MEDICAL MINI REVIEW SERIES IN GASTROENTEROLOGY AND HEPATOLOGY

Efficient Refresher for the Busy Clinical Gastroenterologist

Volume 5

Edited by

A.B.R. Thomson and N. Chande

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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.

LIST OF CONTRIBUTORS

Al Nasser A, MD, FRCP(C)

Al Yatama N, MD, FRCP(C)

Alawadh Y, MD, FRCP(C)

Alghamdi W, MD, FRCP(C)

Beaton M, MD, FRCP(C)

Chande N, MD, FRCP(C)

Driman D, MD, FRCP(C)

Liu L, MD, FRCP(C)

Malhotra N, MD, FRCP(C)

Marotta P, MD, FRCP(C)

McIntosh K, MD, FRCP(C)

Rammal A, MD, FRCP(C)

Sandhu A, MD, FRCP(C)

Segal D, MD, FRCP(C)

Sey M, MD, FRCP(C)

Thomson A, MD, FRCP(C)

Tse F, MD, FRCP(C)

Wilson A, MD, FRCP(C)

Yan B, MD, FRCP(C)

EDITOR BIOGRAPHIES

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.

Dr. Nilesh Chande is an Associate Professor of Medicine in the Division of Gastroenterology at Western University, London, Ontario, Canada. He is the Director of the Gastroenterology Training Program and has interests in inflammatory bowel disease, general gastroenterology, and medical education.

As physicians, learning is life-long.

This book is dedicated to our trainees and

To the patients whom they will care for,

And care about.

Alan Thomson

To the past, present, and future Western Gastroenterology trainees, who challenge and aspire us to excel.

Nilesh Chande

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ESOPHAGUS

Eosinophillic Esophagitis

Amindeep Sandhu

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      - Intestinal parasites
    - Inflammation
      - IBD
    - Infiltration
      - Lymphoma
      - Gastric cancer
      - Colorectal cancer may have eosinophils with ↑ CRC obstruction)
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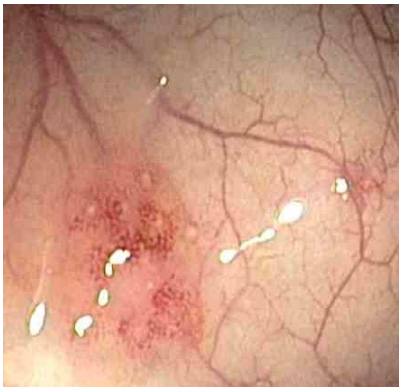
      - Purpura/livedo,
      - Renal disease, mono/polyneuropathy, intestinal angina/mesenteric arteritis
      - GI bleeding
      - Myagia
    - Eosinophilic Granulomatosis with Polyangitis (EGP, aka Churgh-Strauss)
      - Asthma/rhinitis
      - Eosinophilia > 10%
      - Migrating pulmonary infiltrates
      - Mono/polyneuropathy
      - Nasal abnormalities
    - Hyper-eosinophilic syndrome
      - Idiopathic marked eosinophilia
      - Mild GI symptoms and often other sites involved (e.g. heart, lung, brain, kidneys)

- Demography
  - Infancy → 7th decade (3rd – 5th most common)
  - Only 300 – 500 symptomatic cases reported
    - Underestimation
  - Esophagus, Stomach > Duodenum >>> Colon

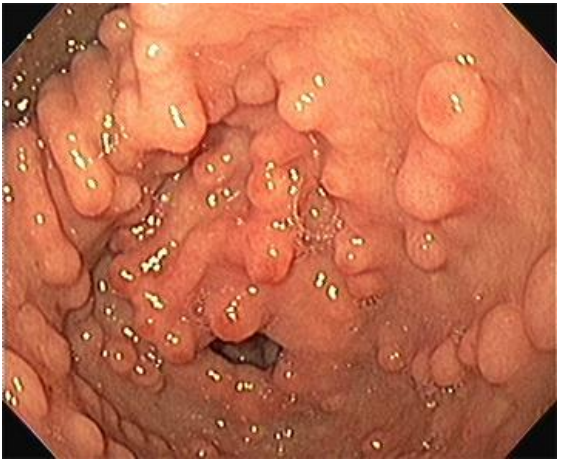
- Pathophysiology
  - Allergic and non-allergic subtypes
  - Food exposure → hypersensitivty reaction → differentiation of IL-5 Th2 cells & mast cell activation → ↑ gut chemokines (g-MSF) → recruit eosinophils with further exposure →gut & peripheral eosinophilia

- Pathology

- Gross endoscopy

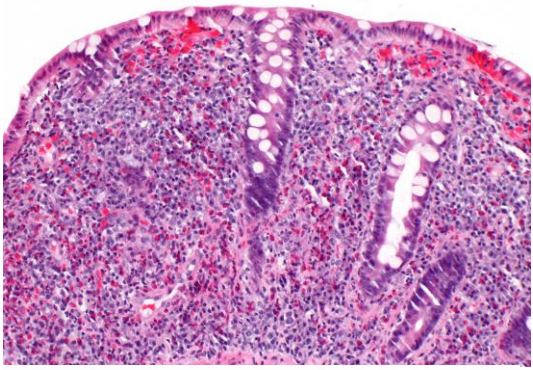


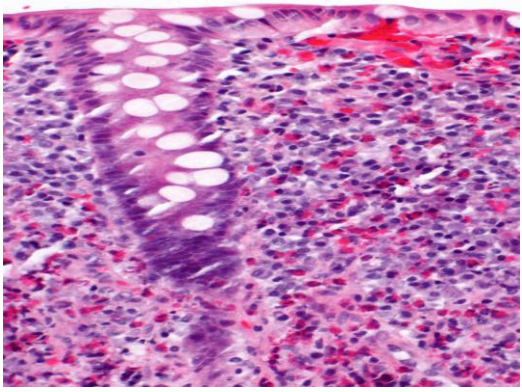
  - Often normal or non-specific erythema
  - Nodularity/Polypoid mucosa
  - Can be classified into mucosal, muscular and serosal
    - Depth of involvement



- Histopathology
  - 4-5 biopsies per site
  - Biopsies
    - Should be taken from normal and abnormal mucosa (normal can also have eosinophilic infiltrates)
    - If found in colon – do EGD with Antral & Duodenal Bx
  - ↑ eosinophilia within lamina propria
    - May be patchy, so beware sampling error)
    - Often > 50/hpf within lamina propria
  - No
    - Crypt architectural abnormalities
    - Dysplasia
    - Granulomas
    - Abundance of neutrophils or lymphocytes
  - Atypical: crypt hyperplasia, epithelial cell necrosis

- Laparoscopic full-thickness biopsy required if
  - Clinical suspicion & negative endoscopy biopsy
  - Change management
  - Extensive endoscopic findings, ascites





- Clinical
  - Based upon
    - Gut damage from mast cell degranulation,
    - Eosinophilic infiltration
    - Location and / or depth of mucosal infiltration with eosinophils

- Mucosa
  - Abdominal pain
  - Nausea / vomiting
  - Early satiety
  - Diarrhea
  - Weight loss with involvement
    - Malabsorption
    - Protein-losing enteropathy
    - FTT
  - Muscle
    - Pseudoachalasia
    - Stricturing
    - Obstruction
    - Perforation
  - Subserosa
    - Ascites
    - Pleural effusion

- Clinical
  - CBC
    - Peripheral eosinophilia (> 80%)
  - Hypoalbuminemia (10%)
    - Protein-losing enteropathy
  - ESR, CRP
    - Almost always normal
    - ↑ IgG (in 25%)
    - Rule out secondary causes: Stool O&P, ANCA's, etc.

- Treatment
  - Dietary therapy
    - Attempt "six-food" (soy, wheat, egg, milk, nuts, fish/shellfish) elimination diet
    - Dietician consultation for compliance difficult
    - Supplements may be required (Calcium, Vitamin D)

- Follow symptoms + peripheral eosinophilia in 6 wks
- Repeat EGD if uncertain response
- Targets 50%

- Food Allergy Testing
  - i.e. skin patch, allergen-specific IgE
  - Not proven to identify culprit foods
  - False positives and negatives muddy the clinical picture

- May be useful to reinforce dietary adherence elimination diet

- Glucocorticoids
  - If dietary measures do not improve symptoms
  - Prednisone 40/d x 2 weeks, then rapid taper over 2 weeks (2.5/d, 5 eod)
  - If symptoms recur at taper – restart at highest dose to blunt symptoms and taper over 2-3 mon
  - If steroids do not resolve symptoms
    - Look for missed secondary cause (parasite, malignancy)
  - If steroids to resolve symptoms
    - Non-systemic steroid budesonide
    - Low-dose prednisone
    - Alternate (asthma) drugs
      - Cromolyn 200 mg qid (inhibits mast cell degranulation)
      - Omalizumab
      - Montelukast

➢ Prognosis

- Chronic waxing and waning condition
  - Many patients in a retrospective case series of 55 patients required > 3 courses of prednisone over a number of years

Hypereosinophilic Syndromes (HES)

Almotasembillah Rammal

Interval History

- She describes longstanding epigastric pain which has remained unchanged over the last 6 to 8 months. The pain is in the epigastric area and increases with food. There are no specific food triggers. It comes and goes 3 to 5 times every week. Improve sometimes with Gravol. The pain is cramping in nature and lasts for several minutes.
- She has had mild nausea with no vomiting.
- She describes intermittent dysphagia in the mid-sternum, predominantly with solids. She has to drink a lot for the bolus to pass and had never had an impaction. She has heartburn and she is not on PPI as she reports because she does not have a drug plan.
- She has regular bowel movements but 2 weeks ago, she had an episode bright blood mixed into the stool.
- She denied melena, weigh loss, fevers, night sweats, noctural symptoms, EIM of IBD.
- She has a history of skin rash but is gone now. No neurologic symptoms.

Examination

- Vital signs stable.
- Abdomen was soft and non-tender with no rebound, guarding, or shake tenderness. Bowel sounds present with no HSM. No cervial or supraclavicular lymphadenopathy, Neurological exam grossly normal.

Plan

- Start PPI
- EGD , C-scope
- Ca , Vit D
- EGD , C-scope are normal
- Patho . Normal

Hypereosinophilic Syndromes (HES)

- Definition
  - Group of disorders marked by the sustained overproduction of eosinophil

- Terms
  - **Hypereosinophilia** (HE) in the peripheral blood is defined as an absolute eosinophil count (AEC) >1.5 x 109/L on two examinations separated in time by at least one month **and/or** pathologic confirmation of tissue HE.
  - **Hypereosinophilic syndrome** (HES) is defined by the association of HE with eosinophil-mediated organ damage and/or dysfunction
  - Must exclude parasitic infection and malignancy
  - Eosinophils
    - Eosinophils are derived from myeloid progenitors in the bone marrow, through the action of three hematopoietic cytokines:
    - Granulocyte macrophage colony-stimulating factor (GM-CSF)
    - Interleukin-3 (IL-3)
    - Interleukin-5 (IL-5) is specific for eosinophil differentiation.

Features of HES variants

Terminology of HES variants	Clinical features
○ Myeloproliferative variants	– ↑ serum B12 – Anemia and/or thrombocytopenia – Hepatomegaly and/or splenomegaly – Circulating leukocyte precursor – May show ↑ serum tryptase + mast cell abnormalities – Occurs almost exclusively in males
○ T cell lymphocytic variants (L-HES)	– Prominent skin findings (including plaques, erythroderma, urticarial) – Polyclonal hypergammaglobulinemia – Usually a benign lymphoproliferative disorder, but may progress to T cell lymphoma
○ Familial HES	– Asymptomatic eosinophilia from birth, autosomal dominant – Progression may occur
○ Idiopathic HES	– Multisystem involvement with varied signs / symptoms

Terminology of HES variants	Clinical features
○ Organ-restricted HES	– Peripheral blood eosinophilia associated with signs / symptoms in a single organ
○ Specific / defined syndromes associated with hypereosinophilia	– Marked eosinophilia in the setting of an underlying disorders associated with eosinophilia. The precise role of eosinophils in the disease manifestations remains uncertain.

➢ Clinical features

○ Skin – Rash	37%
○ Lung – Cough and breathlessness	25%
○ Gastrointestinal	14%
○ Cardiac	5%
○ Neurologic	4%

Gastrointestinal disorders:

- Eosinophilic gastroenteritis, and/or colitis and weight loss, abdominal pain, vomiting, and/or severe diarrhea
- Hepatic involvement may take the form of chronic active hepatitis, focal hepatic lesions, eosinophilic cholangitis, or the Budd-Chiari syndrome.

