humanity infected for 58,000 years
  - More common in developing countries
    - Acquired at early age, before age 10
    - Cycles of eliminated and reinfection
    - Upwards of 80% infected
  - Developed countries have less disease
    - Rate of infection reflects rate of acquisition during childhood
  - While about 50% of the world's population have an H. pylori infection, but only about 15% develop peptic (gastric or duodenal) when disease, and ~1% develop gastric cancer or MALT lymphoma. So, there a disconnect between H. pylori infection in the stomach, and H. pylori-associated diseases
  - Hp positive parent
    - Spouse 68% Hp^+
    - Children 40% Hp^+
  - Hp negative parent
    - Spouse 9% Hp^+
    - Children 3%Hp^+
  - Community Risk
    - Adults - approximately 25-30% (depends on person's age)
    - Higher (30%) in older persons
    - >50% First Nations Canadians, new Canadians from high Hp prevalence areas
    - New Canadians from high prevalence countries

- What predisposes to infection?
  - Crowded living conditions
  - Low socioeconomic status
  - Improving sanitation and hygiene leads to less h. pylori
- Perhaps organism will become extinct
- Transmission
  - Humans are major reservoir
  - Other mammals can harbor infection
  - Don't kiss your cat
  - Viable in contaminated water for days
  - Bottom line = likely oral-oral, fecal-oral
    - Evidence of transmission from household contacts
  - GIs are at increased risk of acquring disease

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

  - Modes of transmission of Hp
    - Gastro-oral vomitus-oral, fecal-oral
  - H. pylori-associated diseases
    - H. pylori may be
      - Associated with, or causative of GU and DU
      - Worsen chance of developing ASA / NSAID-associated GU / DU
      - Worsen effect of smoking on slow healing of peptic ulcer, and higher risk of relapse of ulcer

    (Note: once associated H. Pylori infection has been cured, smoking loses these adverse on ulcer healing and relapse.
      - ↑ risk of ulcer relapse (80% for H. pylori +, 10% for H. pylori-)

- Pathogenesis
  - pH is not a problem
    - Urease hydrolyzes luminal urea to form ammonia
    - Ammonia neutralizes gastric acid forming safe pocket
    - Will move urea within organism to maintain favourable pH
  - Gets into mucus layer
    - Spiral shape
    - Flagella
    - Mucolytic enzyme
    - Basically a corkscrew that is propelled through the mucus while chewing it up
  - Attaches to surface
    - Uses specific receptor mediated adhesion
    - Maybe susceptible hosts express specific receptors that H Pylori likes
    - Attaches to surface
    - Lewis antigens are the mucosal ‘dock’
    - BabA is the bacterial ligand
    - Le and BabA are not the only attachment factors
    - Other implicated proteins include class II MHC, toll-like receptors
  - Survival
    - Decreases expression of antibacterial molecules
  - Hostile actions
    - Bacteria damages epithelium in order to obtain nutrients from inflammatory exudate
    - Cag PAI (segment of DNA) encodes protein that allow bacterial molecules to get into host cell
      - cagE = trojan horse
    - Clear relationship between inflammatory cascade and cagE

- Another implicated protein in attachment and virulence is VacA
  - Cytotoxin causing apoptosis

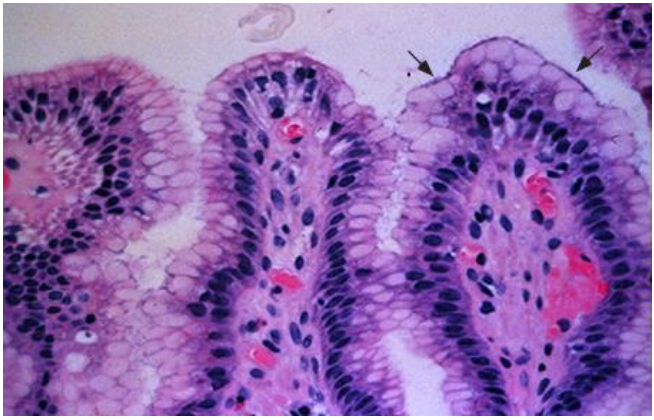
- Role of bacterial enzymes
  - Urease products (Ammonium Chloride) damages epithelium
  - Bacterial phospholipases alter epithelial barrier
  - Catalase enzyme, an anti-oxidant, protects bacteria from host response
  - Proteolytic enzyme

- Host Response
  - The host response is the major cause of disease
    - IL-1beta polymorphisms affect rate of gastric cancer
  - The body attacks!
    - Change epithelial cell morphology
    - Produce cytokines
    - Increase cell proliferation and apoptosis
    - Most studied regulators of response are nuclear factor kappa B (NF-kB) & activated protein 1 (AP-1)

- Cytokines, B cells, and T cells oh my!
  - Disruption of epithelial barrier allows immune system to sample allogenic H pylori epitopes
  - Increased production of IL-1, IL-6, TNF-alpha
  - B cell response, T cell response
  - Increased IgA, IgG, IgM

- Bottom line
  - H Pylori wins titanic battle and persists for life of host unless Abx intervention
  - Immunity is not achieved, impaired T cell response

- Histopathology
  - Infection = Gastritis
    - Much of the damage due to immune response
    - Chronic and active with lymphocytes and macrophages
    - Only colonize stomach (usually antrum) or areas with gastric metaplasia
  - Forms basis for all types of H Pylori associated disease



- Clinical
  - Most infected pts are asymptomatic
  - 10-15% develop PUD, adenocarcinoma, or MALT lymphoma
  - ↓ incidence of Barrett esophagus and esophageal cancer
  - Other associations:
    - Raynaud phenomenon
    - Idiopathic urticarial
    - GBS
    - ITP

- Testing and Treating

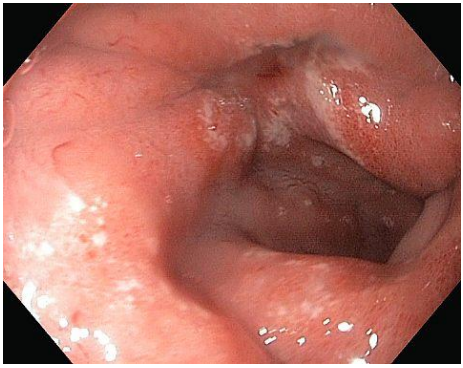
  - Guideline – don't test for H. pylori unless you intend to treat the infection

Indications for diagnosis and treatment of H.pylori

- Established
  - Active peptic ulcer disease
- Controversial
  - Non-ulcer dyspepsia
  - Gastroesophageal reflux disease
  - Persons using nonsteroidal anti-inflammatory drugs
  - Unexplained iron deficiency anemia
  - Populations at high risk for gastric cancer

PEPTIC ULCER DISEASES

- H Pylori present in 80 -95% of DU patients
  - U.S 50-75%
  - OR of 4.0-5.0 for ulcer (predictive)
- Pathogenesis:
  - ↑ gastric acid secretion
  - Elevated gastrin
  - ↑ effect on parietal cells and histamine secreting cells
  - Gastric metaplasia (DU)
    - ↑ gastric acid secretion → lower luminal pH
    - Protective metaplasia
    - H Pylori infection
  - Immune response



- How does H. pylori cause DU?
  - Antrum D cells ↓ - ↓ S - ↓ inhibition of G cells - ↑ G - ↑ HCl - ↑ metaplasia – H. pylori in metaplasia H. pylori infection develops in metaplasia of the duodenum.
  - Why is the rate of symptom relief with Hp-triple therapy higher for dyspepsia in functional dyspepsia in functional dyspepsia with an EGD, than in uninvestigated dyspepsia.
    - EGD shows an ulcer, so pretest probably for symptom relief is higher.

- Hp-associated GI diseases
  - Non-ulcer dyspepsia
  - Acute/chronic gastritis
  - Atrophic gastritis (AG) – acceleration with PPI of AG-IM-Dys-GCa → intestinal metaplasia (IM) → dysplasia (Dys) → GCa (non-cardia gastric cancer)
  - Duodenal and gastric ulcer (DU and GU) (only ~20% of Hp^+ persons develop clinical disease)
  - Accentation of effect of smoking on PUD
  - Accentuation of ASA/NSAID effects on peptic PUD
  - Maltoma

- Fundic gland polyps
- Hypertrophic gastric folds
- Protective against GERD (possible)
- Halitosis
- Carcinoid tumours
- Colorectal cancer (possible association, due to hypergastrinemia)
- Pancreatic cancer (possible association)

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

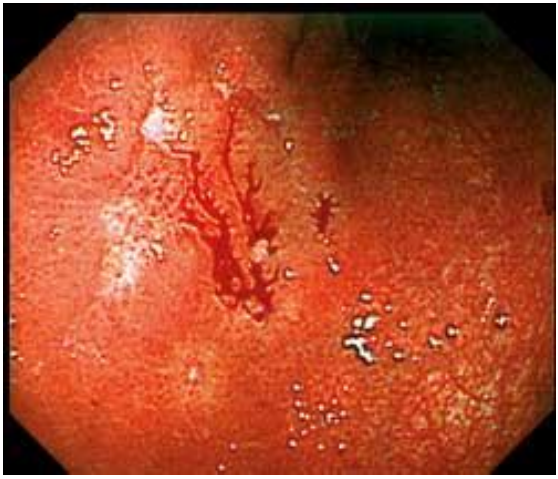
Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DU, duodenal ulcer; GCa, gastric cancer; GERD, gastroesophgeal reflux disease; GU, gastric ulcer; ITP, idiopathic thrombocytopenic purpura; PUD, peptic ulcer disease; SIDS, sudden infant death syndrome.

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

- 12 month ulcer remission rate with HP Rx:
  - 97% gastric ulcer vs. 61%
  - 98% duodenal ulcer vs. 65%
- Rx cost effect for duodenal ulcer after one year, and gastric ulcer over 2 years
- Rx reduces recurrent ulcer bleed from 17% to 4% compared with acid suppression alone
- Do not need ongoing PPI post HP eradication

MALT Lymphoma

- Gastric MALTomas are due to clonal expansion of B cells as a result of chronic gastritis
- HP leads to accumulation of B cells
- HP antigens drive ongoing evolution of disease
- 90% + are HP positive



- HP Rx results in tumor regression in 60-90% of patients
- Longstanding remission
- Perhaps role for HP Rx in HP positive DLBCL gastric tumor

Uninvestigated dyspepsia

- Test and treat strategy endorsed by Canadian and American guidelines
- CADET-Hp, BMJ 2002:
  - ARR 14% when treating HP positive pts versus PPI alone
- Manes G, BMJ 2003:
  - HP eradication reduced endoscopic procedures

H. pylori-associated Non-ulcer Dyspepsia

- Definition
  - Upper gastrointestinal symptoms without and no evidence of structural disease to explain symptoms
- Meta-analysis
  - Eradication of H. Pylori offers 8% benefit for NNT 15!
- Perhaps side benefit of prophylaxis against future ulcers
  - Decreased incidence of subsequent ulcers in NUD
- Decision to Rx should include risk of ulcers and malignancy

Gastroesophageal Reflux Disease (GERD)

- GERD & H Pylori relationship is confusing
- ↑ acid with antral HP
  - Eradication may improve GERD
- ↓ acid with corpus HP
  - Eradication may worsen GERD
- Bottom Line: eradication does not seem to effect GERD

H. pylori and NSAIDs

- *H. pylori* infection and NSAIDs independently and synergistically increase risk for peptic ulcer disease
  - based on systematic review of 25 studies
  - HP + NSAIDs vs NSAIDs (41.7% vs. 25.9%, OR 2.12, 95% CI 1.68-2.67)
  - HP + NSAIDs vs neither (OR 61.1; 95% CI 9.98-373)
  - risk of ulcer bleeding increased
    - 1.79 times with *H. pylori* infection
    - 4.85 times with NSAID use
    - 6.13 times with both factors
  - Still PPI may be just as good in preventing PUD in HP positive individual on NSAID

- Give recommended indications for *H. pylori* eradication therapy (ET) in the patient taking NSAIDs or ASA.
  - Reduce PUD formation
  - Reduce recurrent PUD
  - Reduce recurrent PUD bleeding (in ASA or NSAID high risk users) (ET does not prevent further PUD bleeding in high risk ASA/NSAID users on PPI)

Abbreviation: ET, eradication therapy

Adapted from: Lai LH, and Sung JJY. *Best Pract Res Clin Gastroenterol* 2007; 21(2): pg. 270.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

SST (somatostatin) and gastrin are produced with the gastric antrum, and gastric acid is secreted by the parietal cells in the gastric body.

- Give the explanation why gastric acid secretion falls with acute or chronic H. pylori pancreatits, yet why gastric acid secretion rises with antral gastritis.

➢ Acute or chronic H. pylori pangastritis
  - H. pylori
    - Directly
      - ↓ gene expression of parietal cell H^+ / K^+ - ATPase α-subunit
      - ↓ gastrin release
      - ↓ duodenal HCO_3^-
    - Indirectly
      - Produces anti-secretory cytokines IL-1β and TNF-α
      - Activates CGRP sensory neurons → ↑ SST (somatostatin) → ↓ gastrin
      - ↓ HCl secretion for body parietal cells

➢ Chronic H. pylori antral gastritis
  - ↓ SST
    - Proinflammatory / prosecretory cytokines
    - Prosecretory H_3 agonist (N^3-methyl histamine)
  - ↑ gastrin (from ↑ SST, and from ↑ IL-8 and PAF
  - ↑ gastrin → ↑ ECL cells in fundus / body → ECL hyperplasia
  - ECL hyperplasia → ↑ HCL secretion from parietal cell antibodies

- Combine anti-H. pylori therapy with PPI to
  - ↑ anti-H. pylori effect of antibiotics
  - Accelerate improvement of ulcer healing and symptom relief
- Optimal pH for outcomes for different upper GI disorders (18 hours per day)

≥ 3	GU, DU
4	GERD
5	H. pylori eradication
6	Non-variceal upper GI bleeding

- Recent meta-analysis does not show a statistical difference in H. pylori eradication rates using either triple or quadruple therapy (RR = 1.002; 95% CI 0.936-1.073)
- None of the H. pylori treatment guidelines endorse sequential therapy (Chey 09). Another meta-analysis showed 93% eradication rate with sequential therapy versus 74% for clarithromycin-based triple therapy, particularly in persons with clarithromycin-resistant strains of H. pylori.
- Meta-analysis has shown superiority of a 10-day course of levofloxacin-based triple therapy vs a 7 day course of bismuth-based quadruple therapy (rr = 0.51; 95% CI: 0.34-0.75) for persistent H. pylori infection
- Rifampin has been used as an alternative to clarithromycin, with eradication rates of 38-91%. There may be rare but serious adverse effects (myelotoxicity and ocular toxicity)
- Furazolide used in place of clarithromycin, metronidazole or amoxicillin gives eradication rates of 52-90%.

Helicobactor pylori-negative peptic ulcer disease

- The preparation of all peptic ulcers which are H. pylori-negative is increasing (~25%)
- Ensure that if the diagnosis of H. pylori infection is based on UBT or gastric mucosal biopsies, anti-secretory therapy must be stopped at least 1 week before taking (mucosal gastric) biopsies and biopsies must be taken from antrum (2), body (2), and angularis (1).
- Before deeming that the patient has H. pylori-negative peptic ulcer disease, care must be taken to exclude
  - H. pylori infection, using 2 different types of standard tests
  - Use of ASA, NSAIDs, Coxibs, bisphosphonates (check platelet aggregation or thromboxane B2 levels)
  - Fasting hypergastrinemia (ensure patient not currently taking anti-secretory therapy)

H. pylori-negative (HpN) peptic ulcers are more serious / severe than are H. pylori-positive peptic ulcers (HpP).

- In the absence of use of NSAIDs, give 3 factors which support this statement.

Clinical	HpP	HpN
– Bleeding ulcer	4%	50%
– Recurrent ulcer bleeding	11%	42%
– ASA risk ≥ grade 3	18%	~50%
– Mortality rate	37%	88%

Abbreviations: ASA, American Society of Anesthesiologist

- Theories why Hp-negative are more serious than Hp-positive peptic ulcers (GU / DU)
  - H. pylori involving the gastric body may ↓ secretion of HCl from parietal cells.
  - H. pylori may have an anti-secretory effect, making PPI therapy more efficacious.

The abnormalities in gastric acid secretion and in gastrin metabolism may be worse or different in HpN versus HpP peptic ulcer disease.

- Dyspepsia and pregnancy
  - Upper GI symptoms are common in pregnant women, and when EGD has been performed the findings are esophagitis (34%) and gastritis (25%).
  - Predictors of heartburn during pregnancy include young age of the mother, her parity, increasing gestational age, and the presence of heartburn before pregnancy (which occurs in 14% of mothers) (Marrero JM, et al. *Br J Obstet Gynaecol* 1992:731-4).
  - Only calcium-containing antacids should be used for GERD symptoms, since
    - Aluminum-containing antacids may cause fetal neurotoxicity,
    - Alginic acid (Gaviscon, sucralfate) may cause fetal distress
    - Magnesium-containing antacids may cause renal stones, respiratory distress and cardiovascular impairment, and hypotemia.
  - Nizatidine is not recommended for lactating mothers (FDA C, due to report of growth retardation of rodent pups)

- Give factors to consider when performing endoscopy in pregnant women.
    - A strong indication is always needed, particularly in high-risk pregnancies
    - Whenever possible, endoscopy should be deferred until the second trimester
    - The lowest possible dose of sedative medication should be used (wherever possible FDA category A or B drugs)
    - Procedure time should be short
    - To avoid inferior venal cava or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position
    - Presence of fetal heart sounds should be confirmed before sedation and after the procedure
    - Obstetric support should be immediately available
    - No endoscopy should be performed in patients with obstetric complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)

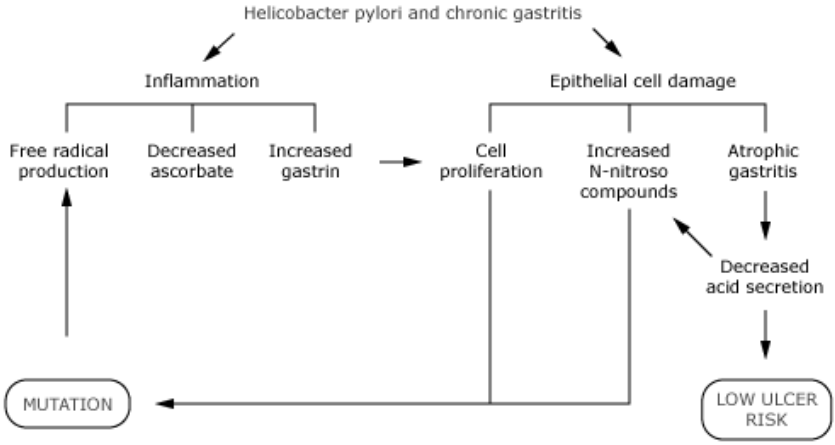
Printed with permission: Keller J, et al. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5(8): 435.

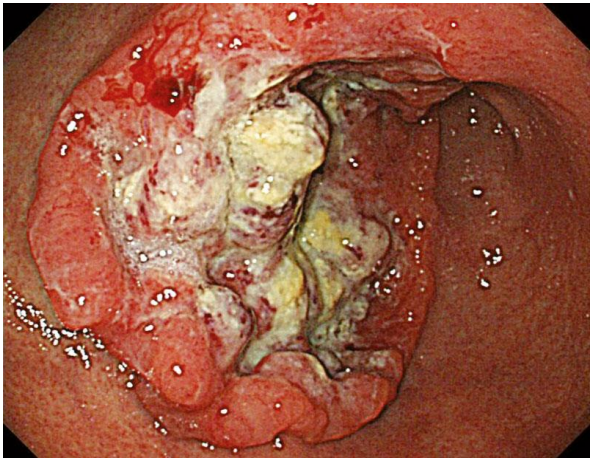
Iron Deficiency Anemia (IDA)

- ↓ HCl secretion, therefore ↓ ascorbic acid co-secretion, and ↓ iron absorption
- Also occult blood loss
- OR for HP and IDA is 2.6
- Treating HP in an Alaskan cohort did not reduce incidence of IDA
- So there is an association but no evidence of cause + effect

Gastric Adenocarcinoma

- 36 – 47% due to H Pylori
- H Pylori causes chronic active and then atrophic gastritis which are steps in carcinogenesis sequence





➢ Disease pathogenesis

- Give bacterial and host factors which are important in the H. pylori-associated development of peptic ulcer, lymphoma and gastric cancer.

➢ The H. pylori organism

  - Adhesion / colonization
    - The genetically 'distinct strains'
    - Bacterial genes encoding proteins in the motility apparatus of H. pylori (movement of organism from lumen of stomach, into the mucus layer) and genes for urease (provides for 2 pH optimum values of 3.0 and 7.2).
    - Colonization occurs only in gastric epithelium or where there is gastric metaplasia.
    - O-glycans in deeper portions of the glandular mucosa present colonization
    - SLPI (secretory leucocyte protease inhibitor) produced by H. pylori reduces colonization.
    - F3 ab A, a bacterial gene product may be liquid for the host Lewis (Le) b receptor or MUC 5AC, enhancing colonization.
    - H. pylori urease binds to MHC (major histocompatibility) class II molecules to ↑ apoptosis.
    - TFF_1 (trefoil protein) on gastric epithelial cells and mucus bind H. pylori
    - TLRs (Toll-like receptors) in the PAMPS (pathogen-associated molecular receptors) family recognize H. pylori or their bacterial products which recognize LPS (lipopolysaccharide) or flagellin.
    - Cag PAI (cag pathogenicity island) is a segment of H. pylori DNA which provides cag E (type N secretion apparatus)

- Cag PAI
  - Allow host gastric cellular membrane translocation
  - ↑ IL-8 expression
  - SRC kinase s phosphorylate tyrosine in Cag A protein
- All H. pylori have the vac A gene, and half produce the protein, Vac A (vacuolating cytotoxin)
- Vc A is a ligand for the cell membrane receptor, protein-tyrosine phosphatase.

- The host
  - Intensity of host inflammatory response
    - OipA (outer inflammatory protein A)
    - ↑ IL-8 → ↑ neutrophil infiltration
    - Peptidoglycan, acting by type IV secretion system
    - HP-NAP (H. pylori neutrophil-activating protein)
      - ↑ chemotaxis of neutrophils, monocytes
      - ↑ ROIs (reactive oxygen intermediates)
    - ↑ recruitment of neutrophils and macrophages → ↑ iNOS (inducible nitric oxide synthase)

  - Host immune response
    - Polymorphism for IL-1β → ↑ IL-1 → intense mucosal inflammation (gastritis)
    - IL-8, IL-10, TNF-α (tumor necrosis factor) also ↑ gastritis
    - Morphological changes in gastric epithelial cells
      - TJ (tight junctions) complexes become broken
      - ↑ epithelial cell proliferation and apoptosis

- ↑ gene expression
- Inflammatory cytokine
  - ↑ signaling mechanism for gene expression
- ↑ MAP (mitogen-activated protein) kinases
- ↑ lost cell redox factor-1
- ↑ activity of NF-kB (nuclear factor kappa B)
- ↑ activity of AP-1 (activator protein-1)
- ↑ oxidative stress
  - ↑ oxidation of DNA
- NOD_1 (nucleotide-binding oligomerization domain-1) in host
  - Sense H. pylori
  - ↑ NF-kB
- GI physiology
  - SST (somatostatin), gastrin effects on secretion of gastric HCl and duodenal HCO_3^-
  - Mucus - ↓ volume
  - ↓ mucosal hydrophobicity
- TNF-α and IFN-γ (interferon-gamma)
  - ↑ effects of HP-NRP
  - Prime neutrophils
- ↑ phagocytosis of H. pylori infected gastric epithelial cells
- ↑ chemokines e.g. ENA-78 GRO-α activate neutrophils
- ↑ cytokine induction
  - TNF-α
  - IL-6, IL-12, IL-17, IL-18
  - Heat shock protein 60

- T cell
  - ↓ IL-4 activation of STAT6 → ↑ Th1 and ↓ Th2 response
  - ↑ Th1 response
  - ↑ apoptosis
  - ↑inflammation
  - ↑ atrophy
  - ↑ dysplasia
- ↑ IL-1β, IFN-α, TNF-α
  - ↑ Fas antigen expression → Fas-FasL (ligand) interactions → ↑ gastric epithelial cell death by apoptosis
- ↓ NFAT (↓ nuclear translocation of a transcription factor) → ↓ IL-2
- Dysregulation of Treg (regulatory T cells)
- ↑ IgA, IgA, IgM and complement
- ↑ monoclonal antibodies to H. pylori cross-react with gastric epithelial cells
- Innate host responses impaired by catalase, urease

- H. pylori treatment risk of recurrence of early gastric cancer (EGCa) after endoscopic mucosal resection (EMR)
- Some evidence that H Pylori eradication reduces gastric cancer incidence
  - Chinese study, 3365 subjects randomized to eradication or placeb
  - 3 vs 4.6 % risk of gastric cancer
  - Similar evidence in Taiwan
- Asian guidelines support population screening and eradication in high risk patients
- ACG guidelines do not
- Perhaps role in 1st degree relatives

- Clinical
  - Majority are asymptomatic (clinically silent)
  - May be associated with dyspepsia or symptoms of peptic ulcer disease (epigastric abdominal pain, upper gastrointestinal bleeding)
  - Acute *Helicobacter pylori* infection may be associated with diarrhea
    - based on prospective study
    - 345 children aged 6 months to 12 years followed for 2 years with *H. pylori* serology every 4 months
    - 12% annual incidence of *H. pylori* infection based on seroconversion
    - seroconversion associated with 2 times more diarrhea days in the subsequent year, strongest effect in first 2 months
  - Past medical history (PMH):
    - Ask about history of peptic ulcer disease (documented ulcer)
    - Ask about any prior testing or treatment for *Helicobacter pylori*
  - Social history (SH):
    - Smoking associated with higher rate of failure of *Helicobacter pylori* eradication
      - Systematic review and meta-analysis of 22 studies with 5,538 patients
      - Smokers had nearly double the risk of eradication failure (summary odds ratio 1.95, 95% CI 1.55-2.45)
      - Absolute difference in eradication rates 8.4% (95% CI 3.3-13.5%) or NNH 12 (95% CI 7-30)

- Diagnosis
  - Only test if there is a plan to treat!
  - No gold standard test
  - Need to pick right test for right situation

Non-endoscopic testing

	Advantages	Disadvantages
○ Antibody testing	– Inexpensive – Widely available – Relatively high negative predictive value	▪ Positive predictive value depends on H. pylori prevalence ▪ Not recommended after therapy (serology may be positive years after infection eradicated)
○ Fecal antigen test	– Identifies active infection – High positive and negative predictive value – Useful before and after therapy	▪ Polyclonal test less well-validated than urea breath test in post-treatment setting ▪ Not affected by concurrent use of PPIs

	Advantages	Disadvantages
○ Urea breath test (UBT) (13C and 14C)	– Identifies active infection – High positive and negative predictive value – Useful before and after therapy	▪ Reimbursement and availability inconsistent ▪ Must be off PPIs / antibiotics > 2 wks at time of testing

Endoscopic testing

	Advantages	Disadvantages
○ Histology	– High sensitivity and specificity	▪ Expensive ▪ Difficult to perform ▪ Not widely available
○ Culture	– Not routinely recommended – High specificity – Permits determination of antibiotic sensitivity	▪ Expensive ▪ Difficult to perform ▪ Not widely available ▪ Marginal sensitivity
○ Rapid urease testing (RUT)	– Inexpensive – Rapid results – High specificity and relatively high sensitivity in appropriately selected patients	▪ Sensitivity significantly ↓ if used after treatment

	Advantages	Disadvantages
○ PCR	– Not routinely recommended – High sensitivity and specificity – Permits determination of antibiotic sensitivity	▪ Methodology not standardized across labs ▪ Not widely available

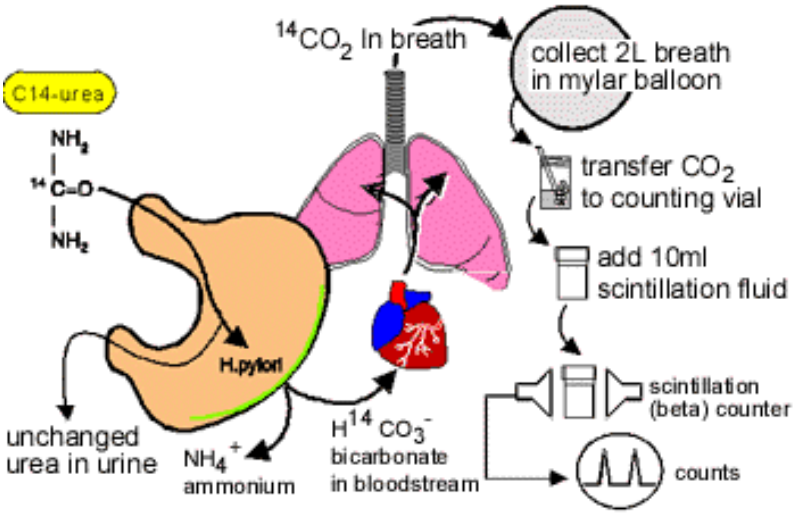
Antibody Testing

- IgG specific to HP in serum
- Develop after 21 days
- Sens = 85%
- Spec = 79%
- Concern about antibody test developed in one part of world not performing well in another
- Positive years post eradication

Urease Breath Test (UBT)

- Reproducible
- Sens. > 95%, Spec. > 95%
- Useful for post-treatment testing
- Once again sensitivity reduced by drugs that reduce organism density or urease activity
  - PPI (hold 2 weeks)
  - Bismuth (hold 1 month)
  - Antibiotics (hold 1 month)

- C^{13} UBT using non-radioactive stable isotope is recommended in children and women of “reproductive potential rather than the radioactive C^{14} UBT



Rapid Urease Testing

- Endoscopic test
- Biopsies placed on pH strip with urea
- Urease creates ammonia and bicarb
- pH paper changes color
- Sensitivity > 90%, specificity > 95%
- Decreased sensitivity:
  - Bismuth
  - Antibiotics
  - PPIs (need to be off 1-2 weeks)

- Histology
  - Gold standard
  - Imperfect due to differential distribution
  - Can assess for gastritis
  - Biopsies:
    - Angularis (2)
    - Greater curvature of corpus (2)
    - Greater curvature of antrum (2)
  - Sensitivity affected by PPI, bismuth, antibiotics

- Laboratory

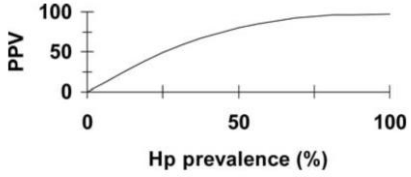
- Culture + PCR
  - Culture
    - Highly specific
    - Get sensitivities
    - Not readily available
  - PCR
    - Very sensitive + specific
    - Will find organisms in 20% of chronic gastritis, HP negative samples
    - Not readily available

- Fecal Antigen Test
  - Identifies H. pylori antigen in the stool
  - Uses antibody immunoassay
    - Antibody may be polyclonal or monoclonal
  - Can screen for infection + test for cure

- Monoclonal antibody performance characteristics
  - Pre-treatment: 96% Sensitivity, 97% specificity
  - Post-treatment: 95% Sensitivity, 97% specificity
- Do 4-8 weeks post Rx
  - Hold: PPI, bismuth, antibiotics (some studies suggest sensitivity not affected by concurrent use of PPI)

Which test to use?

- Endoscopy
  - If endoscopic procedure indicated
    - Do rapid urease test unless pt. on bismuth, PPI, abx
    - Otherwise do biopsy for histology
  - What if the pt. is bleeding?
    - Possible high false negative
    - Prospective cohort study suggested this is not the case
  - Guidelines suggest negative test in setting of bleeding should b confirmed with 2nd test
- Non-Endoscopic
  - Test and treat approach
  - H. pylori serology has high PPV in high prevalence population, low PPV in low prevalence pop.
  - Bottom line = if negative then no H. pylori, if positive in low prevalence population → confirm



When to test for cure

- Those with H. pylori associated ulcer
- Individuals with dyspepsia despite test + treat
- H pylori MALT lymphoma
- Those who have resection of gastric cancer
- Remember to use fecal test or UBT
- Antibody only helpful if negative
- Dyspepsia plus H.pylori infection (HpI)
  - Dyspepsia not responding to treating HpI
- GI bleed from peptic ulcer-associated HpI
  - Prove the HpI has been eradicated, so patient does not need to be on lifelong PPIs
- MALT lymphoma plus HPI
  - Prove that MALT lymphoma and HpI are cured
- Gastric adenocarcinoma plus HPI

- Therapeutic options
  - Uncomplicated peptic ulcer
    - PPI of your po bid for 2 weeks with 2 antibiotics followed by PPI od for 2 weeks
    - If patient experiences frequent recurrent recurrences
      - Perform UBT with patient off PPI for 1 week
      - If UBT positive, retreat H. pylori
      - If UBT negative, consider PI po od continuously as maintenance therapy

- Complicated peptic ulcer
  - Complications of hemorrhage, obstruction, perforation
  - Treat PUD plus H. pylori infection as above for uncomplicated ulcer
  - Either repeat UBT off PPI therapy, and retreat and prove eradication of H. pylori, with no PPI maintenance therapy (PPI po od), or
  - PPI maintenance therapy (PPI od), because of
    - Risk (low) of reinfection with H. pylori
    - Risk (low) of reulceration even without reinfection with H. pylori
    - Possibility that the original ulcer may have been caused by ASA / NSAIDs plus H. pylori infection

- Caution alert
  - Every patient being considered for long-term use of ASA / NSAIDs / Coxibs should be tested (by UBT) and heated for H. pylori of positive
  - Depending upon patient (host) and medication considerations, some persons on long-term on PPI po od, even after eradication of any associated H. pylori infection.

First-Line Treatment

Treatment regimen	Duration	Eradication ratios
○ PPI BID (eso is daily) Clarithromycin 500 mg BID Amoxicillin 1000 mg BID	10-14 days	70-85%
○ PPI Clarithromycin 500 mg BID Flagyl 500 mg BID	10-14 days	70-85%
○ PPI Amoxicillin 100 mg BID Followed by Clarithromycin 500 mg BID Tindazole 500 mg BID + PPI	5 days Followed by 5 days	90%
○ Bismuth 525 mg QID Flagyl 500 mg QID Tetracycline 500 mg QID PPI or H_2RA BID	10-14 days	75-90%

- Treatment Overview
  - In persons with H. pylori (Hp) associated non-ulcer dyspepsia, eradication of Hp results in long term symptomatic relief in about 8% of patients
  - PCM (PPI – clarithromycin – metronidazole) and PCA (PPI – clarithromycin – amoxicillin) regimens are equivalent.
  - It is useful for the physician to have available date on the local rates of Hp resistance to clarithromycin.
  - "PPI – clarithromycin – containing therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is more than 15-20%" (Malfertheiner et al., Gut 2012; 61: 646-664).
  - Smoking reduces Hp – eradication rates by about 8%
  - Extending the duration of triple therapy with PCM or PCA from 7 to 10-14 days increases the Hp – eradication rate by only ~ 5%
  - Bismuth - containing quadruple therapy is also an alternate first-line empirical therapy since compliance with quadruple therapy is high and is particularly useful in areas of high clarithromycin resistance.
  - If Hp – eradication fails with PCM or PCA, use either
    - bismuth – containing quadruple therapy, or
    - levofloxacin – containing triple therapy (PLA, PPI, levofloxacin plus amoxicillin or PCL for 10 days)
  - If Hp – eradication fails after first and then second line treatment, subsequent treatment. "…should be guided by antimicrobial susceptibility testing, whenever possible".

- For persons who cannot take amoxicillin (penicillin allergy), use PCM or bismuth – containing quadruple therapy
- Concomitant therapy (CT) is comprised of PPI, clarithromycin, metronidazole, amoxicillin
  - more effective than standard triple therapy (pooled or, 2.86), and is less complex than ST
- Sequential therapy is comprised of
  - PPI bid plus amoxicillin 1 gm bid for 5 days
  - followed by PPI bid plus clarithromycin 500 mg bid plus metronidazole or tinidazole bid for the next 5 days
  - The place for ST remains to be established.
- Hp tests have a sensitivity of ~95%, so before stating that a patient has a Hp negative duodenal ulcer, perform biopsy- and non-biopsy-based tests for Hp, and for biopsy-based ulcers, ensure that at least 6 gastric biopsies were taken (antrum, 2; angularis, 2; and body 2) within more than 2 weeks of stopping acid inhibitory therapy.

Please see: Thomson ABR. Chapter 61. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 1**:** Drugs used for Dyspepsia and Peptic ulcer disease, page 821.

Please see: Thomson ABR. Chapter 61. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 2**:** Helicobacter pylori Eradication Regimen, page 824-825.

Please see: Thomson ABR. Chapter 62. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 1**:** Parenteral Drugs used in Management of Upper Gastrointestinal Bleeding, page 833.

- First course of Rx is most successful
- Subsequent trials less so (especially if reusing antibiotic)
- Algorithm:
  - H-PAC or bismuth quadruple therapy
    - If allergy: H-PFC
    - If previous macrolide exposure = quad therapy
    - If previous flagyl exposure = quad therapy?
    - Sequential therapy is alternative
    - Consider 2 week course (see below)

Length of treatment

- Vakil N, AP&T, 2004:
  - Compared efficacy of 3, 7, 10 d regimen
  - HPAC at 7 days → 77% eradication rate
  - HPAC at 10 days→ 78% eradication rate
- Paoluzi P, Helicobacter, 2006:
  - Compared efficacy of 7, 14d regimen
  - HPAC for 7 days→ 57%
  - HPAC at 14 days→ 70%

HPAC or quad therapy?

- Meta-analysis Gene (E, AP&T, 2003)
  - 79% eradication for HPAC
  - 80% for quadruple therapy
- HPAC > quad therapy due to complexity of 4 pill regimen

Predictors of Treatment Failure

- Poor compliance
  - Significant side effects reported in 5-20%

- Antibiotic resistance
  - Prior treatment with either macrolide or metronidazole increases likelihood of *H. pylori* resistance to these drugs
- Most likely cause of waning efficacy is increased clarithromycin resistance
- Flagyl R can be overcome with higher dosages
- H Pylori genetic variation
  - CagA negative strains = more treatment failure
  - CagA not cytotoxic, co-expressed with VacA
- Smoking associated with higher rate of failure of *H. pylori* eradication
  - Systematic review and meta-analysis of 22 studies with 5,538 patients
  - Smokers had nearly double the risk of eradication failure (summary odds ratio 1.95, 95% CI 1.55-2.45)
  - Absolute difference in eradication rates 8.4% (95% CI 3.3%-13.5%) or NNH 12 (95% CI 7-30)
- PPI rapid metabolizers (CYP2C19 genotype *1*1) may have lower eradication rates
  - Based on 67 patients aged 20-69 years treated with lansoprazole 30 mg, amoxicillin 750 mg, and clarithromycin 200 mg twice daily for 7 days
  - Eradication rates based on 13C urea breath test 1 month after treatment
    - 70% for rapid metabolizers (CYP2C19 genotype *1*1)
    - 93.9% for intermediate metabolizers (genotype *1*2 or *1*3)
    - 85.7% for poor metabolizers (genotype *2*2, *2*3, or *3*3)

- Treatment Failure
  - Avoid using same antibiotics a second time
  - Culture and sensitivity should be sought after multiple treatment failures
    - Poor evidence for culture guided therapy
  - Since HPAC is standard first line therapy, bismuth quad rx is usual rescue
    - Dore P, helicobacter, 2003:
    - BID quadruple therapy for 14 days was effective in 95% of those who failed prior therapy

Rescue Treatment

Treatment regimen	Duration	Eradication rates
○ Bismuth 525 mg QID ○ Flagyl 500 mg QID ○ Tetracycline 500 mg QID ○ PPI or H_2RA BID	14 days	70%
○ PPI ○ Amoxicillin 100 mg BID ○ Levofloxacin	10-14 days	57-91%
○ PPI ○ Amoxycillin 1000 mg BID ○ Rifabutin 150 mg BID	14 days	60-80%

Common Side Effects

Treatment	Side Effects
○ PPI	– Headache – Diarrhea
○ Clarithromycin	– GI upset – Diarrhea – Altered taste
○ Flagyl	– Metallic taste – Dyspepsia – Disulfiram-like reaction with alcohol
○ Tetracycline	– GI upset – Photosensitivity – Tooth discoloration in children
○ Bismuth	– Darkening of tongue and stool – Nausea – GI upset

SMALL BOWEL

Celiac and Liver Diseases

Yacoub Alawadh

- Classic definition of celiac disease (CD; aka gluten-sensitive enteropathy includes
  - Villous atrophy
  - Symptoms of malabsorption such as steatorrhea, weight loss, or other signs of nutrient or vitamin deficiency
  - Resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months.

- Demography
  - Frequency in the general population ~1%
  - Affects 2.5 % of cirrhotic patients
  - The prevalence of ↑ liver enzymes in the adults with CD ~ 40%
  - Liver enzyme abnormalities are usually mild and respond to a gluten-free diet (GFD)
  - Cirrhosis is rarely described in patients with CD but case reports are emerging in the younger population
  - Recognizing CD in the setting of cirrhosis is essential in order to institute a GFD and potentially prevent further morbidity and mortality associated with both diseases.

Al-Hussaini A, Basheer A, Czaja AJ. Liver failure unmasks celiac disease in a child. Ann Hepatol 2013; 12:501-505

Bardella M T, Vecchi M, Conte D, et al. Chronic unexplained hypertransaminasemia may be caused by occult celiac disease. Hepatology 1999; 29:654-657.

Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003; 163:286-292.

Roumeliotis N, Hosking M, Guttman O. Celiac disease and cardiomyopathy in an adolescent with occult cirrhosis. Paediatr Child Health 2012; 17:437-439.

- Pathophysiology
  - Multi-systemic disease that could affect any organ system including the liver.
  - The most common liver disorders associated with CD are
    - Autoimmune hepatitis (AIH)
    - Primary biliary cirrhosis (PBC)
    - Primary sclerosing cholangitis (PSC)
    - Non-alcoholic fatty liver disease (NAFLD)
  - CD has been found in
    - 3–7% of patients with PBC
    - 3–6% with AIH
    - 2–3% PSC
    - Autoimmune cholangitis (AIC)
    - Does not usually improve after GFD
    - Difficult to establish if the two main kinds of liver injury found in CD (cryptogenic and autoimmune) are discrete entities with a different pathogenesis, or if they are an expression of the same disorder
  - Unproven theories
    - It is still not clear how CD affects the liver but several pathophysiologic mechanisms are proposed

- Malabsorption and long-standing malnutrition
  - ↓ gut mucosal integrity determines malabsorption and secondary malnutrition
  - Rarely observed in CD, but can concur in determining liver dysfunction (mainly steatosis), found in gluten-sensitive enteropathy

Freeman HJ (2006) World J Gastroenterol 12:1503–1508.

- Intestinal permeability
  - ↑ intestinal permeability resulting in the arrival of toxins and antigens in the hepatobiliary system through the portal circulation

Novacek G, Mieshler W, Wrba F, et al. Eur J Gastroenterol Hepatol 1999; 11:283–288.

- Small intestinal bacterial overgrowth
  - ↑ intestinal transit time in untreated CD patients leads to small bacterial overgrowth
  - ↑ bacterial antigen pool available for absorption and enzymatic neoantigen production

Spiller RC, Lee YC, Edge C, et al. Gut 1987; 28:1275-1282.

- Intestinal inflammation
  - Chronic intestinal mucosal inflammation
  - Leads to the exposure of TG2, which is the main autoantigen of CD,
  - Recognized by the specific CD antibodies (anti-tTG andEmA)
  - TG2 is present in the liver
  - Anti-tTG IgA can reach TG2 in extraintestinal tissues and cause liver injury

- Korponay-Szabo IR, Halttunen T, Szalai Z, et al () Gut 2004; 53:641–648.

- Genetic predisposition
  - The main genetic marker of CD is
    - HLA-DQ2 (in 95%)
    - HLA-DQ8 (in 5%)
    - HLA-DQ2 is in strong linkage with HLA-DR3, which is the major HLA risk factor for AIH
  - There is a close correlation between CD and AIH / PSC
    - In patients with PSC, the haplotype HLA-B8/DR3 is found with increased frequency

➢ Serology

- In the past
  - Gold standard for screening has been IgA anti-gliadin by ELISA.
  - Indirect immunofluorescence for IgA anti-EmA is more expensive but has higher sensitivity and specificity than IgA anti-gliadin
  - ELISA anti-tTG using human recombinant tTG is less expensive than anti-EmA, but has comparable diagnostic performance

Burgin-Wolff, A, Gaze, H, Hadziselimovic, F, et al. Antigliadin and antiendomysium antibody determination for coeliac disease. Arch Dis Child 1991;66: 941–947.

- Now recommended
  - Anti-tTG IgA is more sensitive and specific than IgG
  - Necessary to perform both tests to detect the disease in subjects with IgA immunodeficiency, which is found in 10% of all celiac disease patients

Fasano, A, Catassi, C. Gastroenterology 2001;120: 636-651.

- In cryptogenic and autoimmune liver disease, EmA should be preferred to anti-tTG, since the former antibodies, although slightly less sensitive (95% vs 98%), are more specific than the latter antibodies (around 98–100% vs 90%).
- False positives for anti-tTG are prevalently found in patients with liver and autoimmune disorders

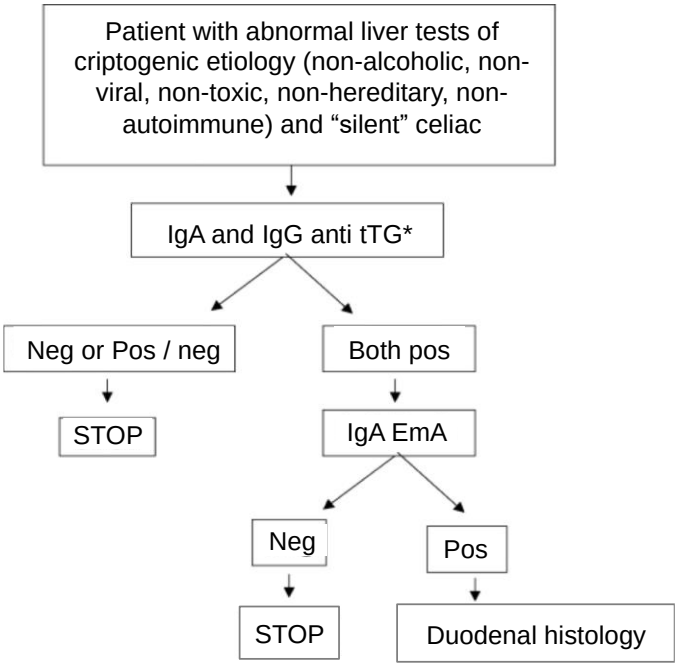
Carroccio, A, Giannitrapani, L, Soresi, M, et al. Gut 2001;49:506-511.

- Use of the **recombinant human antigen** instead of the guinea pig antigen for the antitTG detection **makes the test more specific**
- The human recombinant (or purified) tTG-based ELISA assays are **superior** to those based on guinea pig liver tTG for the detection of anti-tTG antibodies

Vecchi M, Folli C, Donato MF, et al. Scand J Gastroenterol 2003; 38:50–54.

Lo Iacono O, Petta S, Venezia G, et al. Am J Gastroenterol 2005; 00:2472–2477.

- Anti-tTG ELISA assay is less expensive than anti-EmA
- Combine these three non invasive tests in order to reach the maximum pretest probability, and then perform upper EGD plus duodenal biopsy



* human recombinant or purified ELISA test

* only about 10% of persons with chronic liver disease, hypertransaminasemia of unknown origin, and positive CD serology will have a duodenal biopsy compatible with CD

- Management
  - Two main forms of liver damage:
    - Cryptogenic
      - Cryptogenic liver disorder (mild or severe), potentially reversible on a GFD (~ 95%)
    - Autoimmune,
      - Autoimmune liver disorder, generally unaffected by a GFD

Lawson A, West J, Aithal GP, Logan RFA (2005) Aliment Pharmacol Ther 21:401–405

  - Most frequent finding is represented by a cryptogenic hypertransaminasemia
    - The increase in transaminase levels mild (<2×),
    - Normal values of Bil and GGT and ALP
    - Reverting to normal after 6–12 months of a strict GFD

Bardella MT, Fraquelli M, Quatrini M, et al. Hepatology 1995; 22:833–836.