- Treatment
  - Immediate treatment for severe disease
    - Glucocorticoids
      - High-dose glucocorticoids, at doses ranging from 1 mg/kg of prednisone to 1 g of methylprednisolone
    - Anti-IL-5
      - Preparations of antibodies targeted against IL-5 (mepolizumab) have shown promising results in the treatment but are available only in clinical trials
    - Hematopoietic cell transplantation
      - May be necessary in severe HES not responding to usual medications
  - Maintenance
    - Imatinib is the first line therapy
    - Hydroxyurea and interferon-alfa. Are the second line

- Prognosis
  - Lymphocytic variant hypereosinophilic syndromes (L-HES) are usually a benign lymphoproliferative disorder BUT RARLY CAN TRANSFORM TO LYMPHOMA

- Features associated with a poorer prognosis include
  - Findings associated with myeloproliferative disorders, such as
    - Elevated serum vitamin B12
    - Cardiovascular involvement
    - Splenomegaly
    - Lack of response to glucocorticoids
    - Cytogenetic abnormalities
    - Myelofibrosis,
    - Myeloid dysplasia.
- Features associated with a better prognosis include the absence of cardiac or neurologic involvement, lower eosinophil counts, and steroid-responsiveness

Case Report in Gastrointestinal Medicine

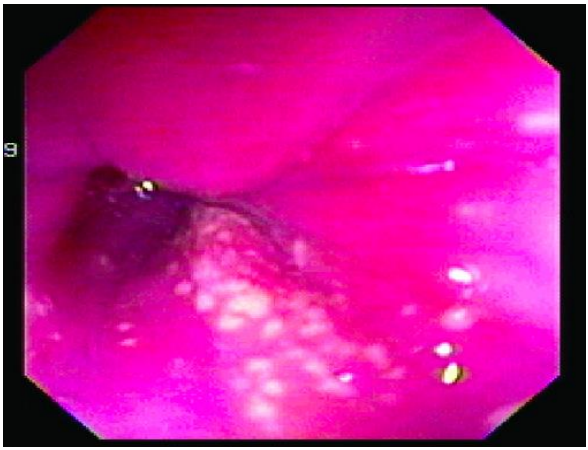
- **A Case Report of Eosinophilic Esophagitis Accompanying Hypereosinophilic Syndrome**

Mahreema Jawairia, Ghulamullah Shahzad, Jaspreet Singh, Kaleem Rizvon, and Paul Mustacchia

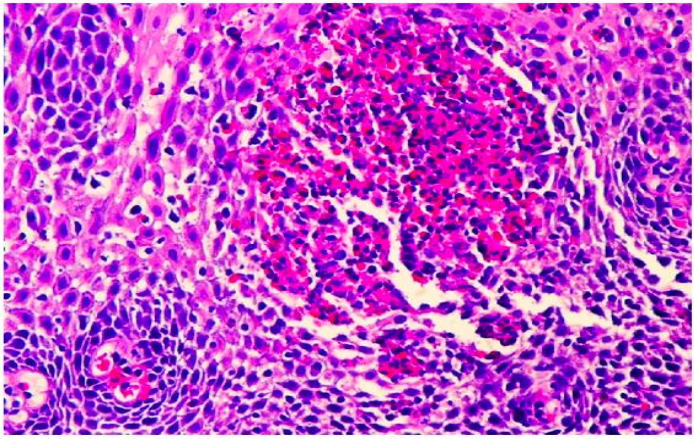
Department of Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, USA (18 May 2012)

- A 39-year-old female presented with complaints of generalized body itching and difficulty in swallowing to both solids and liquids for the past two years.
- Dysphagia was progressively worsening in severity for the past few weeks and was associated with nausea and vomiting.

- Patient denied any weight loss, diarrhea, hematochezia, melena, odynophagia, hematemesis, and abdominal pain.
- Past medical history included asthma and hypereosinophilic syndrome.
- Laboratory findings showed
  - Absolute eosinophil count was increased to 4000/μL
  - Liver-related tests and connective tissue disorder tests were unremarkable.
- EGD revealed whitish exudates noted in the esophagus with normal stomach and duodenum.
- Brushings were negative for *Candida* species
- Antral biopsy was negative for *Helicobacter pylori*.
- A Double Contrast Esophagram examination revealed abnormal peristalsis/motility with the presence of a questionable mild stricture in distal esophagus.
- The patient was started on Fluconazol and pantoprazol 40 mg daily



- Returned to GI clinic four weeks later with persistent dysphagia.
  - EGD was repeated, and it revealed persistent whitish pin-point exudates in the mid and lower esophagus.
  - Then, patient's PPI was increased to 40 mg twice daily and was told to follow-up in GI clinic in two weeks.
  - On follow-up visit, her brushings showed no *Candida* and midesophagus biopsy showed eosinophilic infiltrate and findings were consistent with acute eosinophilic esophagitis and microabscesses with eosinophil count of 65/HPF.
  - Subsequently, she was started on fluticasone 40 mcg twice, daily and on a follow-up visit, she reported marked improvement in her dysphagia.



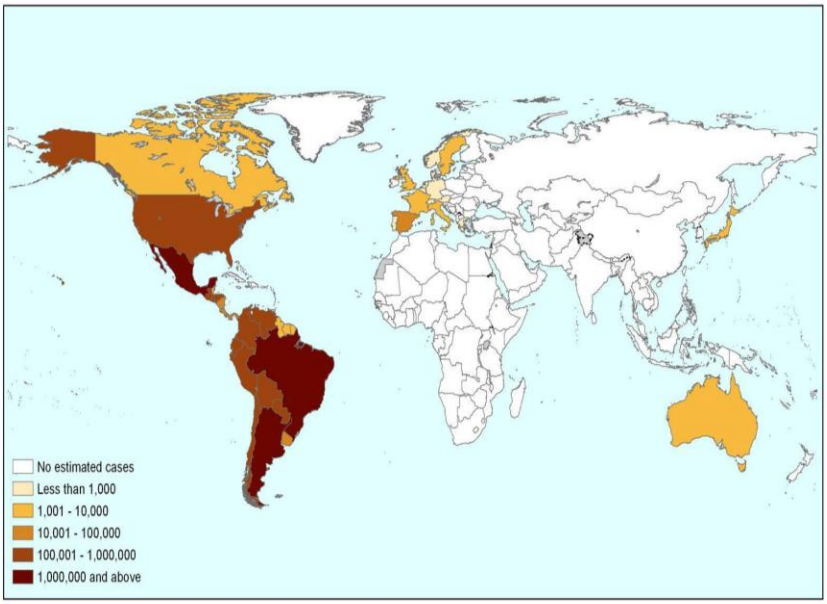
Chagas Disease

Amindeep Sandhu

- Aka American Trypanosomiasis
- Named after the Brazilian physician, Charlos Chagas, who discovered the disease in 1909
- Major complications related to GI disease and cardiomyopathy

- Epidemiology
  - Higher burden of M & M than any other parasite, including malaria
  - Infects humans, and 100 other species of mammals
  - 8-10 million people affected in the Americas
  - Brazil → Chagas = third leading indication of heart treatment
  - Highest prevalence in rural areas of Latin America
  - HIV and organs transplantation increase
    - Incidence of T. cruzi co-infection and rates of re-activation
  - Insecticide resistance cause plagues South America

Estimated global population infected by *Trypanosoma cruzi*, 2009



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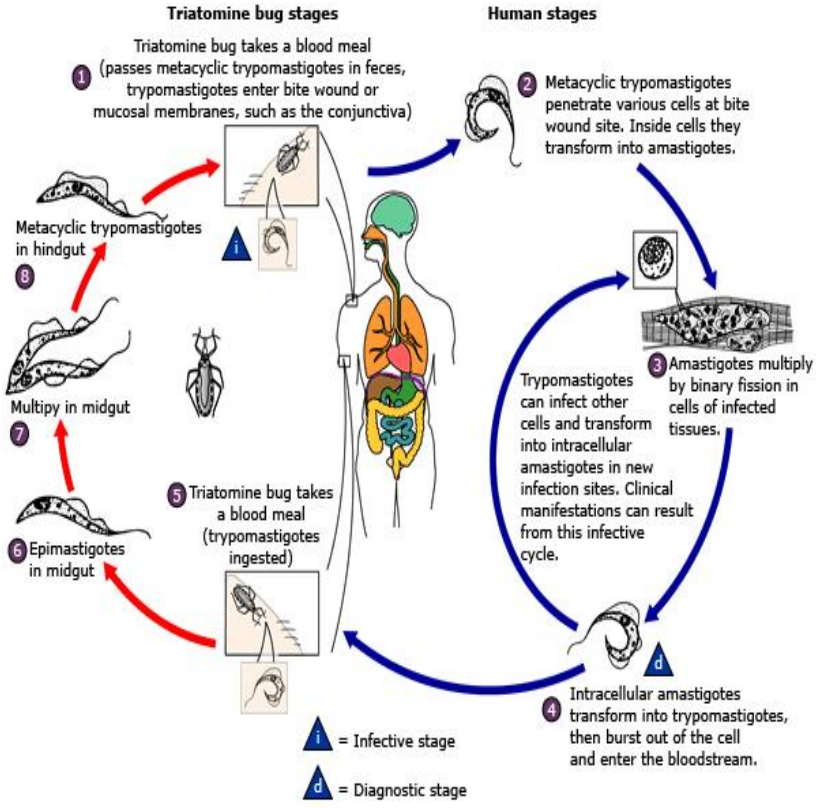
- Microbiology
  - Caused by infection with protozoan parasite Treponema cruzi

- Transmission
  - Vector (70%)
    - T. cruzi consumed by insect vector when it bites human/mammal, and vector transmits it to other humans/mammals
    - Insect vector defecates during blood meal, feces filled with parasite, penetrating skin, conjunctiva or mucous membranes

  - Feed nocturnally, while host asleep!
- Vertical (25%)
  - Growing, now represents 25% of new infections!
  - Infant asymptomatic, can do IgG serology or PCR > 9 mon if risk
- Blood – 1 in 27,000 units infected in 2008 in US
  - 10% of all infections, mostly due to platelets (stored at room T)
- Transplantation
  - Infected organ to uninfected recipient → 19 cases (3 liver)
- Oral (5%)
  - Ingestion of contaminated food containing insect feces (vector, triatomine bug)

- Pathogenesis of GI disease
  - Destruction of neurons in enteric nervous system (ENS)
    - Both parasympathetic & sympathetic fibers affected
    - Denervation occurs in submucosal (Meissner) and myenteric (Auerbach) plexuses
    - Destruction of interstitial cells of Cajal – reduced motility modulation

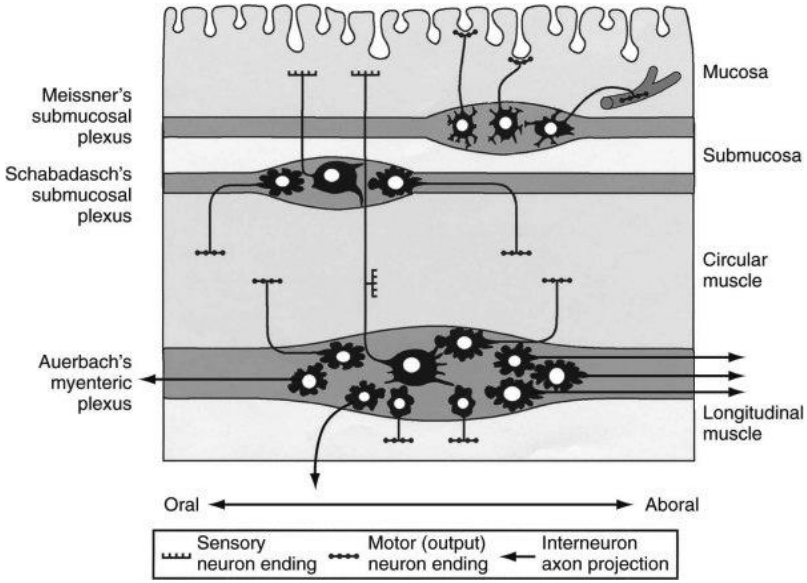


- Pathology
  - Fibrosis
    - Smooth muscle
    - Myenteric plexuse
  - Lymphocytic infiltrates
  - Hypertrophy of muscularis mucosa
  - Esophagus and distal colon usually affected

- Infection
  - Acute (Parasites detected by microscopy)
    - 1 – 2 weeks following exposure (up to 4 mon if infection occurs by blood transfusion or organ transplantation)
    - Asymptomatic → mild viral-like illness: fever, myalgias (diagnosis established here in < 10%)
    - Non-specific abdominal pain
    - < 1% have CHF secondary to myocarditis
    - May cause meningitis
  - Chronic (Parasitemia below level of microscopy)
    - 8-12 weeks after exposure
      - Now can transmit to vector

➢ Clinical

- GI Chagas Disease occurs in 10 – 15% with chronic infection.
- GI symptoms occur in setting of chronic disease
  - Not reactivated disease from HIV or organ transplantation
- Onset most common between 20 – 40 years of age
- Any part of digestive tract affected
  - Esophagus > Rectum > Sigmoid > Descending colon
  - Stomach, Small Bowel, peritoneal involvement rare
- Can start off in esophagus, progress to colon & v/v
- Megacolon is often the final manifestation of the disease



- Esophageal
  - Hypercontractility, from ↑ muscular tone
  - Failure of LES relaxation with swallowing (achalasia)
  - Progressive dilation → megaesophagus
  - Varying symptom severity
    - Asymptomatic motility disorders → mild achalasia → severe megaesophagus (in 80%, associated with megacolon; in 20%, gastric involvement)
    - Usually presents as progressive dysphagia, solids → liquids
    - Spontaneous chest pain, substernal radiating superiorly, common
  - Regurgitation of undigested food

- With increasing severity:
  - Aspiration
  - Food impaction → irritation, ulceration, bleeding, perforation, fistulas
  - Malnutrition
- ↑ risk of esophageal adenocarcinoma

- Stomach
  - 20% with megesophagus
  - Symptoms
    - Gastroparesis
    - Distention
    - Pyloric hypertrophy in late stages
    - Hypochlorhydria

- Small bowel
  - Bacterial overgrowth
  - Recurrent pseudo-obstructions

- Colonic
  - Abnormal basal colonic motility
  - ↓ contractility
  - ↓ relaxation of the anal sphincter
  - Progressive dilation → megacolon
  - Varying symptom severity
    - Asymptomatic but radiographic dilatation (30%)
    - Megacolon often (80%) associated with megaesophagus
    - Slowly progressive constipation (50%)
  - Unable to pass stool for weeks

- Bloating, colicky abdominal pain
- Prolonged stool retention → fecalith formation
- Typically manifest 5-10 years after initial infection
- Complications
  - Recurrent volvulus → secondary bowel ischemic
  - Anorexia, malnutrition

- Diagnosis
  - Two Steps
    - Confirmation of T. cruzi infection
      - Serology
      - PCR
  - Detection organ Involvement
    - Cardiovascular
    - Gastrointestinal
  - Acute phase (within 8 weeks = best yield)
    - Blood cultures – high level of parasitemia,
      - Identifies motile trypomastigotes
      - Parasitemia decreases to nearly zero by 3 months
      - Limiting step is vague presentation not getting cultured
      - PCR → very sensitive, positive even before parasitemia
  - Chronic Phase (8 weeks onwards)
    - Serology: IgG Ab to T. cruzi (ELISA, IFA)
    - Need 2 serological assays to confirm (no assay has enough sensitivity or specificity to be used alone)
      - Antigen-base dassays and/or ELISA/IFA
    - Note
      - PCR not useful

- Esophagus
  - Chest X-ray
    - Dilated esophagus
    - Air-fluid level in esophagus
    - No gastric air bubble
  - Barium esopphagram
    - Stage I
      - Minimal contrast retention (delayed emptying) i.e. Normal diameter esophagus < 10cm
    - Stage II
      - Moderate esophageal enlargement with motor incoordination
      - Moderate dilatation, more contrast retention
      - Relative hypertonicity of inferior third of esophagus
    - Stage III
      - Large achalasic esophagus
      - Substantial contrast retention
      - Hypotonic esophagus
    - Stage IV
      - Atonic esophagus (marked dilation, hypotonic, retention)
  - Manometry
    - Useful if inconclusive barium swallow
    - Loss of peristaltic activity plus incomplete relaxation of lower esophageal sphincter (LES)
    - Cannot distinguish Chagas Megaesophagus from idiopathic achalasia

- Endoscopy
  - Rule out malignancy (of gastric / lower esophagus) → pseudoachalasia
  - Biopsy
    - Chagas Megaesophagus ↑ risk of esophageal Ca
    - Usually only stones
    - Chronic inflammatory infiltrates, lymphocytic infiltration
    - T. Cruzi parasites rarely seen

- Colon
  - Radiography
    - Flat plate of abdomen
    - ↑ intestinal air
    - Fecaloma
    - Barium enema – decreased haustra, dilated atonic colon
      - Dilation usually in distal colon, including sigmoid, rectum
  - Stages
    - Stage 0
      - No alterations
    - Stage 1
      - Mild dilation and atony, ↓ haustra
    - Stage 2
      - Dolichomegacolon, ↑ colon size (descending colon > 6.5cm, Ascending > 8, Cecum > 12)
  - Manometry
    - Slow colonic transit

- Endoscopy
  - Rule out malignancy
  - Treat sigmoid volvulus
  - No utility in biopsy for confirmation of Colonic Chagas infection

- Treatment
  - Early: Anti-trypanosomal pharmacotherapy ↓ progression of GI disease
  - Megaesophagus
    - Symptomatic treatment only
    - Stage I
      - Isosorbide Dinitrate, Nifedipine
    - Stage II-III
      - Heller myotomy and fundoplication
    - Stage IV
      - Esophageal resection
    - No documented efficacy with botulin toxin
  - Megacolon
    - Early
      - High fiber diet, fluids, osmotic laxatives, enemas
    - Late
      - Manual/endoscopy disimpaction of stool
    - Surgery if
      - Rectosigmoidectomy
      - Persistent disimpactions
      - Patient preference
      - Frequent fecaloma, sigmoid volvulus, toxic megacolon

Tumors of the Esophagus

Abdullah Al Nasser

Classification of Esophageal Tumors

EPITHELIAL TUMORS	NONEPITHELIAL TUMORS
Malignant	Malignant
Squamous cell carcinoma	Lymphoma
Adenocarcinoma	Sarcoma, including
Adenocarcinoma of GEJ	malignant GIST
Verrucous carcinoma	Metastatic carcinoma
Small cell carcinoma	
Malignant melanoma	
Benign	Benign
Squamous papilloma	GIST
Adenoma	Leiomyoma
Inflammatory fibroid polyp	Granular cell tumor
	Fibrovascular tumor
	Hemangioma
	Hamartoma
	Lipoma

Epidemiology – Esophageal Carcinoma

Leading New Cancer Cases and Deaths – 2012 Estimates

Estimated New Cases*		Estimated Deaths	
Male	Female	Male	Female
Prostate 241,740 (29%)	Breast 226,870 (29%)	Lung & bronchus 87,750 (29%)	Lung & bronchus 72,590 (26%)
Lung & bronchus 116,470 (14%)	Lung & bronchus 109,690 (14%)	Prostate 28,170 (9%)	Breast 39,510 (14%)
Colon & rectum 73,420 (9%)	Colon & rectum 70,040 (9%)	Colon & rectum 26,470 (9%)	Colon & rectum 25,220 (9%)
Urinary bladder 55,600 (7%)	Uterine corpus 47,130 (6%)	Pancreas 18,850 (6%)	Pancreas 18,540 (7%)
Melanoma of the skin 44,250 (5%)	Thyroid 43,210 (5%)	Liver & intrahepatic bile duct 13,980 (5%)	Ovary 15,500 (6%)
Kidney & renal pelvis 40,250 (5%)	Melanoma of the skin 32,000 (4%)	Leukemia 13,500 (4%)	Leukemia 10,040 (4%)
Non-Hodgkin lymphoma 38,160 (4%)	Non-Hodgkin lymphoma 31,970 (4%)	Esophagus 12,040 (4%)	Non-Hodgkin lymphoma 8,620 (3%)
Oral cavity & pharynx 28,540 (3%)	Kidney & renal pelvis 24,520 (3%)	Urinary bladder 10,510 (3%)	Uterine corpus 8,010 (3%)
Leukemia 26,830 (3%)	Ovary 22,280 (3%)	Non-Hodgkin lymphoma 10.320 (3%)	Liver & intrahepatic bile duct 6,570 (2%)
Pancreas 22,090 (3%)	Pancreas 21,830 (3%)	Kidney & renal pelvis 8,650 (3%)	Brain & other nervous system 5,980 (2%)
All sites 848,170 (100%)	All sites 790,740 (100%)	All sites 301,820 (100%)	All sites 275,370 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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- In the US, 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, and Southern Africa are 10-100 times greater than in the US. 90% are SCC ("*Asian esophageal cancer belt*")
  - US/Canada considered low risk
- 1960s: >90% of esophageal CA was SCC
- In Western countries, adenocarcinoma now of higher incidence

Risk Factors

- **Squamous Cell Carcinoma**
  - Most important etiologic risk factors estimated by a study determining the population attributable risk of each
    - History of smoking, alcohol consumption, diet low in fruits and veg→ accounted for 90% of esophageal SCC in US
  - Other dietary factors:
    - N-nitroso compounds, chewing of areca/betel nuts, high temperature drink/food, red meat consumption, low selenium and zinc
  - Underlying esophageal disease
    - Achalasia
    - Caustic strictures
  - Atrophic gastritis

- Tylosis
  - ASGE suggests screening begin at 30 yr
- Other SCC of aerodigestive tract
- Bisphosphonates
  - Uncertain, but FDA recommends against using in patients with Barrett
- Family history

- **Adenocarcinoma**
  - Most important risk factors:
    - Smoking, BMI higher than lowest quartile, GERD, diet low in fruits and veg→ accounts for 80% of adenocarcinoma in US
  - Helicobacter:
    - Absence of HP may be a RF for distal esophageal adenoCA
    - HP may be a RF for gastric cardia adenoCA, which can be difficult to distinguish from distal esophageal CA
  - Family history

Esophageal Adenocarcinoma and GERD

- >50% of cases of adenocarcinoma have no GERD Sx
- Reflux Sx significantly associated with adenocarcinoma of esophagus (OR 7.7), gastric cardia (OR 2.0)
  - Risk greatest with long-standing Sx (>20y)
  - Weekly Sx increase odds 5-fold
  - Daily Sx increase odds 7-fold

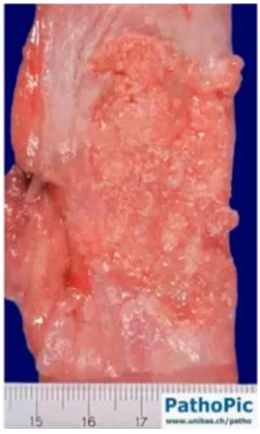
- Barrett increases risk of esophageal cancer at least 30x
  - Absolute risk still low (~0.12% per year in one large study)
- Conditions which predispose to GERD may be RFs

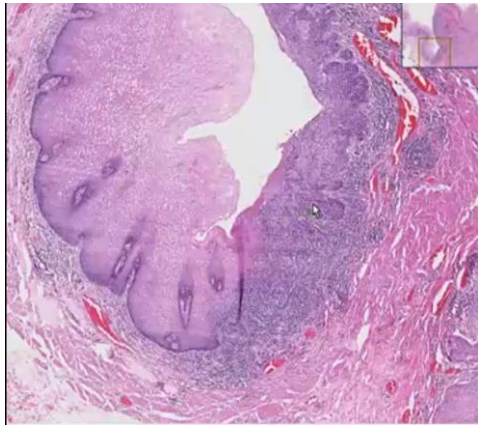
Differences between esophageal SCC and adenocarcinoma

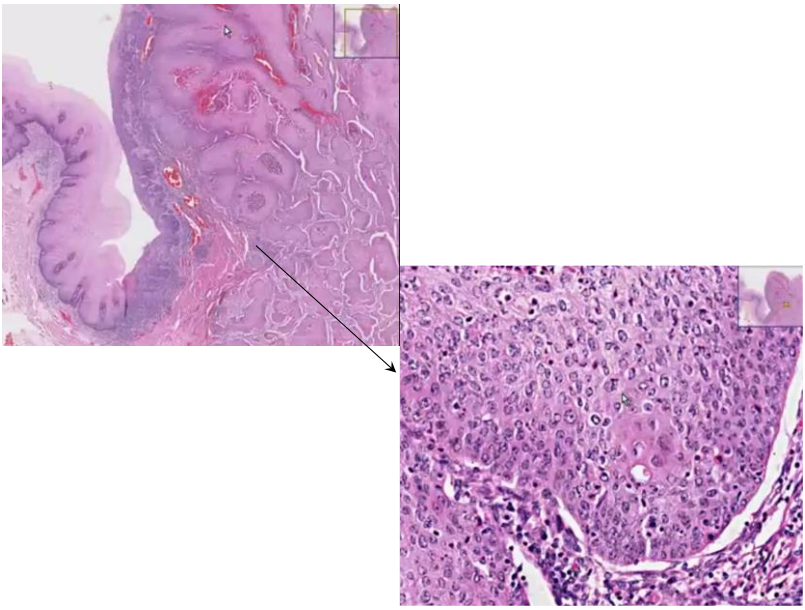
- Demography
  - Gender and ethnicity
    - Adenocarcinoma more prevalent in Caucasian males (6:1 M:F)
    - Esophageal SCC incidence highest in blacks, Asians; sex ratio comparable for all ethnicities
  - Alcohol is likely NOT a RF for adenocarcinoma, and risk may be decreased significantly by wine consumption (not liquor or beer)
  - Obesity associated with adenocarcinoma, not SCC
- Clinical Features
  - Adenocarcinoma much more common in distal esophagus
  - Dysphagia
    - Usually occurs with luminal diameter of <13mm
  - Chronic GI blood loss common, overt GIB uncommon
  - Tracheobronchial fistulae uncommon, late presentation

➢ Pathology

- **SCC**
  - Esophageal SCC 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, include nuclear:cytoplasm ratio, nuclear hyperchromasia, nuclear polymorphism, mitotic figures

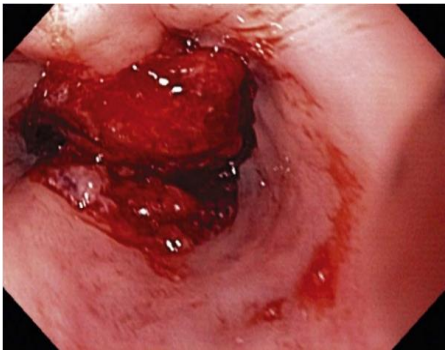


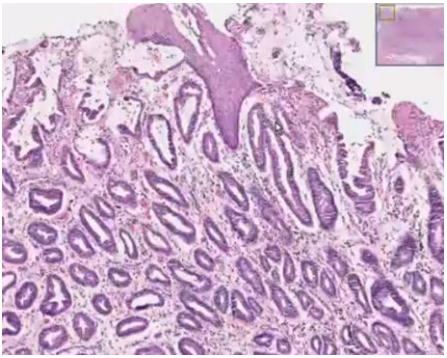


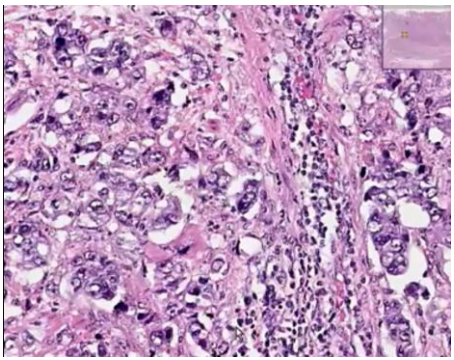


- **Adenocarcinoma**
  - Arises from ectopic gastric-type epithelium which is glandular
    - Almost all secondary to Barrett's (distal third of esophagus)
    - Extremely rarely from foci of gastric heterotopia in cervical esophagus (inlet patch)
  - Dysplasia described as low vs. high grade, similar changes as in SCC
  - "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