Kaukinen K, Halme L, Collin P, et al. Gastroenterology 2002; 122:881–888.

Autoimmune Cholangitis

  - Cholestatic liver disorder with
    - Biochemical evidence of cholestasis,
    - Histological finding of inflammatory bile duct damage,
    - Negativity for antimitochondrial antibodies
    - An association between CD and AIC has been described

Sedlack RE, et al. Am J Gastroenterol 2002; 97:3196-3198.

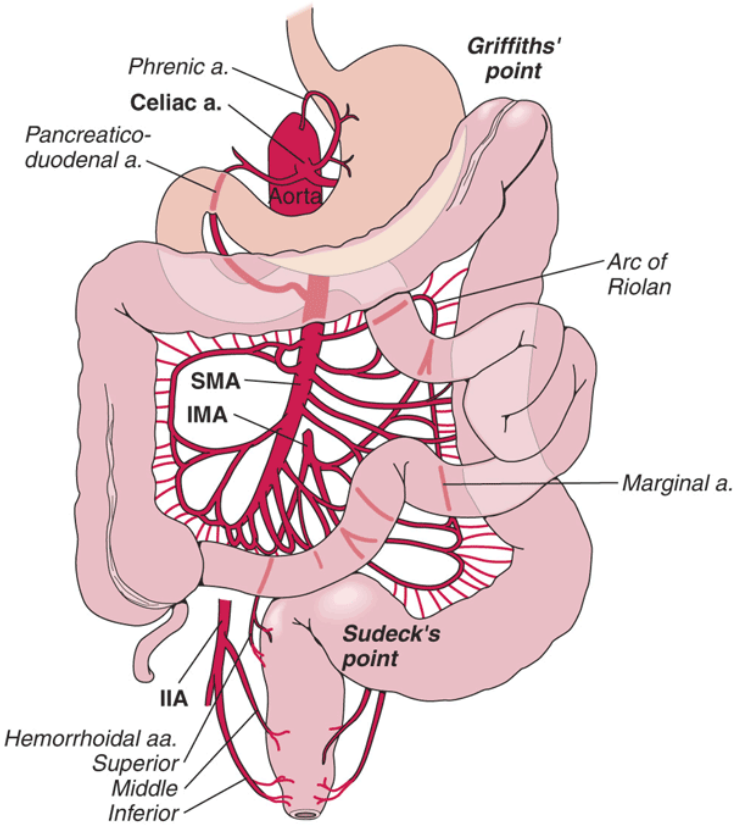
- Conclusion
  - All patients with cryptogenic liver injury
  - (with hypertransaminasemia of unknown origin) and A.I liver disease (including PBC, PSC, and AIH) should be screened for CD
  - High titers for EMA and hTTG levels can be diagnostic of CD in the absence of a SB biopsy in patients with cirrhosis.
  - Transaminase levels should be periodically checked to verify the gluten dependence of liver damage

Intestinal Ischemia

Mansour Alghanem

- Anatomy

Intestinal Circulation



- Celiac axis supplies the stomach and duodenum
- SMA supplies the small bowel from distal duodenum to the Mid transverse colon
- IMA supplies the mid-transverse colon to the rectum

- The celiac axis and the SMA communicate principally through pancreaticoduodenal arteries
- The SMA and IMA communicate through 2 pathways the marginal artery and Arc of Riolan
- Two watershed areas:
  - Sudek Point in the Rectosigmoid regioin
  - Griffith Point at the splenic flexure.

Abbreviations: IMA, inferior mesenteric artery; SMA, superior mesenteric artery

- Physiology
  - Cardiac output to splanchnic circulation
    - Fasting
      - 25%
    - Fed
      - > 35%
  - 70% of blood flow goes to the mucosa
  - Control of intestinal perfusion:
    - Constrictors
      - Angiotensin II
      - Catecheloamines
      - Vasopressin
    - Vasodilator
      - VIP
      - Products of ischemia (lactate, hyperkalemia, and hypoxemia)

Acute Mesenteric Ischemia

- Demography
  - Relatively Uncommon
  - Difficult Diagnosis
  - High Complication Rate
  - High Mortality Rate (50%)

- Etiology
  - Mesenteric artery occlusion
    - Embolic (50%)
    - Thrombotic (15-20%)
  - Non-occlusive mesenteric ischemia (20-25%)
  - Mesenteric venous thrombosis (5-10%)

- Clinical
  - Abdominal pain
    - Sudden
    - Severe
    - Diffuse
    - Pain out of proportion to physical findings”
  - Vomiting-50%
  - Diarrhea-33%
  - Occult gastric/rectal blood-25%
  - 50% with prior symptoms consistent with chronic mesenteric ischemia
  - Physical exam
    - Few findings early
    - Later peritoneal signs and acidosis

- Labs: often normal early Leucocytosis & elevated lactate late

➢ Diagnostic imaging

- Abdominal film
  - Normal in ~ 25%
  - Early
    - May show ileus
  - Advanced may show
    - Bowel wall edema (thumbprinting) (< 40%)
    - Pneumatosis (< 40%)
  - May help rule-out of other causes of abdominal pain, e.g. free air from bowel perforation

- CTA abdomen
  - Confirming embolism or thrombotic occlusion evaluation of bowel
  - Detection of arterial narrowing or occlusion
  - Rule-out of other causes of abdominal pain
  - Initial assessment of bowel perfusion
  - Circumferential bowel wall thickening (most common)
  - Attenuation
    - LOW → Inflammation and submucosal edema
    - HIGH → Submucosal hemorrhage
  - Enhancement
    - ↓ due to compromised blood flow
    - ↑ due to hyperemia

- Pneumatosis indicates
  - Permanent damage to bowel
  - May appear homogeneous or have a "halo"-like appearance

- Angiography
  - Useful for differentiating between embolic and thrombotic occlusions
  - For suspected nonocclusive mesenteric ischemia, consider angiography if
    - Symptoms fail to improve with treatment of underlying disease (ACC/AHA Class I, Level B)
    - Immediate surgery not indicated
  - If used for diagnosis, keep catheter in superior mesenteric artery (SMA) (if possible) for injection of
    - Intra-arterial vasodilators
    - Thrombolytics
    - Angioplasty +/- stenting
  - Findings for non-occlusive mesenteric ischemia include
    - Diffuse, normal venous runoff
    - Narrow irregularities of major superior mesenteric artery branches ("string of sausages" sign)
  - Findings for mesenteric venous thrombosis
    - Generalized slowing and vasoconstriction of arterial flow
    - No opacification of corresponding mesenteric or portal vein outflow tracts (usually segmental)

➢ Treatment

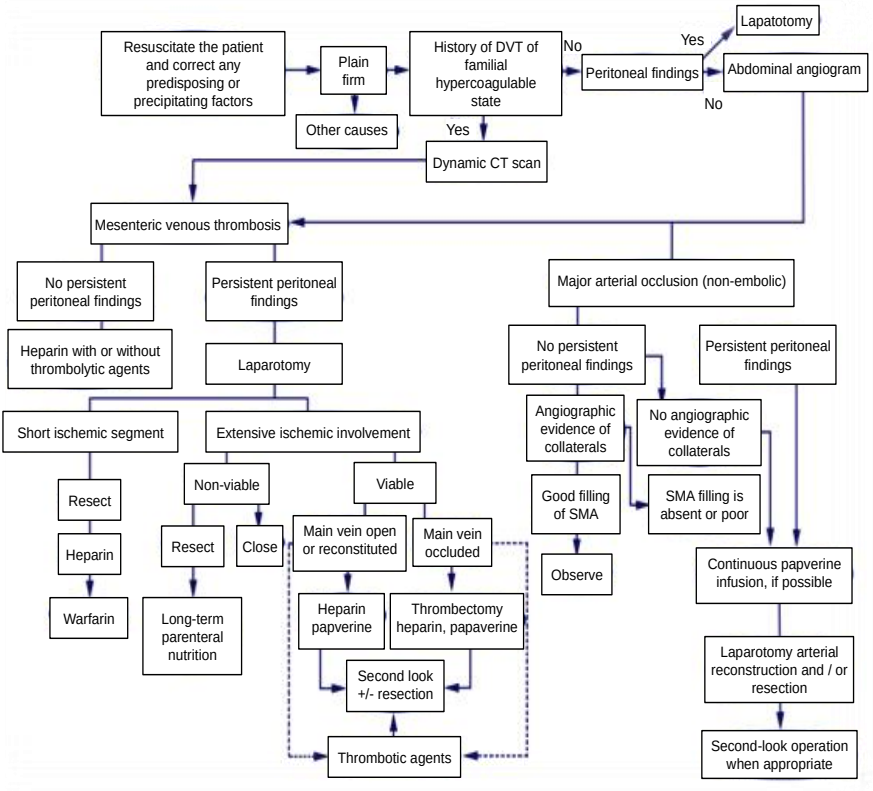
- General
  - Aggressive Fluid replacement to stabilize abnormal hemodynamics
  - Monitoring
    - Hourly urine output
    - Arterial and continuous central pressure monitoring
  - Anticoagulation
    - Heparin (maintain partial thromboplastin time > 2 times normal) to reduce chance of progressive thrombosis
  - Broad spectrum antibiotics (such as metronidazole plus either a second-generation cephalosporin or levofloxacin
  - Vasopressors may be used cautiously for systemic hypotension
    - Warning: May worsen ischemia in marginally viable bowel or exacerbate vasospasm

- Treatment of occlusive disease
  - Revascularization
    - Revascularization associated with better survival in patients with acute superior mesenteric artery occlusion
    - Endovascular management
    - Angioplasty or stenting may be performed during initial mesenteric angiography
  - Catheter-directed thrombolysis

- Surgery indications include
  - Central occlusion of superior mesenteric artery (SMA)
  - Signs consistent with perforated viscous
  - Pre-existing intestinal gangrene
  - Failure of endovascular treatment

- Treatment of non-occlusive disease
  - Treat underlying shock (ACC/AHA Class I, Level C)
  - Consider transcatheter delivery of vasodilators into area of vasospasm for
    - Patients with vasospasm unresponsive to systemic treatment
    - Patients with ischemia due to cocaine or ergot poisoning (ACC/AHA Class IIa, Level B)
  - Vasodilators to interrupt vascular spasm
    - Prostaglandin E1 (PGE1)
    - Prostaglandin I2 (PGI2)
    - Papaverine 30-60 mg/hour via angiography catheter
  - Laparotomy and bowel resection
    - Patients unresponsive to medical treatment (ACC/AHA Class I, Level B)

- Treatment of mesenteric venous embolism
  - Anti-coagulation with Heparin
  - Exploration with resection of non-viable bowel
  - Systemic thrombolytic therapy
    - Systemic, or
    - Catheter directed if viable bowel
  - Thrombectomy
    - Main vein occluded
  - Long term anti-coagulation with Warfarin



Chronic Mesenteric Ischemia

- Demography
  - Fairly uncommon, less than 5% of ischemic intestinal diseases
  - Actual incidence estimated at 2-3 cases/10^5

- Causes / associations
  - Almost always accompanied by mesenteric atherosclerosis
  - 75% of patients with CMI are smokers
- Clinical
  - Crampy abdominal pain 10-30 minutes after eating, lasting 1-3 hours
  - Significant weight loss due to fear of eating
  - May have
    - Nausea
    - Vomiting
    - Diarrhea
  - Often have a history of
    - Coronary artery disease (CAD)
    - Peripheral vascular disease (PVD)
    - Cerebrovascular disease (CVD)
  - Note
    - Important to consider in any patient with predisposition and abdominal pain
  - Physical signs include:
    - Cachexia
    - Abdomen is usually soft and non-tender
    - Even during painful episodes (pain out of proportion to exam)
    - Often have abdominal bruit
- Diagnostic imaging
  - Duplex ultrasound: possible screening tool
    - Fasting peak systolic velocity of > 275cm/s
      - PPV 70% for stenosis
      - NPV, 99%

- MDT CTA or MRA: Highly sensitive to detect proximal lesions (origin of SMA or celiac)
  - Less helpful for distal lesions
- Angiography “Gold standard”

Abbreviations: NPV, negative predictive value; PPV, positive predictive value

- Treatment
  - Low risk patients
    - Surgical revascularization
      - Antegrade or retrograde bypass grafting
      - Aortic reimplantation of SMA
      - Transarterial and transaortic mesenteric endarterectomy
  - High risk patients
    - Percutaneous transluminal mesenteric angioplasty (PTMA) +/- stent
    - Have higher recurrence of symptoms
    - No long term studies to evaluate efficacy of stenting compared to surgical intervention yet

Ischemic Colitis (IC)

- Demography
  - Average patient age at diagnosis is 70 yr Although frequent in the elderly, younger patients may also be affected.
  - M to F ratio is equal
  - Persons > 60 yr

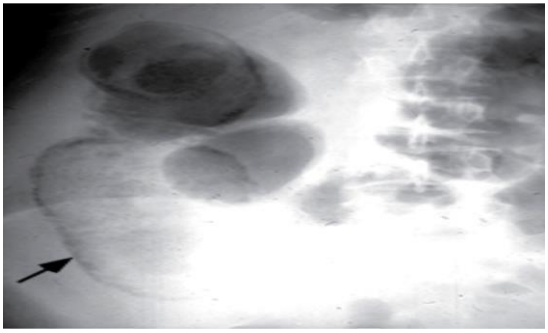
- Types
  - Non-occlusive
    - More common
    - From low-flow states
  - Occlusive colonic ischemia
    - Tumors
    - Adhesions
    - Volvulus
    - Diverticulitis
    - Intestinal prolapse

- Causes / associations
  - Obstruction or potentially obstructing lesions of the colon
    - Carcinoma
    - Diverticulitis
    - Volvulus
  - Vasculitides
    - Systemic lupus erythematosis
    - Periarteritis nodosum
  - Drugs
    - Digoxin
    - Tegaserod
    - Alosetron
    - Cocaine
  - Intra-abdominal inflammatory process secondary to bacterial, parasitic or viral infections
    - *Angiostrongylus costaricensis*
    - CMV
    - *Entamoeba histolytica*
    - Escherichia coli O157:H7
    - Salmonella ileocolitis

- Thrombotic conditions (acquired and hereditary)
  - Antiphospholipid antibodies
  - Factor V Leiden mutations
  - Protein C and S deficiency
  - Anti-thrombin III deficiency)

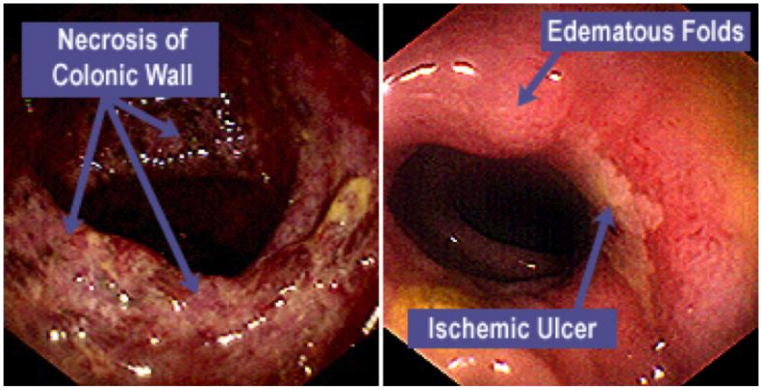
- Laboratory
  - Hyperactive phase
    - Severe abdominal pain
    - Frequent bloody, loose stools
  - Bloody diarrhea
    - Anorexia, nausea, vomiting, or abdominal distension
    - Physical examination usually reveals only mild abdominal tenderness. Peritoneal signs (15%)
  - Paralytic phase
    - Pain diminishes, but more continuous, and diffuse
    - Abdomen more distended, tender, no bowel sound
  - Shock phase (10 to 20%)
    - Massive fluid, protein, and electrolyte leakage through gangrenous mucosa
    - Severe, shock and metabolic acidosis, may develop
    - Rapid life-saving surgical intervention required
  - In severe ischemia or necrosis
    - Leukocytosis
    - Metabolic acidosis
    - ↑ blood lactate concentration

- Diagnostic imaging
  - Plain abdominal x-ray
    - Bowel dilatation
    - Air-filled loops of intestine
    - Mural thickening
    - Loss of bowel haustra
    - Thumbprinting of colonic wall (more specific but less sensitive < 20%)
  - CT abdomen
    - May be normal initially
    - Thickening of bowel wall in segmental pattern
    - Mesenteric stranding
    - Pneumatosis and gas in mesenteric veins in advanced stages



- Colonoscopy
  - Early stages of ischemia
    - Petechial hemorrhages interspersed with areas of pale, edematous mucosa
  - The “single-stripe sign”
    - Single longitudinal ulcerated or inflamed colon strip
    - May characterize milder disease

- Later
  - Segmental erythema, +/-ulcerations and bleeding
  - Mucosa appears cyanotic, dusky, gray, or black.
- Chronic ischemia (weeks or months later)
  - Stricture
  - Decreased haustrations
  - Mucosal granularity



- Treatment
  - Surgery
    - ↓ / occluded perfusion to colon
    - Aortoiliac surgery 1% to 7% develop colonic ischemia
    - Cardiopulmonary bypass
  - Low-flow states leading to impaired arterial perfusion of colon (intestinal blood pressure < 40 mm Hg) in colonic ischemia
    - Post-Myocardial infarction
    - Hemodialysis
    - Shock

- Supportive
  - IVF, bowel rest
  - Empiric antibiotics (moderate / severe)
  - NG tube for ileus
  - Hold meds that can promote ischemia
  - Optimize cardiac and pulmonary function
- Bowel resection if
  - Peritoneal signs
  - Symptoms persisting surgical > 2 weeks
  - Severe complications

➢ Prognosis

- Most patients with non-occlusive ischemia improve within 1 or 2 days
- A minority develop long-term complications
  - Segmental colitis
  - Stricture
- ~15% develop severe gangrene
- Of those that survive surgical revascularization
  - 5 yr survival ~ 80%

Obscure Gastrointestinal Bleeding, and Video Capsule Endoscopy

Terry Ponich

Case 1.

- 78 year old gentleman
- Multiple medical problems
- 3 year Hx GI Bleed
  - Melena 1-2x per month, witnessed
  - Rarely blood per rectum
  - 15 blood transfusions
  - Multiple iron infusions
- \+ ASA use
- Hemoglobin 84 g/L
- EGD - mild esophagitis and gastritis
- Colonoscopy - 2 polyps – removed
- SBFT – Normal
- Started on PPI
- Bleeding continued

- Give what this patient is likely to be bleeding from.
  - Angiodysplasia 53%
  - Crohn Disease 11%
  - Non-specific ulcer 5%
  - Stricture 5%
  - Tumour 3%

Obscure Gastrointestinal Bleeding (OGIB)

- Definitions
  - Bleeding of unknown origin that persists or recurs (i.e. the cause or source of bleeding is obscure)
    - It assumes normal upper & lower endoscopy
    - It also assumes normal small bowel imaging by radiology (SBFT/enteroclysis)
  - Obscure **overt** means bleeding is visible (hematemesis, hematochezia, melena, coffee ground emesis) with cause unknown
  - Obscure **occult** means bleeding not visible (FOBT positive and /or iron deficiency anemia) with cause unknown

Raju GS, et al. Gastroentrol 2007, 133: 1697-717; Leighton JA, et al. GIE 2003, 58: 650-5.

- Demography
  - No source of bleeding found in 29-52% of bleeds after initial EGD/Colon
  - 80-90% eventually identified
  - 10-20% not identified and many resolve spontaneously
  - About 5% remains recurrent without identifiable source – majority of these are from the small bowel.
  - OGI bleed frequency by age
    - < 25 yrs old
      - May have Meckel diverticulum
    - 30-50 yrs old tumors
    - > 50 yrs old
      - Vascular ectasias

- Etiology

Vascular	Inflammatory	Neoplastic	Others
○ Varices	– Esophagitis	▪ Ampullar carcinoma	Diverticulae
○ GAVE	– Cameron erosion	▪ Carcinoid	Biliary
○ PHG	– PUD	▪ GIST	Pancreatic
○ Dieulafoy lesion	– NSAID enteropathy	▪ Adeno-carcinoma	
○ Angioectasias	– IBD	▪ Lymphoma	
○ Radiation enteritis		▪ Metastases	
○ Hemorrhoids			

Vascular Lesions

- Responsible for 70-80% of small bowel bleeding
- Angioectasias
- Telangiectasias – HHT/OWR, Crest syndrome
- Dieulafoy lesion
- Varices
- Portal hypertensive enteropathy
- AVMs
  - Arterial venous malformations
- Vascular
  - Enteric fistulas (aorto/ileo-enteric)

Small Bowel Bleeding Tumors

- Overall 2nd most common cause of SB bleeding, about 10%
- Most common cause in person age 30-50 yrs of age
- Benign
  - Leiomyoma
  - GIST
  - Polyps
  - Peutz-Jeghers
  - FAP
- Malignant
  - Adenocarcinoma
  - Neuroendocrine tumor (aka carcinoid)
  - Lymphoma
    - Leiomyosarcoma
- Metastatic
  - Melanoma
  - Breast
  - Renal cell
  - Kaposi’s sarcoma
  - Colon
  - Ovary

Small Bowel Diverticulae

- Isolated diverticulae
  - Bleed at the edge of the diverticulum from the perforating vessel
- Meckel's diverticulum
  - Most common cause in those <25 yrs old
  - Develops from remnant of vitelline duct in distal ileum
  - Ectopic gastric tissue can ulcerate
  - Also can cause
    - Intususception
    - Inversion
    - Angioectasias
    - Submucosal tumors

Inflammation

- IBD – Crohn disease
- Other ulcers
  - NSAIDS
  - Ischemia
  - ZE syndrome
  - Celiac disease
  - Vasculitis
  - Idiopathic

Very Rare Causes

- Biliary (Hemobilia)
  - Neoplasm
  - Aneurysm

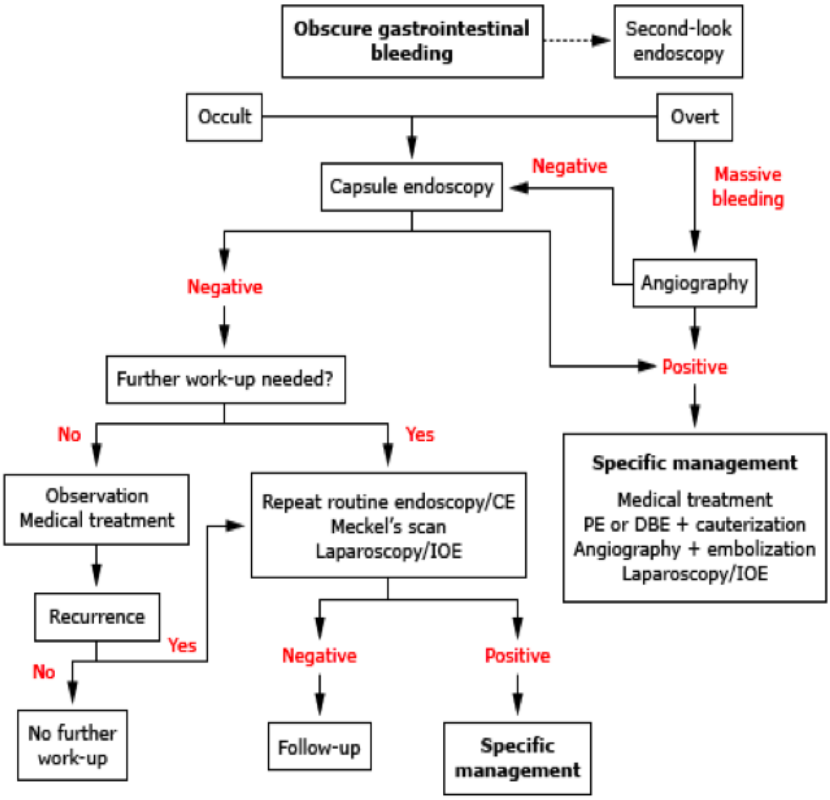
- Trauma
- Abscess (from erosion of vessel in contact with biliary tree)

- Pancreatic (Hemosuccus pancreaticus)
  - Pseudocysts
  - Pancreatitis
  - Tumors (from erosion of vessel in contact with pancreatic duct)
- Infections
  - CMV
  - Histoplasmosis
  - TB
  - Hookworm

- Diagnostic Approach
  - After resuscitation, document objective evidence of GI bleeding
    - Ensure adequate iron intakeor bypass, bacterial overgrowth)
    - Exclude other causes of blood loss and iron deficiency anemia
    - Exclude hematologic causes (check for hemolysis, retic count, response to iron)
  - Rule out upper and lower sources of bleeding
    - Consider 2nd look endoscopy
      - Slow careful procedure
      - Adequate visualization
      - Good preparation
  - Proceed with small bowel imaging with most readily available method

Suggested Algorithm for the management of occult bleeding identified by the presence of IDA and/or fecal occult blood (FOB)

AGA Technical Review on Obscure GI bleeding



Printed with permission: Raju,GS, et al. Gastroenterology 2007; 133: 1697-1717.

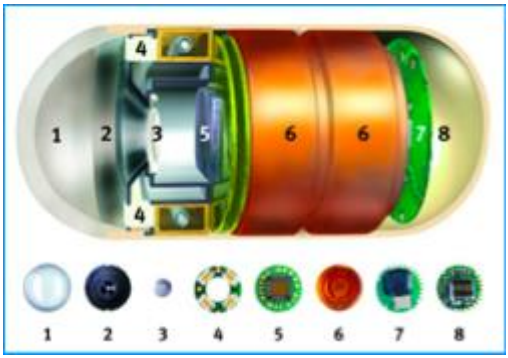
- Diagnostic imaging
  - Push enteroscopy
  - Deep enteroscopy : Single or
  - Double balloon
  - Capsule endoscopy (CE or WCE)
  - Nuclear bleeding study
  - Meckel scan
  - Intraoperative endoscopy
  - Dedicated small bowel X-ray series - Small bowel enteroclysis
  - Abdominal CT scan
  - CT angiography
  - CT enteroclysis
  - MRE – MR enteroclysis - MREG – enterography
  - Angiography
  - Heparinized angiography
- Endoscopy

Review the choices at your institution, discuss with the patient and your involved colleagues how they might want to proceed.

Remember the 3 A's :
- Affability
- Availability
- Ability

Wireless Capsule

PillCam Capsule Components



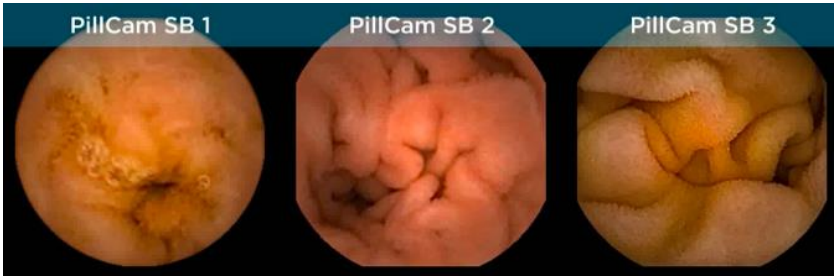
1. Optical dome
2. Lens holder
3. Lens
4. Illuminating LEDs (light emitting diodes)
5. CMOS (Complementary Metal Oxide Semiconductor) image
6. Battery
7. ASIC (Application Specific Integrated Circuit) transmitter
8. Antenna

Photograph kindly provided by the manufacturer

Dimensions:
Height: 11 mm
Width: 26 mm
Weight: 3.0 gr

Pillcam SB3 Capsule

○ Physical	–	Dimensions	▪ Length 26.2 mm; Diameter: 11.4 mm
	–	Weight	▪ 3.0 gr
	–	Material	▪ Biocompatible plastic
○ Optical	–	Illumination	▪ 4 white light emitting diodes
	–	# of imaging heads	▪ 1
	–	Field of view	▪ 156 * ISO-8600-3
	–	Effective visibility	▪ Distance: 3 cm
	–	Min. detectable object	▪ At least 0.07 mm
	–	Frequency	▪ 434.1 MHz
	–	Band width	▪ 3.2 MHz @ 2.7 Mbps; 6.5 MHz @ 5.4 Mbps
	–	Modulation	▪ MSK
	–	RP [nW]	▪ ~20
○ Operational	–	Frame rate	▪ 2 fbs or 2-6 fps
	–	Operating time	▪ ≥ 8 hours
	–	Chemical safety	▪ Resistant to dissolution in pH = 2 to pH = 8
	–	Operating temperature	▪ 20 – 40 ^{o}C
	–	Storage temperature	▪ 0 – 25 ^{o}C
○ Downlink communication	–	Operating frequency	▪ 13.6 MHz
	–	Receiver Bandwidth	▪ ± 150 KHz



Differences between SB Capsule

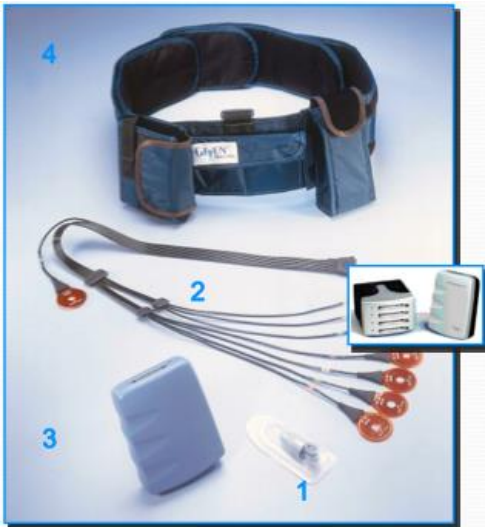
	Given Imaging Pilicam SB2	Olympus Endo Capsule	Intro-Medic MicroCam	Chonqqing Jinshan OMOM
Photography system	CMOS 2-6 Frames / sec	CCD 2 Frames / sec	CMOS 3 Frames / sec	CMOS 2 Frames / sec
Field of view	156 degrees	145 degrees	150 degrees	140 degrees
Transmission	Radio frequency	Radio frequency	Transdermal	Radio frequency
Cost	+++	+++	+++	++
Hours of recording	> 8 (11)	8 – 10	11	8
Size	11.4 x 26.2 mm	11 x 26 mm	11 x 24 mm	13 x 27.9 mm

Patient Experience

- 12 hour fast the night before
- Often a bowel prep (if no diarrhea) e.g. 2 litres PEG +/- Dulcolax after
- Capsule ingested between 7-8 AM, +/- simethicone (+/- domperidone).

- Liquid diet after 2 hours, keep active
- Light meal 4 hours after ingestion
- Return for disconnect after 8 hours
- Capsule passes naturally

Examination Set

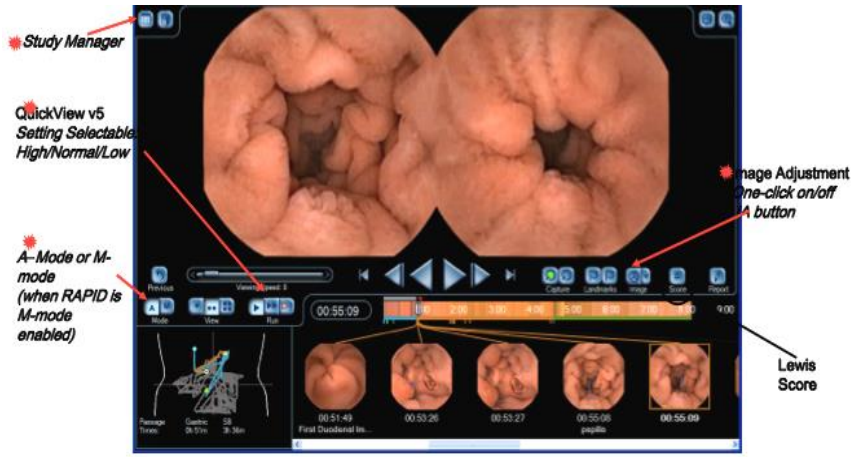


1. The M2A Capsule
2. SensorArrayTM
3. Given DataRecorder
4. Recorder Belt
5. RAPID Booster

PillCam® SB 3

- Components
  - PillCam SB 3
  - RAPID® for PillCam software v8
  - PillCam recorder DR3
  - PillCam sensor belt SB3

RAPID® 5 Features



The QuickView viewing mode does not replace the need to view the complete video.

Image Adjustment

Allows customization of image appearance to help visualization

- Indications for VCE
  - Obscure GI Bleeding including iron deficiency anemia (IDA)
  - Small bowel disease suspected
    - Crohn disease approved in 2011
    - Small intestinal tumors
    - Surveillance in polyposis syndromes
    - Refractory malabsorptive syndromes
- Relative contraindications
  - Achalasia
  - Dysphagia
  - Gastroparesis
  - Other motility disorders (e.g. small bowel diverticulosis)
  - GI obstruction, strictures
  - Fistulas
  - Patients with cardiac pacemakers or other implanted electro-medical devices

- Benefits of capsule endoscopy
  - Non-invasive, painless, no anesthesia, no need for ride home
  - Immediate recovery, patient ambulatory for the day
  - Office procedure, predictable visit, efficient
  - Excellent patient preference and compliance
  - “Physiologic endoscopy”: bowel in normal state without air insufflation or scope trauma
  - Exam can be performed on anticoagulation
  - Good to excellent images – can see flat mucosal lesions (as well as others)
  - Capsule is disposable – no clean up
  - Images can be stored easily

- Complications
  - Major complications mostly associated with strictures
    - Retention of capsule in 0.75%
    - Obstruction in 0.5%, rare aspiration
    - Need deep (balloon) enteroscopy or surgery to retrieve dissolvable capsule in development
  - Uncommon complaints of nausea, vomiting, dysphagia

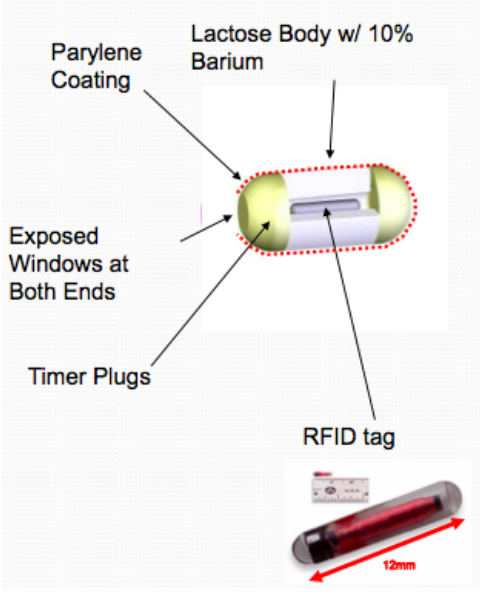
Safety approach: consider Agile Patency Capsule (“dummy capsule”) or SBFT prior to CE in patient with suspected high grade strictures

Disadvantages to capsule endoscopy

- Cost /reimbursement issues if mechanism not in place
- May not see all of the small bowel (delayed transit, bile in ileum, blood in small bowel) Incomplete in 10-25%
- Imprecise localization within the small bowel
- Rare chance of obstruction

- Unable to biopsy, mark or deliver therapeutic intervention
- Until recently, could not be read in real time
- Forethought needed to decide what will be done once information obtained
- Possible management issues: patients have complicated problems and other more important causes of anemia; may need careful repeat endoscopies on many non-GI referrals prior to capsule; expectation we will continue management; need resources for a big program

Agile Patency Capsule (Biocompatible, food-grade components)



Principles of Operation

- Stays intact for minimum 30 hours post-ingestion.
- Disintegrates after 30 hours post-ingestion in GI tract.
- Emits electromagnetic waves at 64 KHz when sensing electromagnetic waves at 128 KHz.(Radiofrequency ID tag)

Delvaux M, et al. Endoscopy 2005; 37(9): 801-807

What are typical VCE Finding in OGIB Patients?

- 92 patients referred for obscure-overt bleeding (n=36) or obscure-occult bleeding (n=56) underwent CE
- All patients had recently undergone at least 2 endoscopic exams of the upper-GI tract and at least 1 ileocolonoscopy, all with negative results
- The CE exam was considered positive in 59.8% of patients (55/92)
- The outcome after CE-guided therapy was favorable in 61 of 92 patients (66.3%), with a mean follow-up of 635.5 days

Hindryckx P, et al. Gastrointest Endosc. 2008;68(1):98-104.

CE Findings in OGIB Patients

- Common
  - Angiodysplasia
  - Active bleeding
  - Erosions/ulcerations
- Uncommon (< 3%)
  - Tumors
  - Ulcerated stenosis
  - Jejunal venous malformations
  - Abnormal mucosal pattern
- ~ 45% of lesions were located in the jejunum- out of reach by upper or lower endoscopy
- The remainder of the lesions are within reach of EGD (esophagus ~5%, stomach ~8%, duodenum ~22%) and colonoscopy (ileum ~22%)

Lepileur L, et al. Clin Gastroenterol Hepatol 2012; 10: 1376-80

Highlights

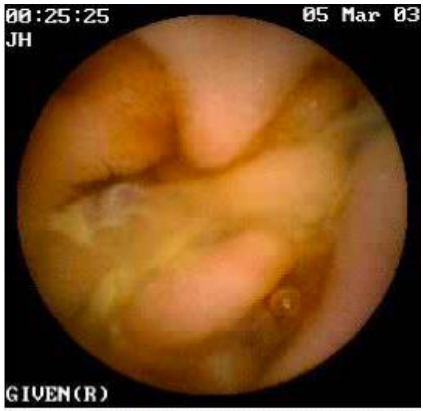
- Capsules were retained in 9 patients – 3 in stomach, 3 at SB tumors and 3 at Crohn strictures (1% overall)
- Mean gastric emptying time 40 min
- Mean SB transit 260 minutes
- CE failed to reach cecum n 137 patients (15%)
- Of the 509 patients with + diagnosis, therapeutic intervention in 356 (278 endoscopy (79%), 75 by surgery (21%) and 3 pts by I.R (0.3%)
- 153 patients (30%) managed by conservative medical treatment.

Lepileur L, et al. Clin Gastroenterol Hepatol 2012; 10: 1376-80.

What did our capsule study show on Patient 1?

Case 1. – Capsule

- Fresh blood in 2nd part duodenum
- Bleeding lesion in jejunum
- Battery life expired before capsule reached cecum
- Push enteroscopy revealed oozing angiodysplasia in distal duodenum and he had push enteroscopy and gold probe (bipolar) cautery



Follow-up

- No further melena, transfusions, iron infusions
- Hb now 98 and rising

- Give what to do if lesion is beyond reach of push enteroscope.
  - Supportive care
  - PRBC and iron therapy
  - Refer to another centre for deep enteroscopy (SBE, DBE)
  - Intraoperative enteroscopy
  - Heparinized angiography and embolization
  - Empiric resection of presumed segment of bleeding

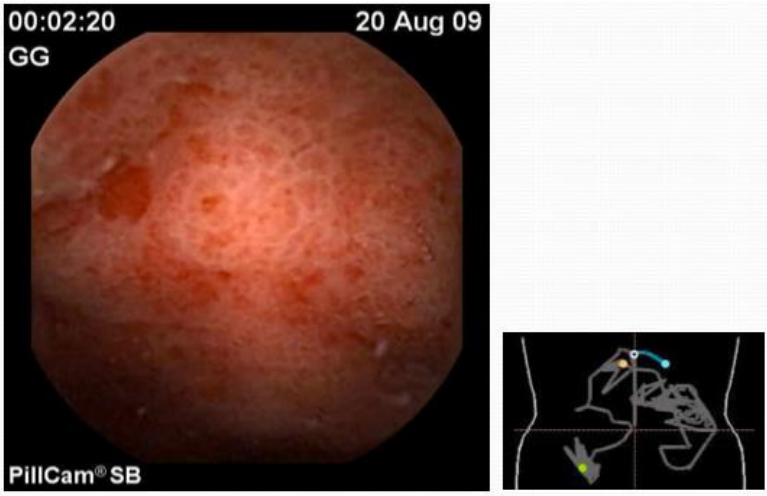
Abbreviation: PRBC, packed blood cell transfusion

Case 2.

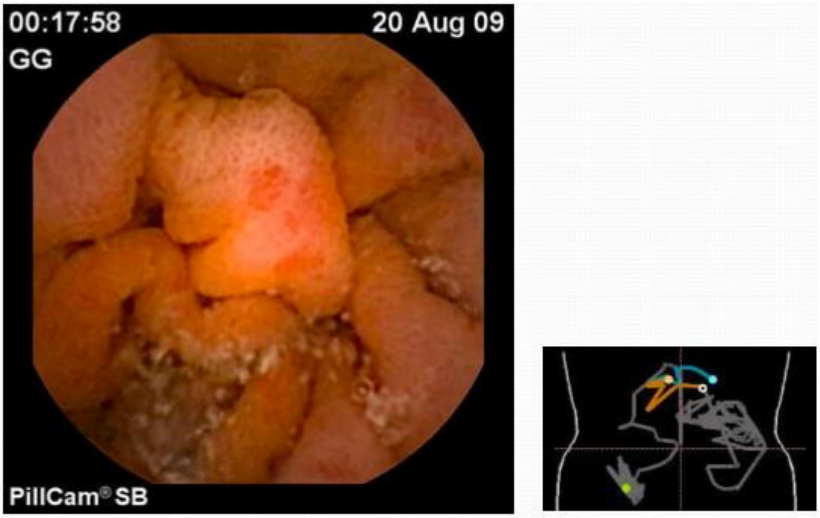
- A 77-year-old man is referred for investigation of obscure gastrointestinal bleeding. He has a 2 year history of recurrent anemia, stool positive for OB, no recent obvious source, and remote history of rectal bleeding.
- Past Medical History:
  - Coronary artery disease, CABG in 2005
  - Diabetes mellitus Type II
  - Hypertension
  - Liver cyst(s) resected – 1970s
  - TIA’s
  - Mild COPD
  - Myelodysplasia

- Past GI History:
  - 2 hospital admissions in Alberta for rectal bleeding, 2-3 yrs ago, patient unaware if source found
  - No history of heart burn, peptic ulcer disease, dyspepsia, ASA/NSAID use, including investigations or treatment for such
  - No family history of bleeding, GI problems or GI malignancies
- Current GI History:
  - Admissions to hospital in Leamington and Windsor, x4, for rectal bleeding and anemia over the past 2 yrs
  - 3 gastroscopies: findings include grade 3 errosive esophagitis with hemorrhagic gastritis once, gastritis another time, benign polyp removed from stomach, and last scope normal except for hiatus hernia and maybe some Barrett's change
  - 3 colonoscopies: findings include hemorrhoids, diverticulosis, tubular andenomas removed with polypectomy, and no clear cause of rectal bleeding
- Other Imaging:
  - CT scan, chest, abdomen, pelvis: finding of splenomegaly
  - Nuclear RBC scan: diffuse hyperemia of the entire abdomen particularly left side, spleen enlarged and very intense, increased activity in the mid and lower abdomen suspicious for bleeding from the small bowel
  - Abdominal ultrasound: splenomegaly 17cm, small liver

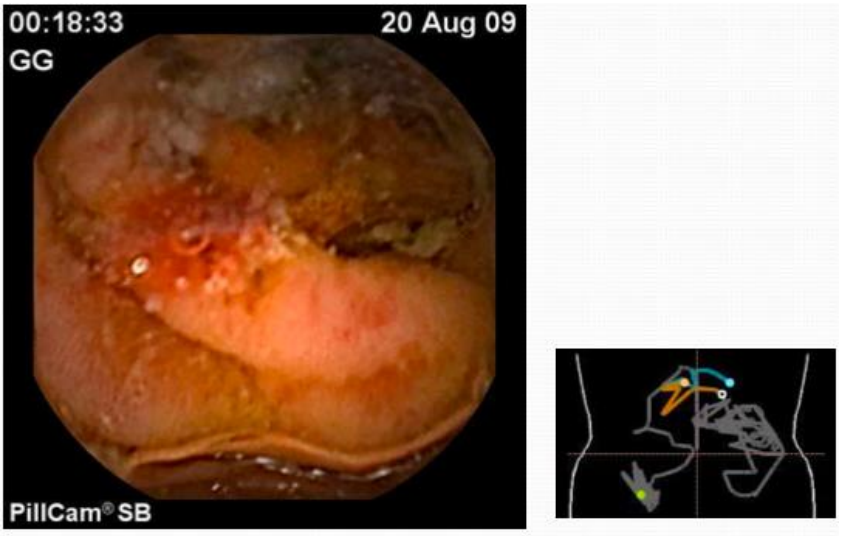
- Other Investigations:
  - Blood work: hemoglobin 86, WBC 5.3, platelets 97, Smear: slight rouleaux formation, INR 1.4, creatinine 130, normal liver enzymes
- Management:
  - Proton pump inhibitors for gastritis
  - Multiple transfusions (15-20 units pRBCs)
  - Patient referred for further small bowel investigations
- While waiting to see us:
  - Patient develops distended abdomen, ascites diagnosed, paracentesis performed and confirms portal hypertension, and diuretics spironolactone and furosemide started – controlled with low dose
  - Liver investigations: HAV, HBV, HCV all negative, other serology negative
  - Liver biopsy: micronodular cirrhosis, likely secondary to NAFLD

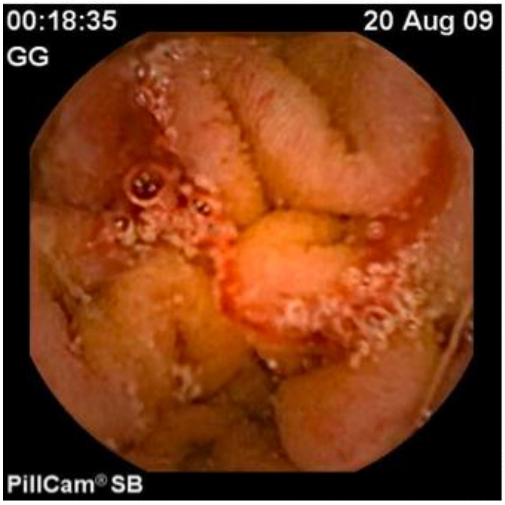


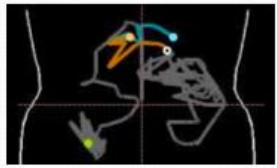
Gastropathy – likely PHG

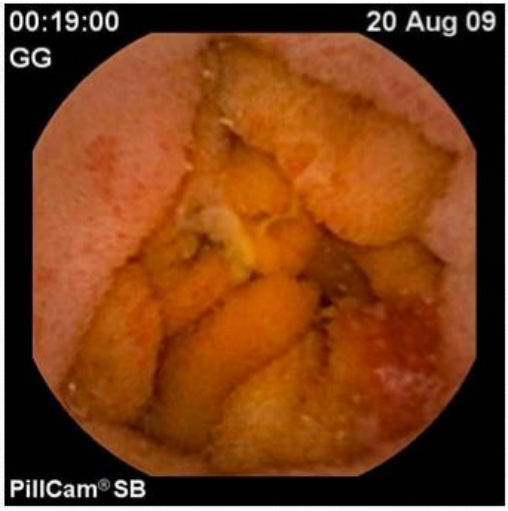


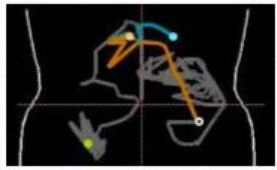
Duodenal Erosion



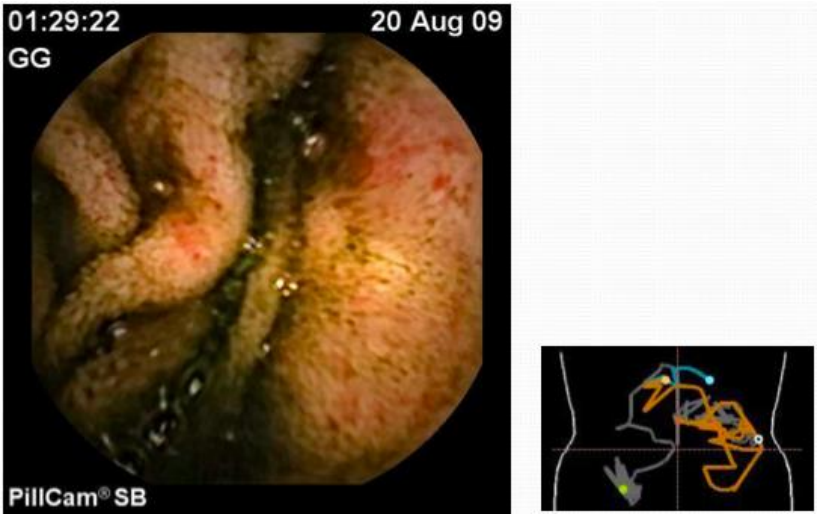




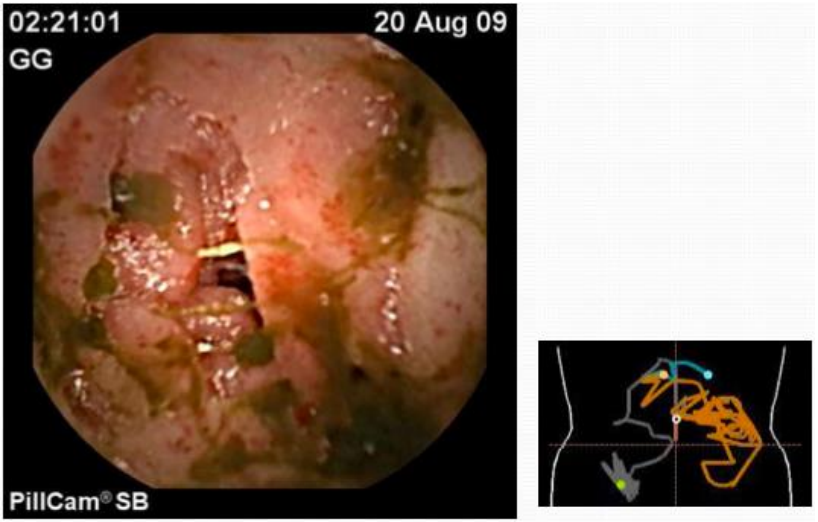




Bleeding duodenal erosion



SB Erosion



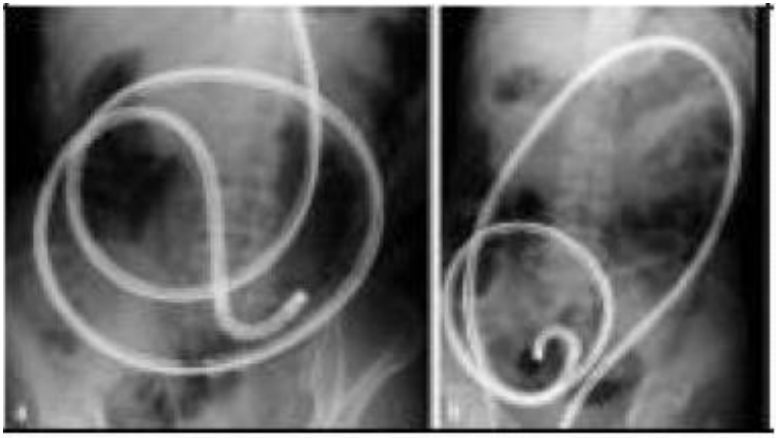
Patchy Erythema

- Conclusion: a few small bleeding points identified in he duodunum/proximal jejunum as well as one spot in the ileum.
  - This may be portal hypertensive enteropathy in a patient with a new Dx of liver cirrhosis.
- Plan
  - Non-selective beta blockers.
  - If bleeding doesn't settle, consider push/deep enteroscopy to cauterize the lesions.
  - Possibly TIPs if extensive and patient eligible

Case 3.