- Staging Esophageal Cancer

Tis	Carcinoma in situ/ high grade dysplasia
T1	Invades lamina propria, muscularis mucosae, or submucosa
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

  - 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%
  - Clinical evaluation, bloodwork – evaluate liver, pulmonary, renal function

Anatomic Stage / Prognostic Groups

*Squamous Cell Carcinoma**

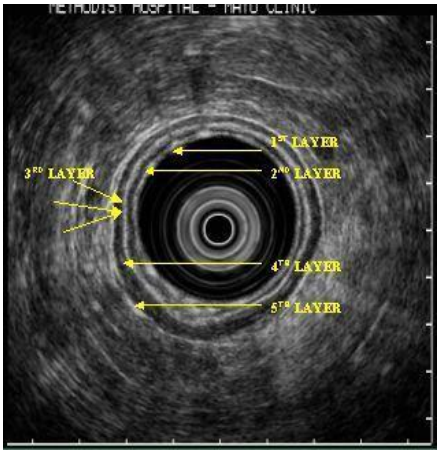
Stage	T	N	M	Grade	Tumor Location**
Stage 0	Tis (HGD)	N0	M0	1, X	Any
Stage IA	T1	N0	M0	1, X	Any
Stage IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
Stage IIA	T2–3	N0	M0	1, X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
Stage IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
Stage IIIA	T1–2	N2	M0	Any	Any
	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

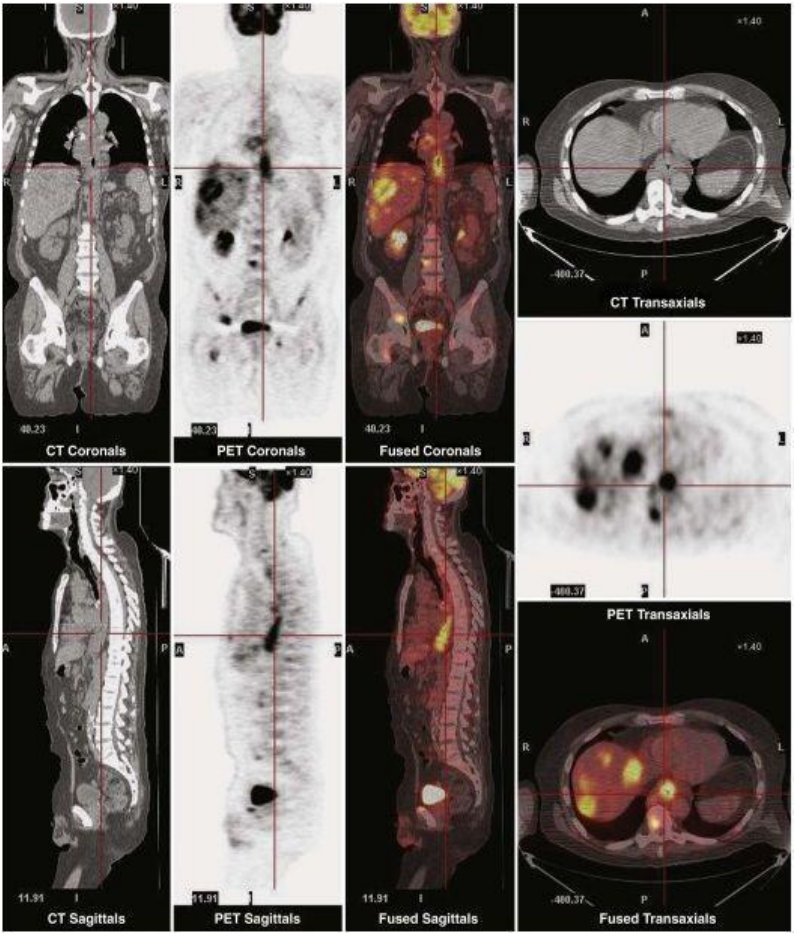
- Diagnosis
  - CT chest/abdo/pelvis
    - Detects metastases in lung, liver, periaortic lymph nodes
    - Poor accuracy for detecting T stage
    - Insensitive for detection of celiac lymph nodes
    - (MRI offers no significant advantage over CT)
  - EUS
    - Best modality for T staging
    - High resolution images of periesophageal tissues (celiac trunk, left lobe of liver, left adrenal gland, thoracic and abdominal aorta, others)
    - Permits FNA of LNs



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

PET and integrated PET/CT scanning

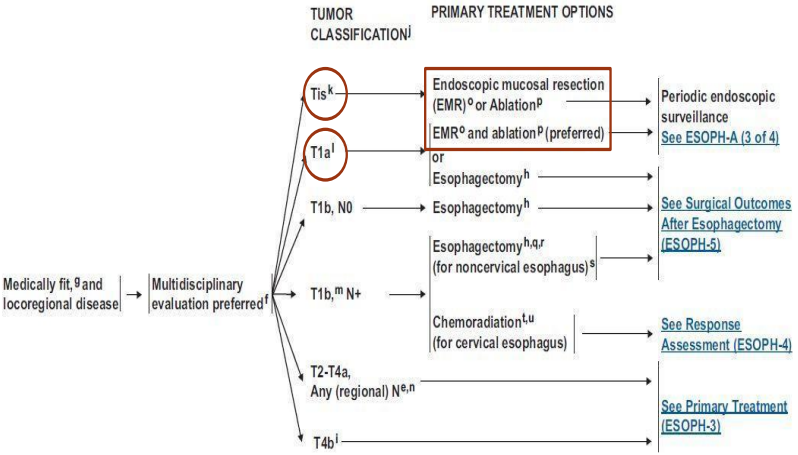


- Upper endoscopy
  - Large forceps, 6-8 biopsies
- Laparoscopy / thoracoscopy?
  - Controversial
  - Sometimes performed to detect occult intraperitoneal mets to limit aggressive treatment in pts with advanced disease (EUS and PET are insensitive for this)
  - Perhaps more accurate for regional lymph nodes than EUS or CT alone, no data exists comparing against EUS + CT or EUS + PET
- Bronchoscopy
  - Can be useful for biopsy and brush cytology in locally advanced nonmetastic tumors at or above level of carina

Staging esophageal cancer – 2012 NCCN Guidelines
**all recommendations are category 2A

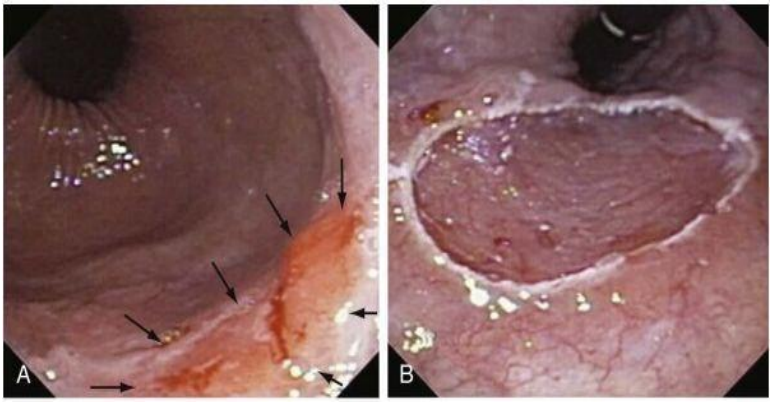
- History and physical, CBC and chemistry profile
- Upper GI endoscopy and biopsy
- CT chest/abdo with oral and IV contrast
- CT pelvis as clinically indicated
- PET evaluation preferred if no evidence of M1 disease (and PET/CT preferred over PET)
- EUS if no evidence of M1 disease, with FNA if indicated
- Bronchoscopy, if tumor at or above carina, no M1 disease
- Laparoscopy (optional) if no evidence of M1 disease, tumor is at EGJ
- [HER2-neu testing if metastatic adenoCA suspected; assign Siewert category; smoking cessation, counseling, pharmacotherapy]

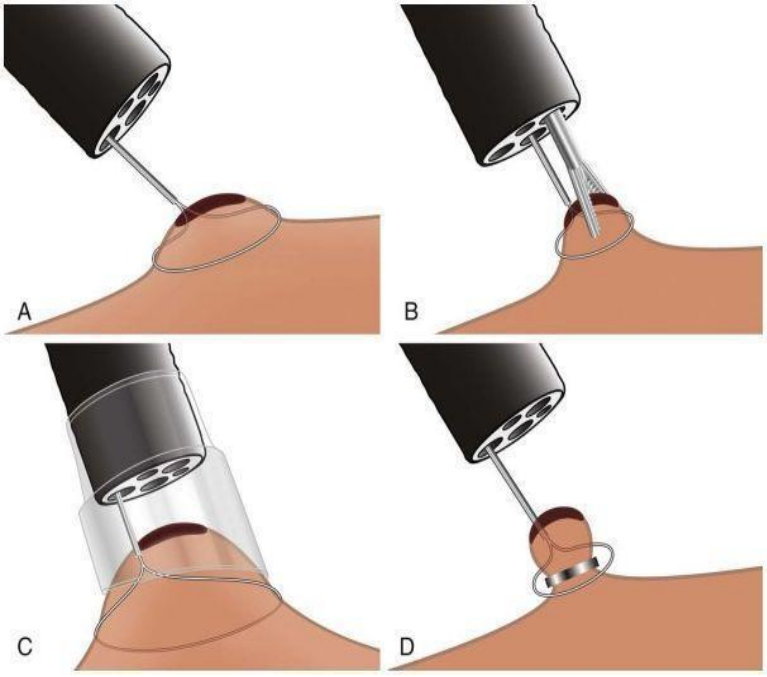
Esophageal cancer – Treatment



NCCN 2012 Guidelines

Methods of endoscopic mucosal resection (EMR)

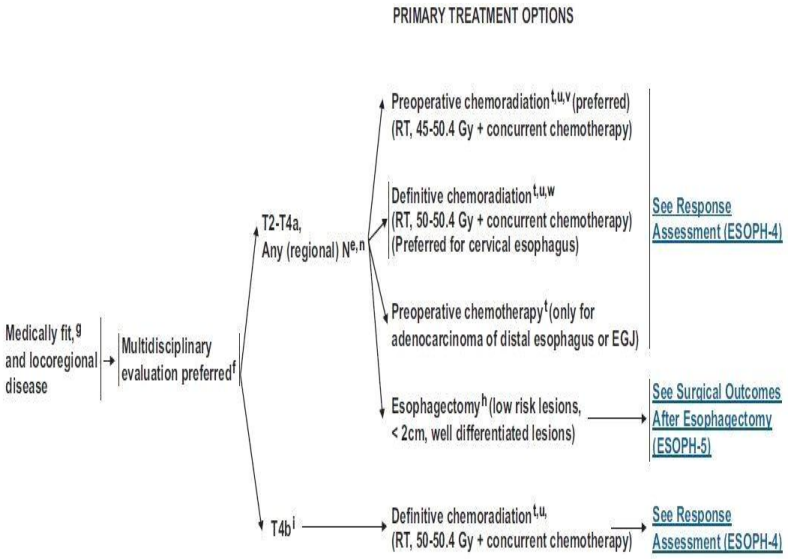




Endoscopic ablative therapies

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

For medically fit, locoregional disease T2 or greater:



NCCN 2012 Guidelines

Screening and Surveillance

- Screening for esophageal SCC cannot be recommended in North America given the low incidence
- Screening for Barrett 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 Barrett:
  - Inability to predict who will have Barrett's
  - Lack of evidence based criteria
  - Invasiveness and expense of endoscopy
  - Large subgroup of pts with Barrett's lacking reflux symptoms (44% in one Swedish study)

- Surveillance of Barrett esophagus

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

Abbreviations: EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal rection

ACG 2008 Guideline

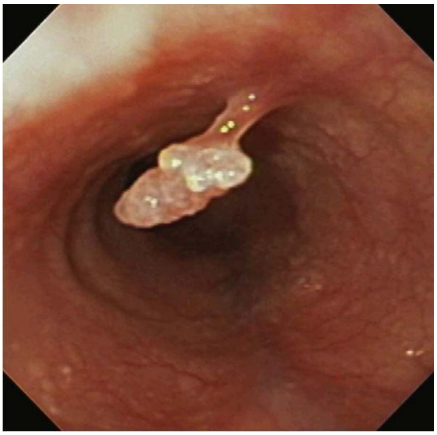
- Post-treatment surveillance
    - Endoscopy ≥ 5-6 weeks post pre-operative therapy, with biopsy and brushings
        - Preop chemo-rad reduces accuracy of EUS staging, of biopsies to diagnose residual disease
        - PET/CT may be emerging as preferred for restaging
    - Pts who have had EMR for 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

Other Malignant Epithelial Tumors

- Small cell carcinoma
    - 1-4% of all esophageal neoplasms
    - Esophagus is most common site of extrapulmonary small cell
    - Early mets 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 mets common (LNs, liver, lung) – poor prognosis

Benign Epithelial Tumors

- Adenoma
  - True adenomatous polyps arise in areas of Barrett, very rare
  - Considered dysplastic with malignant potential → standard snare or mucosectomy techniques usually curative
- Inflammatory fibroid polyp
  - Often related to chronic GERD
  - Usually in distal esophagus at GEJ
  - Endoscopic resection usually indicated to establish diagnosis, also curative



Squamous papilloma

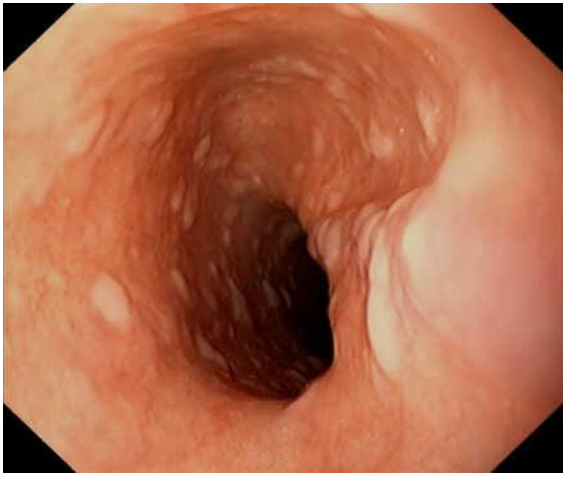
- Usually small, pink/white, sessile or polypoid benign tumors
- Histologically composed of finger-like projections of lamina propria covered by hyperplastic squamous epithelium
- GERD and HPV may be associated

Non-epithelial Tumors

- **Benign non-epithelial tumors**
    - Gastrointestinal stromal tumor (GIST)
        - Rare in esophagus, account for 1% of all GISTs
        - Arise from muscularis propria layer on EUS, from interstitial cells of Cajal
        - Usually found in distal third of esophagus
        - Most GISTs express CD117 antigen (in comparison to leiomyomas and other spindle-cell tumors of GI tract)
        - Risk of malignant transformation variable
            - Very low risk of malignacy: Size <2cm, mitotic rate < five per 50 high powered fields
    - Granular cell tumor
        - From cells of neural origin?
        - Those larger than 4cm or growing should be considered potentially malignant
    - 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
        - Esophgeal lipomas are the rarest of GI lipomas
        - Usually arise from submucosa
        - Pillow sign
        - Endoscopic or surgical resection if symptomatic

- **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 and breast
        - EUS-guided FNA useful to confirm diagnosis

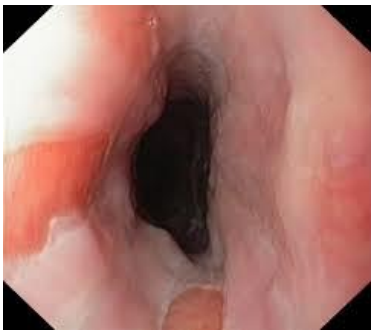
Interesting Common Lesions

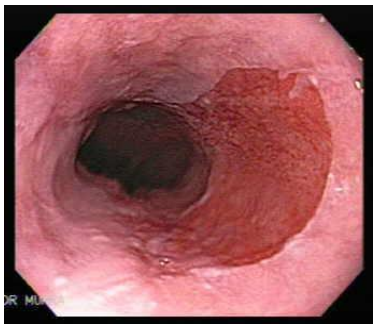


Glycogen acanthosis

- Found in 3.5 to 15 % of all upper endoscopies and in up to 30 percent of patients getting double contrast esophageal imaging
- Age 40's- 50's, for unclear reasons, most are men
- It typically appears as multiple, uniformly sized round elevations in otherwise normal-appearing mucosa, usually in the midportion of the esophagus
  - They are typically 2 to 10 mm in diameter, but lesions up to 15 mm have been described
  - The lesions are believed to grow more numerous and larger with age but do not cause symptoms
- The pathogenesis is unclear
  - They have no relation to glucose metabolism, diabetes, or the presence of acanthosis nigricans.
- Has been described in association with Cowden disease,
  - A rare autosomal dominant disease manifested by multiple hamartomas frequently involving the gastrointestinal tract
- There is also some evidence to suggest an association with celiac disease, especially in children
- Diagnosis can be established by mucosal biopsies with standard cold forceps, which show multifocal plaques of hyperplastic squamous epithelium with abundant intracellular glycogen
  - However, biopsies are rarely needed since the visual findings on endoscopy are highly predictive when the lesions have been confirmed histologically

- Further confirmation can be achieved by application of Lugol solution, which turns the glycogen-containing plaques dark brown, thereby distinguishing glycogenic acanthosis from leukoplakia, moniliasis, and bullous pemphigoid, all of which can have a similar endoscopic appearance.





Inlet patch — An esophageal inlet patch (heterotopic gastric mucosa of the upper esophagus [HGMUE]

- Discreet area resembling gastric mucosa that is typically found in the proximal esophagus.
  - They are most commonly found in the proximal 3 cm of the esophagus, usually just distal to the upper esophageal sphincter,
- The prevalence with endoscopic studies have reported it to be present in 0.4 to 11 percent
- The most common age of detection is in the mid fifties
- The pathogenesis of the esophageal inlet patch is not known precisely

- A wide range of clinical sequelae have been attributed to inlet patches, including:
  - Perforation and a tracheoesophageal fistula
    - The presumed mechanism is related to acid production by the patch.
  - Dysphagia, commonly from strictures, rings, and webs associated with the patch .
  - Helicobacter pylori can be localized in the patch in 19 to 73 percent of patients who are colonized in the stomach, raising the possibility that it acts as a reservoir for oral-oral
  - Up to 20 % have concomitant Barrett's in the distal esophagus
  - Reports of esophageal adenocarcinoma in the upper esophagus
  - Globus sensation, chronic cough, and laryngopharyngeal reflux has been suggested
- Diagnosis
  - Usually be made based upon visual inspection alone. Biopsies can be obtained if there is doubt about the diagnosis.
- Management
  - Treatment is generally required only if complications develop
  - Specific risk factors for malignancy are unclear
    - As a result, consensus has not been achieved on surveillance

STOMACH

A Bariatric Brouhaha: Little Ado About Something

Dan Segal

- Rationale
  - More than a quarter of Canadians are obese (BMI 30+)
  - Since 1981 obesity rates have doubled for both males and females
  - One of the fastest growing groups are the morbidly obese (BMI 40+)
  - Health risks with obesity:
    - Type 2 Diabetes (80% of all cases)
    - Coronary artery disease (27% increased RR per BMI category)
    - Stroke (HR 1.20)
    - Malignancy (breast, colon, uterine)
    - Liver disease
    - Obstructive sleep apnea (60% + of obese)
    - Depression
    - GERD (intragastric pressure?)

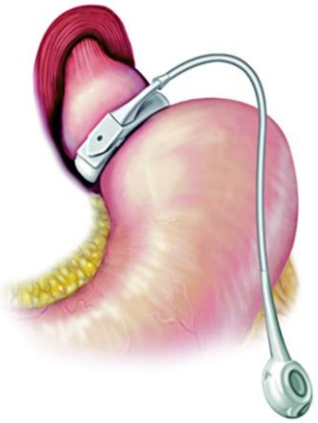
- Indications
  - NIH consensus guidelines, 1991
    - Candidates:
      - BMI 40+
      - BMI 35 – 39.9 with severe weight related comorbidities
      - Previous conservative therapy
      - Multidisciplinary assessment
  - American society of bariatric surgery, 2004
    - Expanded criteria
    - BMI 30 – 34.9 with comorbid conditions that respond well to surgery
    - No need for formal non-operative obesity therapy
    - Still need record of attempted weight loss

- Procedures
  - Restrictive
    - Adjustable gastric banding (AGB)*
    - Vertical band gastroplasty
    - Sleeve gastrectomy (SG)*
  - Combined restrictive and malabsorptive
    - Roux-en-Y gastric bypass (RYGB)*
    - Biliopancreatic diversion with duodenal switch*
  - Malabsorptive
    - Jejunoileal bypass
  - Jaw wiring
    - Failed because subjects drank high calorie liquids

* procedures sanctioned by American Society for Metabolic & Bariatric surgery

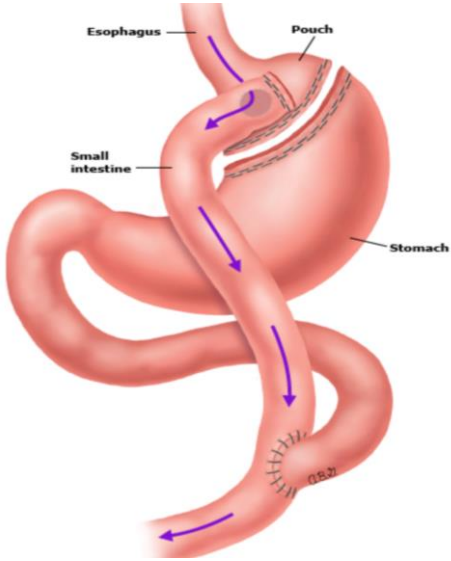
Adjustable Gastric Banding (AGB)

- Silicon band
- 30 mL stomach
- SC injection port
- Band size customizable
- Performed less due to ‘recidivism’



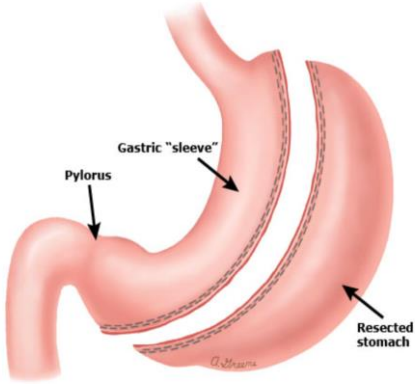
Roux-en-Y Gastric Bypass (RYGB)

- 30 mL stomach
- Gastrojejenostomy
- Bypass stomach, duodenum, proximal jejenum
- Weight loss via:
  - Restriction
  - Dumping syndrome conditioning
  - Malabsorption
  - Ghrelin decrease



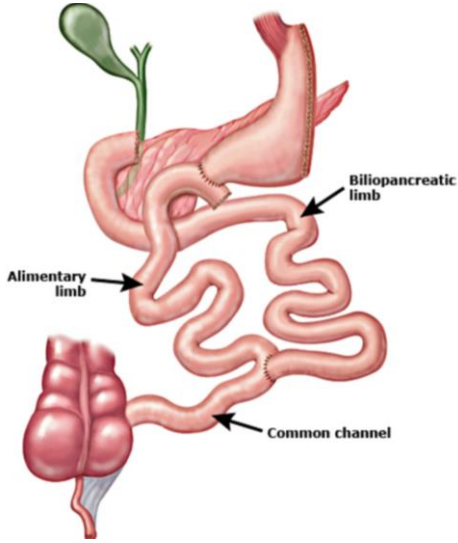
Sleeve Gastrectomy (SG)

- Sleeve size 60 – 120 mL
- Gastric remnant removed
- ↓ ghrelin levels (hunger hormone)
  - ↓ cells to secrete
  - ↑ stretch



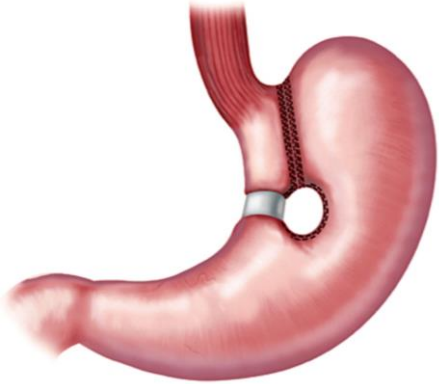
Biliopancreatic Diversion with Duodenal Switch

- Partial gastrectomy
- Pylorus preserved
- Roux limb with short common channel (50 cm)
- In original procedure without switch pylorus not preserved
  - Dumping syndrome



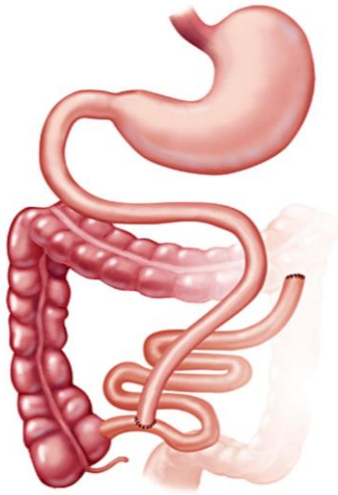
Vertical Band Gastroplasty (VBG)

- Two vertical staple lines
- Outlet stoma
- Polypropylene band
- No longer performed due to complication rates and lack of efficacy long-term



Jejenoileal Bypass

- Duodenum sutured to ileum
- 35 cm of normal absorptive small intestine retained
- Bacterial overgrowth in long blind loop
- Not recommended due to complication rate



- Benefits
  - Weight loss
    - 100 – 120 lbs plateauing at twelve months
    - Less with less invasive procedures like gastric band
  - Diabetes
    - STAMPEDE trial
    - 150 obese, uncontrolled DM2 pts (BMI 27- 43) randomized to surgery (RYGB or SG) and medical therapy or just medical rx
    - 31% surgery vs. 5 % medical therapy had HBA1C < 6% at three years
    - Over 50% of RYGB patients did not require DM meds anymore
    - 24 kg weight loss vs. 4 kg weight loss
    - Outcomes in surgical group better at one year
    - Rationale for surgery

- Hypertension
  - Elevated cholesterol
  - One year post RYGB: LDL -31%, TG -63%, HDL +39%
- Obstructive sleep apnea (OSA)
- GERD +/-
  - May depend on type of surgery
  - RYGB may reduce prevalence (33% post vs. 64% pre)
  - SG may induce GERD
- NAFLD
  - RYGB (12 studies) may improve steatosis, inflammation, and fibrosis
  - VBG (3 studies) may improve steatosis
- Meta-analysis of 160,000+ patients in JAMA
  - 30 day mortality rate 0.31%
  - ~15% ↓ BMI at five years
  - Surgical revision rate 7%
  - RYGB
    - More weight loss, more complications
  - Sleeve gastrectomy (SG)
    - Similar to RYGB
  - AGB
    - Less weight loss, less complications