- This 63 year old woman presented with fatigue and noticed to have anemia. This turned out to be iron deficiency and treated in the past with iron supplements.
- Unremarkable upper and lower GI endoscopy
- With stool continuing to be positive, she was booked for a capsule study see in the next 2 slides..
- Patient underwent a push endoscopy while waiting for the balloon
- Polyp/mass biopsied: adenocarcinoma of the jejunum
- She went to surgery and segment of jejunum resected
- Enteroscopy
  - Push
    - Pentax push enteroscope
  - Deep
    - Single balloon (SBE) (Olympus) 2007
    - Double balloon (DBE) (Fujinon) 2003
    - Spiral endoscope (Spirus Medical□Olympus) 2008
    - Navi–Aid Balloon Guided (Smart medical systems)

- Challenging endoscopy
  - Difficult visualization
  - Length (6+meters)
  - Overlapping loops
  - Free intra peritoneal movement
  - Peristalsis
- We only had the push enteroscope and pediatric colonoscope
- DBE scope use first reported in 2001, and now Yamamoto reports to see entire SB in 86%
- Fujinon DBE is 230 cm total length and 200 cm working length plus 149 cm overtube.
  - It has a 2.8mm channel for biopsies and therapeutic manuevers.
- Can insert the scope antegrade or retrograde
  - Prep' will then be NPO or full bowel preparation depending on direction.



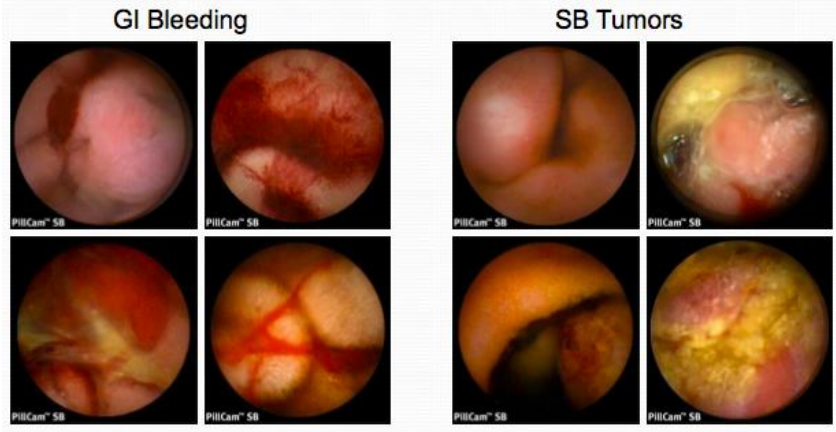
- Indications for Deep Enteroscopy
  - Obscure GI Bleeding
  - Chronic Diarrhea
  - Iron Deficiency Anemia
  - Abnormal SBFT/CTE
  - Abnormal Capsule Endoscopy
  - Peutz-Jegher Polyps
  - Refractory Celiac Disease
  - Retained Foreign Bodies
  - Intestinal Strictures
  - Crohn Disease
  - Small Bowel polyp removal/Bx/Tatoo
  - Unusual Indications
    - Mid Gut Carcinoid
    - ERCP in Roux-en-Y situations
    - Abdominal symptoms in gastric bypass patients
    - Protein wasting enteropathy
    - Jejunal Stenting
    - PEG placement in Gastric bypass anatomy
    - Previously failed colonoscopy

- Therapeutic applications for deep small bowel enteroscopy
  - Treatment of GI bleeding
  - Small bowel polypectomy
  - Stricture dilation
  - Stenting of small bowel obstructions
  - Foreign body removal
  - Endoscopic mucosal resection
  - Placement of direct percutaneous jejunostomy

Masses on CE

Signs suggesting submucosal process	Signs suggesting malignancy
○ Stretching of the mucosa, bridging folds ○ Translucent mucosa ○ Mucosal edema ○ Persistence of the suspect image in a series of frames ○ Appearance of a more congested color than the surrounding mucosa	○ Obstruction of the lumen ○ Thickening/infiltration of the plicae ○ Hypervascularization ○ Bleeding ulcers

Capsule images - GI Bleeding & Tumors



Capsule images – Celiac Disease

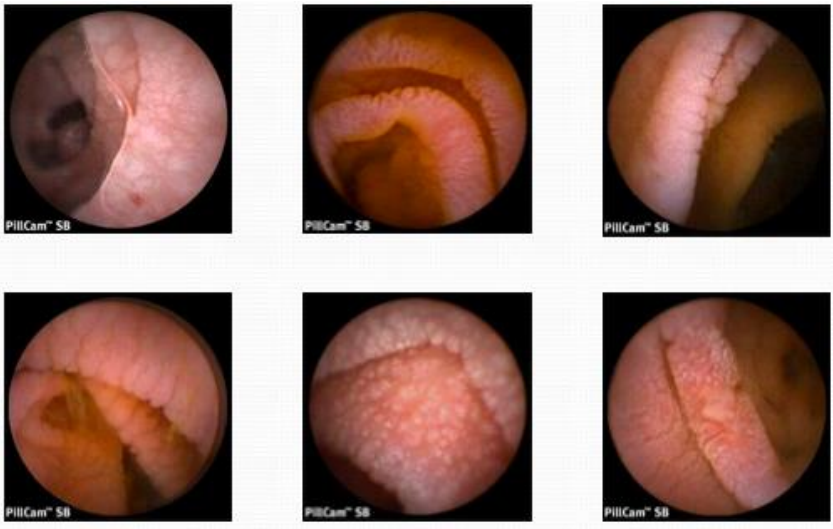
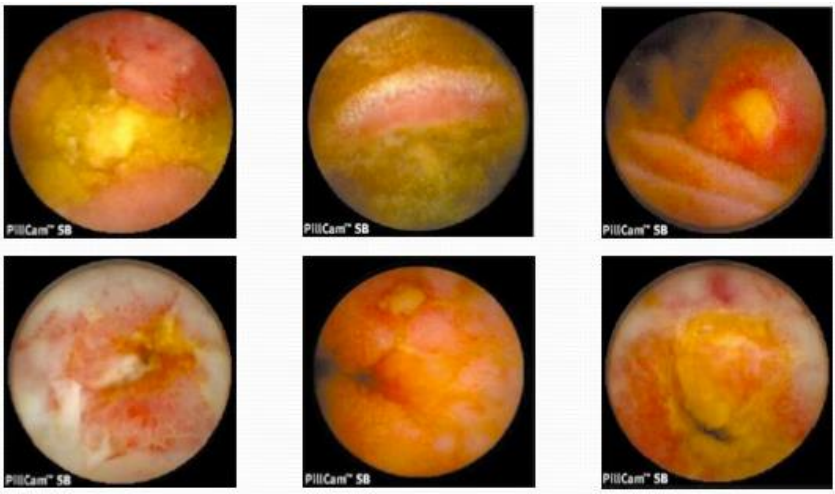


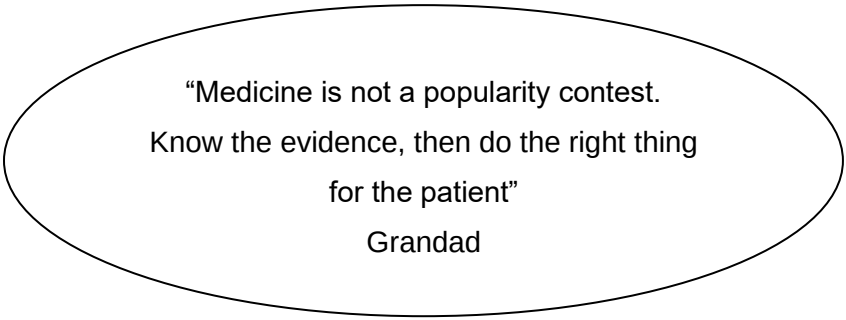
Image Spectrum - Crohn Disease



- Highlight
  - All patients had negative upper and lower endoscopy
  - Randomized but no blinding
  - No bowel prep or promotility agents
  - Results reviewed by 2 staff independently
  - Primary outcome was diagnostic yield
  - Secondary outcome measures included long- term rebleeding rates, further hospital admissions for bleeding or anemia, further blood transfusions and death
  - Patients followed every 12 weeks x 1 year
- Diagnostic Yield
  - For Capsule Endoscopy + in 16 patients:
  - 4 active bleeding bleeding post duodenum (later Dx angiodysplasia in 2 and ulcer in one)
  - 6 small bowel ulcers/eropsions
  - 3 small bowel tumors
  - 3 gastric bleeding lesions not previously seen on EGD
  - For angiography + in 6 patients:
  - Meckel’s diverticulum
  - 1 small bowel tumor

- Further intervention after initial assigned investigations

	Capsule endoscopy (N = 30)	Angiography (N = 30)	P value
○ Crossover to other modality	0 (0%)	4 (13.3%)	0.11
○ Surgery for small bowel diseases	3 (10%)	2 (6.7%)	1.0
○ Balloon directed enteroscopy	7 (23.3%)	1 (3.3%)	0.05
○ Further hospitalization for rebleeding or anemia	5 (16.7%)	5 (16.7%)	1.0
○ Further transfusion	3(10%)	3 (10%)	1.0
○ Death*	4 (13.3%)	4 (13.3%)	1.0



- Causes and timing of rebleeding

Group	Initial findings	Causes of bleeding	Time of rebleeding (month)
○ Capsule endoscopy	– Positive	Vascular ectasia = 1	3
		Small bowel GIST = 1	18
		Unidentified = 1	8
	– Negative	Duodenal varices = 1	6
		Small bowel ulcer = 1	23
○ Angiography	– Positive	Colonic diverticular bleeding = 2	< 1
	– Negative	Small bowel angiodysplasia = 1	2.5
		Duodenal polyp = 1	32
		Small bowel diverticular bleeding = 2	< 1
		Small bowel ulcer = 1	2.5
		Colonic diverticular bleeding = 1	< 1
		Unidentified = 2	31 and 38

Abbreviation: GIST, gastrointestinal stromal tumor

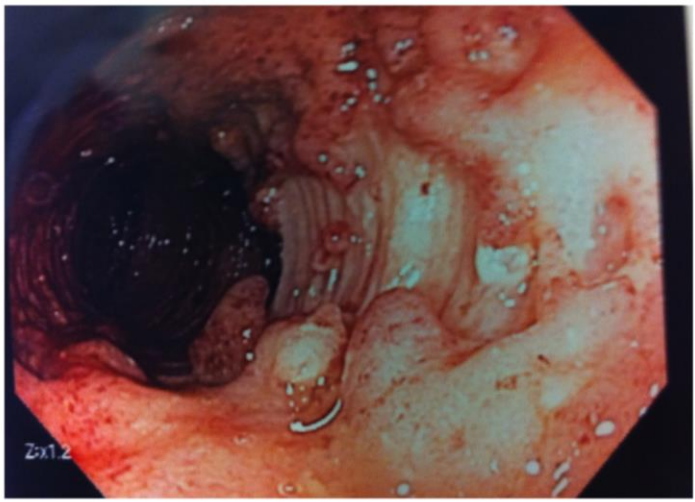
COLON

Skin Manifestations of IBD: Sweet Syndrome and Pyoderma Gangrenosum

Malcolm Wells

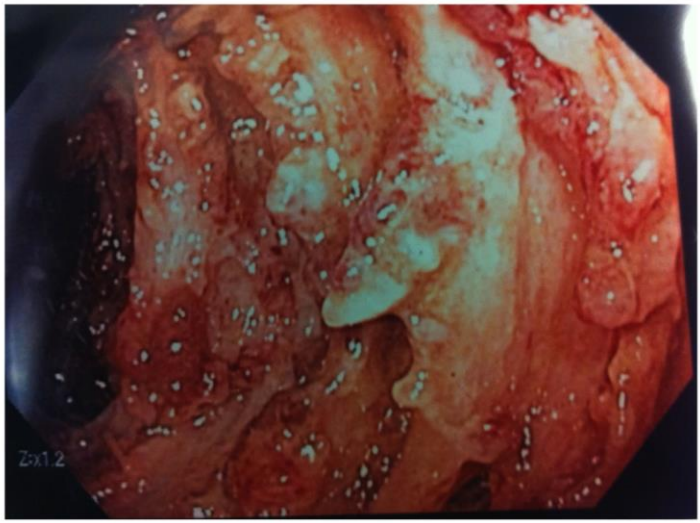
Case 1

- 64-year-old gentleman
- Three-month history
  - Progressively worsening mucousy bloody diarrhea
  - Polyarthritis
  - A rash over his lateral malleolus
- PMHx His history
  - Quadriceps tendon rupture
  - Supraventricular tachycardia
- Medications:
  - Short course of prednisone initiated shortly prior to his hospitalization
- SHx
  - Non-smoker
  - Non-drinker
- FHx non-significant
- Physical exam
  - Fever of 38.2^{o}C
  - Swollen left knee, ankle and foot
  - He had multiple oral ulcers.
  - On the medial aspect of the left malleolus was a 5 cm bullous lesion with erythematous base and draining serosanginous fluid.
  - The remainder of the exam was non-contributory.



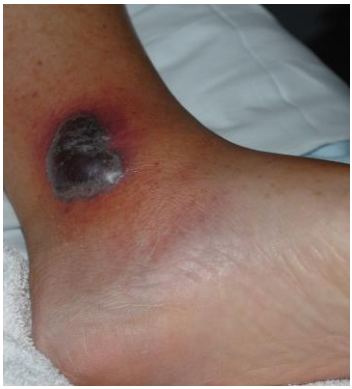
Sweet Syndrome Secondary to Inflammatory Bowel Disease

Printed with permission: Wells, Stecho, Wehrli, Khanna. Canadian Journal of Gastroenterology 2013;**27**(3):124-125

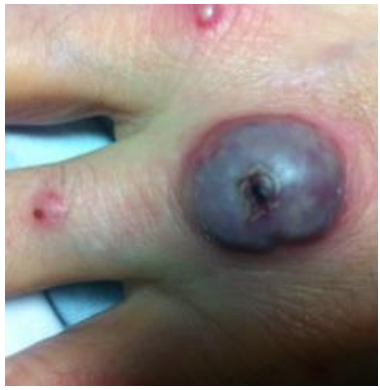


SKIN MANIFESTATION OF IBD

Typical Lesions



64 yr male with severe IBD



65 yr male with lung cancer

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SWEET SYNDROME (aka idiopathic sweet syndrome)

- Epidemiology
  - Age
    - 30-60 most common, but all ages can be affected
  - Sex
    - The sex distribution varies with the subtype of Sweet syndrome and age.
      - In classical Sweet syndrome, 80% of patients are women
      - Drug-induced = 70% women
      - Malignancy-associated = 50-60% women

- Definition
  - Meets the established diagnostic criteria, AND
  - Is not associated with malignancy or drug exposure.

SKIN MANIFESTATION OF IBD

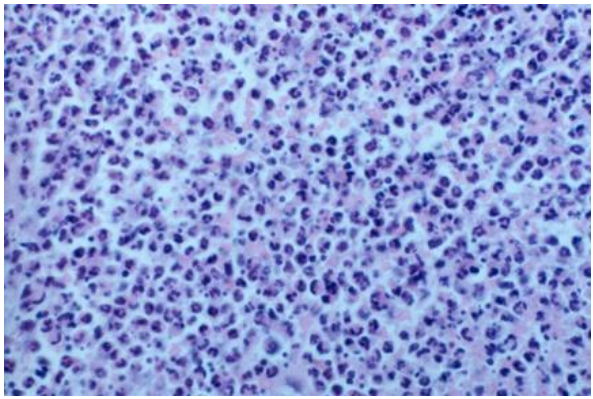
- History
  - Originally described by Sweet RD. 1964
  - Sweet Syndrome (or Sweet Syndrome) is characterized by (Cohen 2007; Burrall B, 1999)
    - Fever
    - Leukocytosis
    - Erythematous tender skin lesions with neutrophilic infiltration of the upper dermis
  - Several types have been described including:
  - Classical/idiopathic Cohen 2007; Burrall 1999; Chan et al., 1994; Bourke et al., 1997)
    - Malignancy-associated (Cohen 1988; Cohen 1993A)
    - Drug-induced, pregnancy-related (Cohen 1993B)
  - Constitutes the majority of cases of Sweet syndrome

- Pathogenesis
  - Not well understood. Several theories
  - Hypersensitivity reaction
    - Antigens stimulating cytokines that promote neutrophil activation and infiltration
  - Cytokine dysregulation
    - G-CSF is compelling
    - Other cytokines are postulated to play roles
      - Granulocyte-macrophage colony-stimulating factor (GM-CSF)
      - Interleukins (eg, IL-1, IL-3, IL-6, and IL-8)
      - Th1 cytokines (IL-1α, IL-1β, IL-2, and interferon-gamma) are elevated, whereas Th2 cytokines (IL-4) often remained normal
  - Genetic susceptibility
    - Abnormalities in chromosome 3q
    - HLA-B54

- Antibodies to neutrophilic cytoplasmic antigens
  - They've have been detected in some
  - A pathogenic role is unknown

- Clinical Manifestations: Cutaneous
  - Lesions typically present as tender, edematous, and inflamed papules, plaques, pustules and nodules
  - Lesions vary in size, shape, appearance, location etc…

- Pathology
  - Skin biopsy remains the gold standard.
  - The characteristic histologic features of Sweet syndrome include:
    - Edema in the superficial dermis
    - Dense infiltrate of neutrophils in the upper and mid-dermis with sparing of the epidermis
    - Leukocytoclasis (infiltrating leukocytes)
    - Endothelial swelling
    - Absence of vasculitis



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SKIN MANIFESTATION OF IBD

Classical Sweet Syndrome Criteria

- Major Criteria

1. Abrupt onset of painful erythematous plaques or nodules
2. Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis

- Minor Criteria

3. Pyrexia >38°C
4. Association with an underlying inflammatory disease, or pregnancy, or preceded by an upper respiratory or gastrointestinal infection or vaccination OR a hematologic or visceral malignancy
5. Excellent response to treatment with systemic corticosteroids or potassium iodide
6. Abnormal laboratory values at presentation (three of four): erythrocyte sedimentation rate >20 mm/hr; positive C-reactive protein; >8,000 leukocytes; >70 percent neutrophils

* Both major and 2/4 minor criteria are required.

* Criteria are the same for malignancy-associated Sweet syndrome, except 4

Su and Liu 1986; von den Driesch 1994)

- Associated Conditions
  - Infections
    - Particularly upper respiratory tract and gastrointestinal infections
    - Sweet syndrome usually develops 2-3/52 after infection
  - Inflammatory bowel disease
  - Pregnancy
  - Less frequent and less definitive associations exist
    - Human immunodeficiency virus [HIV], tuberculosis, chlamydia, viral hepatitis
    - Primary immunodeficiencies
    - Autoimmune conditions

Malignancy-associated Sweet Syndrome

- Accounts for a significant portion of cases of Sweet syndrome (20%) (Cohen 1993A)
- Sweet syndrome may precede, follow, or appear concurrently with a malignancy
- In patients with previous histories of cancer, the development of Sweet syndrome may portend disease recurrence.
- Hematologic malignancies (85%) > solid tumor cancers (15%) (Cohen et al., 1988)
- AML is the most frequently associated malignancy Cohen et al., 1988)
- AML = 42% of the hematologic malignancies (Cohen et al., 1988)
- Myeloproliferative disorders = 22% (Cohen et al., 1988)

- Among solid tumors
- Carcinomas of the genitourinary organs, breast, and gastrointestinal tract are most frequent (Cohen 1993A)

Drug-induced Sweet Syndrome

- Multiple drugs may contribute to Sweet syndrome
- Granulocyte-colony stimulating factor (G-CSF) is the most widely reported
- Timing:
  - About two weeks after first drug exposure
  - Recurrence can be sooner after reexposure to the inciting drug

Antibiotics	Minocycline Nitrofurantoin Norfloxacin Ofloxacin Quinupristin/dalfopristin Trimethoprim-sulfamethoxazole
Antiepileptics	Carbemazepine Diazepam
Antihuman immunodeficiency virus drugs	Abacavir (synthetic carbocyclic nucleoside analogue)
Antihypertensives	Hydralazine
Antineoplastics	Bortezomib Imatinib mesylate Lenalidomide
Antipsychotics	Clozapine

○ Antithyroid hormone synthesis drug	– Propylthiouracil
○ Colony stimulating factors	– Granulocyte-colony stimulating factor – Granulocyte-macrophage-colony stimulating factor – Pegfilgrastim
○ Contraceptives	– Levonorgestrel/ethinyl estradiol (Triphasil) – Levonorgestrel-releasing intrauterine system (Mirena)
○ Diuretics	– Furosemide
○ Nonsteroidal antiinflammatory agents	– Celecoxib – Diclofenac
○ Retinoids	– All-trans retinoic acid – 13-cis-retinoic acid

Drug-induced Syndrome Criteria

A. Abrupt onset of painful erythematous plaques or nodules

B. Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis

C. Pyrexia >38°C

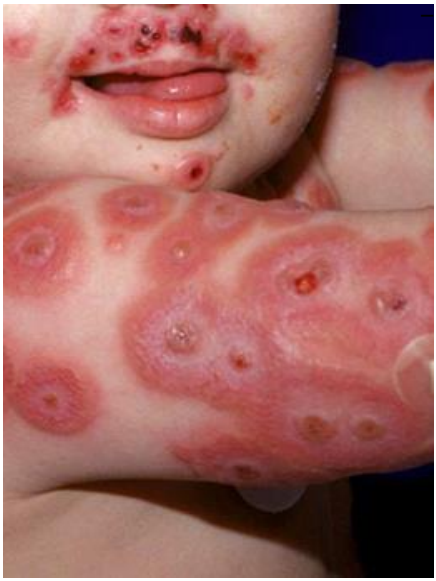
D. Temporal relationship between drug ingestion and clinical presentation, or temporally-related recurrence after oral challenge

E. Temporally-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids

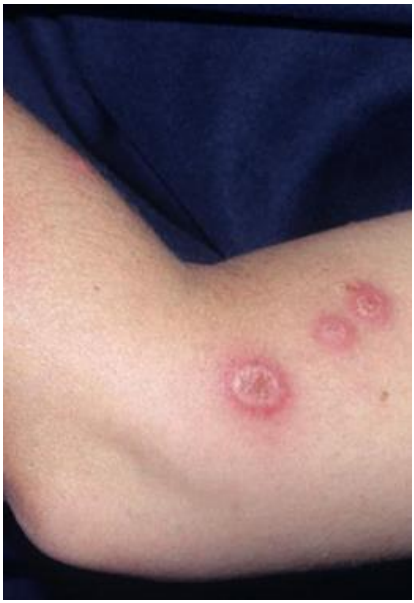
* All 5 criteria are required

Typical Lesions

SKIN MANIFESTATION OF IBD



Multiple inflammatory plaques are present on the face and upper extremities.



- Plaques with a pustular component are present on the upper extremity.

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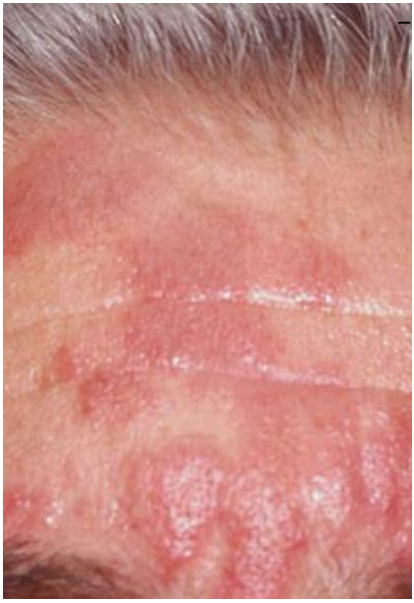
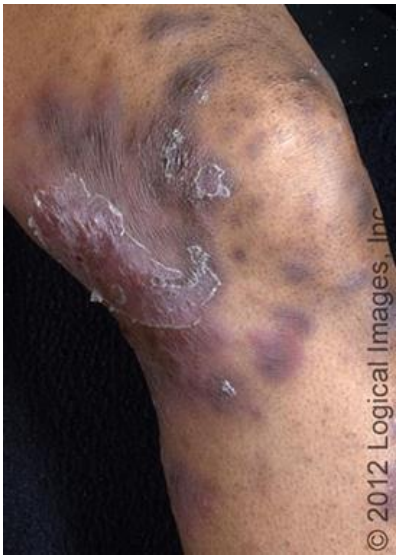
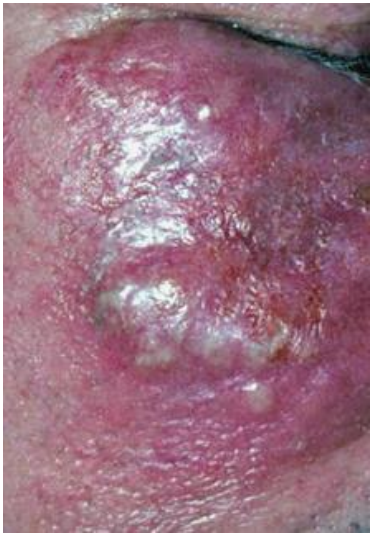
SKIN MANIFESTATION OF IBD



- Erythematous, edematous plaques are present on the face.

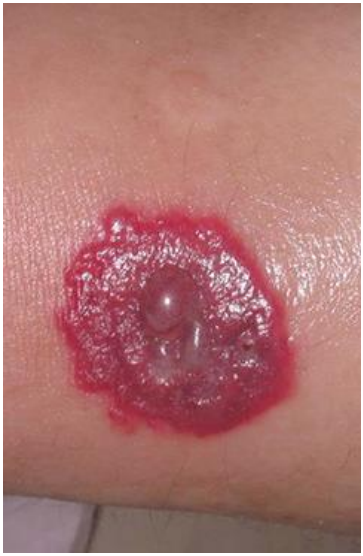


- Inflammatory plaques are present on the extremities.

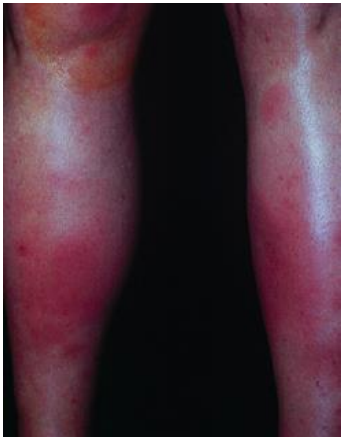


- A brightly erythematous plaque with a pustular component is present on the face of this patient with Sweet syndrome.

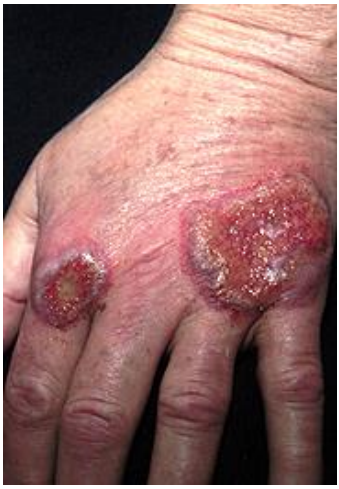
Less common presentations



- Bullous Sweet syndrome
  - Bullous Sweet syndrome is an uncommon presentation of Sweet syndrome in which vesicles and flaccid bullae overly erythematous to violaceous plaques
  - Ulceration resembling pyoderma gangrenosum may occur in bullous Sweet syndrome; this manifestation most commonly occurs in the setting of hematologic malignancy



- Subcutaneous Sweet syndrome
  - In subcutaneous Sweet syndrome, the site of neutrophilic infiltration is in the subcutaneous fat, rather than the dermis
  - This results in the development of erythematous nodules with minimal superficial change.
  - The nodules are usually 2 to 3 cm in diameter, and the extremities are common sites of involvement.
  - Subcutaneous Sweet syndrome can closely resemble erythema nodosum, particularly when it involves the lower legs



- Neutrophilic dermatosis of the dorsal hands
  - Neutrophilic dermatosis of the dorsal hands (also known as pustular vasculitis of the dorsal hands) is a localized disorder that may be on a continuum with Sweet syndrome
  - Affected patients develop inflammatory and pustular plaques on the dorsal surfaces of the hands
  - On the right: painful plaques that have progressed to ulceration. These developed in a 60-year-old female with seropositive rheumatoid arthritis.

- 3 case reports of necrotizing Sweet syndrome
- Pathergy may occur
  - Even minor trauma, such as that obtained with a needle stick, may result in the development of skin lesions

- Evaluation of Malignancy
  - Malignancy testing should only be considered in the setting of:
    - Reasonable clinical suspicion for an underlying malignancy
      - Constitutional symptoms such as weight loss
    - And the absence of another explanation for a Sweet syndrome diagnosis
      - Pregnancy, drug exposure, recent infection, inflammatory bowel disease, rheumatoid arthritis, etc.
  - The screening for malignancy should begin with age-appropriate cancer screening guidelines.

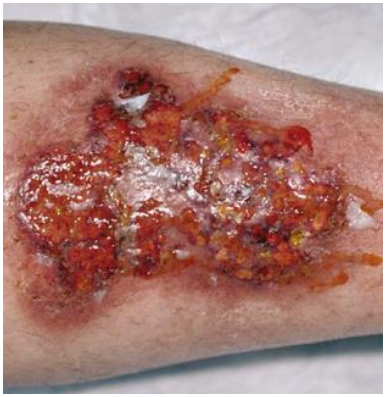
- Treatment
  - Treat underlying conditions
    - Treat malignancy or inflammatory condition
    - Stop the causative medication
  - First Line Treatments
    - Systemic corticosteroids
      - Prednisone 0.5-1 mg/kg daily
      - Symptoms improve within 48 hours and skin lesions usually resolve within 1-2 weeks
      - Once resolution, taper over four to six weeks

- Colchicine
  - 1-1.5 mg daily for a mean of 15 days

- Alternative First Line Treatments
- Dapsone
  - Case reports document successful treatment of Sweet syndrome with dapsone [16, 18]
- Potassium iodide
  - 300 mg TID x 3/52
  - Case series: 7/8 patients treated had a dramatic
  - The mechanism is not well understood

- Prognosis
  - Without treatment, the duration of Sweet syndrome is unpredictable
    - Spontaneous resolution may occur after weeks to months. [33]
  - Prognosis is generally good, with the rash usually responding well to systemic steroids.
  - Death from Sweet syndrome is rare.
  - Relapse
    - Occurs in approximately 30% of patients with classical Sweet syndrome after ending treatment

Pyoderma gangrenosum

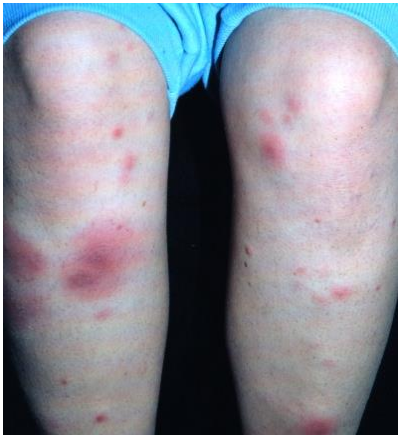


- 64-year-old gentleman
- Three-month history
  - Progressively worsening mucousy bloody diarrhea
  - Polyarthritis
  - A rash
- Endoscopy shows severe IBD
- This purulent ulcer with a ragged and violaceous border is consistent with pyoderma gangrenosum.

- First-lineTreatment – 1
  - Wound Care
  - Surgery is controversial
  - Local corticosteroids often used, but efficacy is questionable
  - Local calcineurin inhibitors — Topical tacrolimus
    - 7/11 patients treated with the tacrolimus and 5/13 treated with clobetasol 0.05% lotion or ointment achieved complete healing
  - Systemic corticosteroids
    - Case reports indicate this is effective
  - Systemic cyclosporine, DMARD’s and biologics

SKIN MANIFESTATION OF IBD

Erythema Nodosum



- 64-year-old gentleman
- Three-month history
  - Progressively worsening mucousy bloody diarrhea
  - Polyarthritis
  - A rash
- Endoscopy shows severe IBD
- Painful erythematous nodules of erythema nodosum are often found in a symmetric distribution on the legs.

- Treatment
  - Usually self-limited or resolves with treatment of the underlying disorder. Thus, treatment is typically symptomatic.
  - Non-steroidal antiinflammatory drugs (NSAIDs)
  - Potassium iodide (360 to 900 mg daily in three divided doses)
    - The basis for the documented benefit of potassium iodide in treating EN is unclear.
  - Glucocorticoids are usually not necessary for idiopathic EN.

Suggested Reading

Bourke JF, et al. Sweet's syndrome and malignancy in the U.K. Br J Dermatol 1997; 137(4): 609-13.

Brooklyn TN, Dunnill MG, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. Gut 2006; 55:505.

Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. Int J Dermatol 2003. 42(10): 761-78.

Hisanaga K, Iwasaki Y. Itoyama Y. Neuro-Sweet disease: clinical manifestations and criteria for diagnosis. Neurology 2005. 64(10): 1756-61.

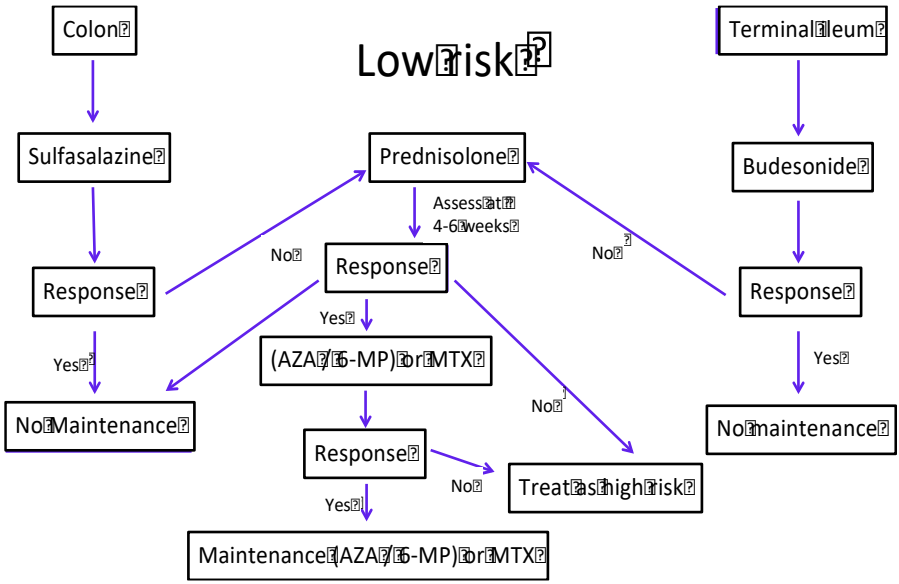
Wells M, et al. Sweet's Syndrome Secondary to Inflammatory Bowel Disease. Can J Gastroenterol 2013; 27(3):124-5.

Crohn Disease Algorithms

Nilesh Chande

Crohn Disease Algorithms

- Establish disease site
- Determine low risk vs. high risk patient
  - Younger age
  - Cigarette smoking
  - Steroids
  - Perianal / other complex fistulizing disease
  - Upper GI disease
  - Extensive disease
  - Severe endoscopic lesions
  - Extra-intestinal manifestations
  - High inflammatory burden



Sulfasalazine

- Mild benefit for colonic Crohn
  - Remission induction but not maintenance
- Good for joint disease
- 500 mg tabs
  - Start slow and titrate up - target dose about 4 g/day
- Split into 4x/day to minimize side effects
- Side effects
  - Common – headache, nausea, diarrhea
  - Less common – cytopenia, hypospermia, folate deficiency

Budesonide (Entocort)

- Controlled ileal release
- For ileal and R colon disease – remission induction but not maintenance
- 3 mg tabs
- Dose 9 mg/d x 8 weeks, then 6 mg/d od x 4 weeks, then 3 mg/d x 4 weeks
- 80% first pass metabolism
- Side effects – similar to placebo except slight cortisol suppression

Prednisone

- For inflammatory disease – remission induction but not maintenance
- Steroid therapy in CD – anything less than 15 weeks is no better than placebo
- 1 and 5 mg tabs
- Dose 40 mg po od x 4 weeks, then taper by 5 mg/week to 20 mg, then taper by 2.5 mg/week until off
- Side effects - lots

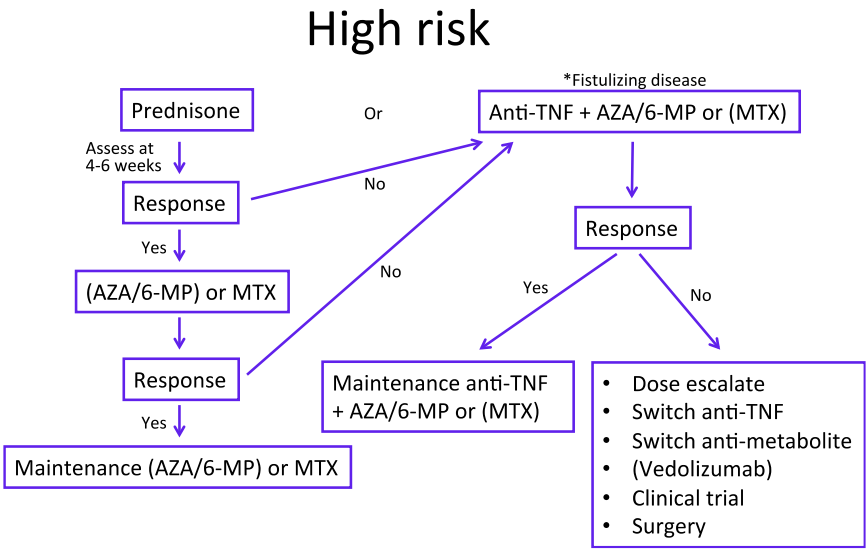
Azathioprine / 6-mercaptopurine

- Mechanism
  - Purine analogue, inhibits DNA synthesis
- Inflammatory disease, slight benefit for fistulizing disease
- Steroid sparing, for remission induction and maintenance
- Takes 3-4 months to work
  - Often started with steroid
- 50 mg tabs
  - Target dose 2-2.5 mg/kg/day (AZA) or 1-1.5 mg/kg/day (6-MP)
- Start 50 mg po od x 1 week, then get blood tests checked, then go to target dose with monthly bloodwork (or titrate up slow and check weekly bloodwork to start)

- Consider TPMT testing prior to starting
- Bloodwork
  - CBC + diff, AST, ALT, ALP, lipase
- Side effects
  - Common – nausea, dyspepsia
  - Less common – neutropenia, hepatitis, pancreatitis, hair loss
  - Rare - lymphoma

Methotrexate

- Mechanism – dihydrofolate reductase inhibitor
- Inflammatory disease
- Steroid sparing, for remission induction and maintenance
- Takes 3 months to work, often started with steroid
- Absolutely contraindicated in pregnancy
- Best given by injection (SC or IM), also 2.5 mg tabs
- Dose 25 mg/ week x 16 weeks, then reduce to 15 mg/week (go back to 25 mg if flare)
- Bloodwork monthly – CBC + diff, AST, ALT, ALP
- Side effects
  - Common – nausea (give folic acid as well)
  - Less common – cytopenia, hepatic fibrosis, pneumonitis, hair loss



Anti-TNF (infliximab – Remicade, adalimumab – Humira)

- Block TNF-alpha which is involved in intestinal inflammation
- Inflammatory and fistulizing disease – remission induction and maintenance
- Work very quickly – within days-weeks
- Reduce hospitalization and surgery, improve quality of life
- Immunogenic – patients often form antibodies against these agents
  - Leads to loss of response or allergic reaction
- Often given with AZA for synergy (only proven for infliximab)
- Usually at least given with low dose AZA (50 mg) or MTX (7.5-12.5 mg) to reduce antibodies

- Side effects
  - Common – immune suppression, reactivation of TB or Hep B → check TB skin test, CXR, Hep B SAg prior to starting - Allergic reaction
  - Rare – CHF, demyelination, lymphoma, non-melanoma skin cancer

Infliximab (Remicade)

- 25% mouse protein
- Given IV
- Dose 5 mg/kg at week 0, 2, 6, then q 8 weeks
- Cost $32,000/year for 60-70 kg patient

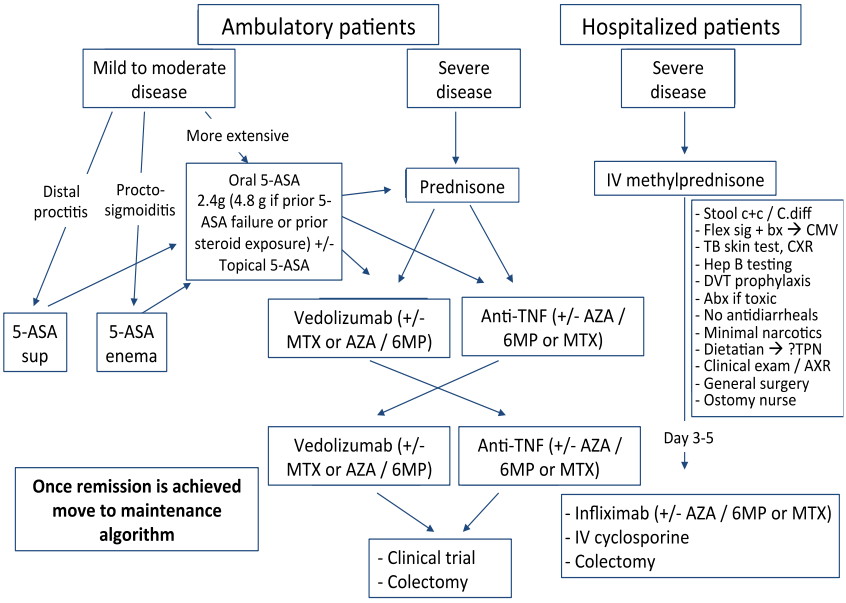
Adalimumab (Humira)

- 100% human protein
- Given sc – comes in syringe or pen
- Dose 160 mg at week 0, 80 mg at week 2, then 40 mg eow
- Cost $24,000/year

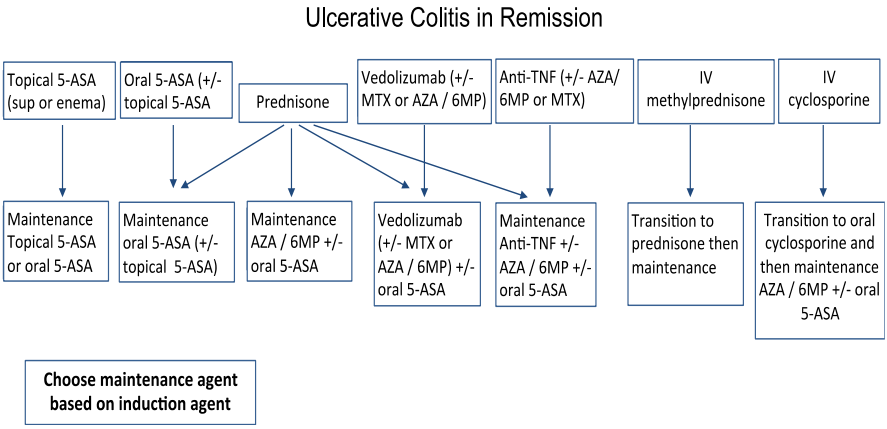
Vedolizumab (MLN-0002)

- Blocks alpha4-beta7 integrin on WBC, stopping migration into inflamed tissues
  - More gut selective than natalizumab which blocks alpha4-beta1 as well and is associated with PML in 1/1000 patients due to reactivation of JC (John Cunningham) virus
- Side effects – immune suppression, headache, nausea, allergic reaction
  - However in clinical trial were similar to placebo

Ulcerative colitis algorithms



Maintenance



Sulfasalazine

- Good for joint disease
- 500 mg tabs - start slow and titrate up - target dose about 4 g/day
- Split into 4x/day to minimize side effects
- Side effects
  - Common – headache, nausea, diarrhea
  - Less common – cytopenia, hypospermia, folate deficiency

Topical 5-ASA (mesalamine)

- Salofalk 500 mg, 1 g sup ; 2 g, 4 g enema (60 cc)
- Pentasa 1 g sup; 1 g, 4 g enema (100 cc)
- Use alone or in combination with oral 5-ASA
- More effective than topical steroids
- Use nightly until symptoms controlled, then maybe use less frequently or prn
- Side effects – headache, interstitial nephritis (rare – check Cr periodically)