➢ Complications

- RYGB
  - Gastric remnant distension due to obstruction
    - Rare, presents with LUQ pain
    - May rupture
    - Emergent operative decompression

- Cholelithiasis
  - Upwards of 38% become symptomatic
  - Due to rapid weight loss changing bile composition
- Abdominal wall hernias
- Dumping syndrome
  - Early: pain and vasomotor symptoms ("dumping")
  - Late: hypogylcemi (insulin response with long $T_{1/2}$)
  - Treat: smaller meals, avoid rapidly absorbable sugars
- Complications

- GB
  - Stomal obstruction (early)
  - Port infection
  - Band erosion through stomach wall
  - Band slippage
  - Esophageal dilation proximal to band
- SG
  - Gastric Leak (5.3%)
  - Reflux
- Nutritional deficiencies
  - More common with malabsorptive procedures
  - Can occur with restrictive surgeries (If not adherent)
  - Protein (60g), calcium, B12, vit D, multivitamin for all
    - Screening BW & DEXA should occur at least yearly
  - Thiamine (B1)
    - 0-30%; specifically those with Vx & poor intake
    - Consequence: Wernicke's – Korsakoff's

- Vitamin B12
  - 0-18%; due to reduced meat, less IF, less acid
  - Consequence: Megaloblastic anemia, SACD
- Folate
- Vitamin D
  - Consequence: osteoporosis and osteomalacia
- Iron, Vitamin A (night vision), Zinc, Copper

- Marginal ulcers
  - Prospective series of 347 patients post- RYGP
    - 4% developed symptomatic marginal ulcers
    - Presented with either UGIB or abdominal pain
    - Mean time to presentation 6.3 months
    - High dose PPI therapy resulted in 100% resolution
    - Suggest post-operative PPI
  - Cause:
    - Acid irritating jejenum
    - Poor tissue perfusion
    - NSAID / H. Pylori infection

Stomal Stenosis

- Demography
  - Occurs in 3 - 27% of subjects
  - Presents with gastric outlet obstruction, nutritional issues

- Pathogenesis
  - Ischemia due to stapler
  - Tension at anastomosis
  - Edema
  - Foreign body reaction

- Associations
  - ↑ gastric pouch
  - ↑ acid secreting cells
  - Chronic stomal ulceration
  - Refractory stricture formation
- Treatment
  - Dilation is mainstay of therapy
  - Surgical revision if refractory
  - Albumin prior to OR should be 30+
  - Technically challenging (mean time 4+ hours)
  - Attempt to downsize pouch to 10 mL

Outcome of Endoscopic Balloon Dilation of Strictures After Laparoscopic Gastric Bypass (Ukleja A, et al. Surg Endosc 2008;22(8):1746-50)

- Retrospective study of 1012 patients who underwent laparoscopic RYGB
  - Evaluated by EGD or UGI series if symptoms
  - Sixty-one (6%) had GJ stenosis (not allowing scope to pass)
  - Mean time to symptoms 2 months (1- 6 mos)
  - 13 % marginal ulcers ulcers
  - TTS balloon dilation from 6 – 18 mm
    - Single dilation in 28% of patients
    - Two dilations in 33%
    - Three dilations in 26%
    - Four dilations in 11.5%
  - All received PPI therapy
  - All patients responded, not requiring surgery
  - 2.2% of procedures resulted in perforation

Refractory Strictures After Roux-en-Y Gastric Bypass: Operative Management (Cusati C, et al. Surg Obes Relat Dis 2011;7(2):165-9.)

- Retrospective study of all patients who underwent revision for GJ strictures post RYGB, Mayo clinic
  - Twenty-four patients identified
  - Five had early postoperative anastamotic leak
  - Seven had gastrogastric fistula
  - Eleven had marginal ulcers
  - 83% underwent previous endoscopic therapy, majority balloon
  - Mean interval to revision 4 years 6 months

Successful Mangement of Gastrojejunal Strictures After Gastric Bypass: Is Timing Important? (Yimcharoen P, et al. Surg Obes Relat Dis 2012;8(2):151-7)

- Retrospective study 591 patients who underwent RYGB, cleveland clinic
  - 72 pts. With strictures; all underwent balloon dilation
  - 63.9% within 90 days of RYGB
    - 98% of early strictures resolved with balloon dilation
  - 61% of late strictures resolved with balloon dilation
    - 38.5% required surgical revision
  - Higher rate of ulceration with late stenosis
- Is timing important?
- Is there different stricture pathophysiology?

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Gastric Antral Vascular Ectasia (GAVE)

Yaqoub AlAwadh

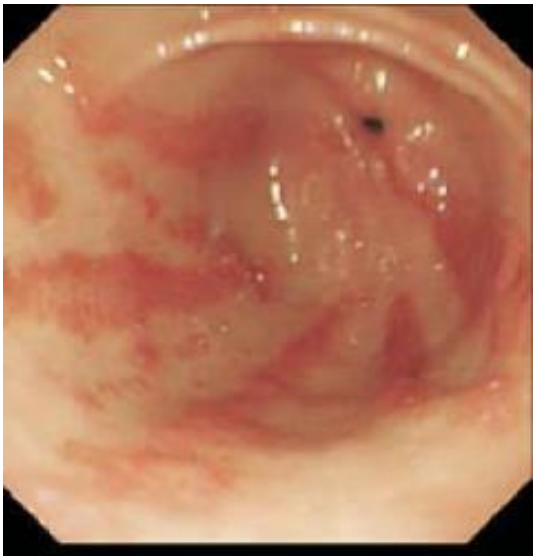
- Background
  - Gastric antral vascular ectasia (GAVE or watermelon stomach) is a rare cause of UGI bleeding (0.3-4%)
  - It was first described in 1953 by Rider et al. as a cause of UGIB
  - The characteristic watermelon appearance was coined by Jabbari et al. in 1984
  - Visible columns of vessels radiating from the pylorus proximally like the ‘stripes of a watermelon’
  - Characterized by mucosal and submucosal vascular ectasia

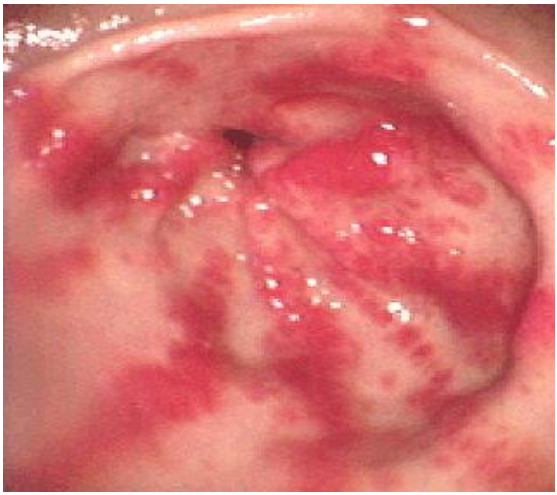
- Clinical
  - Bleeding is most often chronic, with patients presenting with hemoccult positive stools and iron deficiency anemia.
  - Associations

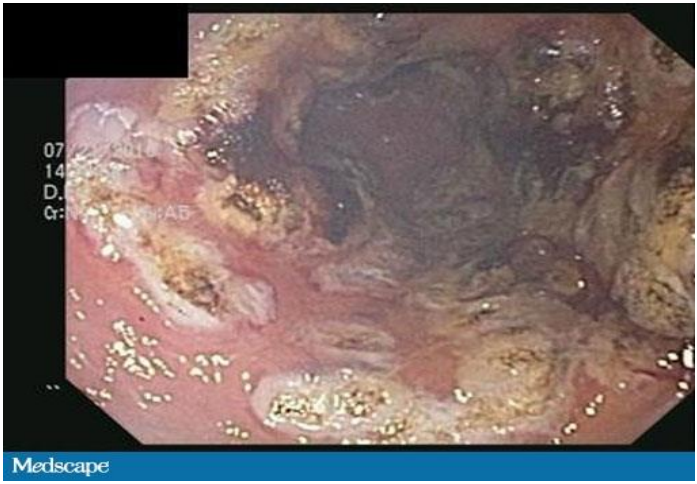
Associated disease	Prevalence (%)
Autoimmune diseases	60
Raynaud phenomenon	
Sclerodactyly	
Sjogren disease	
Systemic sclerosis	
Primary biliary cirrhosis	
Systemic lupus erythematous	
Liver cirrhosis and/or PHT	30
Other	10
Chronic renal failure	
Bone marrow transplantation	
Cardiac disease	

Fuccio L, et al.WJG Endosc. 2013;5(1):6-13.

- Endoscopy







- Treatment
  - Medical Therapy
    - Many medications tried, non with satisfactory results
  - Surgical therapy
    - Antrectomy is curative
    - High morbidity and mortality (up to 10%)
    - Usually reserved for refractory cases
  - Endoscopic therapy
    - First line treatment
    - Options include
      - Argon Plasma Coagulation (APC),
      - Bipolar electrocautery
      - Heater probe,
      - Laser therapy,
      - Band ligation

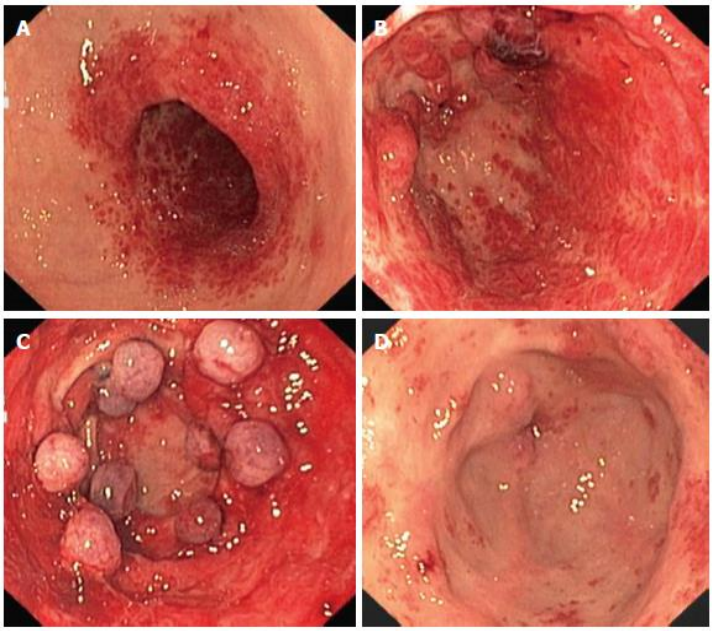
- Laser therapy
  - Neodymium-yttrium-aluminum garnet (Nd: YAG) laser coagulation has been successfully used to control GAVE-related bleeding
  - Reducing or abolishing the need of blood transfusions in about 50% to 80% of cases, with a mean of 3 treatment sessions (range 1-10)
  - The most serious complication is gastric perforation
  - Another complication is pyloric stenosis, that can induce either delayed gastric emptying or true obstruction (8%)

- Argon Plasma Coagulation (APC)
  - A non-contact technique with a controllable depth of coagulation (1-2 mm)
  - Easier to use, more manageable, cheaper and safer
  - Mean of 2.5 sessions are needed to achieve complete eradication
  - APC has become the most common endoscopic therapy for the treatment of GAVE
  - The complications are rare and mostly mild.
    - Intestinal gas distension related to argon flow,
    - Asymptomatic antral stenosis
    - Upper GI hemorrhage
    - No case of perforation during APC treatment of GAVE has been described.

- Cryotherapy
  - A small, prospective pilot study, based on 12 patients, investigated the efficacy of cryotherapy for the treatment of GAVE-related bleeding
  - Achieved a complete response to treatment (i.e., no need for blood transfusion) in 50% of cases
  - 6 patients had a partial response
  - Mean no of PRBC was reduced
  - Increased mean Hb level, from 9.9 to 11.3 g/dL, was noted.
  - Endoscopic cryotherapy is a safe and effective treatment for GAVE
  - The need for specialized equipment and for specific training, represents Cryotherapy's main limitations

- Radiofrequency ablation
  - 6 patients with transfusion-dependent GAVE-related bleeding
  - After 1 to 3 treatments, all but one no longer needed transfusions during the 6 month follow up
  - No adverse event were reported

- Endoscopic Band Ligation (EBL)
  - Well established for the treatment of EV
  - Causes necrosis of the mucosa and sub-mucosa
  - A number of case reports and case series have demonstrated efficacy and safety of EBL for GAVE
  - Many included patients failed APC in the past



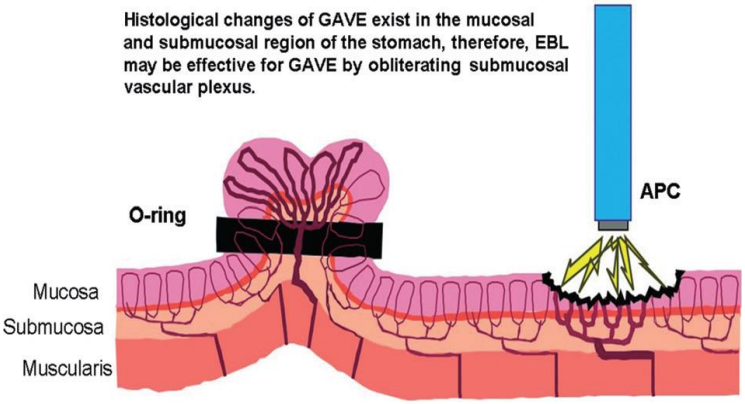
Printed with permission: Keohane J, et al. Digestive Endoscopy 2013; 25: 392–396.

EBL Superior to Endoscopic Thermal Therapy (ETT)

- EBL group required
  - Fewer sessions to control bleeding
  - Higher rates of hemostasis
  - Reduced number of hospitalizations
  - Reduced transfusion requirements.
  - Allowed for a significant increase in hemoglobin values

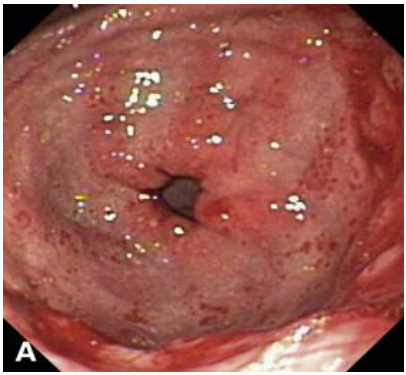
EBL superior to APC

- Rebleeding 8% vs. 68% (p = 0.001)
- EBL maybe more logical treatment than APC given that GAVE involves both mucosa and submucosa

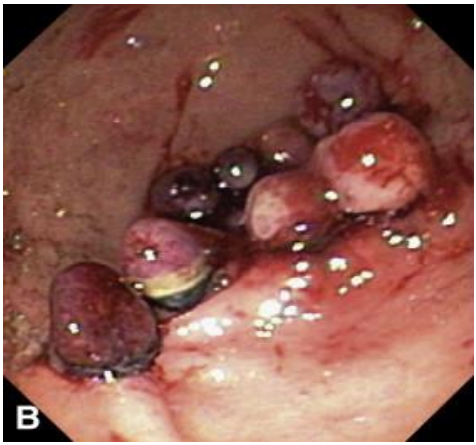


Printed with permission: Sato T, et al. Digestive Endoscopy (2012) 24, 237–242.

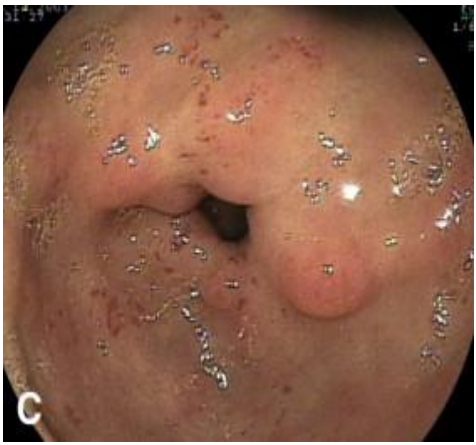
A, Endoscopic image of the gastric antrum with typical linear pattern of vascular ectasia in a patient before treatment with EBL.



B, Endoscopic image of the gastric antrum in the same patient after placement of ligation bands.



C, Endoscopic image of the gastric antrum with minimal residual vascular ectasia after a single treatment with EBL.



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- Summary
  - GAVE is a rare cause of UGIB, but is associated with significant morbidity
  - The treatment of GAVE is mostly endoscopic
  - The optimal endoscopic treatment for GAVE is still uncertain
  - Currently APC is most widely used with good results but with high recurrence rate in the medium and long term
  - Band ligation seems to be an effective therapy and potentially better than APC based on small retrospective studies
  - Prospective studies should be performed to further evaluate this promising treatment modality.

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Gastric Neuroendocrine (Carcinoid) **Tumor**

Azé Wilson

- Differential diagnosis of submucosal lesions of the stomach
  - Benign
    - Leiomyoma
    - Angioma
    - Lipoma
    - Fibroma
    - Pancreatic rest
  - Malignant
    - Leiomyosarcoma
    - Angiosarcoma
    - Liposarcoma
    - Fibrosarcoma
    - GIST
    - Carcinoid

- A historical perspective:
  - 1867 – carcinoid tumor first described by Langhans (*Uber einen drusenpolyp im ileum)*
  - 1888 – Lubarsch credited with discovery
  - 1890 – Carcinoid syndrome described by Ransom
  - 1907 – "*karzinoide"* was coined by Oberndorfer, a German pathologist at the University of Munich
  - 1914 - endocrine-related properties were later described by Gosset and Masson

Wardlaw R1 and Smith JW. Ochsner J. 2008 Winter; 8(4):191-6.

- Definition
  - A slow-growing neuroendocrine tumor with neurosecretory capability
    - Arising from cells of the diffuse neuroendocrine system (enterochromaffin-like cells)
      - Medullary carcinoma of the thyroid
      - Pheochromocytoma
      - Pancreatic neuroendocrine tumors

- WHO redefined “carcinoid” (2004)
  - Neuroendocrine tumor
  - Neuroendocrine cancer

- Demography
  - Overall incidence is difficult to determine – majority asymptomatic
    - Clinical incidence: 1-2/10^5 / yr
    - At autopsy: 8.4/10^5
    - White Americans = African Americans
  - Increasing incidence over 20 yrs
    - True increase vs. improved detection?

- Pathology
  - Sites of NET
    - GI tract 67%
    - Bronchopulmonary (25%)
    - Others 8%
  - Gastric NET
    - <1% of gastric neoplasms
    - ~3% of all carcinoids

- Types
  - Type 1
    - Chronic atrophic gastritis type A (CAG-A) associated
  - Type 2
    - Zollinger-Ellison (ZE) associated
  - Type 3
    - Sporadic tumors

- Give the features which differentiate the 3 types of gastric neuroendocrine tumors (NET).

Features	CAG-A	ZE / MEN1	Sporatic
○ Clinically aggressive	-	-	+
○ ↑ risk of metastases	-	-	+
○ Carcinoid syndrome	+	+	+
○ Histopathology			
– Well-differentiated	+	+	+
– Invasive	-	-	+

Type 1: CAG-A NET

- Demography
  - >50% of patients with CAG-A associated NET have pernicious anemia
  - 1/25 patients with CAG and pernicious anemia develop ECL cell tumors (Rindi et al, World J Surg 1996)
  - Presentation in 6^{th}-7^{th} decade of life
  - F > M
- Pathophysiology
  - Chronic atrophic gastritis (CAG) → serum gastrin – G cell hyperplasia → ↑↑ serum gastrin
  - Because there is CAG, the gastric acid secretion is low (hypochorhydria), despite hypergastrinemia

- Pathology
  - Often diameter < 1cm
  - > 50% multifocal (usually < 5 tumors)
  - Metastasize in < 5% of cases
  - Local post-surgical recurrences reported but no deaths

Kulke MH and Mayer RJ. N Engl J Med. 1999; 340(11):858-68.
Borch K, et al. Ann Surg. 2005; 242(1):64-73.

- Prognosis
  - 5 yr survival rate
    - Localized 73%
    - Regional nodal involvement 65%
    - Distant metastasis 25%

Type 2: Zollinger-Ellison (ZE) **associated NET**

- Represent 5-10% of gastric carcinoids
- Occur almost exclusively in patients with MEN1
- Autosomal dominant
  - Loss of MEN1 gene
- Metastases ~10%

- Treatment
  - Similar to CAG-A associated NET, but tumors
  - Recommend aggressive surgical resection

Type 3: Sporadic Gastric Carcinoid Tumors

- Demography
  - 15-25% of gastric carcinoids
  - M > F
- Pathology
  - Solitary
  - Arise in normal appearing mucosa
  - Diameter > 1 cm
  - Histologically
    - ECL cells
    - May contain other cell types
  - Atypical carcinoid syndrome
- Clinical
  - Asymptomatic
  - Symptomatic:
    - Mass effect
      - Pain
      - Luminal obstruction
    - Constitutional symptoms
      - Malaise
      - Vague abdominal pain
      - Weight loss
    - "Carcinoid syndrome" (10%)
      - Often atypical carcinoid syndrome
    - Usually metastatic at time of presentation
- Treatment
  - Radical gastrectomy

The Carcinoid Syndrome

- Histology
  - First described in 1950
- Symptoms
  - Skin
    - Typical
      - Flushing
      - Pellagra-like skin reactions
    - Atypical presents with a different pattern of flushing:
      - Same head and neck distribution
      - Patchy erythema with central clearing
      - Pruritic
      - Valvular disease and diarrhea unusual
      - Atypical features thought to be due to increased histamine release with gastric carcinoid
  - Lung
    - Bronchospasm
  - Heart
    - Valvular heart
    - Right-sided heart failure (RHF)
  - GI
    - Diarrhea
    - Non-specific abdominal pain
  - Note:
    - Carcinoid syndrome is seen only in the setting of liver metastases

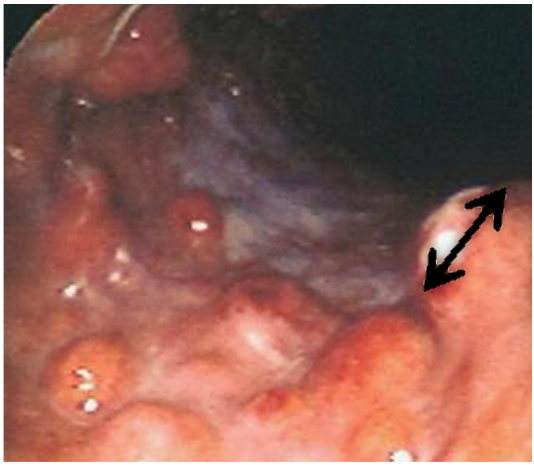
- Pathophysiology
  - Typical Carcinoid Syndrome
    - Tryptophan → 5HTP → Serotonin → Circulation
    - Serotonin ---→ 5-HIAA (5-hydroxy indol acetic acid; urinary excretion)
      MAO + ADH
    - Increased plasma serotonin; increased urine 5-HIAA

- Laboratory

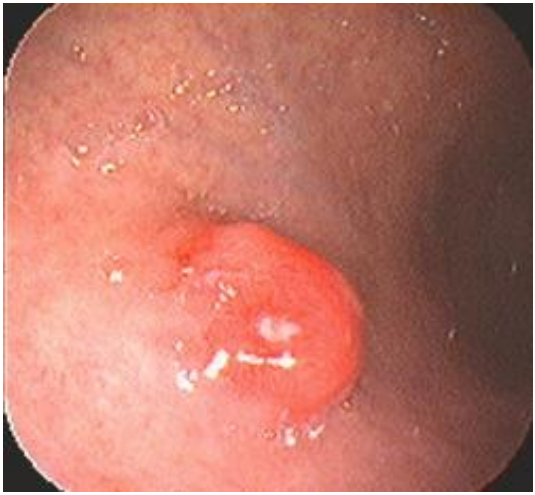
	Carcinoid Syndrome	
	Typical	Atypical
↑ plasma serotonin	+	-
↑ urinary 5-HIAA	+	-
↑ plasma histamine	-	+
↑ serum chromogranin	+	+

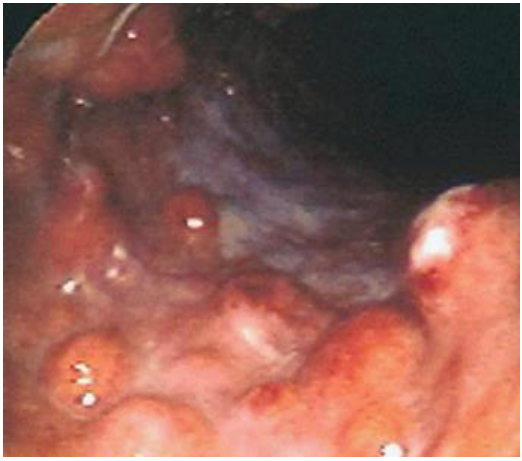
- Diagnostic imaging
  - CT/MRI liver
  - Before contrast
    - Hypovascular
  - After contrast
    - Isodense
  - Scintigraphy (nuclear scanning) with radio-labeled octreotide

- Endoscopy

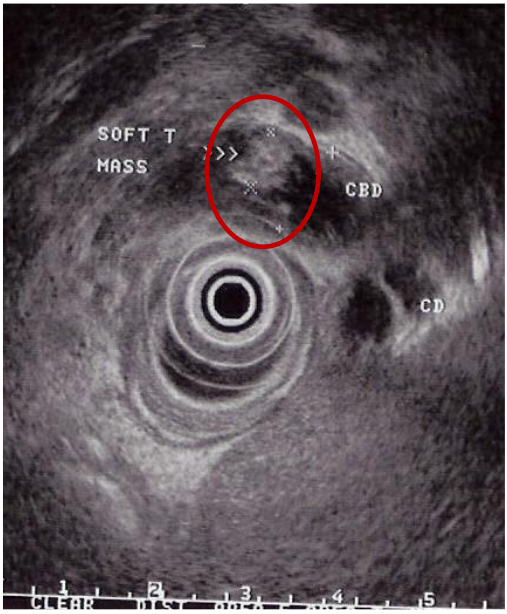


  - Multiple ‘nipple-shaped’ lesions in gastric body
  - Largest 3cm with normal overlying mucosa
  - EGD