Oral 5-ASA (mesalamine)

- Use alone or in combination with rectal therapy
- Can work quickly but may take up to 12 weeks for full response
  - Side effects – diarrhea (especially Dipentum), headache, interstitial nephritis (rare – check Cr periodically)

Medication	Dose	Coating / delivery	Release
○ Asacol	400 mg 800 mg	Eudragit-S polymeric coat	TI + colon (pH>7)
○ Mesasal	500 mg	Eudragit-L polymeric coat	TI + colon (pH>6)
○ Mezavant	1200 mg	Multi-matrix system	Colon
○ Teva-5-ASA	400 mg	Acrylic-based resin	TI + colon (pH>5.5)
○ Pentasa	500 mg 1000 mg	Ethylcellulose microgranules	Small bowel
○ Salofalk	500 mg	Eudragit-L polymeric coat	TI + colon (pH>6)
○ Sulfasalazine	500 mg	Di-azo bond cleaved by colonic bacteria	Colon
○ Dipentum (olsalazine)	250 mg	Cleaved by colonic bacteria to two 5-ASA	Colon

Prednisone

- 1 and 5 mg tabs
- Dose 40 mg po od x 1 week, then taper by 5 mg/week until off
- Side effects - lots

Anti-TNF (infliximab – Remicade, adalimumab – Humira, golimumab - Simponi)

- Block TNF-alpha which is involved in intestinal inflammation
- Work very quickly – within days-weeks
- Immunogenic – patients often form antibodies against these agents
  - Leads to loss of response or allergic reaction
- Often given with AZA for synergy (only proven for infliximab)
- Usually at least given with low dose AZA (50 mg) or MTX (7.5-12.5 mg) to reduce antibodies
- Side effects
  - Common
    - Immune suppression, reactivation of TB or Hep B → check TB skin test, CXR, Hep B SAg prior to starting
    - Allergic reaction
    - Psoriatic rash
  - Rare
    - CHF, demyelination, lymphoma, non-melanoma skin cancer

Infliximab (Remicade)

- 25% mouse protein
- Given IV
- Dose 5 mg/kg at week 0, 2, 6, then q 8 weeks
- Cost $32,000/year for 60-70 kg patient

Adalimumab (Humira)

- 100% human protein
- Given SC – comes in syringe or pen (40 mg)
- Dose 160 mg at week 0, 80 mg at week 2, then 40 mg eow
- Cost $24,000/year

Golimumab (Simponi)

- 100% human protein
- Given sc – comes in syringe or autoinjector (50 or 100 mg)
- Dose 200 mg at week 0, 100 mg at week 2, then 50 or 100 mg q 4 weeks
- Cost $18,000/year

Azathioprine / 6-mercaptopurine

- Mechanism - purine analogue, inhibits DNA synthesis
- Synergistic on top of infliximab (UC-SUCCESS study)
- Not very effective at inducing remission as monotherapy but will maintain a steroid-induced remission
- Takes 3-4 months to work
- 50 mg tabs – target dose 2-2.5 mg/kg/day (AZA) or 1-1.5 mg/kg/day (6-MP)
- Start 50 mg po od x 1 week, then get blood tests, then go to target dose with monthly bloodwork (or titrate up slow and check weekly bloodwork to start)

- Can consider TPMT testing
- Bloodwork – CBC + diff, AST, ALT, ALP, lipase
- Side effects -Common – nausea, dyspepsia; less common – neutropenia, hepatitis, pancreatitis, hair loss; rare - lymphoma

IV corticosteroids

- Methylprednisone preferred over hydrocortisone (less mineralocorticoid effect so less hypokalemia)
- Dose 40 mg IV od
- Side effects - lots

Cyclosporine

- Rarely used anymore
- Similar effectiveness to infliximab but higher toxicity
- Dose 2 mg/kg day IV, then transition to oral
- Side effects – immune suppression, seizures, renal failure, tremor, hair growth

Vedolizumab (Entyvio)

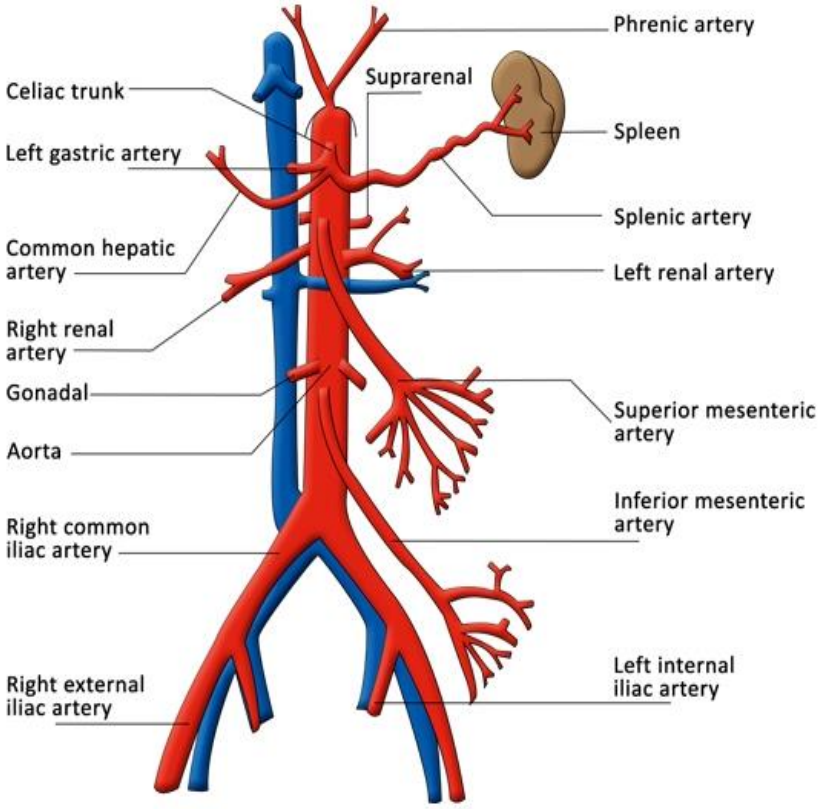
- Blocks alpha4-beta7 integrin on WBC, stopping migration into inflamed tissues
  - More gut selective than natalizumab which blocks alpha4-beta1 as well and is associated with PML in 1/1000 patients due to reactivation of JC (John Cunningham) virus
- Dose 300 mg IV at week 0,2,6 then q8 weeks
- Side effects – immune suppression, headache, nausea, allergic reaction
  - However in clinical trial were similar to placebo

Ischemic Disease of the Colon

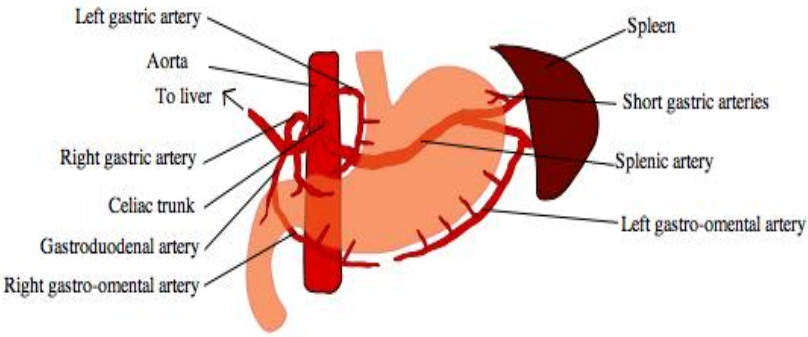
Dan Segal

Topics

- Anatomy



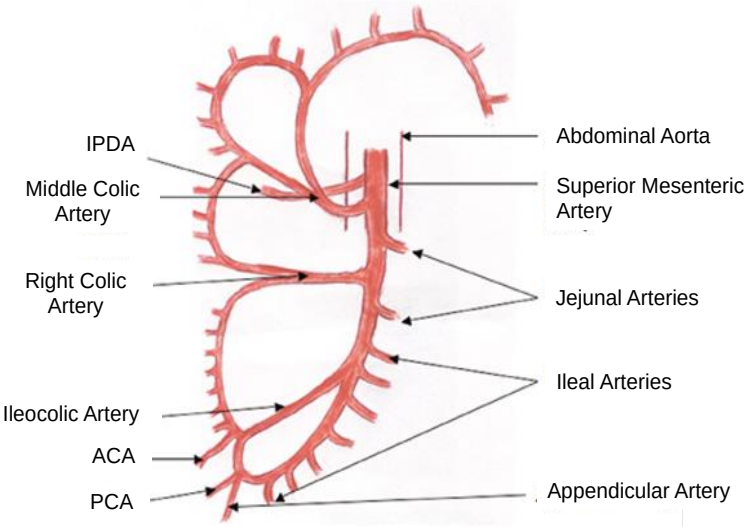
❖ Celiac Axis (CA)



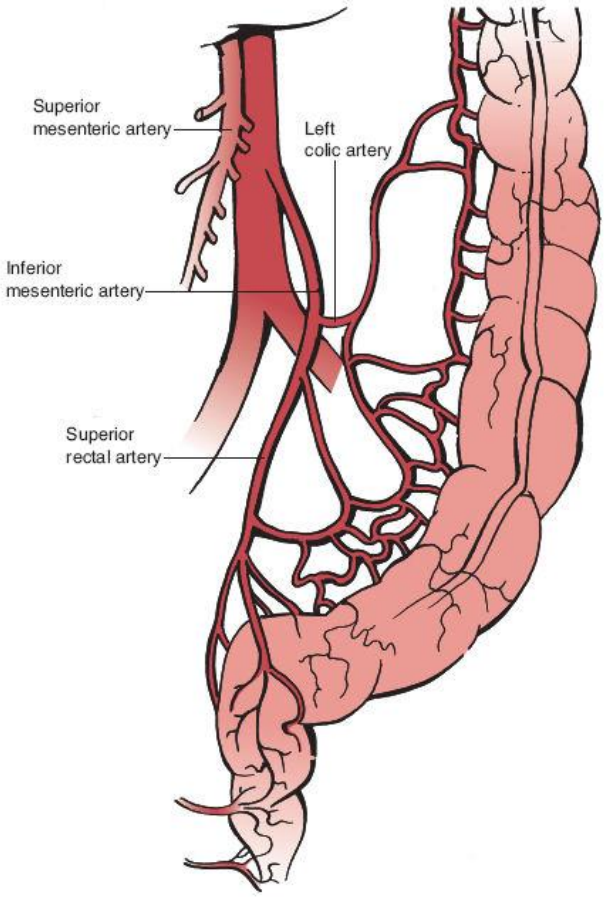
- 3 major branches
  - L gastric artery, common hepatic artery, splenic artery
- Supplies stomach, duodenum, pancreas and liver

❖ Inferior Mesenteric Artery (IMA)

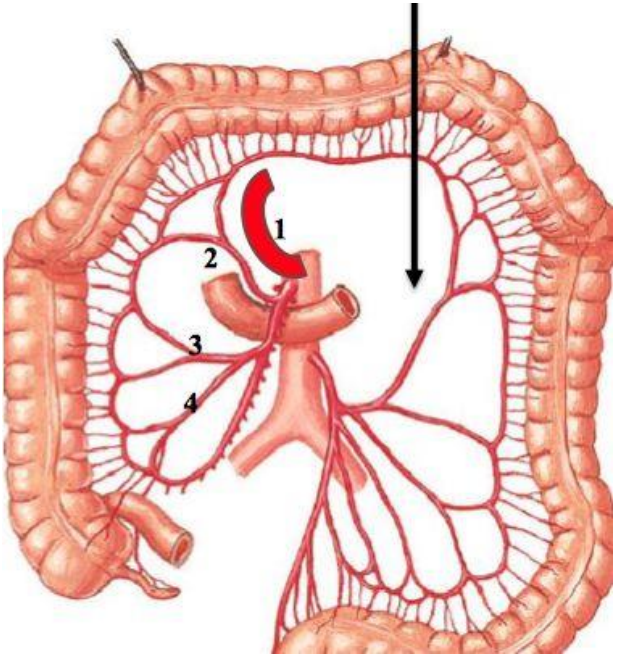
- 5 major branches:
  - Pancreaticoduodenal vessels (2)
  - Middle colic
  - Right colic
  - Ileocolic
- Supply right side of colon, and parts of small bowel



- Arises just above bifurcation
- Branches
  - Left colic
  - Sigmoid branches
  - Superior rectal artery
- Supplies left colon, sigmoid, proximoid, proximal rectum
- Distal rectum supplied by internal iliac



- Collaterals
  - Multiple collaterals throughout splanchnic circulation
  - Splenic flexure and sigmoid have more limited collaterals so more prone to injury



- Pathophysiology
  - Ischemic injury = lack of oxygen and nutrients
  - Bowel can tolerate 75% reduction in blood flow for 12 hours with no changes on biopsy
    - Compensate by increasing oxygen utilization
    - At baseline only 1/5th of mesenteric capillaries are open
  - When vessels occluded, collaterals open immediately
  - After several hours vasoconstriction develops reducing collateral flow

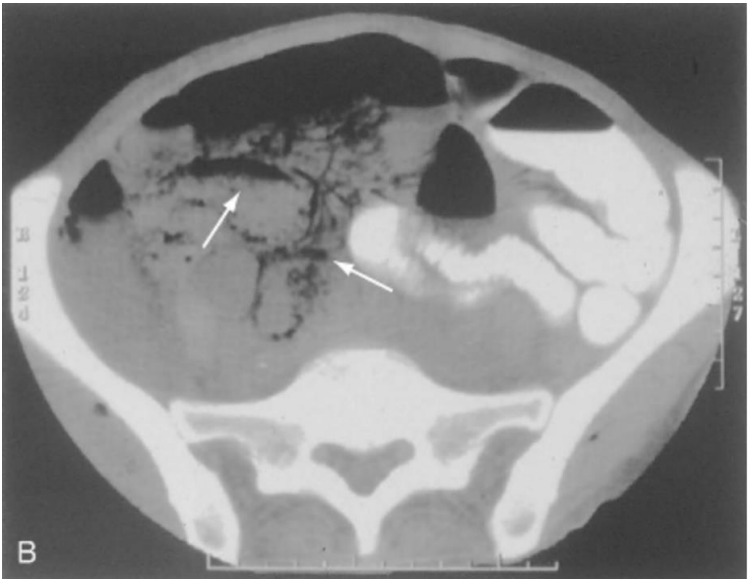
- Vasoconstriction can even be irreversible after precipitant is corrected
- Damage due to initial hypoxia and also reperfusion injury
- Reperfusion = reactive oxygen radicals
  - Damage protein within tissue resulting in cell death etc.
- ROS promote leukocyte adhesion and release of proteases

Acute Mesenteric Ischemia (AMI)

Cause	Frequency (%)
SMA embolus	50
Non-occlusive mesenteric ischemia	25
SMA thrombosis	10
Mesenteric venous thrombosis	10
Focal segmental ischemia	5

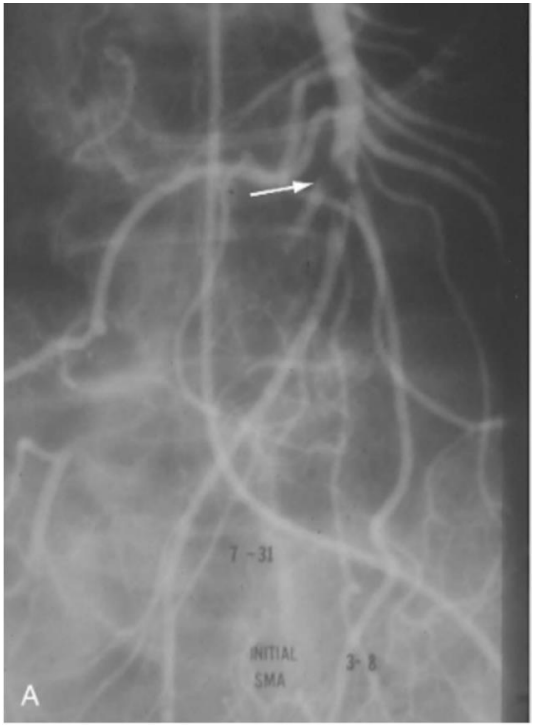
- AMI, 1% of all admissions to tertiary center (high)
- Clinical features
  - Older vasculopathy or younger vasoconstrictor user
  - Severe, unexplained abdominal pain in setting of benign abdomen in early disease

- May see GI bleeding or abdominal distention
  - Sign of abdominal infarction
  - FOBT positive in 75%
- Decreased LOC
- Sepsis
- Lab features + imaging
  - WBC > 15 (75%)
  - Metabolic acidosis (> 50%)
  - Does not mention lactate
  - Pain films usually normal early
    - Sign of abdominal infarction
    - FOBT positive in 75%
  - Ultrasound with dopplers not great
  - CT scan is bottom line investigation (sens 92%; spec 100%)
    - Bowel wall gas, thrombi, embolic infarct in other
    - Early on still non-specific
  - CT angiography increased diagnostic yield of vascular cause by 19% in one study
- Laparoscopy not usually necessary
- Mesenteric angiography is gold standard!

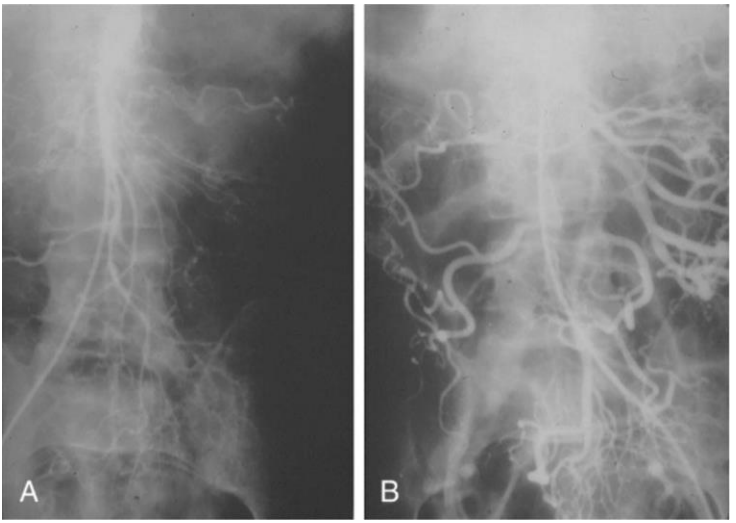


- Principles of therapy
  - High mortality rate without intervention
  - Conventional angiography is diagnostic + therapeutic
  - Angiography can treat obstructive causes and vasoconstrictive causes like NOMI with vasodilators
- Therapy
  - Resuscitation
  - Abx
  - CT imaging followed by conventional angiogram

- Angiogram therapy based on underlying causes + latency of damage
  - Arterial embolus (minor): papaverine + heparin or lytic
  - Arterial embolus (major): papaverine + OR
  - Arterial thrombus (minor): papaverine + heparin or lytic
  - Arterial embolus (major): papaverine + OR
  - Arterial thrombus: heparin + thrombolytic
  - Vasoconstriction: papverine
- If there is persistent peritonitic signs OR +/- papaverine
  - In or attempt revascularization before resection



- A little more on NOMI
  - Splanchnic vasoconstriction due to preceding CV event
  - Appears hours to days after event
  - Angiographic criteria
    - Narrowing of origins of SMA branches
    - Irregularities of intestinal branches
    - Spasm of arcades
    - Impaired intramural vessels filling



- A little more on acute thrombosis of the SMA
  - Usually preceded by chronic ischemic
  - Occlusion usually 1-2 cm from origin
  - Collaterals can help determine chronicity

- With prompt diagnosis and intervention:
  - Mortality less then 50%
- Survival > 90% if no signs of peritonitis
- Diagnosis before intestinal infarction is the key

Mesenteric Vein Thombosis (MVT)

- Can be acute, subacute, or chronic
- Acute MVT can present as AMI
- Subacute MVT is when there is abdominal pain but no intestinal infarction
  - Due to thrombosis with significant collaterals
  - Or acute clot that heals
  - Generally no physical exam or lab findings
- Like other causes if AMI, conventional angiography is gold standard for diagnosis
  - Findings
  - Thrombus in SMV
  - Failure to visualize SMV or portal vain
  - Slow filing of vain
  - Contrast reflux into artery
- Signs at laparoscopy
  - Serosanguineous peritoneal fluid
  - Good arterial pulsations
  - Thrombus in vein when cut
- AMI is treated as mentioned before with heparin + lytic unless peritonitic
  - Ongoing anticoagulation dictated by underlying cause
- Acute Asx MVT may warrant 3-6 mons of anticoagulation
- Chronic MVT goal to prevent variceal bleeding
- Acute MVT has better prognosis than other causes of AMI

Ischemic Colitis (IC)

- Also known as ischemic colon or colon ischemia
- Definition
  - Decreased blood flow to colon
  - Inability to maintain their function resulting in death
- Epidemiology
  - 9-24% of all LGIB
  - 1 in 200 hospitals admissions
  - 1 in 100 colonoscopies
  - Annual incidence of 15.6 / 100,000 pts
    - Underestimated because many do not seek medical attention
    - More common in females and elderly
    - Five year recurrence rate is 10%
- Pathophysiological
  - As mentioned before- hypoperfusion injury
    - Type 1 disease; no specific cause
    - Type 2 disease; systemic hypoperfusion
- Abnormalities on angiography do not correspond with disease
- Colon at risk due to decreased collaterals, sensitivity to autonomic changes
- Risk factors
  - Vasculopathy (DM + cardiac disease)
  - Pulmonary comorbidities (COPD)
  - Kidney disease and dialysis dependence
  - All disorders (RA secondary to increased vasculopathy risk and / or coagulopathy risk)
  - Thrombophilia
  - IBS, diarrhea, constipation
    - Too much vascular sympathetic activity with IBS
    - Constipation compresses submucosal vessels

- Abdominal surgery history
- Drugs
  - Constipation-induced meds
  - Immunomodulators, anti-TNF, interferon
    - Case report evidence
  - Recreational drugs cause vasoconstriction
    - Amphetamines
    - Cocaines
  - Other drug classes with lower evidence (every drug you can think of)

- Clinical presentation
  - Sudden cramping, LLQ pain (87%), urgency
  - BRPBPR within 24 hr (84%)
  - Non-bloody diarrhea (19.4%)
  - Disease of the right colon seems to be more severe with less bleeding (20% 30 d mortality!)
- 75% present within three days
- Symptoms resolve within 2-3 days
- Colon heals within 1-2 weeks
- Sometimes the disease is not reversible
- Sometimes disease takes longer to heal upwards of six months
- Complications do occur
  - Gangrenous colitis 9.9% (transmural infarct)
  - Fulminant colitis 2.5% (frank peritonitis)
  - Stricture
  - Rarely can pass a “colonic cast” (usually mucosa)
    - 20-120 cm in length
    - Passed 2-4 weeks after ischemic insult

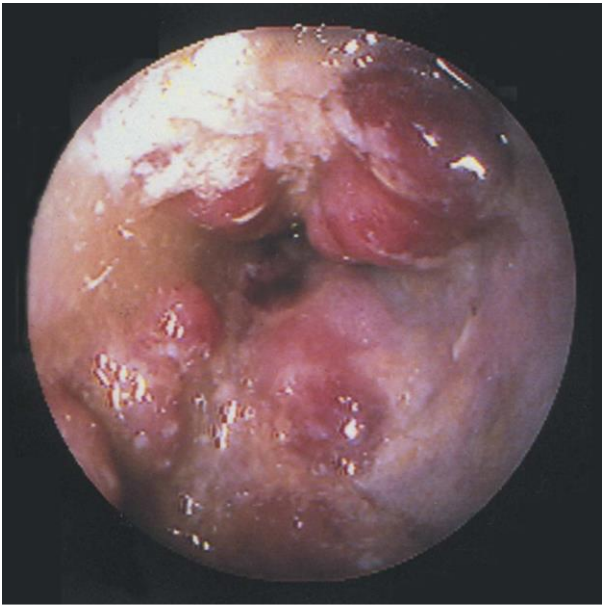
- A spectrum

Type	Frequency (%)
– Reversible colopathy and transient colitis	> 50
– Transient colitis	10
– Chronic ulcerating colitis	20
– Stricture	10
– Gangrene	15
– Fulminant universal colitis	< 5

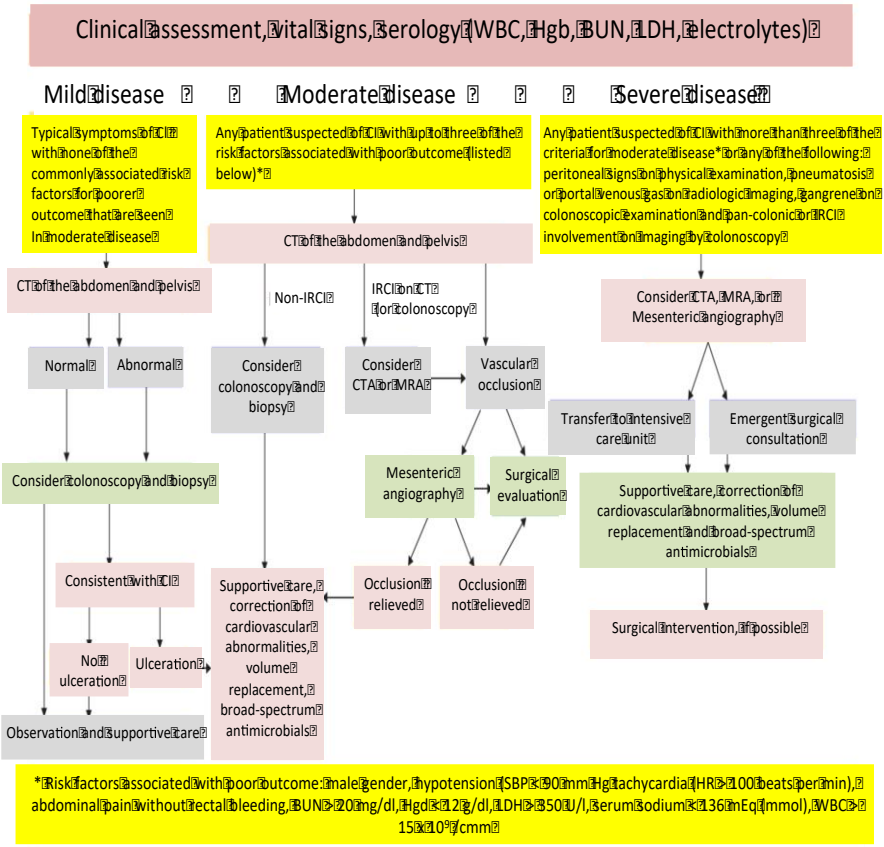
- Pattern of involvement
  - Left colon (32.6%)
  - Distal colon (24.6%)
  - Right colon (25.2%)
  - Entire colon (7.3%)
- Reason for this
  - Watershed areas susceptible
  - Splenic flexure (Griffith's point) SMA to IMA link
  - Sigmoid colon (Sudeck's point) IMA to superior hemorrhoid artery
- Recurrent disease
  - As mentioned, recurrence about 10% at 5 yr
  - AAA and smoking are risk factors for recurrence
- Chronic disease
  - 3+ months of typical symptoms + biopsy confirmation
  - Similar presentation
  - Rate of developing chronicity vary widely and are likely inaccurate
  - Overlap with IBD
  - May not exist

- Laboratory testing
  - Some potential abnormalities
    - WBC, Cre, Urea, LDH
    - Low albumin
- All patients need at minimum
  - Plain film imaging
  - CBC, lytes, renal function
  - Stool testing
- Imaging
  - Plain film can show thumb-printing early; gas late
  - Barium enema used historically
    - May now be used to assess for post event stricture
  - CT scan most prevalent test
    - Can exclude other causes
    - Provides diagnostic clues, area of involvement
    - See segmental wall thickening, pericolic fat stranding, thumbprint
      - ~36% of these patient will have IC as cause of colitis
  - No major role for CT-A or angiography unless concern for AMI
  - Colonic pneumatosis and portal vein gas are bad signs
  - Ultrasound in limited studies has shown utility for diagnosis and determining severity
  - N.B: If IRCI consider CT-A to r/o herald for AMI
- Association with colorectal adenocarcinoma
  - Ischemic segment proximal to tumor
  - Tumoral segment is thicker and shorter than ischemic component
  - Patients should have a colonoscopy at some point for screening

- Colonoscopy
  - C-scope with biopsies is best technique for confirming diagnosis
  - Use minimal insufflation
  - Can do biopsies unless gangrene
  - Avoid C-scope in severe disease at risk of complication
  - Consider within 48 hr for best yield
- Finding
  - Edema, erythema, ulceration, pseudopolyps when healed
  - Dusky, cyanotic mucosa is gansgrenous



- Colon single-strip sign
- Pathology
  - Supportive bit not
  - Usually hemorrhage, neutrophilic infiltrate
  - Pathognomonic: ghost cells cell outline, mucosal infarct
    - Present 7.7% of patients



Indications for surgery in colonic ischemia

- Acute indications
  - Peritoneal signs
  - Massive bleeding
  - Universal bleeding
  - Portal venous gas and/or pneumatosis intestinalis on imaging
  - Deteriorating clainical condition
- Subacute indications
  - Failure of an acute segmental ischemic colitis to respond to treatment within 2-3 weeks with continued symptoms or a protein-losing colopathy
  - Apparent healing but with recurrent bouts of sepsis
- Chronic indications
  - Symptomatic colon stricture
  - Symptomatic segmental ischemic colitis

- Surgery
  - Type depends on amount and location of colon affected
    - Segmental resection
    - Subtotal or total colectomy
    - Left or right hemicolectomy
    - May have diverting stoma or primary re-anastamosis

Risk factors for perioperative mortality

- Low output heart failure (e.g. cardiac ejection fraction < 20% on echocardiogram)
- Acute kidney injury
- Subtotal or total colectomy
- Lactate > 2.5 mmol/L

- Pre- and intraoperative catecholamine administration

Risk factors	Mortality
0	10.5%
1	28.9%
2	37.1%
3	50%
4	76.7%
5	100%

Communicator

- Ability to facilitate doctor patient relationship and dynamic exchanges that occur before, during, and after medical encounter
- Case:
  - 75 y/o female presents to hospital with BRBPR, crampy abdominal pain, and diarrhea for 5 days duration. PMHx of DM. A CT scan shows a segment of thickened large bowel.
  - You chose to admit this patient with a provisional diagnosis of colitis.
  - A. Please explain to patient what you think is going on and what your plan is:
  - B. Please explain to patients family about the process for colonoscopy preparation as inpatient.

Non-pharmaceutical Management of Constipation

Aze Wilson

Introduction

- Constipation affects many people worldwide
- Many beliefs that are held are not evidenced based
- The colon serves 3 purposes:
  - Conserve water;
  - To allow bacteria to split dietary fiber into absorbable nutrients;
  - To retain and expel residue at convenient times and places
- These 3 purposes are seen by 3 functions
  - Absorption
  - Motility
  - Intrinsic and extrinsic sphincter function
- There is no health benefit from colonic cleansing (No scientifically robust studies in support of the use of colonic cleansing (Mishiro R. JFP 2011)
- There is no evidence for “autotoxication” from the normal process of fermentation of unabsorbed dietary fiber by colonic bacteria
- There are no well-designed studies to support the role of dolichocolon (long colon, but not dilated) in the development of constipation (Raahave et al. Dan Med Bull 2009)

Chronic Ideopathic Constipation

- Pathophysiology
  - Slow proximal colonic transit put normal distal transit suggests slow transit constipation. Normal proximal colonic transit but slow distal transit suggests pelvic dyssynergy or anorectal dysfunction
  - Only slow transit constipation will respond to subtotal colectomy with ileorectal anastomosis

- With dilation of both the colon and rectum, as well as normal anal sphincter function proctocolorectomy and an ileoanal anastamosis may be suitable; if anal sphincter function is abnormal, an ileostomy needs to be performed

Please see: Chaun H. Chapter 56. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 3: Constipation, page 741-745.

➢ Causes

- The causes of constipation may be classified as neurogenic, drug-associated, and metabolic. Give causes of constipation in each category.

- Neurogenic
  - Central
    - Multiple sclerosis
    - Parkinson disease
    - Cerebral infarction (CVA)
    - Medullary trauma
  - Spinal
    - Cognitive challenge
    - Dementia
    - Meningocele
    - Spinal cord lesions (trauma, tumour)
    - Cauda equina lesions

- Gut
  - Autonomic neuropathy (paraneoplastic, pseudoobstruction, diabetes)
  - Aganglionosis: congenital (Hirschsprung's) or acquired
  - Cathartic colon (laxative abuse)
  - Narcotic bowel syndrome
  - In a young person, suspect Hirschprung disease (abnormal embryological migration of neural crest cells) when rectal manometry shows
    - ↑ rectal pressure, plus
    - ↑ anal pressure (failure of relaxation)

- Drug-associated
  - Analgesic: narcotics e.g. opiates ("cathartic colon"), non-narcotics
  - Antacid (aluminum)
  - Anticholinergics (dopaminergics)
  - Anti-Parkinson drugs
  - Antipsychotics
  - Antidepressants (tricyclics, but not SSRIs – serotonin reuptake inhibitors)
  - Antidiarrheals
  - Antihypertensives (calcium channel blockers, clonidine)
  - Antiseizure medications
  - Bile acid sequestrants
  - Chemotherapeutic agents
  - Nutrient supplements: calcium, iron
  - 5-HT3 antagonists
  - Somatostatin analogs

- Metabolic
  - Diabetes mellitus
  - Glucagonoma
  - Hypothyroidism
  - Hypoparathyroidism
  - Hypopituitarism (panhypopituitarism)
  - Hypocalcemia
  - Hypomagnesium
  - Hypokalemia
  - Heavy metal poisoning
  - Pregnancy
  - Progesterone level cyclic fluctuation (just before menses)
  - Porphyria
  - Low intake of water

- Pelvis dyssynergy
  - Obstertrical trauma

Printed with permission: Müller-Lissner S. *Best Pract Res Clin Gastroenterol* 2007; 21(3): pg. 475.

- Give the affected structure and pathophysiology of 4 disorders causing functional anorectal outlet obstruction.

Affected structure	Pathophysiology
○ Internal sphincter- Hirschsprung's disease	– No relaxation
○ External sphincter- Pelvic floor dyssynergia ('anismus')	– Paradoxical contraction
○ Pelvic floor- pelvic floor descent	– Loss of pressure
○ Rectal wall – Intussusception	– Luminal obstruction
○ Rectal wall –Anterior, rectocele	– Loss of pressure

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➢ Clinical

- **Rome III diagnostic criteria** for functional constipation, using Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
    - Must include two or more of the following:
        - Straining during at least 25% of defecations
        - Lumpy or hard stools in at least 25% of defecations
        - Sensation of incomplete evacuation for at least 25% of defecations
        - Sensation of anorectal obstruction / blockage for at least 25% of defecation

  - Manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor)
  - Fewer than three defecations per week
- Loose stools are rarely present without the use of laxatives
- There are insufficient criteria for irritable bowel syndrome (IBS).

Source: Longstreth GF, et al. *Gastroenterology* 2006; 130: 1480-9, Table 1.

- Rome III diagnostic criteria for functional defecation disorders using criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
  - The patient must satisfy diagnostic criteria for functional constipation
  - During repeated attempts to defecate must have at least two of the following
    - Evidence of impaired evacuation, based on balloon expulsion test or imaging
    - Inappropriate contraction of the pelvic floor muscles (i.e. anal sphincter or puborectalis) or < 20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG
    - Inadequate propulsive forces assessed by manometry or imaging

Source: Bharucha AE, et al. *Gastroenterology* 2006; 130: 1510-8, Table 2.

- Give the **investigations** which are appropriate for the investigation of persons with constipation.
    - History and physical– social, laxative and drug use, psychological assessment, stool chart; full examination including digital rectal exam (DRE)
    - Laboratory tests
        - CBC
        - HG A, C
        - TSH
        - Electrolytes
        - Mg^{2+}
        - Ca^{2+}
    - Colonoscopy, defecating proctogram (defecogram), colonic transit study, EUS, colonic manometry
    - Diagnostic imaging
    - 3 views of the abdomen
    - Manometry, anorectal manometry
    - Functional testing, balloon expulsion

Abbreviation: DRE, digital rectal exam

➢ Treatment

- Non-pharmaceutical

- Give non-pharmacological treatments of constipation.

    - Treat underlying conditions
    - Bowel management programs, including fiber
    - Psychological management

- Avoid constipating medications
- Exercise
- Adequate water intake
- Dietary measures
- Biofeedback (pelvic floor retraining)
- Total colectomy with ileorectal anastomosis
- Note
  - There is an unproven benefit of fibre to treat constipation, but fiber supplement up to 30 gm per day may be offered on a person-by-person basis.
  - In the absence of dehydration, ↑ water intake does not help constipation

Dietary Fiber

- There are 2 types of fiber:
  - Soluble
    - Legumes, oats, rye, some fruits, broccoli, carrots
    - Readily fermented in the colon into gases and into physiologically active by-products
  - Insoluble
    - Whole grain, nuts, wheat and corn bran, some vegetables e.g. cauliflower
    - Metabolically inert, absorbing water as it moves through the digestive system, easing defecation
- Only poorly fermented insoluble fiber retains the ability to bind water (Stephen et al. Gut 1979)

- In healthy individuals, dietary fiber:
  - ↑ stool bulk
  - ↑ stool frequency
  - ↓ stool consistency
  - ↓ transit time
  - ↑ stool weight
- In constipated patients
  - With either slow transit time or disordered defecation, and were given supplements of dietary fiber, benefit seen in only ~20% (Voderholzer et al. Am J Gastroenterol 1997)
  - With no pathology, ~80% improved with extra dietary fiber
- Some constipated persons given fiber supplements may actually worsen.
- The maximum beneficial fiber supplementation is 30 g /d; higher doses are ineffective but ↑ risk of side effects.
- Caution: the patient have bloating and excess flatus normally occurs in the first 1-2 weeks after dietary fiber intake is increased.
- A systematic review was carried out in APT 2011
- With the 3000 citations
  - Only 6 RCT's were eligible for inclusion:
    - Review of the efficacy of soluble and insoluble fiber supplementation in the management of chronic idiopathic constipation.
    - 6 RCTs eligible – ongoing concern over methodology, bias risk, small patient numbers

- 4 RCTs: soluble fiber – may be of some benefit
- 2 RCTs: insoluble – conflicting results

- Although dehydration is an important cause of constipation, but in some observation studies has been found to slow colonic transit time.
- No studies published show that increasing liquid volume is not effective as a treatment in euhydrated subjects with chronic constipation. Tabbers et al 2011
- 80% of low grade propogated contractions occur during wakefulness, with significant increase after morning awakening or after meals
- In persons with severe chronic constipation, no change in symptoms after 4 week exercise program (Meshkinpour Dig Dis Sci 1998)
- No change in colonic transit time or stool weight in healthy sedentary subjects after 9 weeks of increasing exercise (Bingham et al. Gastroenterology 1989)
- Summary
  - Small amounts of insoluble dietary fiber may improve symptoms of some persons with mild constipation not due to slow transit or pelvic dysynergy, but unpredictable and improven benefit from ↑ intake of water or ↑ exercise

- Pharmacological
  - There is a long menu of choices to treat CIC (chronic idiopathic constipation). Expensive new agents have been developed, but these do not necessarily perform any better than polyethylene glycol, sodium, picosulfate, bisacodyl or lactulose.
  - The NNTs (number needed to treat) to prevent one patient failing to respond to therapy was between 3 and 6. Scan these relative risks (RR) from RCTs reporting old laxatives or new pharmaceuticals versus placebo:

	RR	95% CI
Older osmotic and stimulant laxatives	0.52	0.46-0.60
Newer pharmaceuticals with a big price tag		
- Prucalopride	0.82	0.76-0.88
- Lubiprostone	0.67	0.56-0.80
- Linaclotide	0.84	0.80-0.87

  - Note that none of these newer agents were studied against the older laxatives.
  - Because of the possible heterogeneity of the studies and the variable placebo response rates, the values of the RR or the NNTs (if they had been reported) could not be directly compared. However, the osmotic and stimulant laxatives were certainly not “poor second cousins”
  - It has been suggested that long-term use of the anthraquinone (e.g. cascara, senna) and bisacodyl laxatives may cause changes in the colon on diagnostic imaging (barium studies), and on histopathology.

- "there is no evidence that currently used laxatives can produce "carthartic colon" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 2246).
- Brown discoloration of the mucosa may occur in ~70% of chronic users of cascara or senna laxatives (melanosis coli).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

5-HT4 agonists may be used to treat constipation.

- Give the mechanism of the action of 5-HT4 agonists.
  - 5-HT4 agonists "…act on presynaptic receptors and facilitate release of acetylcholine and CGRP (calcitonin gene-related peptide"

(Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1672).

- Give the **manometric changes** in the colon which occur with severe slow-transit constipation.
  - ↓ high-amplitude of propagating pressure waves
  - ↑ frequency of low-amplitude antegrade and retrograde propagating sequences
  - ↓ nighttime suppression of propagating sequences
  - ↓ colonic response to a high-calorie meal

A middle age women has a normal colonoscopy in association with their constipation. A colonic transit study. Emperic therapy for the constipation has been unsuccessful.

- Give the likely diagnosis and the characteristic findings on anorectal monometry.
  - She likely has pelvic dyssynergy (aka functional anorectal outlet obstruction).
  - Normally, when straining down, as if to have a bowel movement (valsalva maneuver), the pressure measured from the rectal lead on manometry increases, and the pressure from the lead in the anus relaxes.
  - With pelvic dyssynergy, with straining, there is a paradoxical increase in the pressure in the anus (failure of relaxation).

- Give the **FDA category** of laxatives in pregnancy.

Safe (B)	Caution (C)	Unsafe (D)
○ Lactulose ○ Glycerine ○ Polyethylene glycol (PEG) ○ Bulking agents ○ Bisacodyl	– Saline osmotic laxatives – Castor oil – Senna – Docusate sodium	▪ Anthraquinones ▪ 5HT4 agonists ▪ Prostaglandins (misoprostol)

Note: It is recognized that the FDA categories are no longer favoured, but their use continues, and may be asked on examinations.

Adapted from: Cullen G, and O'Donoghue D. *Best Pract Res Clin Gastroenterol* 2007; 21(5): pg. 815.; and Thukral C, and Wolf JL. *Nat Clin Pract Gastroenterol Hepatol* 2006; 3(5): pg. 260.; Printed with permission: Kane SV. *AGA Institute 2007 Spring Postgraduate Course Syllabus:* 511.

- Give causes of **constipation in pregnancy**.
  - Hormonal – slow transit
  - Mechanical
  - Medications
  - Lifestyle
    - Reduced exercise
    - Dietary changes
  - Pre-existing disease:
    - Chronic slow-transit constipation
    - Irritable bowel syndrome
    - Congenital or acquired megacolon
    - Chronic idiopathic intestinal pseudo-obstruction

Adapted from: Quigley EMM. *Best Pract Res Clin Gastroenterol* 2007;21(5): pg. 882.; and Cullen G, and O'Donoghue D. *Best Pract Res Clin Gastroenterol* 2007; 21(5): pg. 810.

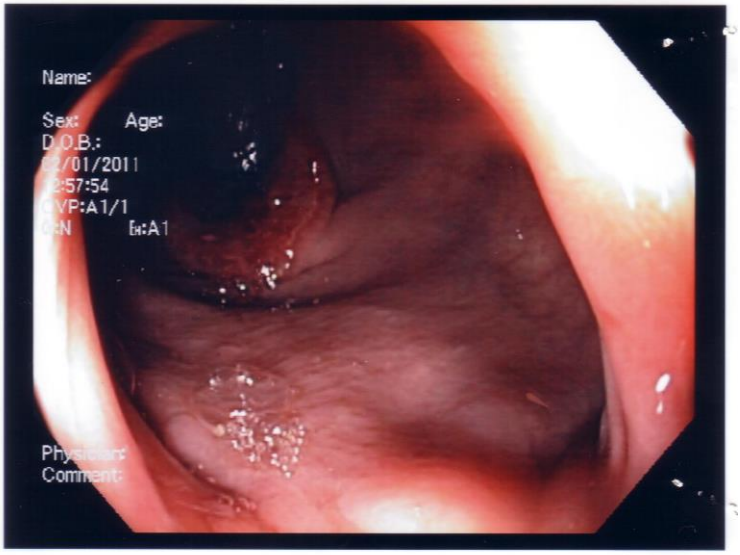
The Digital Rectal Exam

Nilesh Chande

THE DIGITAL RECTAL EXAM

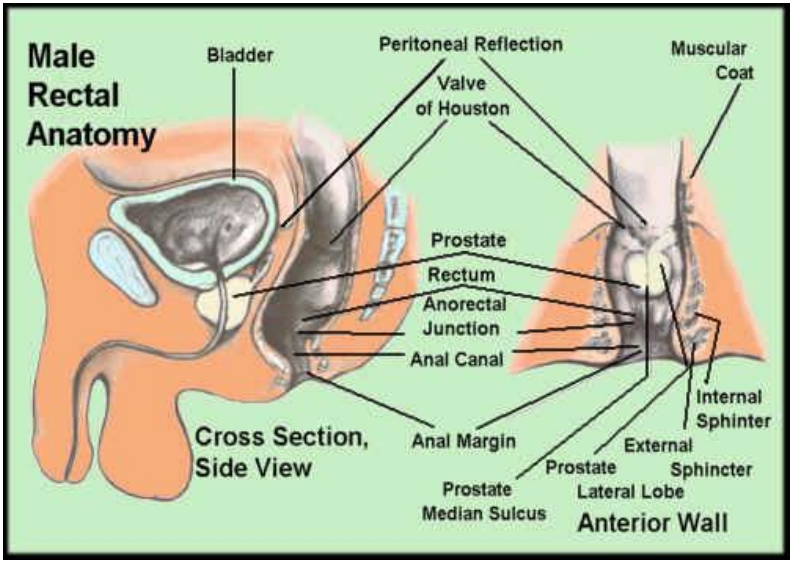
- Objectives
  - Anorectal anatomy review
  - How do you do a digital rectal exam (DRE)?
  - How is the DRE taught in medical school?
  - Is a DRE part of a routine physical?

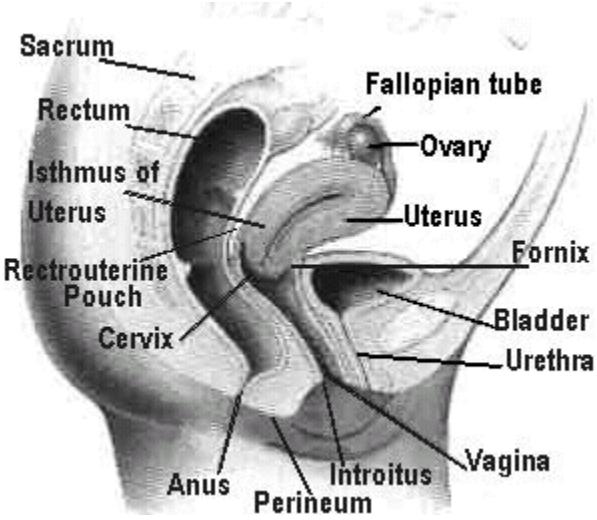
- Colonoscopy



  - Anterior rectal mass – easily palpable

Anorectal Anatomy





THE DIGITAL RECTAL EXAM

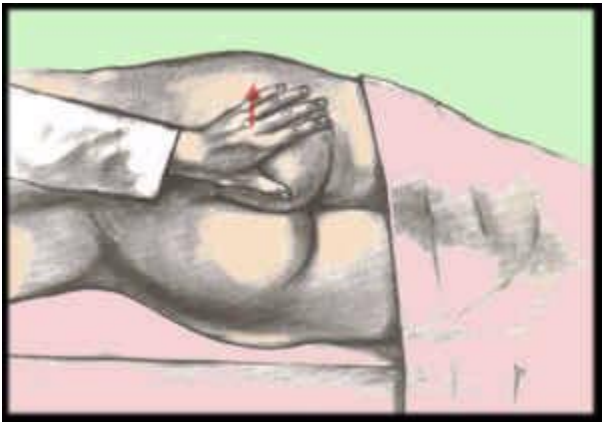
How to do a rectal exam

- Inform patient and obtain verbal consent
- Equipment needed
  - Finger
    - Longer is best for the doctor
    - Thinner is best for the patient
  - Gloves
  - Lubrication

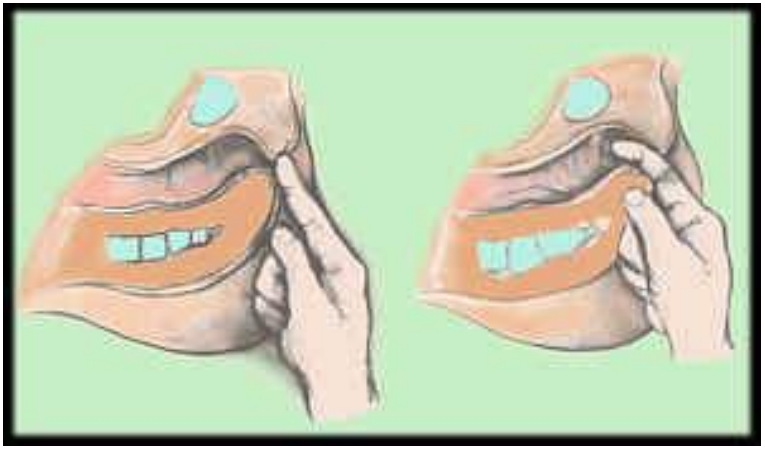
This way please

  - Lighting
    - Bright light
  - Positioning
    - Patient on left side
    - Pull knees up to chest
  - Draping
    - Cover up parts you don't want/need to see
  - Comfort
    - Nurse chaperone if necessary
    - Explain to patient what you are doing
  - Raise exam table so you don't hurt your back and you can get a good look down there
  - Use your left hand to lift up the right buttock
  - If the buttock is big – get a helper!
  - Nurse chaperone is mandatory if MD and patient are of different genders (Canadian Medical Protection Association)

THE DIGITAL RECTAL EXAM



- Inspect / palpate the perianal area
  - Skin
  - Hygiene
  - Fistula
  - Skin tag
  - Rectal prolapse
  - Fissure
  - Abscess
- Insert finger and assess
  - Sphincter tone – rest/squeeze
  - Rectal mucosa – rotate finger
  - Tenderness
  - Prostate
  - Cervix, rectouterine pouch (pouch of Douglas)



Rectal exam teaching

- The evidence

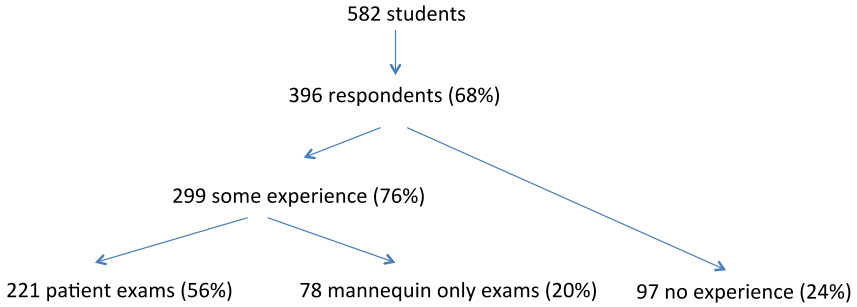
Digital rectal examination: national survey of undergraduate medical training in Ireland

Deirdre Fitzgerald, Stephen S Connolly, Michael J Kerin

Postgrad Med J 2007;**83**:599–601. doi: 10.1136/pgmj.2006.054825

- Survey of 582 final year medical students in Ireland
- Questions about their experience learning performance of rectal exam during training

THE DIGITAL RECTAL EXAM



Mean 1.24 exams/student
>10 exams in 3%
1/3 had 'no confidence' in interpreting results

Fitzgerald D, et al. Postgrad Med J. 2007;83(983):599-601.

Teaching Digital Rectal Examinations to Medical Students: An Evaluation Study of Teaching Methods

Cathy Popadiuk, MD, Madge Pottle, RN, and Vernon Curran, PhD

65 3rd year medical students at Memorial University (Newfoundland)

Lecture presentation and DRE on simulated rectal model

randomization

Control group:
-Rectal model
-Physician supervision
-Peer communication/feedback skills

Rectal teaching associate:
-Trained volunteer patients
-Feedback about interpersonal, technical, cognitive skills

- Results:
  - Control > rectal teaching associate group:
    - Knowledge assessment
  - Rectal teaching associate group > control:
    - OSCE
    - Ability to perform DRE
    - Patient interaction skills

- Conclusions:
  - Rectal teaching associate preferred method
  - Physician instruction for knowledge

Popadiuk C, et al. Acad Med. 2002 Nov;77(11):1140-6.

Examining the Medical Student Body: Peer Physical Exams and Genital, Rectal, or Breast Exams

David V. Power and Bruce A. Center
Department of Family Medicine and Community Health
University of Minnesota Medical School, Minneapolis, Minnesota, USA

- Survey of graduating students at University of Minnesota Medical school
- All had done limited peer exams
- Some had done peer genital / breast / rectal exams (optional tutorial group), including opposite sex

Power DV and Center BA. Teach Learn Med. 2005;17(4):337-43.

A survey of digital rectal examination training in Canadian medical schools

Alysha Nensi BScH, Nilesh Chande MD FRCPC

Summary of methods used to **teach** the digital rectal examination to preclerkship students in Canadian medical schools

	Number of Canadian medical schools
○ Video tutorial	8
○ Standardized patient (SP)	7
○ Physician instruction	7
○ Anatomical rectal models	8
○ Role-playing communication exercises	2
○ Actual patient	1
○ Not taught	1
○ Other	3

Methods used to **evaluate** digital rectal examination training during preclerkship in Canadian medical schools. OSCE Observed Standardized Clinical Exam

	Number of Canadian medical schools
○ Mandatory attendance	10
○ OSCE	1
○ Written exam	2
○ No formal evaluation	4
○ Other	1

Length of time spent on digital rectal examination (DRE) training during preclerkship and clerkship years in Canadian medical schools

Hours	Number of Canadian Medical schools	
	Pre-clerkship	Clerkship
0	1	12
1	2	1
2	6	-
3	2	-
4+	2	1

Number of digital rectal examination (DREs) during preclerkship and clerkship years in Canadian medical schools

Hours	Number of Canadian Medical schools	
	Pre-clerkship	Clerkship
0	1	3
1	7	3
2	3	5
3	2	-
4+	-	1

Western University: teaching rectal exam*

- Preclerkship
  - Video tutorial with physician showing DRE (voice-over instruction)
  - Standardized patients with DRE training
    - One patient per 2-3 students
  - Physician (urologist) instruction at beginning of session (not during standard patient session)
  - Anatomic rectal models to highlight anatomy
  - Prostate exam is also taught
  - Recto-vaginal exam is not taught
    - Total instruction time is 2 hours
    - Student performs DRE on one standardized patient
    - Evaluation – mandatory attendance at training session (no written or OSCE)

* Previously known as University of Western Ontario (London, Canada)

- Clerkship
  - No formal teaching
  - Possible exposure in:
    - Internal medicine
    - Surgery
    - Obstetrics / gynecology
    - Family medicine
  - No evaluation

- Hospital unit where DRE performed
  - Emergency room (ER) 5%
  - Clinical teaching unit (CTU) 16%
  - Consult service 17%

- Documentation of rectal examination performance in the clinical teaching unit of a university hospital
  - Random chart audit of 100 CTU patients
  - Review of DRE performed during patient admission
  - 26% were admitted for primary GI problem
  - DRE least likely with female patient and male resident
  - Only 1 chart mentioned “prostate
  - No documentation of nurse chaperone

Freeman HJ. Can J Gastroenterol. 2000;14(4):272-6.

- Conclusions
  - Rectal exams are important
  - Consultants need to teach students and residents how to perform rectal exam
  - Be patient-friendly
  - Practice makes perfect

The Evidence to Justify Colorectal Cancer Screening

Michael Sey

Burden of Disease

Male 97,700 new cases		Female 93,600 new cases	
Lung	13.7%	Colorectal	11.6%

Canadian Cancer Statistics 2014, Canadian Cancer Society

Cancer Incidence

	Deaths (2014 estimates)			Cases per 100,000		
	Total	Males	Females	Total	Males	Females
Colorectal	24.400	13,500	10,800	48.9	59.4	39.8

Canadian Cancer Statistics 2014, Canadian Cancer Society

Cancer Mortality

	New cases (2014 estimates)			Deaths per 100,000		
	Total	Males	Females	Total	Males	Females
Colorectal	9,300	5,100	4,200	17.9	22.4	14.1

Canadian Cancer Statistics 2014, Canadian Cancer Society

GI Cancers in Canada

	Incidence (M/F) $n/10^5$	Mortality (M/F) $n/10^5$
○ Colorectal	59/40	22/14
○ Pancreas	10/8	10/8
○ Stomach	9/5	6/3
○ Liver	7/2	4/1
○ Esophagus	7/2	7/2

- Note:
  - Incidence rate ~ mortality rate for
  - Major difference between incidence and mortality rates for colorectal cancer

Survival By Stage

Stage	5-year survival
I	93%
IIA	85%
IIB	72%
IIIA	83%
IIIB	64%
IIIC	44%
IV	8%

Canadian Cancer Statistics 2014, Canadian Cancer Society

Effective Screening

- Give the requirements for an effective screening program.

Criteria	Applicable to CRC screening
○ Disease	
– Significant public health concern	✓
– Treatable	✓
– Preclinical state can be detected by the test	✓
○ Test	
– Widely available	✓
– Safe	✓
– Leads to improved health outcome	✓
– Cost is reasonable	Maybe

American Medical Association. Commercialized Medical Screening (Report A-03).

Types of Screening

- Stool tests:
  - gFOBT
  - FIT
- Structural:
  - Flexible sigmoidoscopy
  - Colonoscopy
  - Barium enema (air contrast)
  - CT colonography (CTC)
- Future tests
  - Fecal DNA
  - Colon capsule endoscopy

Abbreviations: FIT, fecal immune testing; gFOBT, guiac fecal occult blood test

Stool Tests

Advantages	Disadvantages
○ 15-30% ↓ CRC mortality ○ Inexpensive ○ Non-invasive ○ Easy public health administration	○ Requires presence of blood ○ Imperfect SN & SP ○ Stool collection ○ Requires serial testing ○ Requirement for colonoscopy ○ For positive tests

gFOBT

- Detects human and animal blood via pseudoperoxidase activity of heme
- Requires avoidance of
  - ASA
  - NSAIDS
  - Vitamin C
  - Red meat
  - Poultry
  - Fish
  - Some raw vegetables
- Uses 2 samples from 3 consecutive BMs (total of 6)
- Sensitivity: 23-69%
- Specificity: 87-98%
  - Varies considerably based on brand, specimen collection technique, number of samples collected, use of rehydration, and screening intervals

Allison JE, et al. N Engl J Med 1996;334:155-9.
Lieberman DA, et al. N Engl J Med 2001;345:555-60.
Levin B, et al. Gastroenterology 2008;134:1570-95.

A Thought Experiment…

- Assuming a prevalence of 1%

	+FOBT	-FOBT	Total
Colon cancer	20	80	100
No colon cancer	180	9720	9,900
Total	200	9800	10,000

- Sensitivity = TP ÷ (TP + FN) = 20 / (20 + 80) = 20%
- Specificity = TN ÷ (TN + FP) = 9720 / (9720 + 180) = 98%
- PPV 20 ÷ (180 + 20) = 10%
  (% of +FOBT with CRC)

What endoscopist sees (positive predictive value, PPV)

- Assuming a prevalence of 10%

	+FOBT	-FOBT	Total
Colon cancer	200	800	1,000
No colon cancer	180	8,820	9,000
Total	380	9620	10,000

- Sensitivity: 20% (same as before)
- Specificity: 98% (same as before)
- Positive predictive value: 200 ÷ (200 + 180) = 53%

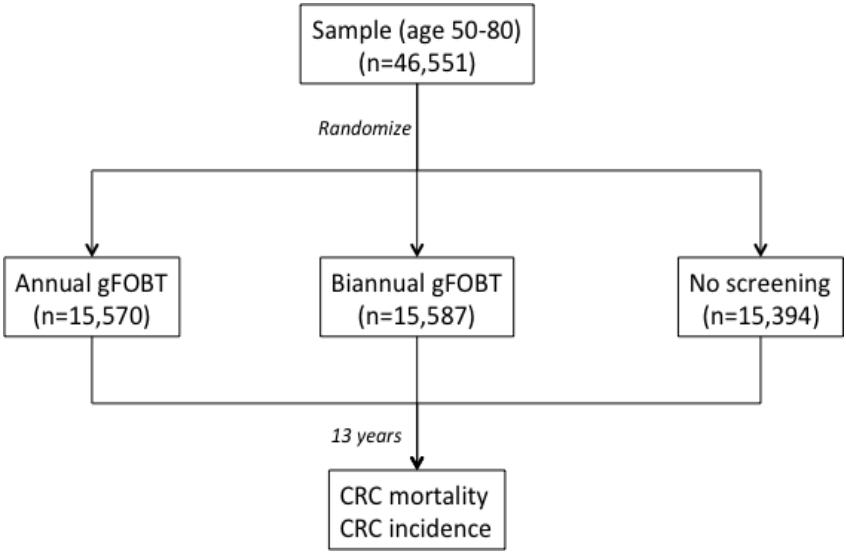
What endoscopist sees (positive predictive value, PPV)

- Note:
  - Comment: The performance of the test in practice, in terms of PPV, depends on the prevalence of the condition to be identified by the gFOBT (↑ PPV with ↑ prevalence, CRC)

Adapted from: Hardcastle JD, et al. Lancet 1996;348:1472-77.

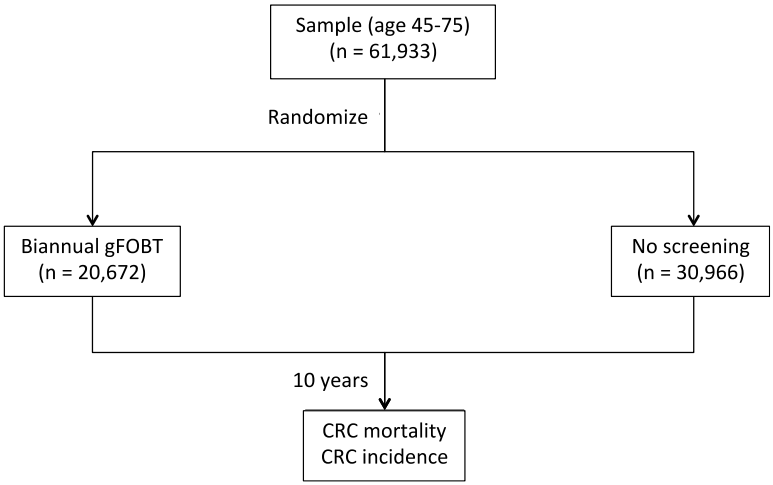
Minnesota gFOBT Study

FOBT screening annually ↓ CRC mortality 33% (no effect on CRC incidence)



- **Major finding**
  - ↓ CRC mortality 13 yr after study of 33%, both with annual and biennial screening, as compared with no screening
  - No evidence for confouding

Denmark gFOBT Study



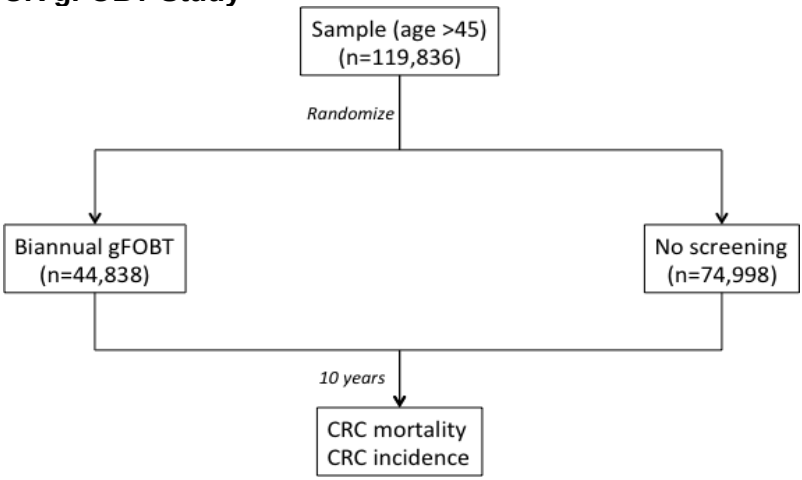
Rate (per 10^5 person-years)	Biannual gFOBT	No screening	95% CI	
CRC incidence rate	171	172	NS	
CRC morality rate	65	82	< 0.05	21% ↓ after 10 yr
Mortality rate from all causes	2209	2240	NS	

Don't forget confounding!!!

- Colon cancer account for only ~10% of positive gFOBT
- The most common finding for a positive gFOBT was polyps (~30%)

Adapted from: Kronborg O, et al. Lancet 1996;348:1467-71.

UK gFOBT Study



Rate (per 10^5 person-years)	Biannual gFOBT	No screening	95% CI	
○ CRC incidence rate	149	144	NS	
○ CRC morality rate	60	70	<0.05	14% ↓ after 10 yr
○ Mortality rate from all causes	2110	2100	NS	

Don't forget confounding!!!

- Colon cancer account for only ~10% of positive gFOBT
- The most common finding for a positive gFOBT was polyps (~45%)
- Colonoscopy was more common in those in the gFOBT arm

Adapted from: Hardcastle JD, et al. Lancet 1996;348:1472-7.

Fecal Immune Test (FIT)

- Utilizes immunohistochemistry rather than pseudoperoxidase reaction
- Advantages over gFOBT
  - No need for special diet due to its specificity for hemoglobin
  - No need to abstain from vitamin C since it does not use the pseudoperoxidase reaction
  - No false positive with UGIB since globin from the UGI tract is rapidly degraded by digestive enzymes
  - Only requires 1-2 stool samples
- Easier to use and less onerous on patient

Abbreviations: UGI, upper GI; UGIB, upper GI bleeding

FIT META-ANALYSIS

Summary operating point
SENS = 0.79 (95%, CI 0.69 – 0.86)
SPEC = 0.94 (95%, CI, 0.92 – 0.95)

HSROC curve
AUC = 0.95%, CI, 0.92 – 0.97)

95% confidence contour
95% prediction contour

Subgroup analysis: pooled sensitivity and specificity for studies using colonoscopy to follow-up of patients with negative fecal immunochemical test results

Lee JK, et al. Ann Intern Med 2014;160:171.

Flexible Sigmoidoscopy

Advantages	Disadvantages
○ 20-30% ↓ CRC mortality ○ Simply bowel prep (Fleet enema) ○ Low risk procedure ○ Sedation not needed	○ Does not examine the whole bowel ○ Colonoscopy needed for those with polyps ○ Sedation not given

Abbreviations: CRC, colorectal cancer; prep, preparation

RCTs of flexible sigmoidoscopy

CRC Incidence (RR, 95% CI)

Study	Any site	Proximal	Distal
Norway*	1.02 (0.83-1.3)	NR	NR
PLCO	0.79 (0.72-0.85)	0.86 (0.76-0.97)	0.71 (0.64-0.80)
SCORE	0.82 (0.69-0.96)	0.91 (0.69-1.2)	0.76 (0.62-0.94)
UK	0.77 (0.70-0.84)	0.98 (0.85-1.12)	0.64 (0.57-0.72)
Meta-analysis	0.82 (0.75-0.89)	0.91 (0.83-0.99)	0.69 (0.63-0.74)

CRC Mortality (RR, 95% CI)

Study	Any site	Proximal	Distal
Norway*	0.73 (0.47-1.13)	NR	0.63 (0.34-1.18)
PLCO	0.74 (0.63-0.87)	0.97 (0.77-1.22)	0.50 (0.38-0.64)
SCORE	0.78 (0.56-1.08)	0.85 (0.52-1.39)	0.73 (0.47-1.12)
UK	0.69 (0.59-0.82)	NR	NR
Meta-analysis	0.72 (0.65-0.80)	0.95 (0.77-1.17)	0.54 (0.43-0.67)

*Based on interim analysis

Hoff B, et al. BMJ 2009;338:1846.
Schoen, RE, et al. N Engl J Med 2012;366:2345-57.
Segnan N, et al. J Natl Cancer Inst. 2011;103:1310-22.
Atkin WS, et al. Lancet. 2010;375:1624-33.
Brenner H, et al. BMJ. 2014;348:g2467

Colonoscopy

Advantages	Disadvantages
○ Complete examination of the colon ○ Ability to perform polypectomy ○ Sedation ○ Indirect evidence supporting CRC mortality reduction	○ No published RCT yet ○ Requirement for full prep ○ Sedation ○ Perforation risk ○ Variable quality in colonoscopy

Abbreviation: RCT, randomized controlled study

Large RCTs are underway but results won't be published until ~2025
NCT00906997, NCT00883792, NCT01239082

National Polyp Study (NPS)

Cumulative incidence of CRC (%)

- "Controls"
  - Mayo Clinical – 226 St. Mark's – 1618
  - Colonoscopy, 0.1% per yr
- NPS (colonoscopy, 0.1% per yr, n = 1418)

} 76% ↓ incidence in CRC

Winawer SJ, et al. N Engl J Med 1993;329:1977-81.

15 Years After NPS

Cumulative CRC mortality (%)

General population 0.2 per yr
NPS adenoma cohort 0.04 per yr
Non-adenoma cohort 0.01 per yr

} 53% ↓ in CRC mortality

Zauber AG, et al. N Eng J Med 2012;366:687-96.

ICES Registry Case-Control Study

Study Groups

Cases: CRC death (n=10,292)
Controls: no CRC death (51,460)
Exposure: colonoscopy

Exposure	OR (95% CI)
○ No colonoscopy	1.0
○ Complete colonoscopy	0.63 (0.57-0.69)
○ Incomplete colonoscopy	0.91 (0.78-1.07)

Baxter NN, et al. Ann Intern Med. 2009;150:1-8.

Meta-Analysis

CRC	RR	95% CI
○ Incidence	0.31	(0.12 – 0.77)
– P	0.44	(0.15 – 1.31)
– D	0.21	(0.10 – 0.31)
○ Mortality	0.32	(0.23 – 0.43)
– P	0.47	(0.29 – 0.76)
– D	0.18	(0.10 – 0.31) ~ 30%

Source:
Cotterchio M. Cancer Causes Control. 2005;16:865-75.
Brenner H, et al. Gastroenterology. 2014;146:709-17.
Kahi CJ, et al. Clin Gastroenterol Hepatol. 2009;7:770-5.
Manser CN, et al. Gastrointest Endosc. 2012;76:110-7.
Doubeni CA, et al. Ann Intern med. 2013;158:312-20.
Nishihara. N Engl J Med. 2013;369:1095-105.
Brenner H, et al. BMJ. 2014;348:g2467

Indirect Comparison: Colonoscopy vs. Flexible Sigmoidoscopy

	CRC Mortality (RR, 95% CI)			CRC Incidence (RR, 95% CI)		
	Any site	Proximal	Distal	Any site	Proximal	Distal
○ Pooled estimate	0.59 (0.30-1.15)	0.49 (0.29-0.85)	0.53 (0.23-1.21)	0.61 (0.23-1.58)	0.58 (1.19-1.74)	0.57 (0.07-4.32)
– P value	0.12	0.01	0.13	0.31	0.33	0.58

Barium Enema

Advantages	Disadvantages
○ Relatively inexpensive ○ Readily available for now	– Poor diagnostic accuracy – No longer recommended by CAG since 2010 – Requires bowel preparation – Mild to moderate discomfort – Ionizing radiation

Barium Enema vs. Colonoscopy

Study	No.	Indication	Sn	Sp
○ Winawer (for any polyps)	862	CRC surveillance	0.35 (NR)	0.54 (NR)
○ Rockey (for polyps > 1 cm)	614	CRC screening +FOBT IDA BRBPR	0.48 (0.35-0.61)	0.90 (0.87-0.92)

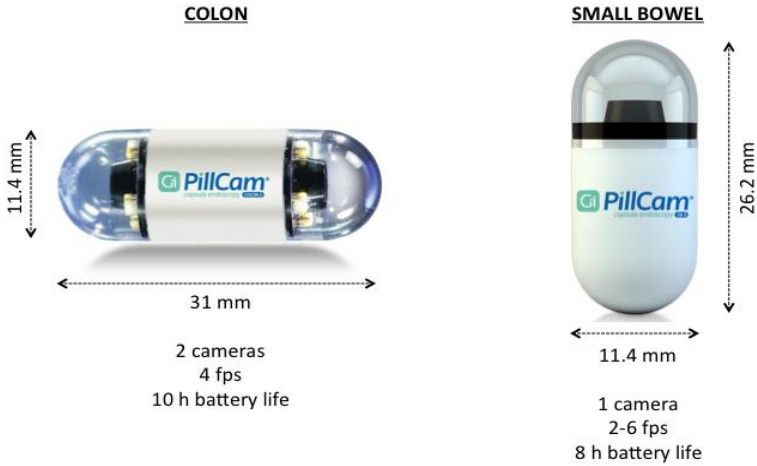
Abbreviations: BRBPR, bright red blood per rectum; IBD, iron deficiency anemia; Sn, sensitivity; Sp, specificity

CT Colonography (CTC)

Advantages	Disadvantages
○ Examination of the entire colon	– May see extracolonic abnormalities
○ No sedation required	– Requires bowel preparation
○ No IV contrast needed	– Mild discomfort (rectal tube)
○ Endorsed by some guidelines	– Ionizing radiation
○ May see extracolonic abnormalities	– Perforation risk (~1:5,000)
	– Need for colonoscopy to confirm findings/polypectomy

*Colonoscopy perforation rate ~ 1:1,1500

PillCam Colon



- Advantages:
  - Non-invasive
- Disadvantages:
  - Diagnostic accuracy unknown
  - Bowel preparation still needed
  - Lack of therapeutics
  - Risk of capsule retention
  - Cost

Fecal DNA

- Detect mutations or methylation in DNA shed by tumor cells
- 1 product commercially available in the US ($599)
- Endorsed by UMSTF only
- Still many unknowns:
  - Accuracy
  - Sample collection strategy
  - Screening interval
  - Target genes for testing

Lesion	Sensitivity % (95% CI)	Specificity % (95% CI)
○ Non-advanced adenoma	17.2 (15.9 – 18.6)	7.6 (6.7 – 8.6)
○ Advanced adenoma	42.4 (38.9 – 46.0)	23.8 (20.8 – 27.0)
○ HGD	83.7 (75.1 – 90.2)	63.5 (53.5 – 72.7)
○ CRC		
– Any	92.3 (83.0 – 97.5)	73.8 (61.5 – 84.0)
– Stage I to III	93.3 (83.8 – 98.2)	73.3 (60.3 – 83.9)

Source: Imperiale TF. N Engl J Med. 2014;370:1287-97.

Hereditary Polyposis Syndromes

Aze Wilson

Inherited Polyposis Syndrome

- Definition
  - A group of conditions in which multiple GI polyps occur in the lumen of the GI tract

- Types
  - These can be subdivided into adenomatous and hamartomatous syndromes of which FAP is the most prevelant of the adenomatous polyposis syndromes.
  - Peutz Jegers syndrome and juvenile polyposis fall under the category of hamartomatous polyposis.
    - Adenomatous: benign neoplasms with gland forming projections
    - Whereas hamartomatous polyps: characterized by an overgrowth of some constituent of the lamina propria, submucosa, or muscular tissues

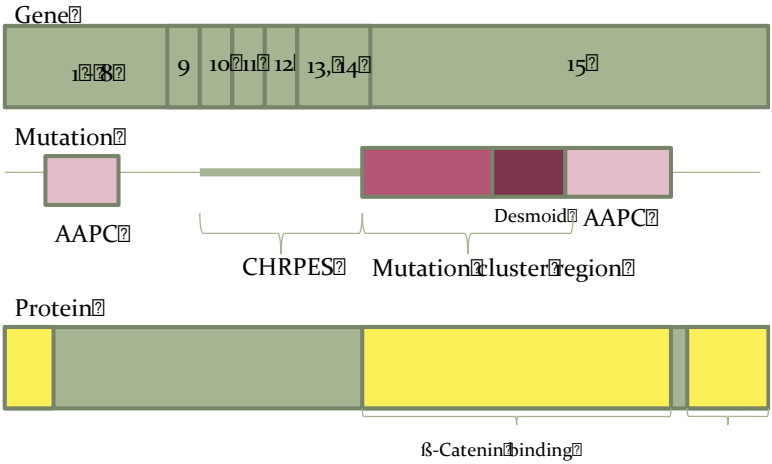
- Give reasons for the clinical interest in inherited polyposis syndrome (IPS).
  - ↑ risk of colon cancer
  - ↑ risk of extra-intestinal tumors
  - Screening and risk reduction through ↑ understanding of
    - Categorization
    - Phenotype
    - Cancer risk

Familial Adenomatous Polyposis (FAP) **Syndrome**

- Useful background
  - The most common adenomatous polyposis syndrome
    - 1 in 5000-7500
    - M=F
  - Characterized by 100's-1000's of adenomatous colon polyps (age 16, age 7-36)
    - 75%-80% will have an affected parent
    - Offspring of an affected individual have a 50% risk of inheriting the mutated APC gene
  - Age 35: 95% of individuals with FAP have polyps
  - Without colectomy, CRC is inevitable
    - Mean age: 39 yrs (34-43)

- Genetics
  - FAP arises from mutations of the adenomatous polyposis coli (APC) gene
    - Long arm of chromosome 5 (5q21-q22)
  - More than 825 different mutations have been found in families with FAP
    - 90% of APC mutations causing FAP give rise to a truncated protein product with loss of function
    - Location of APC mutation correlates with the #of colonic polyps, extracolonic manifestations

- APC Gene Schematic



FAP gene: Sleisenger & Fordtran's Gastrointestinal and Liver disease Vol 2 Ch126 Colonic Polyps and Polyposis Syndromes

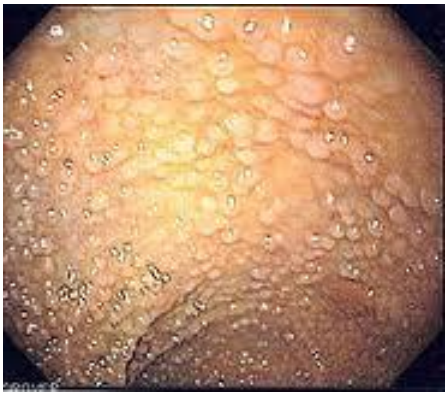
- APC gene consists of 15 exons.
- CHRPES is associated with mutations downstream of exon 9.
- The mutation cluster is at center of gene.
- Most mutations give rise to florid polyposis. Desmoid tumors are associated with the region shown.
- APC is a tumor suppressor gene
- In FAP:
  - 1st mutated allele is inherited
  - 2nd allele is damaged or lost leading to adenoma formation
- Loss of both alleles is needed for tumorigenesis to occur

- In this condition one mutated allele is inherited from an affected parent and adenomas develop when the 2nd allele is lost or damaged. In contrast, in sporadic adenomas, the APC alleles must both be damaged or lost by acquired mutations for adenoma formation to begin.
- This why they typically occur at a later age than in FAP.
- Normally, the APC protein of the APC gene:
  - Localizes to the nucleus and cytoskeleton of human epithelial cells
  - Binds to and regulates the function of other cell proteins e.g. Beta-catenin (maintains cell-cell junctions)
- Regulates colonic epithelial cell homeostasis and participates in cell proliferation, migration, differentiation, apoptosis and chromosomal segregation.
- It regulates the actin cytoskeleton affecting cell morphology
- APC forms a complex with other cell proteins to bind B-Catenin which leads to its downregulation through phosphorylation.
- With mutations:
  - Loss of beta-catenin downregulation – promotes cell growth and suppresses apoptosis
  - Loss of cytoskeleton regulation and chromosomal stability
- APC gene mutations occur in all epithelial cells of the body; therefore, tumors can develop in areas other than the colon.

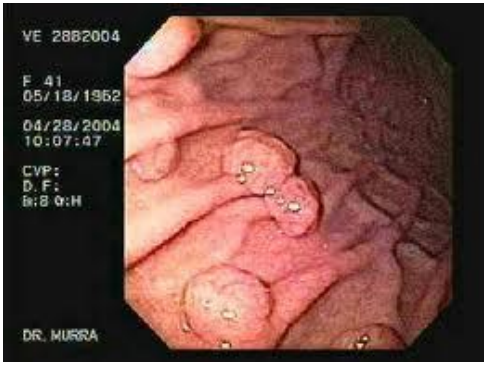
- If a mutation occurs at the beta-catenin binding region (central portion of the gene), beta-catenin is no longer down-regulated.
- The nucleus and upregulate target genes that promote cell growth and adenoma formation and suppress apoptosis.
- If, as in the majority of APC mutations, the APC protein is truncated, the domain that contributes to proper chromosomal segregration and cytoskeleton regulation is lost.
- This has the dual effect of disrupting the breakdown of beta-catenin, promoting activation of cancer associated genes AND creates abnormal chromosomal segregation.

➢ Clinical features

- Colonic:
  - 100s-1000s of polyps by age 10-12
  - Polyps are tubular, tubulo-villous, villous
  - Most polyps are less than 1 cm and are identical to those found in the general pop
  - Polyp size/number correlates with latent period between time to diagnosis and the onset of disease.
  - CRC is inevitable
    - 10-15 yrs after dx; multiple tumors common
  - Despite screening, 25% have CRC at time of colectomy



- Upper GI tract:
  - Gastric polyps (30-40%)
    - Mostly fundic gland polyps
    - Can occur in 1st decade
    - Mostly non-neoplastic
    - May occur prior to the development of colonic adenomas in the 1st decade of life.
    - 5% will develop gastric adenomas with progression to gastric adenocarcinoma occuring very rarely (more frequent in Japan than in NA)

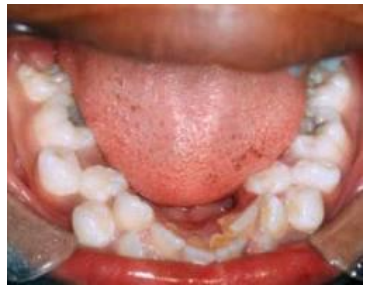


FAP colon polyps: http://www.medthical.com/familial-adenomatous-polyposis.html

- Duodenal adenomas
  - Periampullar region
  - 4-12% lifetime risk of duodenal Ca
  - Develop in 60-90% of FAP patients.
  - Cause biliary/ pancreatic duct obstruction in 50-85% of cases.
- Jejunal/ileal adenomas
  - Rare malignant transformation
  - Seen in 40% and 20% of cases respectively

➢ Extra-intestinal

- Gardner Syndrome
  - Inherited polyposis associated with
    - Benign osteomas of the jaw, skull, long bones
    - Dental abnormalities such as mandibular cysts, supernumerary and or impacted teeth.



- Congenital hypertrophy of the retinal pigmented epithelium (CHRPES)
  - Benign lesions of the optic fundus
- CHRPES are seen in 90% of patients with Garderners (vs. 5% of general population)

- Usually bilateral multiple benign pigmented lesions of the ocular fundus. These are a reliable marker of gene carriage
- They are an asymptomatic curiousity and do not need to be sought in someone with an established diagnosis of FAP

Fundic gland polyps:
http://www.gastrointestinalatlas.com/english/gastric_polyps_ii.html

- Desmoid tumours: diffuse mesenteric fibromatosis
  - Occur 4-32% of FAP patients.
  - Estimated risk is 2.56/1000 patient years
  - 10-50% mortality
  - Familial aggregation
  - The result of progressive growth of mesenteric fibroblasts that occur typically after laparotomy; they can cause obstruction, and constrict arteries, veins, ureters

- Surgery/radiation generally NOT effective
- Some response to systemic chemotherapy
- 1st line: tamoxifen, NSAIDS, sulindac
- Radiation is helpful in localized and accessible disease
- Most are inaccessible in the mesentery.

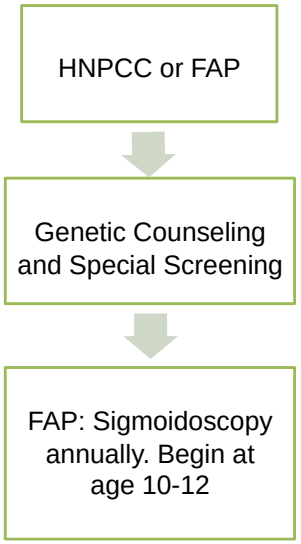
- Benign
  - Epidermoid cysts,
  - Lipomas
  - Fibromas
- Malignant
  - Neoplasms of
    - Biliary tree
    - Liver
    - Adrenals
  - Papillary carcinoma of
    - Thyroid
    - Hepatoblastomas
    - Medulloblastoma

- Genetic Testing
  - Genetic testing is key component of disease management
  - More than 825 different mutations have been found to date in FAP families.
  - 90% of these mutations result in a truncated APC protein.
  - The CAG guidelines recommend genetic testing for all patients with a possible diagnosis of FAP or relative with this diagnosis.

- Screening usually delayed to age 10-12 yr when clinically screening starts.
- Three laboratory techniques:
  - Protein truncation testing (PTT)
    - Detects mutations at the protein level that lead to premature translation termination.
    - The translation products are detected on immunoblots via chemiluminescence
    - PTT infers but does not specifically identify the gene mutation causing the disease
  - Linkage testing
    - Used when no disease-causing mutation can be identified in an affected individual AND when there is more than one affected family member in different generations.
    - The markers used are closely linked with the APC locus and have a predictive accuracy of 98%
  - Gene DNA sequencing
    - Test of choice
    - 90% chance of finding mutation in index case with FAB
    - DNA sequencing is more accurate than PTT and has replaced PTT as the test of choice.
    - The accuracy for mutation finding in relatives after a mutation has been identified in an index case is 100%

- CAG Screening Guidelines

Colonic screening:



Some recommend colonoscopy to appreciate the full phenotype and exclude proximal carcinoma.

Extra-colonic screening

- UGI screening at time of colonic diagnosis or age 20 with forward and side-viewing endoscopes q1-3 yr
- Evaluation of entire small bowel at baseline (4-12% duodenal cancer)
- Possible periodic abdominal ultrasound starting at age 20 (2% pancreatic cancer)
- Annual thyroid exam starting 10-12 yr (2% thyroid cancer)
- Annual physical with hepatic u/s and alpha-fetoprotein for 1st decade (hepatoblastoma 1.6%)

- Management
  - Surgical
    - ONLY reasonable option
    - Timing and extent
      - Any mucosa left behind is at risk for CRC
    - Optimal procedure: total proctocolectomy with IPAA

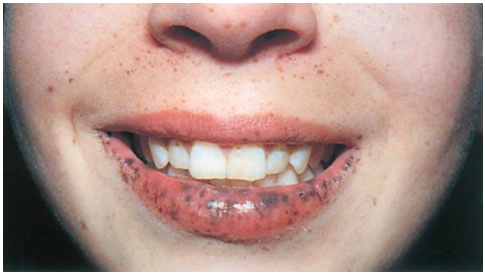
- Alternative subtotal colectomy with ileorectal anastomosis and frequent screening of rectal stump
- Note
  - ¼ of these patients will eventually go on to have a proctectomy for caner or intractable polyps.

- Conflicting recommendations
  - Mayo Clinic experience – favours total colectomy
  - Cleveland clinic, St Mark's London – favour rectal-sparing ORs

- Medical
  - Historical interest
    - Ascorbic acid (Bussy *et al*, Cancer 1982)
    - Calcium supplementation (Stern *et al*, Surgery 1990)
    - NSAIDS: sulindac
      - Decreases size and number of polyps
      - Mechanism of action – inhibition of COX activity
      - Cochrane review of 3 RCTs shows
        - polyp regression over short-term (Giardello 1993, Labayle 1991, Steinbach 2000)
          - No protection from rectal cancer was seen
          - Drug effect

Peutz-Jegher Syndrome (PJS)

- Demography
  - 2nd most common polyposis syndrome
  - Incidence ~$1/10^5$ live births
  - Affects all racial groups equally
  - Males = females
- Genetics
  - Autosomal dominant disease with incomplete penetrance
    - Hamartomatous polyps in the GIT
    - Mucocutaneous pigmentation
  - Mutation in STK11/LKB1 gene
    - 30-70% sporadic cases (mutation rate unknown)
    - 70% of familial cases
  - STK11/LKB1 is a tumour suppressor gene
    - 9 exons
    - Encodes a 435 AA protein = STK
  - Lack of identification of an STK11 mutation in all cases suggests there may be another locus/loci
- Clinical presentation
  - Mucocutaneous pigmentation:
    - Occurs in infancy, avg age 2; fades in adolescence
    - 1-5mm in size
    - Involves vermilion border of lips (94%); buccal mucosa (66%); hands (74%); feet (62%)
    - Secondary to pigment-laden m/ps depositing in the dermis



Supranummary teeth:
http://www.intelligentdental.com/2012/02/06/the-extra-tooth/

- Give the clinical way to differentiate the pigmentation of PJS from freckles
    - Freckles are never in mouth or around the lips or nostrils.
    - Polyps
        - Polyps grow during first decade of life
        - Symptoms at 10-30 years
        - Average age of diagnosis: men 23yrs; women 26 yrs
            - Intestinal obstruction (43%)
            - Abdominal pain (23%)
            - Bleeding (14%)
            - Anal extrusion of polyp (7%)
            - Melanin pigmentation (13%)
            - Intussuception in young most common complaint

- Cancer Risk
  - Meta-analysis (210 pts; 6 papers) of cancer risk:
    - RR all cancers 15%
    - Life time cancer risk = 93%
    - Mean age of CA dx = 43 yrs
  - GIT malignancies:
    - Pancreatic (36%)
    - Colon (39%)
    - Esophagus (0.5%)
    - Stomach (29%)
    - SB (13%)
  - Non-GIT malignancies:
    - Lung (15%)
    - Testes, sertoli cell (9%)
    - Breast (54%) – similar to BRCA1/2
    - Uterus (9%)
    - Ovarian (21%)
    - Cervix (10%)

Site	Polyps	Cancer
▪ Esophagus	-	0.5%
▪ Stomach	49%	29%
▪ Small bowel	64%	13%
▪ Colorectum	96%	39%
▪ Pancreas	-	36%

- Diagnostic criteria
  - Hamartomatous polyps with at least 2 of:
    - Labial melanin deposits
    - A family history of PJS
    - Small bowel polyposis

- Pathology
  - Hamartomatous polyps:
  - Affect 88% of affected individuals
    - Occur most frequently in SB (64%)
    - 1-20 polyps per segment of affected bowel
    - 0.1-5 cm in diameter
    - Site
      - Stomach, 49%
      - Small bowel, 64%
      - Colon, 64%
      - Rectum, 32%
  - Branching framework of connective tissue and smooth muscle lined by normal intestinal epithelium, rich in goblet cells
  - Elongated and convoluted glands
  - Arborizing pattern of growth

- Management
  - Screening at risk individuals:
    - 1st degree family members: annual hx/px for melanin spots, testicular tumors
    - If asx by age 8: offer genetic testing
    - If no mutation identified in family:
      - Small bowel imaging q2yrs until age 25
      - +/- endoscopy at 12, 18, 24

- If genetic testing negative
  - Same risk as general population
- If genetic testing positive
  - Polypectomy for stomach, colon >1cm
  - OR for sx or rapidly growing SB polyps or asx polyps >1-1.5cm
  - Polyps > 1 cm polypectomy stomach, colon
  - Asymptomatic > 1.5 cm
  - Symptomatic polyps
  - Rapidly growing small bowel polyps

➢ Surveillance

Site	Age to begin surveillance	Surveillance interval
	Birth	History / physical examination q 1 yr
○ Stomach, small bowel	8	EGD and SBFT at baseline
○	18	EGD and SBFT q 2-3 yr
○ Colon	18	Colonoscopy q 2 yr
○ Breast	18	Monthly self-exam
○ Uterus / cervix	21	Annual pap
○ Ovaries	25	TV US with CA-125 q 1 yr
○ Pancreas	25-30	EUS q 1 yr (CT +CA19-9 as options)

Juvenile Polyposis Syndrome (JPS)

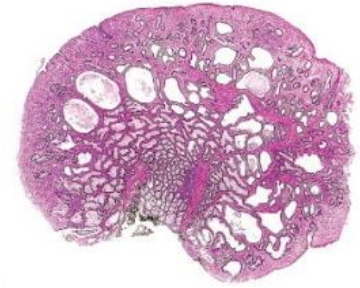
- Demography
  - 3rd most common polyposis syndrome
  - Incidence: 1/100,000 live births
    - 1/3 of individuals will have family hx
  - Mean age of presentation: 18.5yrs
  - Dozens-100s of polyps

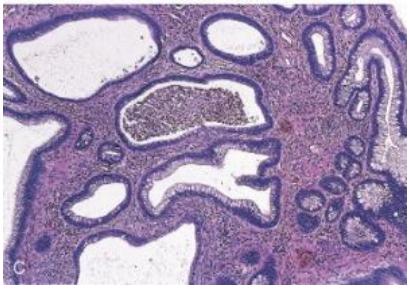
- Types
  - Autosomal dominant inheritance pattern, with no congenital abnormalities
    - SMAD4
      - Mediates gene transcription of proteins responsible for inhibition of cell proliferation
      - Mutations = cell proliferation
    - BMPR1A
      - Activates SMAD4
      - Mutation = inactivation of SMAD4, primary event involved in transformation to polyp
    - 50% of JPS families have one of 2 mutations:
      - SMAD4 (MADH4 or DPC4) gene (chr 18)
      - BMPR1A gene (chr 10)
    - PTEN is another mutation (less commonly seen) in JPS families
  - Sporadic
    - Occurs in 2% of pediatrics population
    - Associated with congenital heart ds, hydrocephalus, intestinal malrotation, clubbing

- Clinical
  - Polyps grow during first decade of life
    - Rectal bleeding with anemia
    - Abdominal pain
    - Passage of tissue per rectum
    - Intussusception

- Cancer Risk
  - Colorectal cancer (CRC) risk = 9-68%
    - Cancer risk is dependent on adenomatous changes occuring within 50% of the JPs
    - Mean age of diagnosis of CRC = 34yrs (15-68yrs)
  - Non-colorectal cancers
    - Stomach
    - Duodenum
    - Pancreas
    - Biliary tree

- Histology
  - Prominent stroma with mixed inflammation
  - Cystically dilated glands lined by mature epithelium





https://quizlet.com/19135686/small-intestine-colon-pathology-flash-cards/ Diagnostic criteria

- Multiple hamartomatous polyps of the colon and rectum
  - >4 juvenile polyps (JP) in the colorectum, or in the GIT, or
  - Any number of JPs in a person with a known family history of JPS
- Rule out
  - Cowden Syndrome
  - Gorlin Syndrome
  - Bannayan-Ruvalcaba-Riley syndrome

➢ Management

- Screen at risk family members with genetic testing
- Annual EGDS/cscopes starting at age 15 yrs
  - Small number of polyps = polpectomy at time of endoscopy
  - Annual surveillance until polyp free then q3yrs
  - Numerous polyps = colectomy (if subtotal colectomy, ongoing rectal surveillance needed)
  - No polyps = surveillance q3yrs

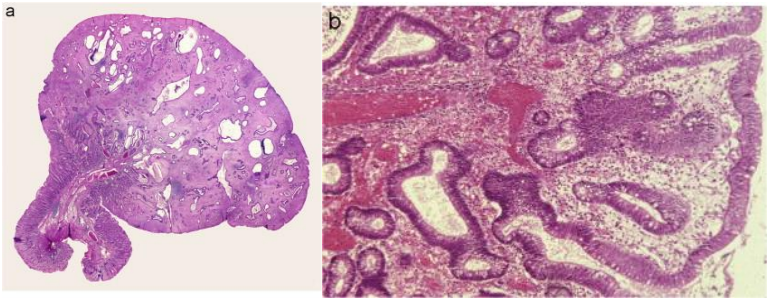
Cowden Syndrome (CS)

➢ Demography

- 1/200,000 live births
- By age 20, 99% have developed mucocutaneous stigmata
- Mutation of PTEN (chromosome 10)
  - 90% of families with PTEN mutation have the CS phenotype

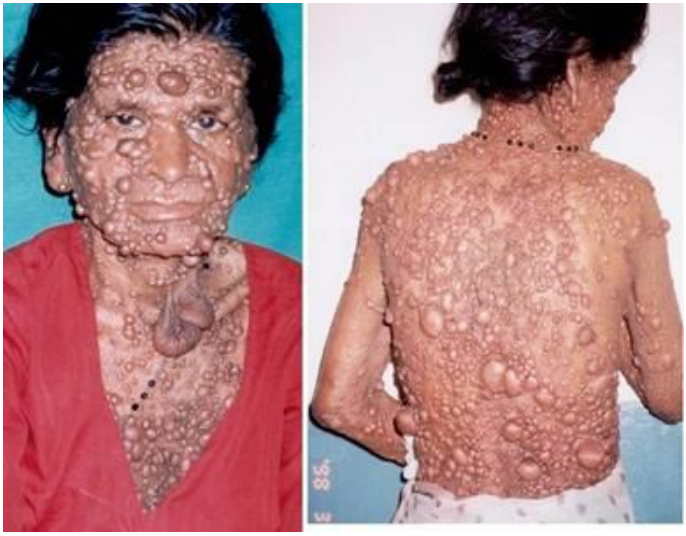
- Clinical
  - Multiple hamartoma syndrome
    - Hamartomatous polyps of the stomach, small bowel, and colon
    - Extra-intestinal manifestations:
      - Multiple facial trichilemmommas (eyes, nose and mouth/ Orocutaneous hamartomas
      - Acral keratosis

- Pathology
  - Different types of hamartomas
    - JPs
    - Lipomas
    - Ganglioneuromas
  - Rare hamartomatous overgrowth syndrome characterized by focal or diffuse enlargement of cerebellar folia that presents as a slowly growing posterior fossa mas
  - Disorganization and proliferation of the muscularis mucosae
  - Normal overlying colonic epithelium



http://www.hereditarypathology.org/categories.php?parent_id=2170Diagnosis

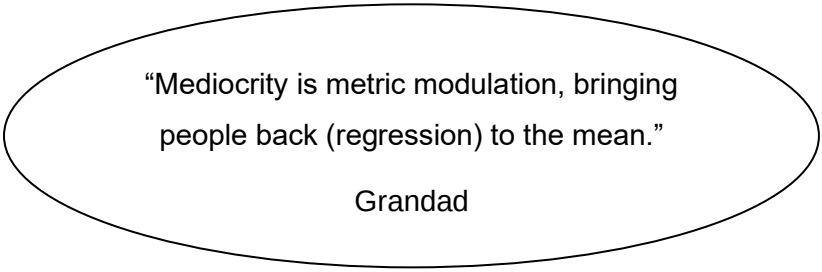
- Major criteria
  - Macrocephaly
    - Extraintestinal cancers
    - Lhermitte-Duclos Disease
- Minor criteria
  - Hamartomas



http://www.allhealthsite.com/cowden-syndrome-signs-symptoms-criteria-prognosis-treatment.html

- Cancer Risk
  - No increased risk of GIT cancer
  - Non-GIT cancers:
    - Breast (50%)
    - Thyroid
    - Uterus

- In the context of inherited hamartomatous polyp syndromes, give the meaning of the Bannayan-Ruvalcaba-Riley (BRR) syndrome
    - Rare autosomal dominant syndrome
    - PTEN mutation (50-60%)
    - Hamartomatous GI polyps with:
        - Macrocephaly
        - Developmental delay
        - Other developmental abnormalities
        - Pigmented spots on penis
        - Thyroiditis



Radiation Proctopathy

Dan Segal

- Definition
  - Epithelial damage to the rectum due to radiation that is not associated with inflammation, so radiation proctitis is a misnomer

- Types
  - Radiation proctitis (RP)
  - Divided into acute vs. chronic
  - Acute RP occurs during or within six weeks of therapy
  - Chronic RP usually presents within 9 to 14 months of radiation, but can occur anytime post radiation

- Demography
  - External beam radiation is employed in treating 70 % of cancer patients
  - Cancers of the rectum, anus, cervix, uterus, prostate, bladder, and testes may all be treated with radiation
  - 90% of patients develop permanently altered bowel habits
  - 50% have associated reduction in quality of life
  - Rate of RP with brachytherapy (internal radiation) is around 10 %
  - 10 – 80 % require procedural intervention

- Pathophysiology
  - Gastrointestinal tract uniquely susceptible because of rapidity of cell turnover
  - High-energy photons collide with electrons which leave orbit of atom
  - Electrons cause ionization of other molecules or generate ROS
  - These interactions damage DNA, proteins, lipids
  - Failure to repair even one DNA break in a cell nucleus could cause cell death
  - Amount of damage based on radiation energy, absorbed dose, fractionation schedule
  - 1 gray (Gy) = 1 joule of energy / kilogram of absorbing material (tissue)
  - Absorbed dose based upon a number of factors including location in cell phase, i.e cells in mitosis absorb most radiation
  - Inflammatory colonic cytokines seem to protect against injury (FGF-2, TNF-α)
  - Some luminal microbes may sensitize cells to injury via inducing certain proteins
  - Increased risk depending on combination therapy with other modalities
  - Apoptosis:
    - In animal models cell apoptosis is dose related
    - P53 promotes apoptosis while bcl-2 protects the mucosa after irradiation

- P53: the regulator of the genome
  - Following damage it is upregulated, causing arrest of cell cycle, apoptosis
- Early changes include apoptosis of lamina propria lymphocytes + epithelial cells
- Damage to vascular cells
- Loss of polarity of cells lining the crypts leading to swelling and loss of mucus secreting goblet cells
- Stem cells generally survive and repopulate epithelium
- If dose too high then lose stem cells, barrier becomes destroyed
- Get bacterial translocation, infection etc.
- TGF-β
  - Radiation activates translation of transforming growth factor β
  - TGF-β is a potent fibrogenic and inflammatory cytokine
  - Stimulates intestinal fibrosis by causing increased expression of collagen genes
  - TGF-β is upregulated in the majority of tissues in the acute phase after radiation
  - It is only present in vascular endothelial cells at 26 weeks
- CTGF:
  - Connective tissue growth factor increased in radiation
  - Its increase may be mediated by TGF-β
  - Mediator of intestinal fibrosis
- Delayed effect from 6 months to 5 years

- Vascular injury and regeneration
- Myointimal thickening in medium sized vessels predisposes to ischemia
- Ulceration in areas overlying these vessels
- Telangiectatic vessels in submucosa due to increased collagen infiltration?

- Risk Factors
  - Dose of radiation (< 45 Gy cause minimal long-term side effects)
  - Area of exposure (anterior wall of rectum)
  - Method of delivery
    - External beam radiation results in greater exposure to surrounding organs
    - Brachytherapy, administered via radioactive implants, has smaller field
  - Concomitant disease
    - HIV/AIDS
    - IBD
  - Previous surgery to pelvis
  - Decreased blood flow to bowel wall
    - Hypertension
    - Diabetes

- Prevention
  - Many strategies attempted to prevent sequelae of radiation on colon

- Reducing or abolishing inflammatory response?
  - Steroid enemas, 5-ASA
- Mechanically shielding colon?
  - Sucralfate
- Preventing free radical damage with scavengers?
  - Amifostine
- Not a ton of great evidence…
- Beclomethasone dipropionate
  - **Fuccio L**. "Randomized clinical trial: preventive treatment with topical rectal beclomethasone dipropionate reduces post-radiation risk of bleeding in patients irradiated for prostate cancer." Aliment Pharmacol Ther, 2011.
    - 120 patients randomized to BDP enema or placebo for four weeks
    - Follow up to twelve months
    - No significant differences between groups for main outcome of rectal side effects
    - Did have lower risk of rectal bleeding, NNT 5

➢ Clinical

- Acute RP presentation
  - Symptoms:
    - Diarrhea in 50 – 75 %
    - Mucus discharge
    - Urgency, tenesmus
    - Constipation
    - Bleeding uncommon in acute RP
    - Bleeding very common in chronic RP

- Laboratory
  - Exclude other causes of symptoms
    - History: recent travel (amebiasis), recent abx (C Diff), STI hx (proctitis)
      - Atherosclerotic risk factors (ischemic bowel)

- Acute
  - Endoscopic and mucosal biopsy
    - Non-specific
    - Mucosa may have pallor, exhibit friability
    - Telangiectasias→ single or multiple or serpiginous
    - Edema, inflammation, friability

- Chronic
  - Symptoms
    - Rectal urgency
    - Incontinence
    - Pain
    - Strictures
    - Mucous Discharge
    - Rectal bleeding (common)
  - Imaging
    - MRI if concern for fistula
    - CT if obstructive symptoms
  - Endoscopic Imaging
    - Rectum pale and noncompliant
    - Strictures, ulcerations
    - Fistulas due to poor wound healing
    - Mucosal hemorrhage
    - Telangiectasia

- Clinical caution
  - Persistent rectal bleeding should prompt you to think of colorectal malignancy!
  - Rate of colorectal malignancy increases significantly 5-10 years after prostate Ca therapy
  - Think of this especially if really late presentation of chronic RP
  - Be careful not to “mess about” early on after radiation therapy as high risk of causing rectal fistula formation with something as innocuous as rectal biopsy

- Treatment

- Acute
  - Supportive therapy
    - Hydration
    - Antidiarrheals
    - Butyrate enemas may accelerate healing
      - Example of short-chain fatty acid
      - Major metabolite of bacterial fermentation in colon
      - Butyrate inhibits colonic tumor cells and promotes healthy colonic epithelial cells
      - Has been used as fishing bait and as a stink-bomb due to strong odour
      - **Vernia P.** Topical butyrate for acute radiation proctitis: randomised, crossover trial. Lancet, 2000.
        - RCT post external beam rad. Therapy for pelvic cancer (n=20) comparing butyrate enemas to placebo for three weeks
        - Butyrate enemas improved symptoms, endoscopy, histology
  - Self-limiting issue
    - 15-20% will require altered therapeutic course

- Chronic
  - 56% of those who receive pelvic irradiation develop bleeding
  - Up to 5% become transfusion dependent
  - Bleeding typically starts one year out, persists or worsens for three years, then slows spontaneously over the next decade

Type of therapy	Proposed mechanism	Summary
○ Medicinal therapies		▪ Historically used as first-line therapy with mixed results; few randomized trials available ▪ HBOT appears to be effective
– 5-ASA	– Anti-inflammatory	
– Sucralfate	– Anti-inflammatory	
– Steroid enemas	– Anti-inflammatory	
– Short-chain fatty acid enemas	– Promote healing	
– HBOT		
○ Endoscopic therapies		▪ More effective than medical therapies but associated with higher rectal complication ▪ Rate; APC is preferred over laser coagulation
– Topical formalin	– Chemical cauterization	
– Heater and bipolar cautery	– Thermoelectric cauterization	
– Nd: YAG and KTP laser	– Noncontact electrocoagulation	
– Argon plasma coagulation	– Noncontact electrocoagulation	
○ Surgical therapies		▪ High risk of postoperative morbidity ▪ Reserved for severe rectal strictures and rectal fistulas
– Proctectomy		
– Diverting colostomy		

Abbreviations: APC, argon plasma coagulation; HBOT indicates hyperbaric oxygen therapy; KTP, potassium titanyl phosphates; Nd:YAG, neodymium / yttrium aluminium garnet argon

- Topical Pharmacotherapy
  - 5-ASA po / pr
    - Active component of sulfasalazine
    - Anti-inflammatory effects including reducing prostaglandin production
    - Mixed results
    - “Failure of 5-aminosalicylic acid enemas to improve chronic radiation proctitis” Baum Ca. Dig Dis Sci, 1989.
      - Case series of four patients treated with 4 g enemas for two – six months
      - No endoscopic healing and only one patient had symptom improvement
  - Sucralfate enema
    - Aluminum salt that adheres to mucosal cells and stimulates prostaglanding production
      - “Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate.” Kochhar R. Dig Dis Sci, 91.
      - **“**Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension.” Kochhar R. Dig Dis Sci, 99.
    - Sucralfate enemas better tolerated, better clinically, similar endoscopically
    - 92% had reduction of bleeding by 16 weeks of treatment

- 71% had no further bleeding at a mean of 46 month follow up
- Sucralfate better for symptoms but similar endoscopic response in comparison to prednisolone enemas bid and sulfasalazine po for 4 wk

“Making Your Own Sucralfate Enemas”

- Sucralfate suspension
- Add to 30-50 mL tap water
- Draw up in bladder syringe
- Fit a soft Foley catheter to the syringe
- Lubricate the catheter and pass into the rectum
- Inject the sucralfate mixed with water twice a day into the rectum
- Retain the enema for as long as possible
- Initially roll through 360^{o} to coat the entire rectal surface
- Lying prone then best covers anterior wall rectal telangiectasia, the likely area of greatest bleeding
- Short-chain fatty acid enemas (e.g. butyrate)
  - Fifteen patients comparing two weeks of butyrate enemas to placebo with crossover of both groups
  - No change in symptoms, endoscopy, or histology
  - Talley NA. “Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled cross-over pilot trial. Dis Colon Rectum, 1997.

Therapy	No. of studies	Results	No. of sessions needed	Complications	Study(s)
- Topical formalin	5	Initial response rate, 59% - 100%; PR rate at 1 y, 19% - 38%	1-3	Rectal strictures, < 1%; perianal ulcers fissures, 5%	Wilson & Rex 2006, Matthai & Seow-Chen 1995, Seow-Chen 1993, Saclarides 1996, Biswal 1995, Counter 1999, Roche 1996, Yegappan 1998
- Heater and bipolar probe	2	Response rate, 100%	1-4	None	Fuentes 1993, Davila 1996,
- Nd:YAG and KTP laser	5	Response rate at 1-3 y, 75% - 90%	2-5	Ileus, pain, 1% - 5% rectal fistula, < 1%	Taylor 1993, Buchi 1991, Buchi & Dixon 1987, Chapuis 1996, Taylor 200
- Argon plasma coagulation	5	Response rate at 1-2 y, 90% - 100%	2-3	Rectal strictures, 2%	Tam 2000, Silva 1999, Fantin 1999, Sebastian 2004, Rotondano 2003

Abbreviations: KTP, potassium titanyl phosphate; Nd:YAG, neodymium / yttrium aluminium garnet argon; PR indicates partial response;

- Endoscopic therapy

- Argon Plasma Coagulation (APC)
  - APC is trademarked name from Erbe
  - Monopolar electrosurgical procedure whereby electrical energy zaps tissue without actually touching probe to mucosa
  - Instead, conductive gas (argon) facilitates electrical transfer via the path of least resistance
  - Benefits
    - Consistent depth of penetration
    - Less charring of tissue
  - "Argon plasma coagulation therapy for hemorrhagic radiation proctosigmoiditis." Silva RA. Gastrointest Endosc 1999; 50(2): 221-224.
    - Report of 28 patients had improvement of bleeding and anemia after median of 2.9 sessions
    - All visible lesions treated each session
    - Follow up procedures scheduled in 4 week intervals
    - Mean hemoglobin rose by 12 g/L
    - Some patients experienced post-procedure rectal pain and cramps
    - Can use 5-ASA suppositories to treat rectal ulceration from APC
    - Hanson B. "Endoscopic and medical therapy for chronic radiation proctopathy: a systematic review." Dis Colon Rectum. 2012.
      - Meta-analysis of all treatments for CRP
      - 27 studies with endoscopic therapy
      - Meta-analysis shows only low level evidence for short-term efficacy of APC, but insufficient evidence for long-term benefit

- Risks
  - Rectal pain, rectal stenosis, altered bowel habits, rectal wall injury
  - Rate of rectal ulceration leading to fistulization <1% - 2%
- Be careful using this within two years of radiation therapy due to potential risk of rectourethral fistula

- Bipolar cautery and heater probes
  - Heater probes apply direct heat reaching 250 F
  - Bipolar cautery coagulate tissue with electricity with max temp. of 100 F
  - Widely available, relatively inexpensive
  - Jensen DM. “A randomized prospective study of endoscopic bipolar electrocoagulation and heater probe treatment of chronic rectal bleeding from radiation telangiectasia.” Gastrointest Endosc, 1997.
    - Case series of twenty-one patients treated with bipolar or heater probe
    - Only patients who failed medical therapy
    - Both modalities decreased severe bleeding compared to baseline
    - Anemia improved in both groups
    - No major complications
  - Unclear if APC has better safety and efficacy data

- Lasers (Nd:YAG, argon, KTP)
  - All are different laser systems
  - Nd:YAG
    - Shown reasonably good short-term control of symptoms
    - Limitations: depth of penetration (5 mm), need to aim directly at telangiectasias
  - Argon + KTP
    - Lower depth of penetration (1-2 mm)
    - Taylor JG. “KTP laser therapy for bleeding from chronic radiation proctopathy”. Gastrointest Endosc, 2000.
      - Twenty-three patients treated a median of two times and followed for 29 months
      - Significant reduction in bleeding, improved ADLs
      - Two patients had rectal ulcers
  - Major disadvantages
    - High cost
    - Limited availability
    - Associated risk of bowel perforation
    - Rectal ulcers and fistula development on order of 1-6%

- Cryoablation
  - “wart therapy” i.e noncontact application of liquid nitrogen
  - “Treatment of chronic radiation proctitis with cryoablation.” Hou JK. Gastrointest Endsoc. 2011.
    - One pilot study, 7/10 patients had improvement in symptom severity
    - Endoscopic improvement in telangiectasia score
    - One patient had cecal perforation from gas overdistension

- Formalin
  - Induces coagulative skin necrosis on contact
  - Developed for radiation induced cystitis
  - APC considered more effective
  - May run into serious complications like fistulas and bowel necrosis in up to 27% of patients because you know.. It's formalin!
  - Several techniques have been employed for application of formalin
    - By direct application during flexible sigmoidoscopy
    - By 16-inch cotton tip applicator
      - In this series 3 patients complained of anal pain
    - Documented complications:
      - Ulceration
      - Fissures
      - Anal stenosis
      - Fecal incontinence

- Hyperbaric oxygen
  - Clarke RE. "Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up." Int J Radiat Oncol Biol Phys. 2008.
    - RCT of 150 patients randomized to sham air vs. hyperbaric 100% oxygen
    - Higher clinical response based on scoring system, NNT 3
  - Extremely expensive
  - Need > 20 sessions

- Antibiotics
  - Immunomodulatory effects and selective toxicity to microorganisms that contribute to pathogenesis
  - Cavcic J. “Metronidazole in the treatment of chronic radiation proctitis: a clinical trial. Croat Med J, 2000.
    - Sixty patients assigned to 5-ASA plus betamethasone enemas +- flagyl 400 PO Q8H
    - Rectal bleeding, diarrhea, and rectal ulcers were less common in the flagyl group out to one year

- Vitamin A (antioxidant agents)
  - Ehrenpreis ED. “A prospective, randomized, double-blind, placebo controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy.” Dis Colon Rectum, 2005.
    - RCT of nineteen patients assigned to vitamin A versus placebo for ninety days
    - Five placebo nonresponders were crossed over to vitamin A
    - No significant difference in patients that responded (P = 0.057), but significant difference in the mean symptom scores

- Surgical therapy
  - Usually for complications such as rectal strictures or fistulas
  - Different procedures offered: excision, diversion, and reconstruction
  - Seem to have higher rates of postoperative complications
    - Sepsis, wound dehiscence, bowel obstruction, new fistula

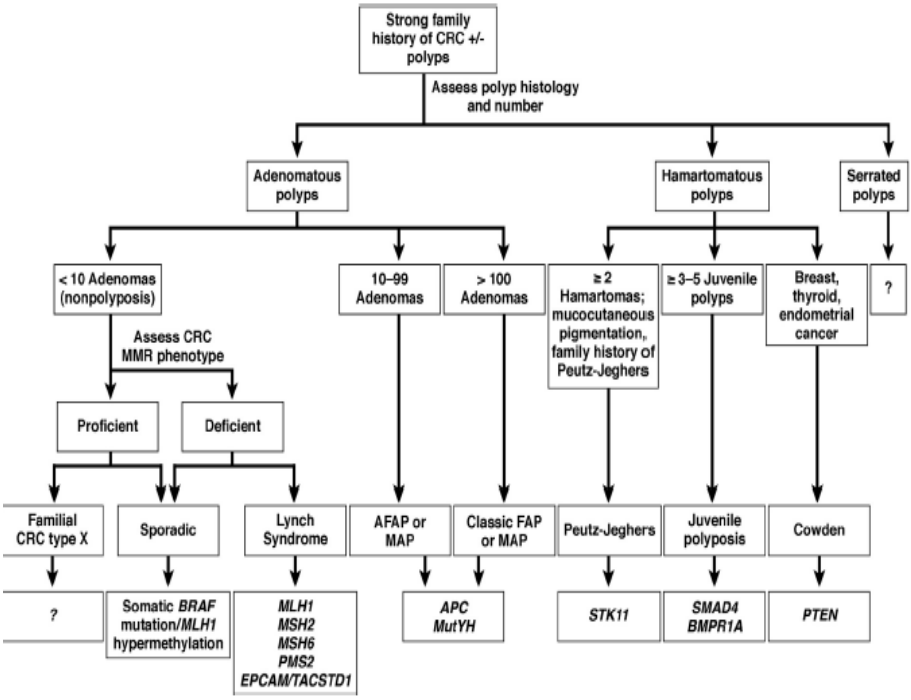
- Classic case series from Mayo Clinic in Am J Surg, 1986
  - Sixty-two patients with radiation colitis + proctitis (acute and chronic)
  - 13% mortality during OR, 65% complication rate
  - Majority of operations were ostomies for fistula and stricturing
- Newer data suggests mortality rate 3 % and morbidity rate is 9 %

UK guidelines (Andreyev HJN, et al. Gut 2012; 61: 179-192)

- Step 1: Investigate with flexible endoscopy
- Step 2: Optimize bowel function and stool consistency
- Step 3: If bleeding not affecting QOL reassure and do nothing
- Step 4: If bleeding affects QOL stop/reduce anticoagulants and if really severe start sucralfate enemas
- Step 5: Discuss definitive treatment to ablate telangiectasias
  - Hyperbaric oxygen therapy
  - APC
  - Formalin therapy

Familial Colorectal Cancer

Neel Malhotra



Approach to patients with familial CRC, AFAP, attenuated familial adenomatous polyposis; MAP, MutYH-associated polyposis

Mutation in Known Genes

Lynch Syndrome

- Most common of the hereditary CRC syndromes (Lifetime risk: 22-75%)
- Develop colorectal, endometrial and selected other cancers (ovarian, gastric, brain, pancreatic)
- Autosomal dominant pattern

- > 90% have high DNA microsatellite instability (MSI-H) and loss of expression of mismatch repair proteins (MLH1, 2, 6, PMS2)
- Tumor develop at younger age groups and accelerate progression
- Frequent surveillance is effective in reducing CRC incidence and mortality
  - Surveillance with colonoscopy Q1-2 years (Starting at age 20 to 25)
  - Upper GI endoscopy at 3-5 year intervals (Starting at age 30 to 35)

Lynch syndrome	– MMR deficiency phenotype in tumors (MSI) – Accelerated adenoma-carcinoma sequence – CRC risk 30-70% over lifetime – Risk for extracolonic cancers	MLH1 MSH2 MSH6 ▪ PMS2 TACSTD1 / EPCAM ▪ Mutations detected in 70%	– Colonoscopy every 1-2 yr starting at age 20-25 yr – Consider upper endoscopy every 3-5 yr, starting at age 30-35 yr – Consider endometrial cancer screening vs. prophylactic hysterectomy	Cohort studies Expert opinion

Familial Adenomatous Polyposis (FAP)

- Second most common of the inherited CRC syndrome
- Classic phenotype: hundred to thousands of adenomatous polyps in the colon
- Most develop adenomas by the second or third decade of life
- Lifetime risk of CRC with no surgical colectomy: >90%

- Increased risk of papillary thyroids, adrenal carcinomas, CNS tumors
- Classic FAP
  - 90% due to **APC gene** mutations (tumor suppressor gene)
    - Multiple adenomas at a very young age
    - Most are Autosomal Dominant inherited
- 30% have no family history
  - De-novo mutation in APC or biallelic mutations in MutYH (a DNA excision repair gene involved in the repair of oxidative damage)
  - MutYH associated polyposis is an autosomal recessive pattern of inheritance. More attenuated phenotype (<100 adenomas)
- Begin surveillance at age 10 to 12 years
- Test negative for mutations: screen according to population based

Classic

– 100-1000 colorectal adenomas – Risk for duodenal and ampullary adenocarcinoma – Risk for desmoid tumors, thyroid cancer – CRC risk 90% without surgery	▪ APC mutations detected in 90% ▪ MutYH (biallelic)	– Colonoscopy every 1-2 yr, starting at age 10-12 yr colectomy for large polyp burden – Upper endoscopy every 1-3 yr – Consider thyroid ultrasound	Expert opinion

Attenuated			
– 10-99 colorectal adenomas – CRC risk is variable	▪ APC, MutYH mutations detected in ~ 10%	– Colonoscopy every 1-2 yr, beginning at age 20-25 yr – Upper endoscopy every 1-3 yr	Expert opinion

Hamartomatous Polyposis Syndromes

- Defined as more than 3 to 5 hamartomatous polyposis polyps in the GI tract
- Peutz-Jeghers Syndrome (PJS): multiple intestinal hamartomatous polyps, mucocutaneous pigmentation and a high lifetime risk of GI, pancreatic and breast cancers.
  - Incidence: 1 in 150,000
  - Diagnosis requires (2 or more of the following):
    - Mucocutaneous Pigmentations (freckling in mouth/lips, fingers)
    - 2 or more Peutz-Jegher type GI hamartomas
    - Family history if PJS
  - Risk of cancer up to 90%
    - GI cancers (colon, small intestine, stomach, pancreas)
    - Breast
  - Mutation in the serine threonine kinase 11 (STK-11) tumor suppressor gene.
  - Gene testing can confirm diagnosis (But not informative for those with a clinical diagnosis)
  - Screening as per recommendations
- Juvenile polyposis syndrome (JPS): multiple (≥3-5) juvenile polyps and increased risk for GI cancers (Gastric and colorectal)
  - Risk: 40-50% (lifetime)
  - Often present in childhood with abdominal pain, anemia and bleeding

- Polyps mostly found in stomach or colon
- Mutations in SMAD4 and BMPR1A genes in 50%
  - Encodes proteins involved in the transforming growth factor pathways (TGF-Beta). Considered a transcription factor also based on the downstream effect
- Genetic testing is clinically uninformative
- Screening (personal or family history: upper and lower endoscopy starting at age 15

- Cowden Syndrome
  - Caused by mutations in the PTEN (phosphatase and tensin homolog) gene → another tumor suppressor gene
  - Increased risk for cancers:
    - Breast, thyroid, endometrial
  - Wide heterogeneity in polyp number and histological type

PJS

- ≥ 2 hamartomatous polyps in small bowel - Mucocutaneous pigmentation (mouth / lips, fingers) - Cumulative lifetime cancer risks 80-90% (colorectal, breast, gastric, pancreatic)	▪ STK11 mutations detected in 50-70%	- Upper endoscopy every 2-3 yrs starting in late teens - Small bowel visualization (e.g. capsule endoscopy, CT/MR enterography, small bowel follow-through) every 1-3 yr starting at age 8-10 yr - Colonoscopy every 2-3 yr, starting in late teens - Pancreas screening (MRCP or EUS) every 1-2 yr, starting at age 25-30 yr - Mammogram and breast MRI, yearly, starting age 10 yr - Transvaginal ultrasound, yearly, starting at age 18 yr	Expert opinion

JPS			
– 3-5 juvenile polyps in gastrointestinal tract – Some associated with congenital heart disease, hereditary hemorrhagic telangiectasia	▪ SMAD4 BMPR1A ENG ▪ Mutations detected in < 50%	– Upper endoscopy every 1-3 yr starting at age 15 yr – Colonoscopy every 1-3 yr starting at age 15 yr	Expert opinion
Cowden syndrome			
– Macrocephaly – Increased risk for cancer (breast, thyroid, endometrial) – Variable colorectal polyp phenotype (adenoma, hamartoma, sessile serrated, ganglioneuroma) – CRC risk can be variable	▪ PTEN ▪ Mutations detected in 65-85%	– Colonoscopy every 3-5 yr, beginning at age 30-35 yr – Mammogram and breast MRI, yearly, starting at age 30-35 yr – Annual thyroid ultrasound starting at age 18 yr	Expert opinion

Familial Colorectal Cancer without Identifiable Gene Mutations

- Familial Colorectal Cancer Type X
  - Patients that meet the Amsterdam Criteria
  - MMR proficient phenotype on testing
  - Unknown cause for increased risk of cancer
  - Difficulty to implicate a single gene, possible polygenic hypothesis
  - Lower Methylation

- Risk of colorectal cancer appears to be lower than Lynch syndrome
- Screening: 5-10 yr earlier than when the youngest family member diagnosed
  - Repeat Q5 years

- Attenuated Adenomatous Polyposis
  - > 10 but <100 adenomatous colonic polyps
  - Genetic evaluation for MutYH and APC genes are considered
    - Can be helpful for management of family members, but generally genetic testing considered uninformative
  - Goal: removal of all adenomas (surgery if not)

- Serrated Polyposis
  - Large and/or multiple serrated polyps
  - Believed to be the precursor lesions of serrated colorectal cancers
  - Mechanism of carcinogenesis: hypermethylation resulting in silencing of tumor suppressor genes
  - Somatic mutations in the BRAF proto-oncogene
  - Found mostly in the proximal colon
  - Classification from the WHO
    - More than 5 serrated polyps (proximal to the sigmoid colon) with at least 2 measuring greater than 10 mm
    - Any number of serrated polyps in the proximal colon in an individual who has a first degree relative with serrated polyposis
    - More than 20 serrated polyps of an size distributed throughout the colon
  - Clinical genetic testing is low yield
  - Goal (based on expert consensus) → removal of as many polyps as possible. Surgical resection considered

Abbreviation: CLD, chronic liver disease

- Familial Colorectal Cancer (Not otherwise specified)
  - 30% of patients with CRC report having some relatives diagnosed with CRC.
    - Germline mutations are implicated in only 5-6%
    - Red Flags that should promt further evaluation
    - Young age at diagnosis
    - Strong family history
    - National Comprehensive Cancer Network Guidelines:
- Overall
  - Screening of CRC tumors for MMR deficiency to ensure those at risk for Lynch syndrome undergo genetic evaluation is becoming the expected standard of care
  - Identify high risk individuals early enough to change the natural history of the disease

National Comprehensive Cancer Network Criteria for Further Risk Evaluation for High-Risk Syndromes Associated with CRC

- Individuals meeting the revised Bethesda Guidelines
- Individuals with a family history that meets Amsterdam Criteria
- Individuals with > 10 colorectal adenomas
- Individuals with multiple gastrointestinal hamartomatous polyps or serrated polyposis syndrome
- Individuals from a family with a known hereditary syndrome
- Individuals with desmoid tumor

Note: Data are from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, version 1.2013 (available at: www.nccn.org)

LIVER

Oral Anticoagulation in Patients with Chronic Liver Disease

Vidya Sujana Kumar and Alison Martin

Chronic Liver Disease (CLD)

- Gradual destruction of liver tissue over time
- Wide variety of etiologies
  - Infectious
  - Toxin/Drug induced
  - Genetic
    - Alcohol
    - Non-alcoholic fatty liver disease
  - Immune/autoimmune
- Vascular
- Cardiac
- Malignant
- Systemic disease
- Progression early → advanced → pre-cirrhotic → cirrhotic
- Classification/Prognostication (grading and staging) systems:
  - Child-Turcotte-Pugh (CTP)
  - MELD score

Abbreviation: MELD, model for end stage liver disease

Child-Turcotte-Pugh Classification for Severity of Cirrhosis

Clinical and Lab Criteria	Points* 1	2	3
○ Hepatic encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
○ Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
○ Bilirubin (mg/dL)	< 2	2-3	> 3
○ Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
○ Prothombin time			
– Seconds prolonged	< 4	4-6	> 6
– International normalized ratio	< 1.7	1.7-2.3	> 2.3

1 year survival
- ○ Class A – 100%
- ○ Class B – 80%
- ○ Class C – 45%

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (lease severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

Model for End Stage Liver Disease (MELD)

MELD score = 10 x [0.957 x log e (creatinine) + log e (bilirubin) + 1.12 x log e (INR)] + 6.43

3 month mortality according to MELD score

	Cirrhotic	≤ 9	10-19	20-29	30-39	≥ 40
○	Hospitalized	4%	27%	76%	83%	100%
○	Outpatient	2%	6%	50%		

- Complications of CLD and cirrhosis
  - Portal Hypertension (varices, congestive splenomegaly and hypersplenism)
  - Ascites
  - Infection (SBP)
  - Hepatic encephalopathy (HE)
  - Hepatorenal syndrome (HRS)
  - Hepatopulmonary syndrome (HPS)
  - Hepatocellular carcinoma (HCC)
  - Malnutrition
  - Hematologic abnormalities
  - Abnormalities in coagulation

CLD and Coagulopathy

- CLD puts patients at an ↑ bleeding risk through multiple mechanisms
  - ↓ production of coagulation factors
    - V, XI, Vit K dependant factors (II, VII, IX, and X)
    - Fibrinogen
    - Plasminogen
  - Abnormalities of platelet number and function:
    - ↓TPO
    - Sequestration
    - Auto-antibody destruction
    - Bone marrow suppression
    - Platelet dysfunction
  - Infection
    - Overt sepsis or low levels of endotoxemia can
      - ↓ platelet function, production, and adhesion
      - ↑ endogenous heparinoids and predispose to disseminated intravascular coagulopathy (DIC.
  - Hyperfibrinolysis
    - Systemic fibrinolysis
    - Accelerated intravascular coagulation and fibrinolysis (AICF)
  - Other culprits for bleeding tendency
    - Portal hypertension
    - Endothelial dysfunction
    - Renal failure
    - Infection

- Patterns of prohemostatic and antihemostatic drivers in the different phases of hemostasis in patients with chronic liver disease

Hemostasis phase	Prohemostatic drivers	Antihemostatic drivers
Primary hemostasis (platelet-vessel wall interactions)	High von Willebrand factor, low ADAMTS 13	Low platelet count
Blood coagulation (thrombin generation and inhibition)	Low anticoagulant factors: antithrombin, protein C	Low procoagulant factors: fibrinogen factors II, V, VII, IX, X, XI
Fibrinolysis (clot dissolution)	Low plasminogen, high PAI	High t-PA, low TAFI, low plasmin inhibitor

Problems of diagnosing coagulopathy in CLD

- Don't we trust the INR
  - Standardized ratio (INR) was calibrated for patients on vitamin K antagonists, not for people with CLD
  - Plasma of cirrhotic patients generates as much thrombin as plasma from healthy subjects, when measured by methods that reflect the action of procoagulants and anticoagulants (Tripodi et al, 2005)
  - Plasma and reagents that are used to measure the prothrombin time do not appropriately assess the balance of thrombin generation and inhibition (i.e. protein C/thrombomodulin)

Prothrombotic State in CLD

- ↓ production of endogenous anti-coagulants
  - Protein C&S
  - Anti-thrombin
- ↑ procoagulant factors
  - Factor VIII (acute phase reactant)
  - vWF (↓ADAMTS 13 and chronic inflammation)
- Restoration of platelet function
  - ↑ vWF
  - ↓ ADAMTS 13 may restore platelet adhesion and function
  - Platelet counts as low as $60x10^9$ can produce low normal amounts of thrombin (Tripodi et al, 2006)

Macro- and microvascular disease in CLD

- ↑ risk (~ 2x ↑) of developing
  - Macrovascular (DVT/PE/PVT)
  - Microvascular (hepatic microthrombi)
  - Portopulmonary hypertension complications (despite an ↑ INR)

➢ Summary

- CLD promotes both pro and anti-coagulant states
- INR may not be a good reflection of coagulability in CLD
- The theory of “auto-anticoagulation” is a misconception
- Need for a method of identifying CLD patients who may benefit from or be at high risk of bleeding with anticoagulation
- What is known
  - Patients with chronic liver disease may require anticoagulation for unrelated conditions, but little is known about its safety in these patients.

        - Novel anticoagulants are not approved for use in patients with liver disease; thus, warfarin will likely continue to be the predominant agent used in this patient population.

    - What is needed
        - Albumin plus creatinine = only meaningful predictors of ↑ bleeding risk

Proposed clinical predictive tool for evaluation of risk of major hemorrhage in patients with chronic liver disease with indication for anticoagulation:

- One point each for serum creatinine 4 – 2 mg/dL and / or albumin 2.50 – 3.49 g/dL, for creatinine > 2 mg/dL, and for albumin < 2.5 g/dL

Efird, LM, et al. Circ Cardiovasc Qual Outcomes. 2014;7(3):461-7.

➢ Self testing on the **coagulopathy of chronic liver disease.**

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

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

A Practice Curiosity

In cirrhosis, the necessarily reflected in INR predicts a bad prognosis, but the risk of spontaneous bleeding is not increased by ↑ INR (of course ↑ INR is associated with serious bleeding, if and when bleeding occurs from a pathological cause, such as bleeding esophageal varices.

- So what is the curiosity? The evidence is not strong that the severity of bleeding esophageal varices is reduced by giving
  - Vitamin K
  - FFP (fresh frozen plasma)
  - rVIIa (recombinant factor VIIa)
  - Platelets
  - Desmopressin
- So, why do we sometimes do this in common everyday practice?
  - Well, because it “makes sense”, or “it’s the local standard of care”, or “if I don’t, the lawyers will eat we alive”!

Stratifying the Risks of Oral Anticoagulation in Patients With Liver Disease

- Methods
  - Veterans Affair Study to Improve Anticoagulation Database 2006-08 from 100 sites
  - 102,134 patients who received warfarin
  - Warfarin use was determined by:
    - Dispensed by pharmacy
    - INR checks every 6 weeks
    - Verified duration of prescriptions + 30 day grace period
  - Inclusion Criteria:
    - International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)
    - Chronic Liver disease = >1 ICD-9 codes for chronic liver disease
  - Exclusion Criteria:
    - First 6 months of Warfarin Use
    - Portal vein thrombosis was not among indications for anticoagulation
    - Anticoagulation for mechanical valves

* patient with valvular heart disease or mechanical heart valves were excluded from the study

Efird, LM, et al. Circ Cardiovasc Qual Outcomes. 2014;7(3):461-7.

  - Definition of Hemorrhagic Events
    - Major bleeding event into critical anatomic site
    - Death within 30 days
    - Associated with blood transfusion
    - Main reason for a hospitalization

- Definition of Liver Disease Severity
  - Mean values of the following laboratory parameters:
    - Albumin
    - Aspartate transaminase (AST)
    - Alanine transaminase (ALT)
    - Bilirubin
    - Creatinine
    - Cholesterol
- Stratification of Bleeding Risk

HAS-BLED Score

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (I point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age > 65 years)	1
D	Drugs or alcohol (I point each)	1 or 2

Age and TTR = covariates for labile INR

Abbreviation: TTR, time in therapeutic [anticoagulation] range

- Results

Time in Therapeutic Range (TTR)

- Liver Disease TTR = 53.5 %
- Non-Liver Disease TTR = 61.7%
- Poorer TTR seen with:
  - ↑ levels of the following:
    - Creatinine
    - AST
    - Bilirubin
  - ↓ levels of the following:
    - Albumin
    - Cholesterol
- Factors Associated with Bleeding
  - Any type of liver disease = ↑ hemorrhagic risk
  - ↑ bleeding risk associations = same factors for TTR!

For the time to event analysis of any hemorrhagic event in patients with chronic liver disease receiving oral anticoagulations, stratified by laboratory values, please see Efird, LM, et al. Circ Cardiovasc Qual Outcomes. 2014; 7(3): 461-7.

TTR Score

↑ risk of bleeding (No significant hemorrhagic events (p=0.59)

	TTR
0	56.7%
2	50%
4	30%

More hemorrhages ($p < 0.001$)

- Risk and recommendation for patients with liver disease with indication for anticoagulation, based on total points of proposed clinical predictive tool

Liver disease and total points	Risk and recommendation
0 1	Normal or slight risk – Consider coagulation as per general population
2 3	Moderate – Consider usual risks / benefits of anticoagulants
4	High risk – Consider alternatives to anticoagulation

Adapted from: Efird, LM, et al. Circ Cardiovasc Qual Outcomes. 2014;7(3):461-7.

- Study Limitations
  - Retrospective, based on automated data
  - Mostly male population
  - Excluded
    - Portal vein thrombosis (PVT)
    - Mechanical valves
  - Did not compare to outcomes of patients not receiving anticoagulation
  - Unable to control for numerous confounders, e.g.
    - Antiplatelet pharmacotherapy
    - Thrombocytopenia
    - Baseline INR

- Limited follow-up (over 2 year)
- Difficult to know if there is a dose-response gradient
- Also difficult to know effect of anticoagulation in absence of baseline INR and Platelet count
- Prediction tool used in study may not be valid in all settings

- Summary
  - What the study adds: the “take home message”
    - Patient with chronic liver disease receiving warfarin have poorer anticoagulation control and more bleeding, even after controlling for bleeding risk factors.
    - However, these effects are not uniform, and specific
    - A 4-point scoring system using albumin and creatinine can risk-stratify patients with liver disease in regard to risk of major hemorrhage while taking warfarin

Suggested Reading

Violi F, et al. Coagulopathy of chronic liver disease. N Engl J Med. 2011;365(15):1453.

Tripodi A, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41:553-8.24.

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Søgaard KK, et al. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol. 2009;104(1):96-101.

Saleh T, et al. Venous thromboembolism with chronic liver disease. Am J Med. 2011;124(1):64-8.

Northup PG, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol 2006;101(7):1524-8

Eid LM, et al. Stratifying the risks of oral anticoagulation in patients with liver disease. Circ Cardiovasc Qual Outcomes 2014;7(3):461-7.

Aggarwal A, et al. Deep vein thrombosis and pulmonary embolism in cirrhotic patients: systematic review. World J Gastroenterol. 2014;20(19):5737-45.

Sanyal AL. Chronic portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management" Uptodate Article, 2014

Hepatocellular Cancer (HCC)

Amindeep Sandhu

- Epidemiology
  - Commonest primary malignant tumor of the liver
  - 5th most common cancer in men, 8th in women
  - 2nd most common cause of cancer-related deaths
  - 250,000 – 1 million deaths globally per year
  - Under-diagnosed/under-reported, often by as much as 50% in low-income, developing countries
  - 80% of cases are due to HBV and HCV infection worldwide
  - ↑↑ incidence since 2000
  - Highest incidence regions = sub-Saharan Africa, China, Hong Kong, Taiwan
  - 40% of ALL cases occur in China
  - North, South America, Europe, Australia – lowest incidence rates
  - Men > Women, 5.7:1
  - ↓ mean age at presentation – better screening modalities guidelines

- Risk Factors

Please see later table on groups in whom HCC surveillance is recommended because of incidence of HCC

- Liver

HBV infection (even in absence of cirrhosis, 20%)

  - Associated with viral load, +HBeAg, +HBsAg if not cirrhotic
    - All of the above carry independent risks

- HBV DNA
  - Independent predictor of HCC
  - Highest risk is 10^6 million copies/mL (regardless of ALT levels)
- Relative risk of HCC
  - ↓ 50-60% post-INF or
- Inactive carriers: Risk persists if +HBsAg but HBeAG negative
- ↑ risk of HCC reduced by 50-60% post-INF or nucleos(t)ide Rx
- Men > Women risk of HCC if HBsAg +
- ↑ risk with HCV, HDV co-infection
- EtOH consumption habitually, smoking, elevated ALT
- Accounts for 80% of all HCC
- HBV DNA integrated into cellular DNA of 90% of HBV-related HCC
- Virus is both directly and indirectly carcinogenic
  - Direct - Cis-activation, X protein activation, changes in DNA repair
  - Indirect – chronic inflammation, cirrhosis

- Hepatitis C
  - Accounts for 33% of all HCC in the USA
  - Male = Female HCC incidence in those with HCV
  - HCC &HCV
    - Exclusively occurs in those with advanced fibrosis/cirrhosis
    - 10% have less fibrosis

- Does not integrate into host DNA
- HCC induced by chronic inflammation
- Treatment of HCV ↓ HCC risk
  - SVR vs. no SVR, RR = 0.24

- Cirrhosis
  - Often co-exists with HCC, regardless of cause
  - 5% Risk in 3.6 years of cirrhosis duration, poor data afterwards
  - Risk factors for cirrhotics to develop HCC:
    - Obesity
    - Thrombocytopenia
    - HBcAg+
    - Older age
    - Male gender
  - 40% with HCC have undiagnosed cirrhosis worldwide
  - Compensated cirrhotics – 1-8% annual incidence of HCC
  - Chronic Hepatitis – 1% annual risk
    - With Elevated AFP – also have higher risk than low AFP (< 20mcg/L)
  - Cirrhosis + HCV or HBV or HH → carry highest risk of HCC

Abbreviation: AFP, alpha fetoprotein; HH, hereditary hemochromatosis

- Environmental
  - Aflatoxin B1
    - Mycotoxin → contaminates corn, soybeans, peanuts
    - Derived from *Aspergillus flavus/parasiticus*
    - Molds contaminate food stuffs
    - Strong association with HCC, especially if HBV+ (synergistic)
    - Important risk factor in Africa and Asia
  - Contaminated Drinking Water
    - Pond-ditch > well water (algae toxins in ponds)

- Life-style
  - Smoking – some studies
  - Dietary – Red meat, saturated fat
  - Systemic diseases
    - DM – 2.2x ↑ risk
    - NAFLD/NASH - likely via cirrhosis
    - Iron Overload – even without cirrhosis in HH
    - Alpha-1 Anti-trypsin deficiency, even without cirrhosis
    - Wilson's Disease, only with cirrhosis
    - Membranous IVC obstruction – 40% get HCC
    - Incidence increased in HIV

Abbreviations: HH, hereditary hemochromatosis; IVC, inferior vena cava

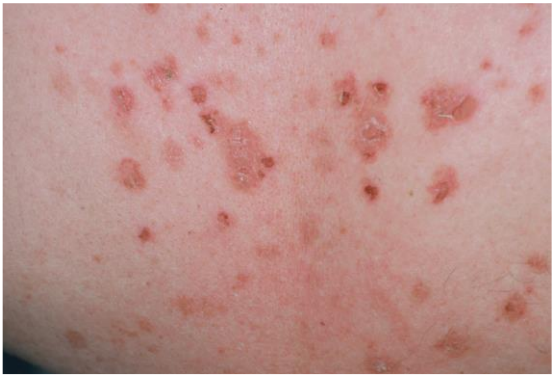
➢ Pathology

- Appearance
  - Nodular, Massive, Diffusely infiltrating
  - Nodular most common – usually coexists with cirrhosis
    - Irregular nodules of various sizes scattered throughout liver
  - Massive
    - Large circumscribed mass, small satellite nodules
    - Prone to rupture
      - In younger patients
      - In non-cirrhotics
  - Diffusely infiltrating (rare)
  - Infiltrated homogenously by indistinct minute nodules
  - Can be hidden by cirrhosis
  - Infiltrate portal vein and its branches

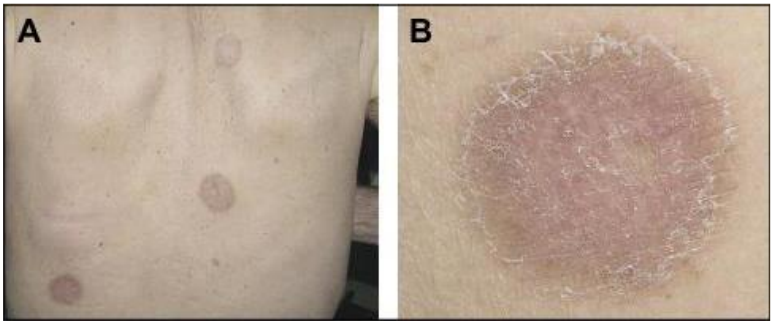
- Histopathology
  - Well Differentiated
    - Most common
    - Trabecular
    - Acinar pattern
  - Moderately Differentiated
    - Solids
    - Clear cell varieties

- Undifferentiated (Pleomorphic)
  - Large bizarre giant cells
  - Spindle-shaped
  - Globular hyaline structures

- Clinical
  - Often no symptoms, other than from their chronic liver disease
  - Suspicion if compensated cirrhosis → decompensates
    - Sudden ascites, encephalopathy, jaundice, variceal bleeds
    - Extension of tumor into hepatic/portal veins or AV shunting
  - Other non-specific symptoms / signs
  - Uncommon
    - Obstructive jaundice from biliary tree invasion
    - Diarrhea
    - Bone pain
    - Dyspnea from mets pulmonary metastses
    - Intraperitoneal bleeding from tumor rupture -> sudden onset abdominal pain, acute Hct drop, hypotension – often fatal
    - Fever – can be from central tumor necrosis
    - Paraneoplastic manifestations
      - CNS
        - Neuropathy, Polymyositis
      - Skin
        - Cutaneous
          - Dermatomyositis
          - Pemphigus foliaceus



- Pityriasis rotunda



- GI
  - Watery Diarrhea – often profound
  - Carcinoid – serotinin
- Endocrine
  - Hypoglycemia – tumors high metabolic needs, typically mild, can secrete IGF-II → severe, life threatening
  - Hypercalcemia – even without osteolytic mets, PTHrp+
  - Sexual changes – gynecomastia, feminization
  - Thyrotoxicosis

- Bone
  - Hypertropic osteoarthropathy, Osteoporosis
- Blood
  - Erythrocytosis – tumor secretes EPO, <10%

SYMPTOMS	FREQUENCY (%)
Abdominal pain	59-95
Weight loss	34-71
Weakness	22-53
Abdominal swelling	28-43
Nonspecific gastrointestinal symptoms	25-28
Jaundice	5-26

SIGNS	
Hepatomegaly	54-98
Ascites	35-61
Fever	11-54
Splenomegaly	27-42
Wasting	25-41
Jaundice	4-35
Hepatic bruit	6-25

➢ Surveillance

- WHO
  - High risk for HCC should enter a surveillance program
  - Patients on transplant waiting list
    - Screen for liver HCC
    - In USA
      - Development of HCC is given increased priority for LT
      - Failure to identify HCC in these patients → Cancer may progress beyond listing criteria

Groups for whom HCC surveillance is recommended or in who the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

Surveillance recommended

Population group	Threshold incidence for efficacy of surveillance (> 25 LYG) (% / year)	Incidence of HCC
Asian male hepatitis B carries over age 40	0.2	0.4-0.6% / year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6% / year
Hepatitis B carrier family history of HCC	0.2	Incidence higher than without family history
African / North American Blacks with Hepatitis B	0.2	HCC occurs at a younger age
Cirrhosis hepatitis B carrier	0.2-1.5	3-8% / yr
Hepatitis C cirrhosis	1.5	3-5% / yr
Stage 4 primary biliary cirrhosis	1.5	3-5% / yr
Genetic hematochromatosis and cirrhosis	1.5	Unknown, but probably > 1.5% / year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5% / year
Other cirrhosis	1.5	Unknown

Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2% / yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5% / yr
Non-cirrhotic NAFLD	1.5	< 1.5% / yr

➢ Screening Tests

- How
  - The old serological (not AASLD recommended)
    - AFP → Cut-off of 20 ng/mL = optimizes SN and SP
      - Sensitivity still only 60% (AFP could miss 40% of HCC)
      - Can be elevated in ICC, mets from CRC – thus, not HCC
      - Overall, regardless of cut-off, not considered an adequate screening test for HCC
  - The new – Diagnostic imaging (AASLD recommended)
    - Ultrasound → may show
      - Non-specific changes echogenic lesions (fat cells), or
      - Hypoechoic, nodules with “target lesion”
      - SN = 65%-80%, SP >90% for screening purposes
      - Difficulties with obese (NAFLD/NASH)
    - AASLD offers a single recommendation of q6 month for all sub-groups
    - Based on tumor growth rates, not risk of HCC
    - i.e. higher risk does not = more surveillance
    - CT → Would require 4 phases, ++radiation, little data as a screening test

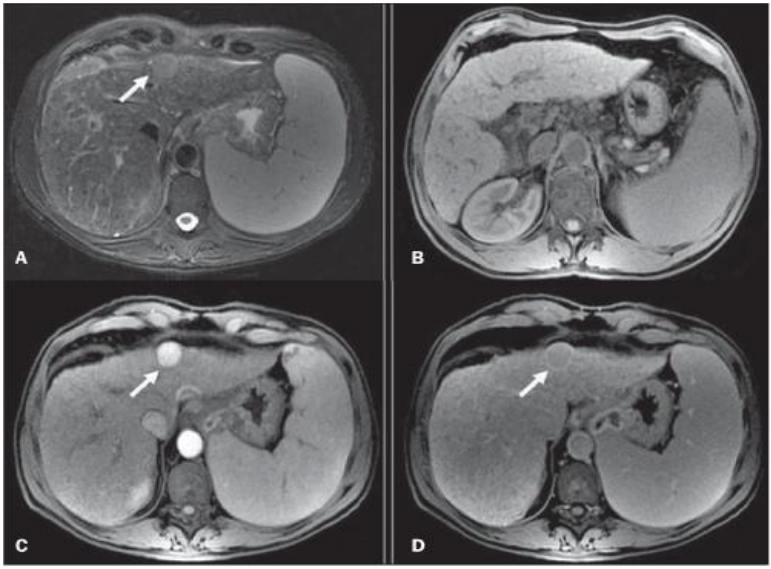
Abbreviations: SN, sensitivity; SP, specificity

➢ Diagnosis

- 4-phase MDCT
  - HCC can be diagnosed without the need for liver biopsy
  - Requires contrast enhanced study – dynamic CT or MR
  - Arterial phase
    - HCC enhances over surrounding liver
    - R`HCC contains only arterial blood, liver diluted by arterial and venous blood
  - Venous phase
    - HCC enhances less
    - Has no portal blood supply
    - Its Arterial blood now has no contrast, portal blood does (washout)
  - Delayed phase: Washout persists
  - Unenhanced phase: Baseline

- Contrast enhanced MRI
  - High resolution images without nephrotoxic contrast or ionizing radiation
  - Similar SN for Dx of HCC vs. helical CT
  - Better SN and SP vs. CT or U/S in cirrhotics (HCC difficult to distinguish from regenerative nodules)
  - High cost
  - Often used if 4-phase CT inconclusive of typical findings

Abbreviations: SN, sensitivity; SP, specificity



Hepatolcellular carcinoma at MRI (arrows)
A: FSE: at-saturated T2-weighted image, echo time = 90 ms;
B: GRE: fat-saturated T1-weighted image;
C: arterial phase, contrast-enhanced GRE T1-weighted image;
D: equilibrium phase, contrast-enhanced GRE T1-weighted image.

Note signs of hepatopathy, with small, sparse, regenerative siderotic nodules more clearly seen with hypointense signal on T2-weighted image. The hepatocellular carcinoma in the left lobe presents a remarkable arterial enhancement and washed in the equilibrium phase, with contrast-enhancement of the fibrotic pseudocapsule

AASLD Guidelines on Biopsying Hepatic Nodules

- Useful if imaging modalities do not clarify diagnosis
- Stain for tumor markers
  - CD34
  - CK7
  - Glypican
  - HSP-70
  - Glutamine synthetase
- If biopsy negative
  - Imaging q3-6 months until it disappears, enlarges, or displays diagnostic characteristics
  - Can repeat liver biopsy if lesion enlarges but remains atypical on imaging

➢ Staging

- Solid tumors prognosis depends on staging at presentation, but
- More complex with liver
  - Underlying liver function affects prognosis
- BCLC staging system most commonly used, because it includes
  - Tumor stage
  - Liver function
  - Physical status
  - Cancer-related symptoms
  - Links staging to treatment allocation

Performance Status Score (ECOG)

ECOG	Description
0	○ Fully active ○ Able to carry all pre-disease performance without restriction
1	○ Restricted in physically strenuous activity, but ○ Ambulatory and able to carry out work of a light or secondary nature (e.g., light house work, office work)
2	○ Ambulatory and capable of all selfcare, but ○ Unable to carry out any work activities ○ Up and about more than 50% of waking hours
3	○ Capable of only limited selfcare ○ Confined to bed or chair more than 50% of waking hours
4	○ Completely disabled ○ Cannot carry on selfcare ○ Totally confined to bed or chair

CHILD-Turcotte-Pugh (CTP) **Class**

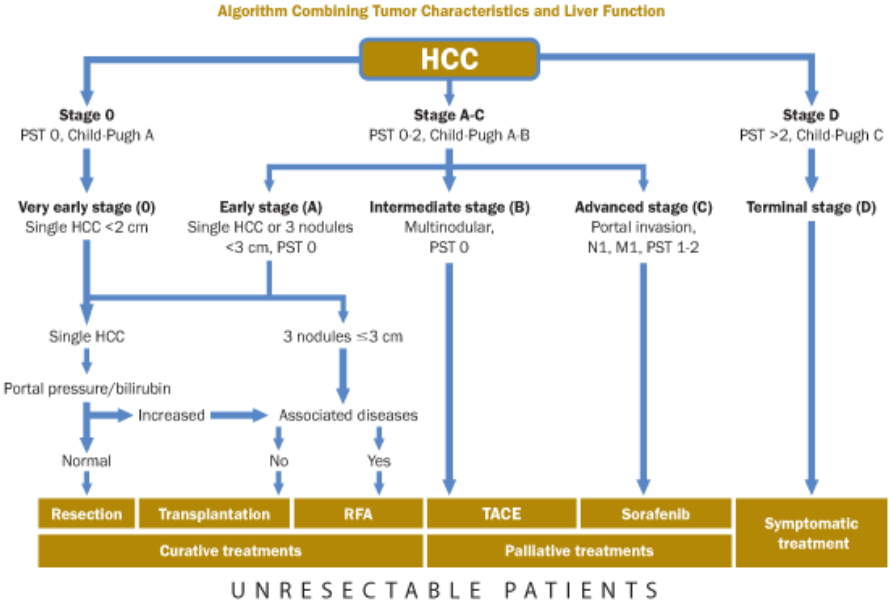
Clinical and Lab Criteria	Points*		
	1	2	3
○ Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
○ Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
○ Bilirubin (mg/dL)	< 2	2-3	> 3
○ Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
○ Prothrombin time			
International normalized ratio (INR)	< 1.7	1.7 – 2.3	> 2.3
Seconds prolonged	< 4	4 – 6	> 6

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (mild liver disease)
Class B = 7 to 9 points (moderate)
Class C = 10 to 15 points (severe)

➢ Treatment

- Algorithm

HCC Treatment Algorithm based on CTP class (BCLC)



BCLC Summary

- Early Stage Disease (0 or A)
  - Preserved Liver Fxn (Child-Pugh A & B)
  - Solitary HCC, or up to 3 nodules ≤ 3cm
  - Options
    - Resection
    - Transplantation
    - Percutaneous ablation
  - Long-term cure possible, 5-year survival 50-75%

- Intermediate Stage (B)
  - Preserved Liver Function
  - Large/multifocal HCC
  - No cancer-related symptoms
  - No macrovascular invasion
  - No metastases
  - 3-year survival without Rx up to 50%
  - Optimal candidates for TACE

- Advanced Stage (C)
  - Cancer-related symptoms
  - +/- portal/vascular invasion / extrahepatic spread
  - 1 year survival 50%
  - Candidates for Sorafenib

- End Stage (D)
  - Extensive tumor involvement
  - Severe deterioration of physical capacity
  - Major impairment of liver function (Child-Pugh C)
  - Median survival < 3 months
  - Symptomatic/Palliative treatment

- Surgical Resection
  - Single lesion, plus
  - Non-cirrhotic or cirrhosis with
    - Well-preserved liver function (C/P-A), normal bilirubin
    - Hepatic vein pressure gradient, < 10 mmHg

- No vascular invasion
- No metastasis
- Long-term relapse-free survival > 40%
- 5 year survival 90%
- No uniform eligibility criteria for size of tumor cut-off
- Resection for C/P – B
  - Controversial

- Liver Transplantation (orthotopic)
  - Unresectable tumors due to:
    - Degree of liver dysfunction
    - Less often due to tumor extent
  - No Vascular invasion or metastases (nodal nor distant)
  - 3 year survival 80%
  - Lifelong immunosuppression, long wait times
  - Living donor Tx can be offered for HCC
    - If waiting time so long that it risks tumor progression, leading to wait list exclusion
  - Can attempt “bridging therapies”
    - TACE
    - RFA
    - Partial Hepatectomy while patient wait-listed (controversial)
  - Criteria
    - Milan criteria are applied as a basis for selecting patients with cirrhosis and hepatocellular carcinoma for liver transplantation.
      - One lesion smaller than 5 cm.
      - Up to 3 lesions smaller than 3 cm.
      - No extrahepatic manifestations
      - No vascular invasion

- Percutaneous Ablation
  - Best option for those not suitable for resection or transplantation
  - Destruction of cells by:
    - Chemical injection (ethanol, acetic acid, boiling saline)
    - Temperature modification (radiofrequency, microwave, laser, cryo)
  - RFA is current first choice, ethanol injection still widely used
  - Ethanol injection well studied
    - Necrosis rate
      - 90-100% if < 2 cm
      - 70% if 2-3 cm, 50% if 3-5 cm
    - Rarely complete necrosis > 3 cm because
      - Volume too large, intra-tumor septa
      - Can first perform arterial embolization, then ethanol injection
  - 50% survival at 5 years

- Radiofrequency Ablation
  - Application of radiofrequency thermal energy to lesion
  - High frequency alternating current through electrode, > 60 ^{o}C
  - Safe and effective in
    - Those who cannot undergo resection
    - As a bridge to transplant
  - Contraindicated
    - Subscapular tumor
    - Poor tumor differentiation → risk of peritoneal seeding

- Efficacy
  - Similar to ethanol when tumors < 2 cm
  - Better if tumors > 2 cm – better disease control
  - Worse for tumors ≥ 3 cm
  - Efficacy = resection (controversial)
- High cost
- High rate of adverse events – pleural effusion, peritoneal bleeding (10%)
- Requires fewer treatment sessions than ethanol
- Many restrict RFA with Child-Pugh A or B, not based on size
- Few retrospective studies report long-term outcomes
  - RFA may be considered after failed ethanol ablation
    - CT with contrast → lack of contrast uptake suggests necrosis, while uptake suggests Rx failure

- Transarterial Embolization and Chemoembolization (TACE)
  - TACE = 1st line non-curative Rx for non-surgical patients with large/multifocal HCC with no vascular invasion/mets
  - Arterial embolization combined with prior chemoembolization with agents mixed with lipiodol
  - Takes advantage of the angiogenic activity of HCC
    - Early HCC → poorly vascularized, blood from portal vein
    - With growth → arterialization, supply from hepatic artery
  - TACE → hepatic arterial obstruction → ischemic tumor necrosis

- Procedure:
  - Catheter into hepatic artery, then to lobar/segmental branches
  - Distal better
    - Minimal injury to surrounding non-tumor tissue
- TACE for multifocal HCC
  - Understudy: complete hepatic artery obstruction
- Induces tumor necrosis in >50%
- Markers of efficacy:
  - Decrease in tumor markers
  - Intra-tumor necrosis on CT/MRI
- ↓ tumor progression → ↓ risk of vascular invasion
- ↑ survival 20-60% at 2 years (Barcelona, Hong Kong trials)

- Chemotherapy
  - Chemotherapy with Lipiodol
  - Lipiodol retained within tumor, oily contrast agent, expands exposure of chemo to rest of tumor
  - TAE/TACE – for non-surgical patients
  - Ineligible for percutaneous ablation
  - No metastases
  - Main contraindication
    - Lack of portal blood flow (PVT)
      - Not safely tested for safety, prognosis poor
      - ↑ risk of ischemic necrosis of viable liver
      - Death
  - Avoid if Child Pugh B/C +/- clinical symptoms of end-stage cancer
  - Systemic or Selective Intra-arterial chemotherapy not recommended

- Sorafenib
  - Multi-kinase inhibitor: Raf-1, B-Raf, VEGFR2, PDGFR, c-kit, TKR
  - For those who have preserved liver function, plus cannot benefit from or have failed more effective treatment resection transplantation TACE
  - SHARP Trial
    - 602 patients, advanced HCC
    - Stopped at interim analysis because of its survival advantages
    - Included only Child-Pugh A (B/C = sparse data)
    - HR 0.69 Sorafenib/placebo → 31% decrease in risk of death
    - Median survival 10.7 months vs. 7.9 months (placebo)
  - Adverse effect
    - Diarrhea
    - Skin reactions
  - 1st line if no resection, Tx, TAE/TACE, preserved liver function

- Other Therapies
  - Radioembolization with “Yttrium90-lebeled” glass beads
    - Can induce extensive tumor necrosis, acceptable safety profile
    - No known survival benefit
  - Tamoxifen
  - Anti-androgens
  - Octreotide
  - Hepatic artery ligations are not recommended

Acute Liver Failure

Neel Malhotra

AASLD Practice Guidelines: 2011 Update

Lee WM, Stravitz T and Larson AM. Introduction to the Revised American Association for the Study of Liver Diseases Position Paper on Acute Liver Failure 2011

- Demography
  - Rare condition affecting individuals without known pre-existing liver disease
  - In the U.S: 2,000 cases per year

- Definition
  - Evidence of coagulation abnormality and any degree of mental alteration in a patient without pre-existing cirrhosis
    - Coagulation abnormality: INR ≥ 1.5
    - Mental alteration: Encephalopathy
    - Duration of illness: < 26 weeks

- Causes
  - Most prominent causes:
    - Drug Induced Liver Injury (DILI)
    - Viral Hepatitis
    - Autoimmune liver disease (AIH), if developed in < 26 wk
    - Shock / Hypo-perfusion
    - Ideopathic cause (~15%)

- Stratification
  - Can include: Wilson Disease, Vertically acquired hepatitis B or Autoimmune hepatitis (if it has developed in < 26 weeks)

- Terms used to further stratify the disease do not necessarily have prognostic significance
  - Not routinely used
- Hyperacute (< 7 days) → Often Acetaminophen toxicity (tend to have better prognosis)
- Acute (7-21 days)
- Subacute (>21 days and < 26 weeks)

- Diagnosis
  - Diagnosis → hospital admission is mandatory
  - INR ≥ 1.5 (Prothrombin time prolonged by ~4-6 seconds)
    - Any evidence of alteration in sensorium

Recommendations: Grade III (based on opinions of respected authorities)

- Patients with ALF should be hospitalized and monitored frequently, preferably in an ICU
- Contact with a transplant center and plans to transfer appropriate patients with ALF should be initiated early in the evaluation process
- The precise etiology of ALF should be sought to guide further management decisions

- Clinical
  - History of possible exposures (may require collateral)
    - Viral Infections
    - Drugs
    - Toxins

- Physical Exam
  - Mental status examination
  - Stigmata of chronic liver disease
  - Jaundice
  - RUQ tenderness and Liver palpation for liver enlargement

➢ Grades

Grades of Encephalopathy

Grade	Definition
I	Changes in behaviors with minimal changes in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, in appropriate behavior
III	Marked confusion; incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Note: Some patients will overlap grades; clinical judgement is required.

Adapted from: Conn HL, et al. Gastroenterology 1977; 72: 573-583.

- Laboratory

Suggested initial laboratory analysis

- Prothrombin time / INR
- Chemistries
  - Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose
  - AST, ALT, alkaline phosphatase, GGT, toltal bilirubin, albumin creatinine, blood urea nitrogen
- Arterial blood gas
- Arterial lactate
- Complete blood count
- Blood type and screen
- Acetaminophen level
- Toxicology screen
- Viral hepatitis serologies
  - Anti-HAV, IgM, HBsAg, anti-HBc IgM, anti-HCV RNA*, HSV1 IgM, VZV
- Ceruloplasmin level**
- Pregnancy test (females)
- Ammonia (arterial If possible)
- Autoimmune markers
  - ANA, ASMA, immunoglobin levels
- HIV-1, HIV2***
- Amylase and lipase

* Done to recognize potential underlying infection

** Done only if Wilson disease is a consideration (e.g. in the patients less than 40 years without another obvious explanation for ALF); in this case uric acid level and bilirubin to alkaline phosphatase ratio may be helpful as well.
*** Implications for potential lier transplnatation

- Pathology
  - Role of a Liver Biopsy
    - Usually not necessary unless the following are suspected (although not required for the diagnosis)
      - Autoimmune Hepatitis
      - Metastatic Liver disease
      - Lymphoma
      - Herpes Simplex Hepatitis

Acetaminophen Hepatotoxicity

- Demography
  - Leading cause of Acute Liver Failure in US and Europe
  - Dose related toxin
  - Most ingestions leads to ALF exceed 10 g/day (~150 mg/kg)

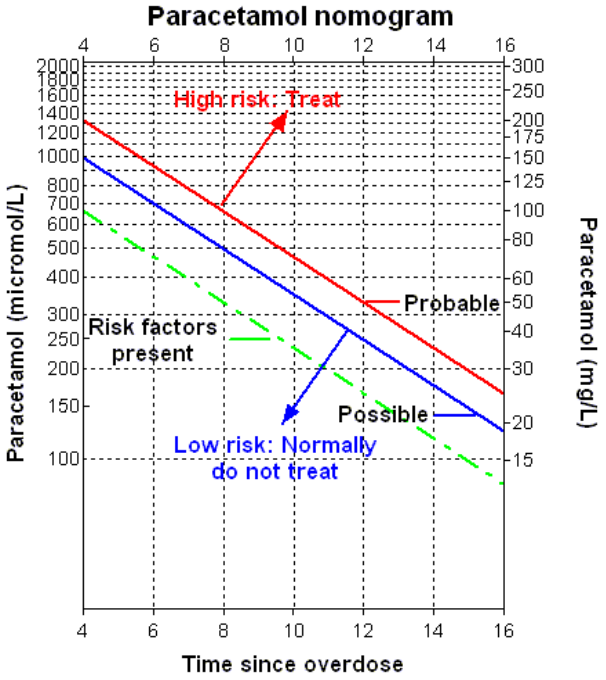
- Laboratory
  - ↑↑↑ Aminotransferase levels are typically seen
    - ≥ 3500 are highly correlated with acetaminophen poisoning
    - ↓ bilirubin levels

- Treatment
  - Activated charcoal
    - Most effective if given within 1 hour (up to 3-4 hours) after ingestion
    - Dose: 1 g/kg orally (slurry)
  - For patients with known or suspected Acetaminophen overdose within 4 hours of presentation: Give activated Charcoal just prior to starting NAC dosing (Grade I)

N-acetylcysteine (NAC)

- Recommendation
  - Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferase indicate impending or evolving liver injury (Grade II)
  - NAC may be used in cases of ALF in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate but aminotransferases suggest acetaminophen poisoning (Grade III)

Acetaminophen Hepatotoxicity



- Antidote therapy: NAC (N-acetylcysteine)
  - Recommended in any case of ALF with overdose suspected
  - May be of value up to 48 hours or more after ingestion
  - Dose: 140 mg/kg orally → 70 mg/kg Q4H (17 doses)
  - Dose: 150 mg/kg IV (over 15 minutes) → 50 mg/kg maintenance dose given over 4 hours → 100 mg/kg over 16 hours (or 6 mg/kg/hr)
  - Duration: 72 hours period vs. continuation until liver chemistry has improved

Mushroom Poisoning

- Usually Amanita Phalloides: Known as the “death cap”
- Widely found across Europe
- Toxin: α Amantin → Damages liver and kidneys
- May have killed Roman Emperor Claudius in AD 54
- No available blood test to confirm toxin

➢ Clinical

- Nausea, Vomiting, Diarrhea, Abdominal Cramping)
- Occur within hours to a day of ingestion

➢ Treatment

- Suspected cases
  - Gastric Lavage
  - Activated Charcoal
  - Fluid resuscitation
- Accepted Antidotes (lack of controlled trials)
  - Penicillin G
  - Silibinin (Silymarin or milk thistle): 30-40 mg/kg/day (IV or PO) for 3-4 days
    - Thought to be more successful (based on reports)
    - Not available as a licensed drug in the US

➢ Recommendations (Grade III)

- Patients with ALF secondary to mushroom poisoning
  - Consider administration of Penicillin G and NAC
  - Listed for liver transplantation (often the only lifesaving option)

Drug Induced Liver Injury (DILI)

- Many prescription and over the counter medications have been implicated
- Diagnosis of exclusion
- Dose-related toxicity
  - Acetaminophen
  - Antibiotics
  - NSAIDs
  - Anticonvulsants
- Most cases occur within 6 months of drug initiation (De novo damage unlikely the cause if being used for 1-2 years)
- NO antidote and Steroids NOT indicated
- Steroids considered for DRESS (drug rash with eosinophilia and systemic symptoms) or an autoimmune reaction is suspected

Some Drugs Which May Cause Idiosyncratic Liver Injury Leading to ALF

- Combination agents with enhanced toxicity
  - Trimethoprim-sulfamethoxazole
  - Rifampin-isoniazid
  - Amoxicillin-clavulanate
- Some herbal products / dietary supplements that have been associated with hepatotoxicity include:
  - Kava Kava
  - Harbalife
  - Hydroxycut
  - Comfrey
  - Senecio
  - Greater celandine
  - He Shon Wu
  - LipoKinetix

- Carbamazepine
- Valproic acid
- Doxycycline
- Diclofenac

- Recommendations (Most Class III)
  - Obtaining details (including onset of ingestion, amount and timing of last dose) concerning all prescription and non-prescription drugs/herbs and dietary supplements taken over last year
  - Determine ingredient of non-prescription medications whenever possible
  - In the setting of ALF due to possible drug hepatotoxicity, discontinue all but essential medications
  - NAC may be beneficial for ALF due to DILI (Class I)

VIRAL HEPATITIS

- Role in Acute Liver Failure
  - USA: 12%
  - Hepatitis B (HBV) 8%
  - Hepatitis A (HAV) 4%
- Role of Hepatitis C alone causing ALF is controversial
- Hepatitis E significant cause in endemic areas:
  - Russia
  - Pakistan
  - Mexico
  - India

HAV Infection

- Recommendations (Grade III)
  - Viral Hepatitis A (and E) related liver failure treated with supportive care as
    - No virus-specific treatments

HBV Infection

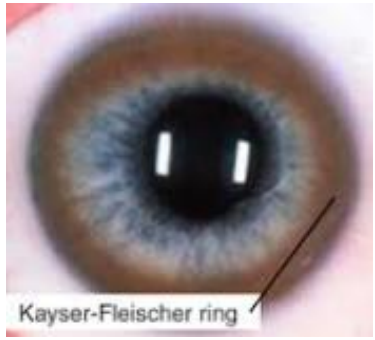
  - Reactivation of chronic or inactive HBV may occur in the setting of chemotherapy or immunosuppression
    - If HBSAg positive
      - Treat prophylactically with a nucleoside/nucleotide analog for 6 months after completion of immunosuppressive therapy

- Recommendations (Grade III)
  - Nucleoside / Nucelotide analogues should be considered for hepatitis B associated acute liver failure and for prevention of post-transplant recurrence

HSV / HZV Infection

  - Patients with known or suspected herpes virus or varicella zoster as the cause of acute liver failure should be treated with acyclovir (5-10 mg/kg IV Q8H) and may be considered for transplant

Wilson Disease



- Uncommon cause of ALF: 2-3% of cases in US
- Typically in young patients
- Associated with abrupt onset of Coombs negative Hemolytic anemia
- High serum bilirubin levels (> 20 mg/dL)
  - Due to hemolysis: high indirect bilirubin
- Kayser Fleischer rings: present in 50% of patients
- Ceruloplasmin: typically low
  - 15% have normal levels
  - Low levels in ~50% of other forms of ALF

➢ Laboratory

- High urinary copper levels along with hepatic copper levels: Confirm diagnosis
- Other findings
  - ↓↓ Alkaline Phosphatase
  - ↓ uric acid
  - ↑ bilirubin (mg/dL) to ALP ratio (> 2.0)

➢ Treatment

- Acutely lower serum copper to ↓ hemolysis
  - Dialysis
  - Plasmapheresis
  - Plasma Exchange
  - Liver transplantation for ALF

- Penicillamine
  - Do **not** use penicillamine in acute setting (risk of hypersensitivity)

- Recommendations (Grade III)
  - To exclude Wilson disease one should obtain ceruloplasmin, serum and urinary copper levels, slit lamp examination for Kayser-Fleischer rings, Hepatic Copper levels when liver biopsy is feasible and total bilirubin/alkaline phosphatase ratio
  - Patients in whom Wilson disease is the likely cause of acute liver failure must be promptly considered for liver transplantation

Autoimmune Hepatitis (AIH)

- Recommendations (Grade III)
  - Liver Biopsy is recommended when Autoimmune Hepatitis is the suspected cause of acute liver failure and autoantibodies are negative
  - Patients with coagulopathy and mild hepatic encephalopathy due to autoimmune hepatitis
    - Consider for corticosteroid treatment (prednisone 40-60 mg/day)
  - Patients with autoimmune hepatitis should be considered for transplantation even while corticosteroids are being administered

Acute Fatty Liver of Pregnancy / HELLP

Acute fatty liver of pregnancy		<500 may be as high as 1000	↑	WBC ↑ PT ↑ PLTS ↓ glucose ↓ uric acid ↑	HELLP, drug toxicity, fulminant hepatic failure	Maternal mortality <3 percent; fetal mortality as high as 35 to 45 percent; recurrence uncommon.

- Occurs near the end of pregnancy
- Presentation:
  - Jaundice
  - Coagulopathy
  - Low platelets
  - +/- hypoglycemia
- Associated features of pre-eclampsia: HTN, proteinuria are common
- Imaging: Findings of Steatosis supports diagnosis
- Managements: Prompt delivery
- Prognosis: Recovery is typically rapid after delivery

➢ Recommendations (Grade III)

- For acute fatty liver of pregnancy or the HELLP syndrome, expeditious delivery of the infant is recommended.
- Transplantation may need to be considered if hepatic failure does not resolve quickly following delivery

Acute Ischemic Injury (aka “shock liver”)

- Causes / associations
  - Occurs after periods of significant hypovolemia/hypotension
    - Cardiac arrest
    - HF
    - Sepsis
    - 2/3 of patients suffer from cardiac disease
- Clinical caution
  - Hypotension is not always found
  - Drug induced Hypotension or Hypoperfusion:
    - Long acting Niacin
    - Cocaine
    - Methamphetamine
- Laboratory
  - ↑↑ ALT, AST
  - ↑ LDH
- Prognosis
  - Determined by underlying condition
  - Liver transplantation seldom indicated
- Recommendations (Grade III)
  - In ALF patients with evidence of ischemic injury, cardiovascular support is the treatment of choice

Budd-Chiari Syndrome (BCS)

- Acute hepatic vein thrombosis can present with ALF
- Often presents with striking
  - Hepatomegaly
  - Abdominal pain
  - Ascites
- Confirmed by
  - Dopper Ultrasound
  - CT
  - MR venography
- Testing for hypercoagulable conditions e.g.
  - Polycythemia
  - Malignancy
- Poor prognosis if hepatic failure is present.

➢ Recommendations (Grade III)

- Hepatic Vein thrombosis with acute hepatic failure is an indication for liver transplantation, provided underlying malignancy is excluded

➢ Treatment

- General Considerations
  - NAC improve the outcome of ALF
    - ↑ liver blood flow and function in patients with septic shock
  - Admit to ICU if altered mental status
  - Supportive care
    - Fluid management
    - hemodynamic and metabolic parameters
- Note
  - Aminotransferase levels correlate poorly with prognosis

Cerebral Edema

- ↑ intracranial pressure (ICP)
- Mechanisms
  - Osmotic disturbances in the tissue
  - ↑ cerebral blood flow (from loss of cerebrovascular auto regulation)
- Interventions
  - Limited evidence
  - No uniform protocol
  - Stepwise approach is advised

HEPATIC ENCEPHALOPATHY (HE)

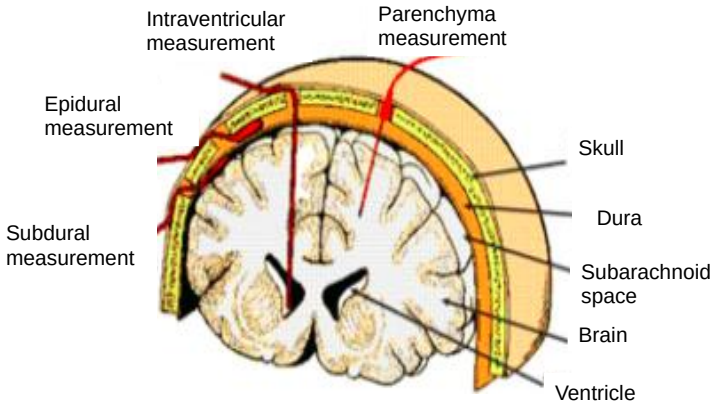
Grade I-II encephalopathy

- CT head to exclude other causes of decline in mental status
- Sedation avoided
- Unmanageable agitation
  - Short acting Benzodiazepines in small doses
- Lactulose
  - Based on role of ammonia

Grade III-IV encephalopathy

- Intubation and Mechanical ventilation are mandatory
- Propofol
  - ↓ the already ↑ ICP and ↑ cerebral blood flow
- Elevate head of bed at 30 degrees
- ↓ maneuvers that may ↑ ICP
  - Pain
  - Valsalva during suctioning

- ICP Monitoring not routinely recommended
  - Rationale: Improve early recognition of ICH
  - Clinical signs: Cushing's Triad (Systemic HTN, bradycardia, irregular respirations) aren't always present
  - CT not reliable at early stages
  - Allows monitoring of ICP (goal < 20 mmHg) and CPP (goal > 60 mmHg)



- Mannitol
  - Osmotic agent which is transiently effective in ↓ cerebral edema
  - First line for those with mild ↑ ICP
  - Not helpful if ICP > 60 mm Hg
  - Dose: 0.5-1.0 g/kg (can be repeated as long as serum osmolarity is < 320 mOsm/L)
  - Risk
    - Volume overload in those with renal impairment
    - Trigger hyperosmolarity or hypernatremia

Elevated ICP

- Consider hyperventilation mannitol fails (Goal PaCO2 of 25-30 mmHg)
  - Goal: restore cerebrovascular auto regulation → vasoconstriction → reduction in ICP
- Prophylactic hyperventilation
  - No ↓ in the incidence of cerebral edema / ICH
  - No survival benefit
  - May worsen ↑ hypoxia
- Hypertonic Saline
  - Prophylactic induction of hypernatremia (goal: 145-155 mEq/L) → lower incidence of ICH.
  - No survival benefit
  - Recommended in those at highest risk of cerebral edema
    - High serum ammonia
    - High grade Hepatic encephalopathy
    - Acute Renal Failure
    - Requirement of Vasopressors

Infection

- Periodic Surveillance (chest x-ray, periodic sputum, urine and blood cultures) is appropriate
- Low threshold for starting therapy
- Deterioration of mental status may represent infection
- Association between infection and/or SIRS with progression in encephalopathy stages
- Early stages of HE
  - No roles of antibiotic prophylaxis

- Later stages of encephalopathy: prophylactic antibiotics may reduce risk of infection
- Hypothesis: perhaps prophylactic antibiotics
  - May decreased risk of cerebral edema

➢ Recommendations- Grade III

- Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens as early as possible. Antibiotic treatment should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of SIRS)
- Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes in ALF and therefore cannot be advocated in all patients, particularly those with mild hepatic encephalopathy

Coagulopathy

- In the absence of bleeding
  - Not advisable to correct the INR with plasma
- Arbitrary correction of INR may obscure the trend (follow for prognosis)
- Risk of transfusion
  - Acute Lung Injury
  - Volume overload
- Although commonly corrected prior to invasive procedures
  - No studied regimen
- Approach
  - Vitamin K 5-10mg SC

Recommendations

- Replacement therapy for thrombocytopenia and/or prolonged prothrombin time is recommended only in the setting of hemorrhage or prior to invasive procedures
- Patients with ALF in the ICU should receive prophylaxis with H2 blockers or PPI (or sucralfate as second line) for acid related GI bleeding associated with stress (Grade I)

Hemodynamics and Renal Failure

- Pathophysiology
  - In ALF: ↓ systemic vascular resistance (similar to sepsis)
  - ↓ splanchnic pooling of blood (seen in cirrhosis)

- Pathophysiology
  - Goal: maintain renal and cerebral perfusion
    - MAP ≥ 75 mmHg
    - CPP 60-80 mmHg

Abbreviations: CPP, cerebral perfusion pressure; MAP, mean arterial pressure

- Approach to management
  - First Resuscitation with Normal saline
    - Switch to 0.45 NS with bicarbonate if acidotic
    - Addition of dextrose to prevent hypoglycemia
  - Treatment of Potential Infection / Sepsis

- Inotropic / Vasopressor support
  - General consensus
    - Norepinephrine (α1 > β1) → preserving splanchnic blood flow
    - Vasopressin addition (second line) may potentiate norepinephrine

- Prognosis
  - Multifactorial
    - Etiology of ALF
    - Grade of Coma on admission
    - Ability to regenerate healthy liver
    - Absence of significant and often unpredictable complications
  - Prognostic scoring systems have not yet been successful in determining who will survive without transplantation
  - Clinical Predictors:
    - The etiology of ALF was found to be one of the most important predictors of outcome
    - Acetaminophen, Hepatitis A, Shock Liver, Pregnancy related causes: Transplant free survival ≥ 50%
    - All other etiologies: <25% transplant free survival
    - Those with grade III or IV encephalopathy are less likely to survive without receiving a liver transplant
  - Most widely applied prognostic system: King's College Hospital Criteria
    - Developed from a retrospective cohort of nearly 600 patients
    - Sensitivity: 68-69%
    - Specificity: 92-92%

Potential Helpful Indications* of Poor Prognosis in Patients with ALF

- Etiology
  - Idiosyncratic drug injury
  - Acute hepatitis B (an other non-hepatitis A viral infection)
  - Autoimmune hepatitis
  - Mushroom poisoning
  - Wilson disease
  - Budd-Chiari syndrome
  - Indeterminate cause
- Coma grade on admission

➢ Transplantation

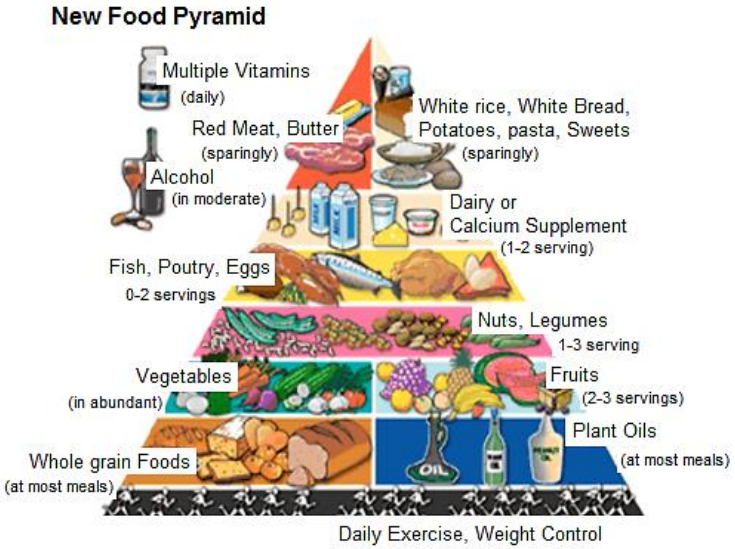
- ~ 50% of patients with ALF undergo transplant
- Liver transplantation has ↑ overall survival rates for ALF to > 60%
- Mortality
  - Highest within the first 1-3 months after transplant
  - Neurologic complications
  - Sepsis
- Overall survival (when compared to patients who are transplanted for chronic liver disease)
  - Lower in the first year
  - Better long term survival
- Living Donor Transplantation related transplant use is controversial
  - Accounted for 2% of transplants
  - Compressed Donor Evaluation (risk of being incomplete / coercion)
  - Right lobe used → 75% survival at 1 year

- Auxiliary transplant: leaves recipient's liver in place
  - Uses a partial left or right lobe from the donor (acts as temporary support)
  - Survival rates: ~ 65%
  - Immunosuppression withdrawn in 65-85% by 1 year post transplant
- Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death (Grade II)
- Living donor or auxiliary liver transplantation may be considered in the setting of limited organ supple, but its use remains controversial (Grade II)

NUTRITION

Protein and Carbohydrate Digestion

Jayesh Patel and I. Abdelghadir



http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php

Protein Digestion

- Exogenous origin (dietary intake)
  - Major source of amino acids
  - Provide 10-15% of energy intake
  - Recommended dietary requirements vary, ranging from 0.75 to 1 g/kg of body weight per day
  - Plant proteins are less digestible than those derived from animals
  - Digestion and absorption of proteins are remarkably complete (approximately 3% to 5% of ingested nitrogen is lost in the stool because of the resistance of some peptide bonds to hydrolysis)

- Endogenous origin
  - Almost half of all protein that enters the intestine is derived from endogenous sources:
    - 20 to 30 g per day are derived from secretions of salivary, gastric, biliary, pancreatic, and mucosal origin
    - 30 g per day of protein are provided by epithelial cells desquamated from the villus tips
    - 2 g of plasma proteins are delivered into the intestinal lumen each day

- Intraluminal digestion
  - Pepsins
  - Pancreatic Proteases
  - Digestion at the Brush Border Membrane and in the Cytoplasm

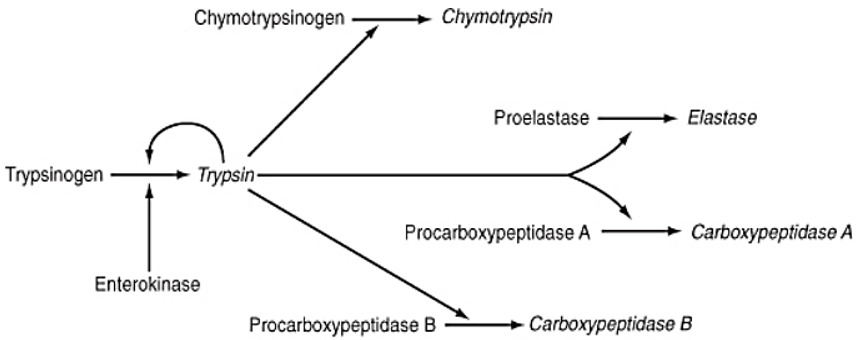
Pepsins

- Digestion of proteins begins in the stomach with the action of pepsins secreted by gastric mucosa
- Pepsins are a group of proteolytic enzymes:
  - Immunologically: group 1 and group 2
    - Both are secreted by chief cells
    - Group 2 isoforms also are present in the mucus cells of the oxyntic and pyloric areas of the stomach and in Brunner's glands of the duodenum
  - Electrophoretically: eight fractions
- Chief cells is stimulated by gastrin and histamine and also from cholinergic stimulation pepsinogen auto activation in an acid pH with the loss of a small basic peptide
- Pepsins action will produce a mixture of peptides with a small proportion of amino acids

- Gastric proteolysis depends on:
  - Rate of gastric emptying
  - pH of intragastric contents
  - Types of protein ingested
- Gastric proteolysis is not an essential component of digestion

Pancreatic Proteases

- Each of the pancreatic proteases is secreted as a proenzyme and therefore must be activated within the lumen
- The proteases are classified as endo- and exopeptidases, according to the sites of the peptide bonds against which they are most active
- In addition to nutrient protein hydrolysis, pancreatic proteases have other functions:
  - Split vitamin B_{12} from the R protein
  - Increase the turnover of brush border membrane hydrolytic enzymes
  - Initiate the final steps in the processing of the sucrase-isomaltase complex
  - May have a role in the inactivation of some organisms



Enzyme	Action	Products
○ Trypsin	Endopeptidase; cleaves internal bonds at lysine or arginine residues; cleaves other pancreatic proenzymes	Oligopeptides and proteolytic enzymes
○ Chymotrypsin	Endopeptidase; cleaves bonds at aromatic or neutral amino acid residues	Oligopeptides
○ Elastase	Endopeptidase; cleaves bonds at aliphatic amino acid residues	Oligopeptides
○ Carboxypeptidase -A	Exopeptidase; cleaves aromatic amino acids from C-terminal end of proteins and peptides	Aromatic amino acids and peptides
○ Carboxypeptidase -B	Exopeptidase; cleaves arginine or lysine from C-terminal end of proteins and peptides	Arginine, lysine, and peptides

Peptidases in the BBM (bush border membrane) and Enterocyte Cytoplasm

- A range of peptidases are present in the brush border membrane and in the cytoplasm of villus epithelial cells for the hydrolysis of oligopeptides up to approximately eight amino acid residues in length
- Synthesis of each specific peptidase occurs in the rough endoplasmic reticulum, and following transfer to the Golgi apparatus, the proteins are transported to the brush border membrane, where they are inserted by exocytic fusion

Peptidases

Substrate	Brush Border Membrane (%)	Cytoplasm (%)
Dipeptides	5-10	80-95
Tripeptides	10-60	30-60
Tetrapeptides	90	1-10
Higher peptides	98	Nil

Cytoplasmic Peptidases	Action	Products
Dipeptidases	Cleave most dipeptides	AA.
Aminotripeptidase	Cleaves tripeptides	AA.
Proline dipeptidase	Cleaves proline-containing dipeptides	Proline and AA.

- Action and products

Peptidase	Action	Products
Amino-oligopeptidases	– Cleave AA. from C terminal end of 3 to 8 amino acid peptides	AA. and dipeptides
Aminopeptidase A	– Cleaves dipeptides with acidic AA. at N terminal end	AA.
Dipeptidase I	– Cleaves dipeptides containing methionine	AA.

Peptidase	Action	Products
○ Dipeptidase III	– Cleaves glycine-containing dipeptides	AA.
○ Dipeptidyl aminopeptidase IV	– Cleaves proline-containing peptides with free α-amino groups	Peptides and AA.
○ Carboxypeptidase P	– Cleaves proline-containing peptides with free C-terminal end	Peptides and AA
○ Gamma glutamyl transpeptidase	– Cleaves gamma-glutamyl bonds and transfers glutamine to amino acid or peptide acceptors	Gamma-glutamyl amino acid or peptide
○ Folate conjugase	– Cleaves pteroyl polyglutamates	Mono-glutamate

Abbreviation: AA, amino acids

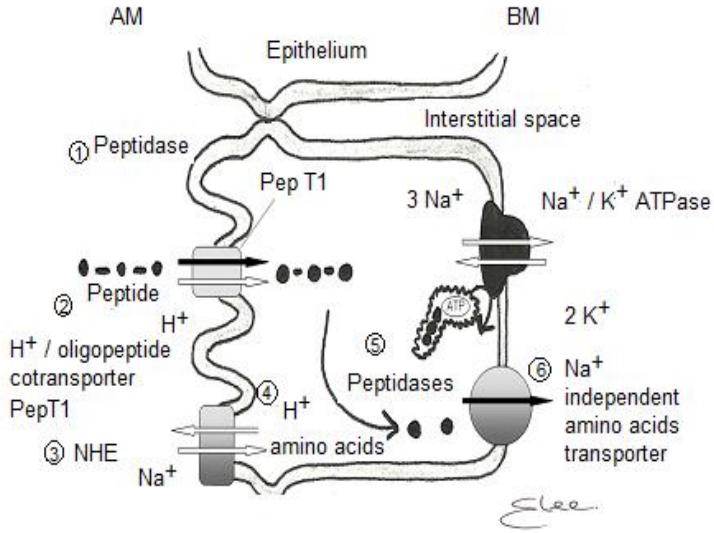
Absorption

- Tri- and dipeptides inhibit uptake of either from the lumen
- Small peptides utilize a separate transporter system from those used by single amino acids

- Tetrapeptide absorption is inhibited by single amino acids, suggesting that tetrapeptides are split before absorption
- Dipeptide absorption greater than single-amino-acid absorption
- Factors influence digestion and absorption:
  - Presence of amino acids in the lumen inhibits peptide hydrolysis (product inhibition)
  - Luminal glucose and luminal acidification each inhibit amino acid and peptide absorption
- BLM amino acid transport systems are different from those in the BBM.
  - Import amino acids into the enterocyte from the portal circulation for cellular metabolism during fasting
  - Export amino acids from the enterocytes into the portal circulation during feeding

Peptides

- Di- and tripeptides are taken up by a single type of transporter with some stereospecificity
- Affinity is greater for dipeptides than for tripeptides because of the following:
  - L Form of AA. in dipeptides
  - Neutral AA. in dipeptides
  - Long-side-chain AA. in dipeptides
- The driving force of transport process is a transmembrane electrochemical H^+ gradient



Enterocytes and Uptake of Amino Acids and Peptides

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009;Figure 45-8, page 958.

Amino Acids

- Multiple transport mechanisms are available for the 20 amino acids
- These mechanisms are located on BBM (brush border membrane) or BLM (basolateral membrane) of enterocytes on upper portion of villi
- Involve carrier-mediated active transport or facilitated diffusion processes
- Several amino acids utilize a number of different transport systems

Transport System	Substrate
• Brush Border Membrane (BBM)	
○ Neutral amino acids	
– NBB (SLC6A19)	▪ Broad specificity for neutral amino acids
– PHE	▪ Phenylalanine and methionine
– IMINO (SLC36A1)	▪ Imino acids; proline, hydroxyproline
○ Basic amino acids	▪ Lysine, cysteine, basic amino acids
○ Acidic amino acids X-GA (SLC1A1)	▪ Glutamate, aspartate
• Basolateral Membrane (BLM)	
○ L	▪ Broad selectivity
○ A	▪ Broad selectivity
○ ASC (SLC1A5)	▪ Neutral amino acids, alanine, serine, cysteine
○ N	▪ Glutamine, histidine, asparagine

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 100-9, page 1716, Ninth Edition, 2010

Exit from the enterocyte across basolateral membrane (BLM)

- Transport across the BLM
- Different mechanisms that involve
  - Active transport
  - Passive diffusion
- Active sodium-dependent processes exist at BLM
  - Supplies nutrients for crypt cells and for villus enterocytes during fasting
- Villus enterocytes receive the amino acids necessary for production of their own protein from luminal nutrients
- Crypt cells obtain their supply from the portal circulation
- Glutamine is the major source of energy for enterocytes.
- Ammonia is an important metabolic by-product of this process

Water Soluble Vitamins

- Several of these vitamins are present in the diet as conjugates or coenzymes that require hydrolysis before or during their absorption
- Absorption of water-soluble vitamins is dependent either on passive diffusion across the intestinal mucosa or specific carrier-mediated processes

➢ Ascorbic Acid (Vitamin C)

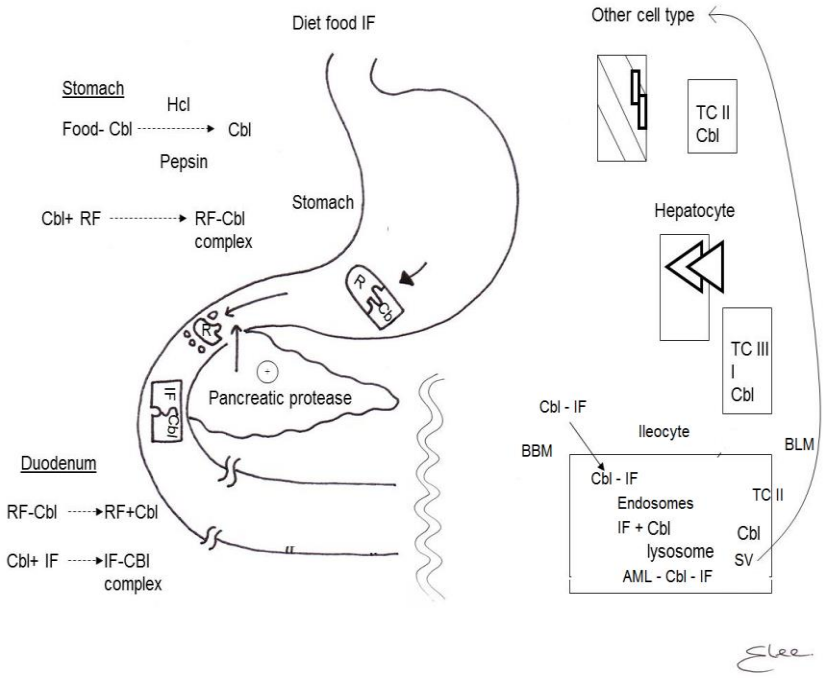
- Recommended daily intake is 40 mg
- Ingestion of 10 mg per day prevents scurvy
- Absorption of ascorbic acid decreases with increased intake and varies from 16% at high (greater than 10 g) to 98% at low (less than 20 mg) intakes
- Transport across the BBM of enterocytes occurs by an active sodium-dependent process

- This active absorption mechanism becomes saturated when the mucosal concentration of vitamin C is greater than 6 mmol/L

- Folic Acid
  - Recommended dietary intakes are of the order of 200 mg per day in adults and 400 mg per day during pregnancy
  - Dietary sources of folate include green leafy vegetables, orange juice, grains (in particular, breakfast cereals that are fortified with folic acid), and organ meats such as liver.
  - Dietary folate is in the form of polyglutamates consisting of at least six glutamic acid residues.
  - Folates are absorbed in the duodenum and upper jejunum.
  - Dietary polyglutamates undergo BBM hydrolysis to monoglutamates.
  - Monoglutamate are taken into enterocytes by active transport into the cytoplasm.
  - Two intestinal proteins— glutamate carboxypeptidase II (GCP II) and the reduced folate carrier (RFC) —are required, respectively.
    - For this sequential hydrolysis of dietary folylpolyglutamates
    - Transport of folylmonoglutamate derivatives across the enterocyte BBM and BLM
  - Uptake is achieved by a specific carrier-mediated, concentrative, sodium-dependent, pH-sensitive process that is active at acidic pH
  - Whereas luminal bacteria consume cobalamin, folic acid is a product of bacterial substrate fermentation.
  - An important clinical observation in small-intestinal bacterial overgrowth (SIBO) is therefore the finding of low serum B12 and high folate levels

- Vitamin B_{12} (Cobalamin)
  - Cobalamin exists largely as hydroxycobalamin, methylcobalamin, and adenosylcobalamin, whereas cyanocobalamin is the pharmaceutical and interchangeable form of the vitamin
  - Mainly animal sources (Liver, kidney, beef, fish, eggs, and milk)
  - 10 to 20 µg is ingested per day in an average diet, and of this, approximately 1 to 2 µg is required to provide for normal daily needs

ABSORPTION OF VITAMIN B_{12} (Cbl)



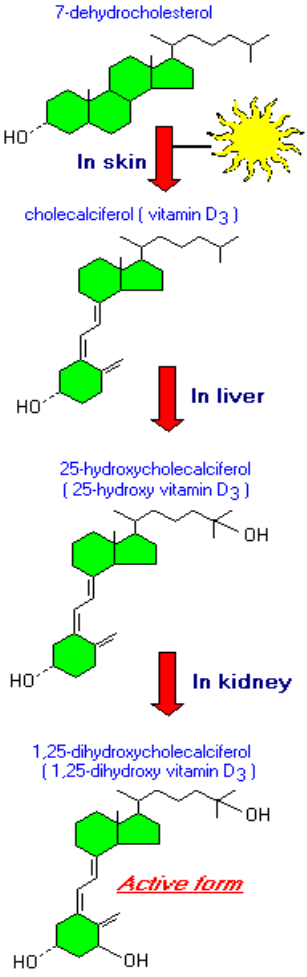
Abbreviation: Cbl, cobalamin (vitamin B12); PP, pancreatic proteases; SV, secretory vesicle; TC II, transcobalamine II; TC III, transcobalamine III

- Digestion and absorption of vitamin B_{12}
  - The initial two steps of the gastric phase require an acid pH. In the presence of gastric acid and pepsin, cobalamin is released from its protein bond and then transferred to R-binding protein (haptocorrin) that is present in saliva and gastric juice.
  - The release of cobalamin and its transfer to R factor is optimal at pH 1 to 1.3**,** a level not achieved by achlorhydric individuals, who include most persons older than 65 years.
  - Similarly, patients using proton pump inhibitors such as omeprazole do not absorb food-bound protein normally and are presumably at risk for cobalamin deficiency.
  - The third gastric step involves the secretion of an additional cobalamin-binding protein, intrinsic factor (IF), from acid-secreting parietal cells.
  - However, IF is ineffective as a cobalamin binder at the acid pH of the healthy stomach, and it follows the haptocorrin-cobalamin complex into the duodenum.
  - Here, the complex is degraded by pancreatic proteases, and at the neutral pH of the duodenum, cobalamin is quickly bound to the protease-resistant IF and in this state traverses the small intestine to the ileum

- Vitamin A
  - Vitamin A includes provitamin dietary carotenoid precursors of retinol and dietary retinol in its esterified form
  - Vitamin A (retinol) is found in the diet in milk and milk products, egg yolk, and fish oils

- Carotenoids are defined by their chemical structure:
  - Hydrocarbon carotenoids are known as carotenes
  - Oxygenated derivatives of these hydrocarbons are referred to as xanthophylls
  - Beta-carotene is the principal carotenoid in carrots, consists of two conjoined molecules of retinol and is a precursor of the active vitamin
- Carotenoids are found predominantly in green vegetables and carrots
- Both retinol and carotene are absorbed in the small bowel
- Within the intestinal lumen, dietary retinyl esters are hydrolyzed by a specific pancreatic esterase to retinol, which is incorporated into micelles, then transported into enterocytes by a specific carrier protein. Transport is active and saturable at low concentrations, and passive at high concentrations
- Before entering the mucosal layer of the intestine, carotenes first are solubilized into micellar solution, along with other fat-soluble compounds (transported by passive diffusion)
- Carotenes are converted into retinol in the enterocytes
- Free retinol (from retinyl ester and carotenes) in the mucosal cells is re-esterified, mainly with palmitic acid, before being incorporated into chylomicrons, which is how vit-A mostly leaves the mucosa

- Vitamin D
  - Vitamin D comprises a group of sterols
  - Only two nutritionally important members
    - Vitamins D_2 (ergocalciferol)
    - Vitamin D_3 (cholecalciferol)
  - Both are produced by UV irradiation of their precursor sterols, ergosterol and 7-dehydrocholesterol
  - Vitamin D_3 (major dietary form) is found in the oils of fatty fish
  - Most of a person's requirement for vitamin D is supplied by endogenous synthesis in the skin during exposure to sunlight.
  - Vitamin D absorption occurs by simple passive diffusion in the small intestine
  - Bile salts are unnecessary, but luminal pH influences absorption (Absorption is reduced at neutral pH and increased in acid)
  - Most absorbed vitamin D passes into the lymphatics unchanged in chylomicrons



- Vitamin E
  - Vitamin E comprises eight tocopherols, of which two, α- and γ-tocopherol, are significant to human nutrition
  - The major food sources of vitamin E are polyunsaturated vegetable and seed oils, whole grains, nuts, and green leafy vegetables.
  - The intestinal absorption of dietary vitamin E includes deesterification by pancreatic esterases, followed by bile-dependent incorporation into intralumenal micelles, subsequent passive diffusion into enterocytes, and incorporation into chylomicrons for transfer to the lymphatics and the circulation

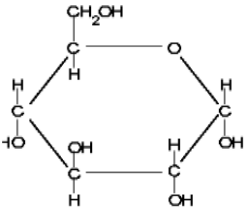
- Vitamin K
  - Recommended daily intake is 1 μg/kg/day
  - Vitamin K is found in two forms:
    - Phytomenadione (K_1) –
      - Derived largely from plants
      - Absorption from the small intestine is dependent on luminal bile salts, and uptake is achieved by a carrier-mediated process
    - Menaquinones (K_2) –
      - Found in green vegetables, beef liver and also produced by colonic bacteria
      - Absorption form the small intestine is by passive diffusion

Carbohydrate Digestion

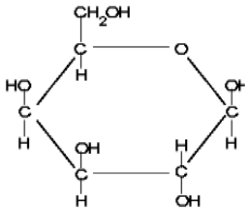
- 45% of total energy requirement is provided by carbohydrate
- Chemically, carbohydrates are organic molecules in which carbon, hydrogen, and oxygen bond together in the ratio: $C_x(H_2O)_y$
- All carbohydrates are made up of units of sugar (also called saccharide units)
  - Monosaccharides (one sugar unit)
  - Disaccharides (two sugar units bonded together)
  - Complex Carbohydrates (polymers of the simple sugars)

➢ Monosaccharides

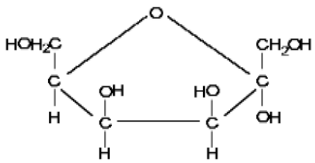
Structure of Common Monosaccharides



Glucose



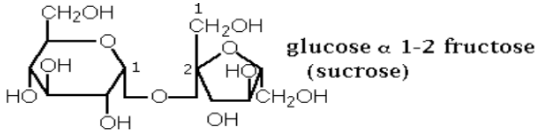
Galactose

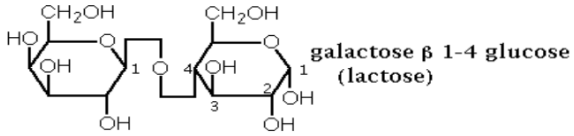


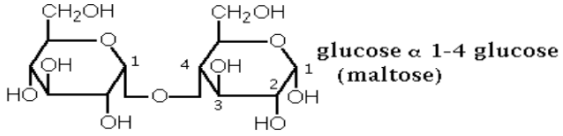
Fructose

- All have the same chemical formula ($C_6H_{12}O_6$); however, they have different structures

- Disaccharides



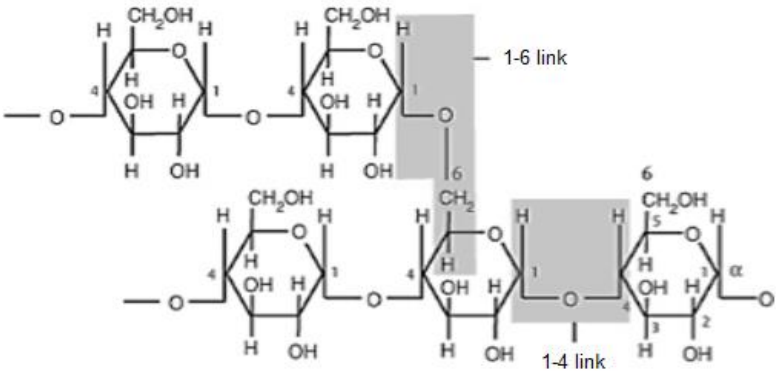




Complex Carbohydrates

- Oligosaccharides- carbohydrates with 3-9 sugar units
- Polysaccharides
  - Starch
  - Glycogen
  - Dietary fibers

- Starch
  - Made up of long chains of glucose
    - Amylose-a linear polymer in which each glucose molecule is coupled to its neighbor by α1-4 linkage, has a molecular weight of 10^6
    - Amylopectin-a branched-chain polymer in which α1-6 links provide the angulations between adjacent chains of α1-4-linked glucose molecules. It has a molecular weight greater than 10^9
  - Starches contain more amylopectin than amylose



- Glycogen
  - Major storage form of polysaccharide in animals
  - Structure is similar to that of amylose and consists of straight chains of α1-4-linked glucose monomers
  - Branched chains α1-6 link every 4-8 glucose monomers
  - Less osmotic pressure

- Non-starch polysaccharides
  - Mainly dietary fiber
  - Found in cereals, peas, beans, carrots, and peanuts
  - Consisting predominantly of :
    - Celluloses- made up of α1-4-linked glucose molecules in straight chains
    - Hemicelluloses- made up of pentose and hexose polymers with both straight and branched chains
  - Both resistant to amylases, but can be broken down partially by colonic bacteria to SCFA.

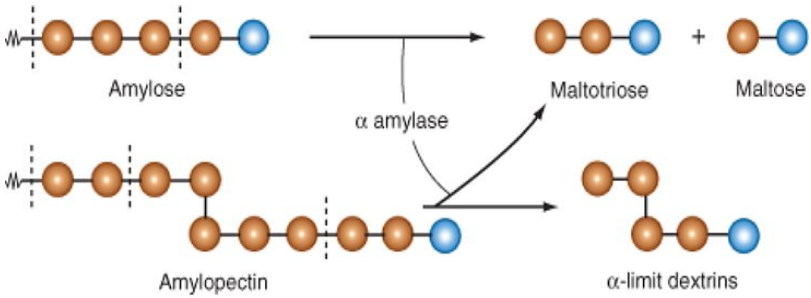
- Others: pectins, gums, and alginates, which are metabolized only partially in the colon.
- Lignins, elaborated by plants in the process of becoming woody, are completely indigestible.
- Dietary fiber has different roles:
  - Eases constipation by increasing fecal bulk
  - Delays absorption of sugars and fats
  - Curtails the insulin response to CHO meals
  - Lignins- may lower serum cholesterol by binding bile salts
  - Satiety is achieved more rapidly from a diet rich in fiber

- Dietary sources of carbohydrate
  - Glucose/fructose: fruit, honey, corn syrup
  - Galactose: driedbeans and peas ,fruit
  - Sucrose: beet, cane sugars, maple syrup, molasses
  - Lactose: milk, milk products
  - Maltose: plants, processed food
  - Starch: granula, cereals
  - Glycogen: meet products, sea food
  - Cellulose: vegetables, fruits and coverings of seeds

Salivary and Pancreatic Amylase

- Both are endoenzymes
- They cleave the α1-4 links internal to, or at the second or third bond from, the end of the polysaccharide chain

- The products of amylase digestion consist of short, linear oligosaccharides with maltotriose and maltose
- α1-6 links, and the adjacent α1-4 bonds, in the branched chains of amylopectin are not hydrolyzed by amylase
- The products of amylopectin digestion include short, branched oligosaccharides, termed α-limit dextrins



➢ Salivary amylase

- Its effect depends on its proximity to the ingested starches and the time they spend within the mouth.
- Salivary amylase is inactivated rapidly by gastric acid.
- Short-chain oligosaccharides offer some protection for the enzyme against inactivation at acid pH.
- However, it is uncertain what proportion of dietary starch is digested before it reaches the duodenum.

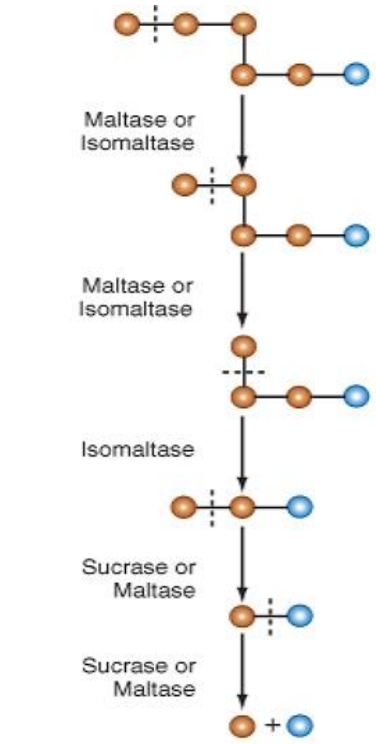
- Pancreatic amylase
  - Major enzyme of starch digestion
  - Produces short oligosaccharides, maltotriose, maltose, and α-limit dextrins
  - Glucose monomer is not produced
  - Hydrolysis mainly occurs within the intestinal lumen
  - Some digestion may occur at the brush border membrane of enterocytes

BBM Hydrolases

- Terminal products of luminal starch digestion, together with the major disaccharides in the diet, need further hydrolysis by brush border membrane hydrolases
- Maximally expressed in the villi of the duodenum and jejunum
- Combination of sucrase-isomaltase, maltase, and α-limit dextrinase serves to liberate glucose monomers very rapidly and in proximity to hexose carriers, thus encouraging efficient absorption
- The transport process of glucose by hexose carriers is the rate limiting step for uptake into the epithelium

Characteristics of Brush Border Membrane Carbohydrases

Enzyme	Substrate	Product(s)
○ Lactase	Lactose	Glucose, Galactose
○ Maltase (glucoamylase)	α-1,4-Linked oligosaccharides; up to 9 residues	Glucose
○ Sucrase-isomaltase (sucrose α-dextrinase)		
– Sucrase	Sucrose	Glucose, Fructose
– Isomaltase	Small α-Limit dextrin α-1,6 Link	Glucose
– Both enzymes	α-Limit dextrin at α-1,4 Link at non-reducing end	Glucose
○ α-limit dextrinase	Penta- and hexa-α-limit dextrins	Glucose



α-limit dextrin digestion

- Note: Isomaltase is necessary to split the α1-6 link

BBM Transport of Carbohydrate

- The three major diet-derived monosaccharides-glucose, galactose, and fructose-are absorbed by saturable carrier-mediated transport systems located in the BBM of enterocytes in the proximal and mid-small intestine

- Active glucose transport is driven by the sodium gradient across the BBM generated by the (Na^+,K^+-ATPase) pump located in the BLM of the enterocyte
- Na^+, K^+-ATPase pump transports 3 Na^+ out of the cell and 2 K^+ into the cell
- 2 Na^+ ions bind to the outer face of the transporter, which produces a conformational change that permits subsequent sugar binding
- The 2 Na^+ ions and the glucose molecule then are transferred to the cytoplasmic face of the membrane through another conformational change
- At the cytoplasmic surface, glucose dissociates first, and then the 2 Na^+ ions dissociate into the cytosol to produce a ligand-free transporter
- Types of glucose transport:
  - High affinity Na dependent SGLT1
  - Low affinity transporter (not Na dependent) GLUT2, SGLT4 and SGLT6
  - Passive (diffusive): at jejunum mediated by GLUT2
- Some of the glucose that crosses the BBM fuels the enterocyte metabolism
- The rest passes out of the enterocyte across the BLM by facilitated diffusion
- For every glucose that enters, 2 Na^+ and 2 anions are transported
- Fructose transport:
  - Transport occurs by facilitated diffusion via GLUT5 transporter protein
  - Then, Transported across the basolateral membrane and metabolized rapidly by the liver

Exit from Enterocyte across the BLM

- Most hexoses are exported from the enterocyte by way of the BLM.
- Exit across the BLM by facilitated diffusion (not requiring energy), which is mediated by a specific carrier, into the portal circulation.

Large Intestine

- Not all potentially digestible carbohydrate is absorbed in the small intestine
- 20% of dietary starch may escape into the colon
- This is metabolized by colonic bacteria and produces SCFA, hydrogen & methane.
- This component becomes quantitatively important in persons with extensive loss of the small intestine, resulting in SBS (short bowel syndrome).

Useful websites

http://www.celiac.ca/

http://pancassociation.org/

http://www.dietitians.ca/

http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php

PREGNANCY AND LACTATION

What to Expect When you're Expecting: Guidelines for Endoscopy in Pregnant and Lactating Women

Aze Wilson

- Useful background: by the numbers
  - In the USA, pregnant women comprise
    - >2% of the female population
    - >1% of the total population.
  - Annually, >12,000 pregnant women have strong indications for EGD
  - Annually, >6,000 pregnant women have strong indications for colonoscopy
  - Thus, having a clear understanding of the safety and efficacy of these procedures is important to give patient best experience, and care

Abbreviations: EGD, esophagogastroduodenoscopy; USA, United States of America

- Endoscopy in pregnancy
  - The safety and efficacy of endoscopy in the pregnant patient is not well-studied
  - Any invasive procedure during pregnancy is justified when the *failure* to perform it could expose mother and/or baby to harm
  - Informed consent should include:
    - Risks to mother
    - Risks to fetus
  - Maternal-Fetal circulation
    - Umbilical Aa – deoxygentated fetal blood to placenta
    - Maternal circulation replenishes the nutrients
    - Umbilical V carries oxygenated blood to the fetus

- Limited data on safety of endoscopy in pregnancy
- Case Series/Case-control studies = EGD is safe in pregnancy
  - CCS – 83 EGDs in pregnant women = 95% diagnostic for GIB (Cappell et al 1996)
    - No premature labour
    - No congenital malformations
- Case-control studies = Colonoscopy is safe
  - Case-control study – 20 pregnant women; same number of poor outcomes (2/20) as in the controls (Cappell et al 2010)
  - Case control study – 8 pregnant women – no adverse events with cscope (Cappell et al 1996)

- Physiological background
  - The physiologies of the fetus and the mother are tightly interwoven.
  - Any compromise to maternal circulation will affect the developing child.
  - The fetal-placental circulation allows the umbilical arteries to carry deoxygenated and nutrient-depleted fetal blood from the fetus to the villous core fetal vessels in the placenta.
  - The placenta is fed by the maternal circulation.
  - After the exchange of oxygen and nutrients, the umbilical vein carries fresh oxygenated and nutrient-rich blood circulating back to the fetal systemic circulation.
  - At term, maternal blood flow to the placenta is approximately 600–700 ml/minute.

- Risks
  - The fetus is sensitive to maternal hypoxia and hypotension
    - Maternal oversedation = hypoventilation, hypotension
    - Improper maternal positioning = IVC compression by the gravid uterus causing decreased uterine blood flow and fetal hypoxia
  - Teratogenicity/Abortifacients
    - Medications
    - Ionizing radiation
- On balance
  - Where therapeutic intervention is necessary, endoscopy offers a relatively safe alternative to radiologic or surgical interventions.
- **ASGE recommends…**
  - Every endoscopic procedure requires a pre-procedure consultation with a obstetrician regardless of gestational age.
  - Always have a strong indication, particularly in high risk pregnancies.
    - Close monitoring for fetal distress

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy

- Give contraindications for endoscopy in pregnancy.
  - Uncontrolled eclampsia
  - Placental abruption
  - Ruptured membranes
  - Imminent delivery

- Give the Indications for endoscopy in pregnancy.

➢ ESD
  - Dysphagia or odynophagia
  - Significant or continued GI tract bleeding
  - Severe or refractory nausea and vomiting, or abdominal pain

➢ Colon
  - Severe diarrhea with negative non-invasive evaluation
  - Strong suspicion of colon mass

➢ ERCP
  - Biliary Pancreatitis
  - Symptomatic choledocholithiasis
  - Cholangitis
  - Biliary or pancreatic duct injury

Abbreviations: EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreaticogram

Recommended for Maternal and fetal monitoring

- The decision to monitor fetal heart rate should be individualized
  - Gestational age
  - Available resources
- < 24 weeks gestation
  - Confirm presence of fetal HR pre/post procedure

- > 24 weeks gestation
  - Simultaneous HR and uterine contraction monitoring throughout the procedure (if possible)

- **ASGE recommends for conscious sedation**
  - Use lowest effective dose of sedative medications
  - Use category ‘B’ drugs whenever possible
  - “None of the currently used anesthetic agents, when used in standard concentration at any gestational age, have been shown to have any teratogenic effect in humans.” (American Society of Anesthesiologists and the American College of Obstetrics and Gynecology)

- It is recognized that these FDA categorize are not widely used, but they are still favoured by some clinicians, and do appear on exam.
- The FDA lists 5 categories of drugs with regard to safety during pregnancy.
- Category A drugs are safe during pregnancy.

- Category B drugs may generally be used during pregnancy.
- Category C drugs may often be used if required during pregnancy.
- Category D drugs are relatively contraindicated, and when used should be administered with extreme caution.
- Category X drugs are absolutely contraindicated during pregnancy.

Safety during pregnancy of medications commonly used for endoscopy

- For endoscopic procedures, 'B' and 'C' drugs are recommended1 (There are no 'A' drugs used for endoscopy)

Propofol (B)
Meperidine (B)
Narcan (B)

Morphine (C)
Fentanyl (C)

Caution

- Meperidine is rated a category B drug during pregnancy, but rated **category D** when used for prolonged periods (>36 h) at high doses at term.
- Meperidine use should be **limited to 50–75 mg** during routine endoscopy during pregnancy.

Do not use benzodiazepine (D) in pregnancy

- Caution should be used in administering any level of sedation to a pregnant patient:
  - Increased risk for aspiration
    - Decreased LES pressure
    - Increased intragastric pressures
    - Altered GEJ angle
    - Delayed gastric emptying

- Potentially difficult airway
  - Swelling of oropharyngeal tissues
  - Decreased calibre of the glottic opening
- Hormonal changes to the vascular structures of the resp tract lead to capillary engorgement and swelling of the oropharyngeal structures

Propofol (B)

- No demonstrated risk to the fetus.
- Should be administered by a trained anesthesia provider
- Safe in T1

Abbreviation: T1, first trimester of pregnancy

Meperidine (B/D)

- Merperidine (B) does not appear to be teratogenic and is preferred over morphine (C)
  - Morphine crosses the fetal blood-brain barrier more rapidly
  - Merperidine may cause loss of fetal beat-to-beat cardiac variability (does not indicate fetal distress)
  - Mostly supplanted by short-acting analgesics due to theoretical concerns about toxicity
    - As respiratory depression
    - Seizures

  - Toxicity occurs from progressive accumulation of meperidine's mildly toxic metabolite, normeperidine, after high-dose, repeated, and prolonged administration

- Give the clinical setting when meperidine is rated FDA category B, yet at other times is rated C.

  - Fentanyl (C) has a rapid onset of action and shorter patient recovery time (vs Merperidine)
    - Not teratogenic; is embryocidal in rats
    - Appears safe in pregnancy in the low doses used in endoscopy

Narcan (B)

- Crosses the placenta within in 2 minutes of IV administration
- Does not appear to be teratogenic
- Used only for respiratory depression, hypotension or unresponsiveness in a closely monitored setting

Benzodiazepines (D)

- Diazepam should **NOT** used for sedation in pregnant women
  - Associated with cleft palate and neurobehavioural disorders
- Midazolam is not associated with congenital abnormalities
  - It is the “preferred” benzodiazepine
  - Should be avoided in T1

Abbreviation: T1, first trimester of pregnancy

Topical Anesthetics

- Lidocaine (B)
  - No fetal malformations in 293 infants with T1 exposure to lidocaine (Heinonen et al 1982)
  - Recommended to have patient gargle and spit rather than swallow

Colonoscopy in Pregnancy

- Cleansing Agents
  - PEG, sodium phosphate and magnesium citrate preparations are classified as pregnancy category C
  - Sodium Phosphate and magnesium citrate preparations
    - May cause fluid or electrolyte imbalances and
    - Use with **caution**
  - Tap water enemas may be sufficient for flexible sigmoidoscopy in a pregnant patient

- Timing
  - If strongly indicated
    - Colonoscopy should be deferred to T2
      - T2 pregnant women were the main study subjects evaluated
  - Theoretical risks:
    - T1 – hypoxia associated with cscope could lead to impairments in fetal brain/organ development
    - T3 – increased risk for preterm labour

Abbreviations: T1, 2, and 3: 1st, 2nd or 3rd trimester of pregnancy

- Patient positioning
  - Pregnant patients are at an increased risk for aspiration
  - Pregnant uterus can compress the aorta or IVC resulting in maternal hypotension and decreases placental perfusion
  - Patients in T2 or T3 should not be placed on their backs DURING, BEFORE or AFTER the procedure
    - Left lateral decubitus position during procedure
    - Left pelvic tilt before and after

- Experience
  - Only an experienced physician should perform the endoscopy in a pregnant patient, so as to minimize the duration of the procedure

Interventions Therapeutic Endoscopy in Pregnancy

- Electrocautery
  - Bipolar electrocautery should be used
  - Minimize use
    - Ok for sphincterotomy or hemostasis
    - Polypectomies should be delayed until postpartem
  - If monopolarised, rounding pad should be placed so that the uterus is NOT between the electrical catheter and the grounding pad (amniotic fluid conducts

- Endoscopic hemostasis (for non variceal bleeding)
  - Insufficient data (limited to 4 cases) to characterize fetal outcome
  - Recommendations based on expert opinions extrapolated from non-pregnant patients with PUD
  - Exercise caution, individualized treatment

Endoscopy During Lactation

- Same diagnostic and therapeutic value as in others
- Drugs excreted in breast milk:
  - Propofol
  - Fentanyl
  - Merperidine
  - Midazolam

Drug	Need to delay after endoscopy
Propofol	No
Fentanyl	No
Meperidine	Use fentanyl instead
Midazolam	AAP recommends with holding breast milk 4 hr post procedure

Abbreviations: AAP, American Academy of Pediatrics

Note: If there is concern then mothers should be counselled to pump and discard breast milk after the procedure is complete.

- Summary
  - Every endoscopic procedure requires a pre-procedure consultation with a obstetrician regardless of gestational age. Fetal monitoring may be required
  - Always have a strong indication, particularly in high risk pregnancies.
  - Use lowest effective dose of sedative medications
  - Use category ‘B’ drugs whenever possible
    - Do not use benzodiazepine
  - Minimize procedure time
  - Defer endoscopy to second trimester (T2) whenever possible
  - Position patient in left pelvic tilt or left lateral decubitus position
  - If needed, bipolar electrocautery should be used.
  - Take caution with drugs used in lactating women

The Burden of Pregnancy on the Liver

Karim Qumosani

Case Presentation

Ms SK is 35 year old lady live in London, presented to ER with few days history of

- Itching (palm and feet)
- Jaundice
- Tea coloured urine
- Minimal generalized abdominal discomfort
- Past medical history
  - Oxycodone misuse; currently on methadone
  - Cholecystectomy in 2003 with an ERCP and papillotomy
- Home Medication
  - Methadone 18 mg Daily
  - Prenatal Vitamins
- Allergy
  - Not know any drug allergy
- Social History
  - Binge drinker every few weeks 8 – 12 beer
  - Smoke 7 – 8 cigarettes per day
  - Oxycodone misuse, but never used IV drugs
  - Her partner “Ex-husband” use IV drugs and he is HCV positive, they do not live together but he come to visit his kids very often and kids go to his place occasionally
  - Needle stick injury while she was cleaning her partner house few weeks prior to her presentation
- Review of systems
  - No recent travel
  - No new drug use or herbal medication
  - No contact with sick person
  - No neurological symptoms
  - No fever, chills, or night sweating

Obstetric History

Physical examination

- Conscious, oriented, GSC 15
- Vitals; BP 121/65 mmHg, HR 90 bpm
- General; Jaundice, no paler
- Abdomen; soft, no tenderness, no Hepatosplenomegaly, no stigmata of CLD
- Lower limb; no edema

Sodium	135	WBC	6.3
Potassium	3.6	Hemoglobin	118
Urea	2.0	Platlets	165
Creatinine	45	Ethanol	< 2.2
Lactate	1.2	TSH	0.49
Total Bilirubin	165	Glucose	3.5
Direct Bilirubin	125	HA1C	0.050
INR	1.0	Calcium	2.13
Albumin	28	Phosphate	0.84
AST	786	Lipase	21
ALT	489	Amylase	37
ALP	107	Magnesium	0,72

- Differential diagnosis

In pregnancy

- Hyperemesis gravidarum (HG)
- Intrahepatic Cholestasis of pregnancy
- HELLP
- Acute Fatty Liver of pregnancy (AFLP)
- Pre-eclampsia

Not in pregnancy

- Viral hepatitis

- Drug / toxin induced liver injury (DILI)

AIH

- CBD obstruction

- Vascular disease

Hyperemesis gravidarum (HG)

- Affect 0.3 – 2 % of all pregnancy
- First trimester, or before 22 week of pregnancy
- Sever intractable nausea and vomiting
- Pathophysiology unknown but may related to hCG level
- Risk Factors;
  - Younger age
  - Primiparous
  - Non Caucasian
  - H*. pylori*

HELLP Syndrome

- Affect 0.1 – 0.8 % of all pregnancy
- Third trimester, after 28 weeks but late second trimester
- Nausea, vomiting, and abdominal pain
- Hypertension and proteinuria 85%
- Pathophysiology
  - Unclear
  - Abnormal placentation; Systemic inflammatory disorder and the complement cascade is the key mediator
  - LCHAD deficiency

H; Hemolysis (MAHA)
EL; Elevated Liver enzymes (AST, LDH and Bilirubin)
LP; Low Platelets
< 100,000 cell/microL

Acute Fatty Liver of Pregnancy (AFLP)

- Rare; 1 in 13,000 deliveries
- Third trimester
- Nausea, vomiting, abdominal pain and jaundice
- Hypertension 50%
- Central DI

Mitochondrial Beta-Oxidation of Fatty Acids

- Aminotransferase and Bilirubin
- Hypoglycemia
- Elevated ammonia level
- Coagulopathy
- Encephalopathy

- Liver Biopsy;
  - Microvesicular fatty infiltration
  - Foamy appearing cytoplasm
  - Central and mid zonal sparing Periportal area

Microvesicular vs. Macrovesicular Fat

Macrovesicular Steatosis	Microvesicular Steatosis
○ Obesity, type2 diabetes, metabolic syndrome and dyslipidemia (non-alcoholic fatty liver disease) ○ Excessive alcohol consumption ○ Hepatitis C (genotype 3) ○ Wilson disease ○ Lipodystrophy ○ Starvation ○ Jejuneal bypass ○ Parenteral nutrition ○ Abetalipoproteinemia ○ Medications (amiodarone, methotrexate, tamoxifen, corticosteroids, antipsychotics)	– Reye syndrome – Medications (valproate, antiretroviral medicines, intravenous tetracycline) – Heat stroke – Acute fatty liver of pregnancy – Hemolysis devated liver enzymes and low platelets (HELLP) syndrome – Inborn errors of metabolism (lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman disease

Physiological changes during pregnancy

- Cardiac output is increased but blood flow to the liver remains constant and the liver usually remains impalpable during pregnancy
- Spider angiomas and palmar erythema are normal findings in pregnancy and are caused by the hyperoestrogenic state
- Increase in the blood volume more than 50% during pregnancy resulting in dilutional effect on albumin and bilirubin
- Increased Alkaline phosphatase activity due to placental secretions

➢ Liver Biochemistry in Pregnancy

- Liver tests affected by pregnancy
  - Albumin and total protein (decreased from the first trimester)
  - Alkaline phophatase levels (increased in second and third trimester)
  - Bilirubin levels (slightly decreased from the first trimester)
  - Gamma glutamyltransferase levels (slightly decreased in late pregnancy)
- Liver tests not affected by pregnancy
  - Serum aminotransferase levels (ALT, AST)
  - Prothrombin time
  - Serum concentration of total bile acids (fasting state)
  - Lactate dehydrogenase (LDH)

Intrahepatic Cholestasis of Pregnancy (ICP)

- Definition
  - Pruritus with elevated serum bile acids occurring in the second half of pregnancy, which resolves after delivery
  - 0.2% and 2% of all pregnancies, most common in South America and northern Europe
  - Serum Bile Acids 268 which > 40 fold upper limit of normal

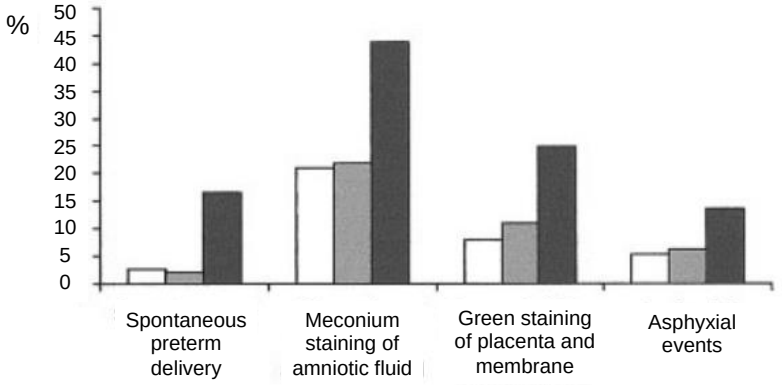
- Risk factors
  - Multiple pregnancy (up to 22% in one Study)
  - In vitro fertilization treatment (2.7% compared with 2%)
  - Women older than 35 years of Age
  - Seropositivity for hepatitis C (0.7% compared with 0.2%; hazard ratio 4.16, CI 3.14–5.51)
  - Women who develop cholestasis secondary to the oral contraceptive pill
  - Family history of the condition

- Pathogenesis
  - Related to the effect of reproductive hormones on cholestasis in genetically predisposed individuals
    - Hormonal evidence
    - Timing in pregnancy (Peaks in 3rd trimester)
    - Twin pregnancies display both a higher incidence of ICP and more pronounced rises in hormone levels
    - Resolves after delivery when hormone levels are decreased

- Bile Acids are the end products of the cholesterol metabolism in the liver.
  - Genetic component
    - 10% occurrence in 1st degree relatives
    - Regional clustering
    - Defects in multidrug resistance type -3 gene (MDR-3)Encodes for the canalicular phospholipid pump protein

  - Disruption of the transport of bile acids from the liver to the gall bladder and there is compensatory transport of bile salts from the hepatocytes into the blood

Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates



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- Clinical Features
  - Pruritus
    - Defining feature
    - Affects mainly palms and feet
    - Worse at night
  - Jaundice
    - 10%-25% of patients
    - 2-4 weeks after the pruritus
  - Symptoms of cholestasis: dark urine and pale stools
  - Steatorrhea

- Laboratory
  - Liver function test;
    - Alk phos (1 – 4x)
    - Aminotransferases (2 – 10x)
    - GGT normal or mild increase
    - Jaundice in 15 % of cases
  - Serum bile salts;
    - Most sensitive and specific marker
    - Elevated fasting serum total bile acids {cholic acid/chenodeoxycholic acid (CA/CDCA) ratio of approximately 4:1 vs. normal pregnancies of <1.5}
  - Liver Biopsy;
    - Cholestasis without inflammation

- Treatment
  - Ursodeoxycholic acid
    - ↓ plasma bile acid and sulphated progesterone metabolite concentrations
    - ↑ bile salt export pump expression
    - ↓ pruritus, improve liver function tests, and reduces fetal complications
    - Doses of 10–15 mg/kg BW safe to mother and fetus
  - Dexamethasone
    - Less effective than UDCA in reducing pruritus and aminotransferase levels
    - Advantage of promoting fetal lung maturity
  - Cholestyramine
    - Effective at reducing pruritus
    - No improvement in serum bile acid levels or liver function tests
    - Can exacerbate diarrhea or /and vitamin K deficiency

- Hydroxyzine
  - Dose (25 to 50 mg/day)
  - May improve pruritus only
  - Can aggravate respiratory difficulties in preterm babies.
- Obstetrical care
  - Monitor pregnancies beginning at 32-34 weeks and deliver fetus early
    - Deliver by 37 weeks for mild disease
    - Deliver by 36 weeks for cases with jaundice
    - Deliver as soon as possible if fetal distress is identified
    - May need to deliver earlier if mother has disabling pruritus

➢ Prognosis

- Mother
  - Pruritus usually disappears in the first few days following delivery, accompanied by normalization of serum bile acid concentrations and other liver tests
  - Cholestasis recurs during subsequent pregnancies in 60 – 70 %
  - Rarely progress to cirhosis and only reported in cases of underlying familial intrahepatic cholestasis
  - No contraindication to breast feeding or use of OCP after delivery
- Fetus
  - ↑ risk of;
    - Prematurity (60%)
    - Meconium stained amniotic fluid,
    - Intrauterine demise (1%)
    - Respiratory distress syndrome (20-40%)

- Fetal complications correlate with maternal bile acids levels

Viral Hepatitis and Pregnancy

- Most common cause of jaundice in pregnancy
- Increased risk of transmission of hepatitis A and B during delivery if mother viremic
- Less risk for transmission of hepaitis C unless coinfected with HIV. No effective passive immunoprophylaxis
- Fortunately, the course of most viral hepatitis infections is unaltered by pregnancy with the exception of hepatitis E
- Prevalence of HCV antibody 1.16%, and the prevalence of HCV RNA ranges between 42.5% and 72%
- Acute HCV infection is rare
- Natural course of Chronic HCV
  - Significant reduction in the mean alanine aminotransferase (ALT) levels has been reported with rebound during the postpartum period.
  - HCV RNA titer rises during the third trimester
  - Liver fibrosis: conflicting evidence regarding progression of fibrosis during pregnancy

HCV and Pregnancy

- Effect of HCV on Pregnancy
  - ↑ risk of Obstetrical complications
    - Studies reports higher rates of C – Sections in HCV positive women
    - Increase risk of Intra-hepatic cholestasis of pregnancy
  - Fetal outcomes
    - ↑ prevalence of low birth and preterm deliveries
    - ↑ risk of Intensive care and assisted ventilation

- Vertical transmission of HCV
  - Risk of vertical transmission from chronically infected mother ~5%
  - Risk factors
    - ↑ levels of hepatitis C RNA
    - HIV coinfection
    - Long duration between membrane rupture and delivery

- Hepatitis C and infant
  - ↑ rate of spontaneous clearance 25 – 30%
  - Variable incubation period of HCV that can range from 2 weeks to 6 months
  - Test infants with HCV RNA on 2 occasions between the ages of 2 and 6 months and/or test for HCV antibody after 12 months

- Treatment
  - Anti HCV treatment is contraindicated during pregnancy
    - Peg interferon causes psychiatric S/E which confound post partum depression
    - Ribavirin are teratogenic
    - Sofosbuvir and ledepasvir can be used in pregnancy FDA class B
  - Avoidance of invasive procedures pre or during delivery (amniocentesis, instrumented vaginal delivery)
  - Breast feeding; acceptable unless clear nipple trauma or abrasions
  - No advantage of performing Caesarian section for birth of child

FDA Approved Medications for Treating HBV and HCV

Drug	Category	Indication
Adefovir (Hepsera)	C	HBV
Entecavir (Baraclude)	C	HBV
Incivek (Telaprevir)	B	HCV
Interferon (Intron A)	C	HCV and HBV
Ledipasvir (Harvoni – ledipasvir + sofosbuvir)	B	HCV
Pegylated interferon alfa-2a (Pegasys)	C	HCV and HBV
Pegylated interferon alfa-2b (Peglntron)	C	HCV
Sofosbuvir (Solvaldi, Harvoni (sofosbuvir / ledepasvir)	B	HCV
Simeprevir (Olysio)	C	HCV
Ribavirin (Rebetol, Copegus, etc.)	X	HCV
Telbivudine (Tyzeka)	B	HBV
Tenofovir (VIread)	B	HBV and HIV
Victrelis (Bocoprevir)	B	HCV

HEV and Pregnancy

- Demography
  - Rare in the developed world but in developing worlds where it is more common
- Virology
  - It is a waterborne virus spreading through faecal – oral transmission
  - Outbreaks occur after flooding
- Diagnosis
  - Serum or feces by polymerase chain reaction (PCR) or by the detection of IgM antibodies to HEV
- Treatment
  - Supportive treatment only
- Prognosis
  - Maternal
    - 2.7-fold higher rate of fulminant hepatic failure and
    - A 6-fold higher mortality rate
    - Antepartum hemorrhage (relative risk, 4.1) and intrauterine fetal death (RR, 1.9)
    - Responsible for high level of fulminant hepatic failure and mortality;
      - Pregnant women 20% (1st TM 1.5%, 2nd TM 8.5%, 3rd TM 20%)
      - 1% in non pregnant
    - Reason of high fatality is unknown

- Fetal outcomes
  - Intrauterine fetal death (RR, 1.9),
  - Preterm delivery
  - Stillbirth.

Summary

- Acute HCV during pregnancy is very rare; however it should be considered in high risk patients
- Intrahepatic Cholestasis of Pregnancy should be considered in any pregnant woman with pruritus and elevated liver enzymes
- Bile acid level is very useful tool to diagnose Intrahepatic Cholestasis of Pregnancy but it could be elevated with other cholestatic disorders like PSC, PBC

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