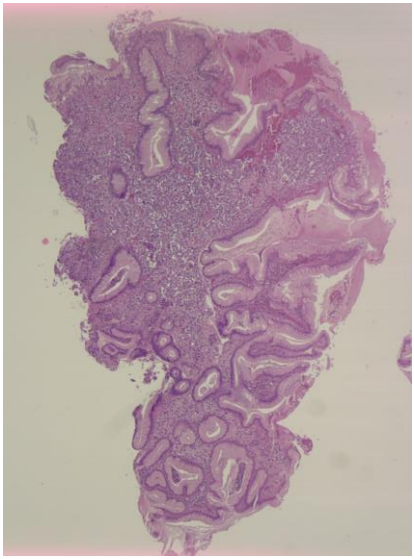


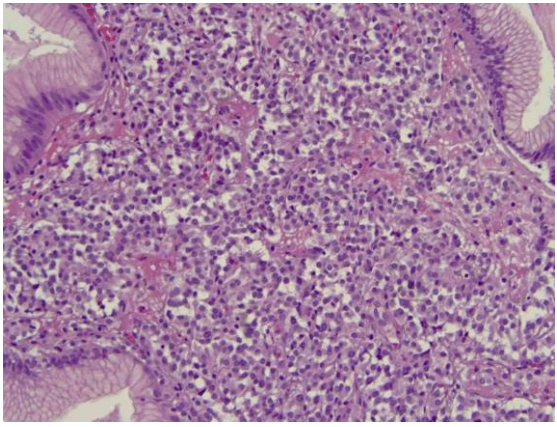


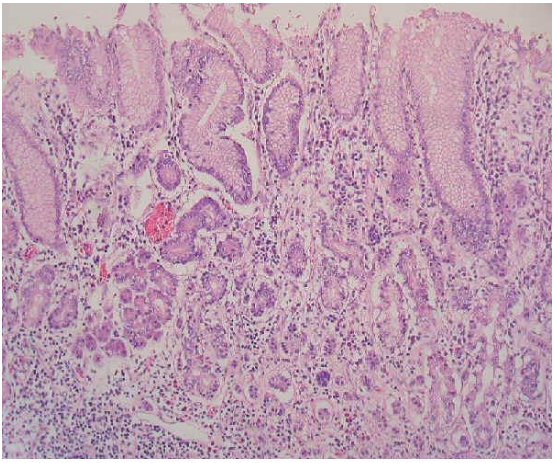
- Endoscopic ultrasound (EUS)



- H&E
  - Monomorphic nests
  - Trabeculae (aka festoons)
  - Central nuclei
  - “Salt & Pepper” chromatin

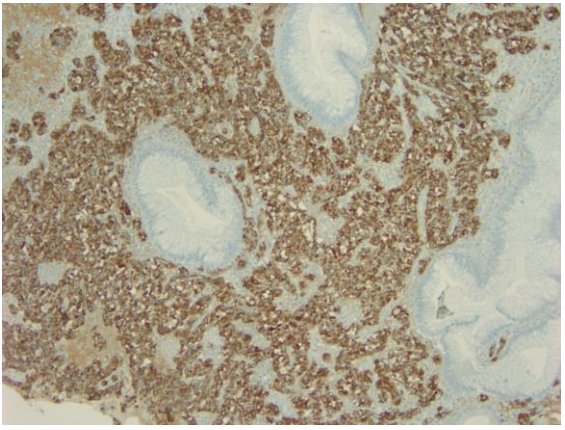




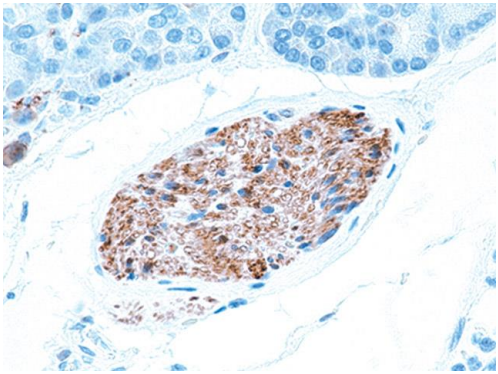


Chronic Atrophic Gastritis Associated NET

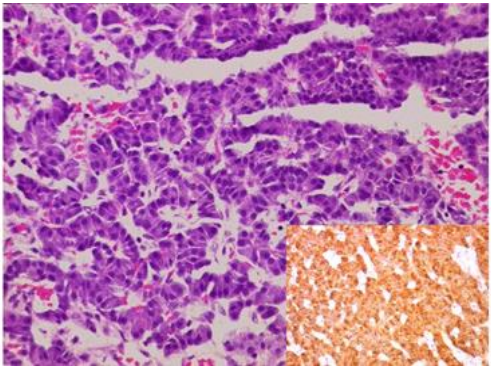
- Immunohistochemistry
  - Gastric tissue



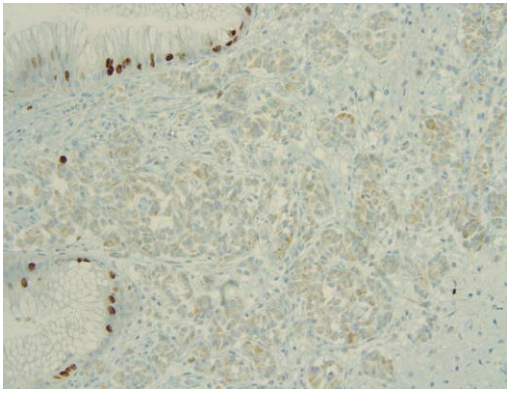
Chromogranin A



NSE



Synaptophysin



Ki-67 Index

- Virtually no positive nuclear reaction for the proliferation marker KI-67
  - This supports its low grade. Non-specific cytoplasmic staining is present
  - Proliferative activity is evident in the foveolar epithelial cells.

- Treatment
  - Small tumors
    - Small tumors
      - Endoscopic mucosal resection plus
      - Endoscopic surveillance
  - Large lesions (> 2 cm), multiple (> 5), recurrent or invasion into muscularis propria
    - Antrectomy
    - Invasion of serosa or beyond
    - Total gastrectomy, plus lymph node dissection
  - Octreotide
    - Controls symptoms of carcinoid syndrome in midgut carcinoids
    - In CAG-A NET
      - ↓ ECL cell numbers
      - ↓ plasma gastrin
    - Malignant midgut carcinoids and endocrine pancreatic tumours (interferon or octreotide or both)
      - Sometimes ↓ size of metastases (Granburg et al. Gut 1998)

- Cytotoxic chemotherapy (metastatic NET)

Selected chemotherapy trials in metastatic carcinoid tumors

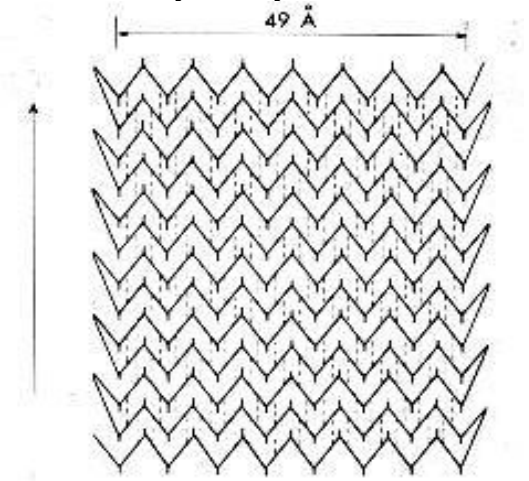
Phase II trials				
Regimen	**Number of patients***	**Tumor response rate, percent**	**Median overall survival, months**	**Reference**
Dacarbazine	56	16	20	Bukowski, R; 1994
Dacarbazine (second-line)	61	8	11.9	Sun, W; 2005
Etoposide	17	12	NR	Kelsen, D; 1987
Paclitaxel•	24Δ	8	18	Ansell, S; 2001
Docetaxel	21	0	24	Kulke, M; 2004
Gemcitabine	18◇	0	11.5	Kulke, M; 2004
Streptozocin + fluorouracil + doxorubicin + cyclophosphamide	56	30	10.8	Bukowski, R; 1987
Streptozocin + fluorouracil + cyclophosphamide	9	22		
Streptozocin + fluorouracil + cisplatin	33	25	31.5§	Turner, N; 2010
Temozolomide + thalidomide	15	7	NR	Kulke, M; 2006
Gemcitabine + oxaliplatin	18 (previously treated¥)	17	23.4	Cassier, P; 2009
Randomized trials				
Regimen	**Number of patients***	**Tumor response rate, percent**	**Median overall survival, months**	**Reference**
Streptozocin + cyclophosphamide **VS.** Streptozocin + fluorouracil	47 42	26* 33*	12.5 11.2	Moertel, C; 1979
Doxorubicin **VS.** Streptozocin + fluorouracil	81 80	21 22	11.1 14.9	Engstrom, P; 1984
Doxorubicin + fluorouracil **VS.** Streptozocin + fluorouracil	88 88	16 16	15.7 24.3 (p=0.03)	Sun, W; 2005

- Outcomes
  - Tumor response 33%
  - Median survival 12-32%

Gastrointestinal Amyloidosis

Keith McIntosh

- Chemistry of Amyloidosis



  - Generic term for extracellular deposition of insoluble, misfolded protein
  - Precursor proteins (LMW) undergo transformation to fibrillar pattern
  - Fibrils align in an antiparallel β-pleated sheet
  - Appear homogenous under microscope
  - When stained with congo red and viewed in polarized light see green positive birefringence

- Types of Amyloidosis
  - Primary (AL)
    - Initially syndrome without preceding disease → primary
    - Fibrils composed of fragments of antibody *light chains*
    - Occult immunocyte secreting abnormality
    - May have other dyscrasia→ MM (6 %), MGUS, Waldenstroms

- Reactive/secondary (AA)
  - Fibrils composed of fragments of serum *amyloid A protein* (acute phase reactant) in chronic disease
    - CTD (RA, Ank Spond, Reactive)
    - GI (IBD, PBC)
    - Infections (TB, osteomyelitis, leprosy)
    - Tumors (RCC, GIST)
- Dialysis related
  - Fibrils composed of retained β2-microglobulin (decreased GFR)
  - β2MG is a light chain that is part of MHC1
  - When cells break down this usually ends up in urine
  - Can occur 15 yrs after dialysis start
- Others types
  - Senile usually over age 80 (~25 %), involves heart and GI tract
  - Most common hereditary is familial amyloidotic polyneuropathy (FAP)
    - Due to abnormal transthyretin (prealbumin) produced by liver

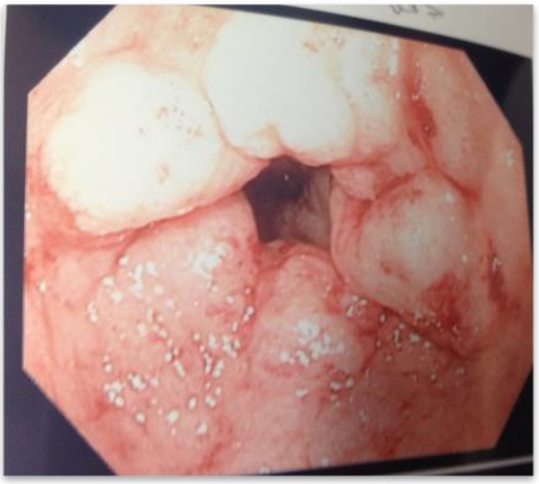
Gastrointestinal Amyloidosis

- Types
  - AL classically involves GI tract
    - 6% of AL patients have MM
  - AA classically involves liver and spleen
    - 48 % of AA patients have RA
    - If a patient has RA and diarrhea → 62 % have amyloidosis
    - Ratio of AA to AL ~ 1:25

- Diagnostic imaging
  - AL typically forms polypoid protrusions
    - More often obstructing phenotype
  - AA has a granular appearance
    - More often malabsorption, bleeding

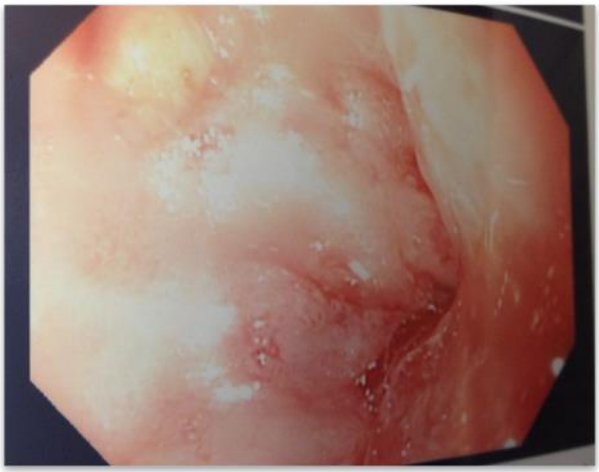
- Endoscopy
  - Most radiological abnormalities are in small intestine:
    - Coarse mucosal appearance
    - Thickened folds
    - Ulcerated nodular polyps
  - In large intestine
    - Mucosal nodularity
    - Thickened folds
    - Loss of haustrations

Prepyloric folds



Kindly provided by Dr. Jeremy Parfitt, MD, FRCP, Department of pathology, Western University, London, Canada.

1st Part of Duodenum (distal)



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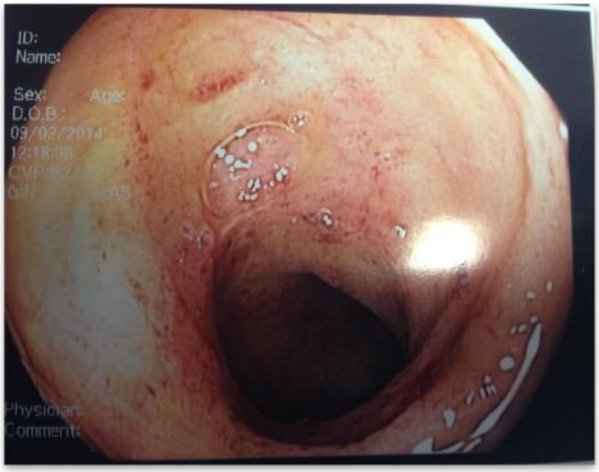
Cecum



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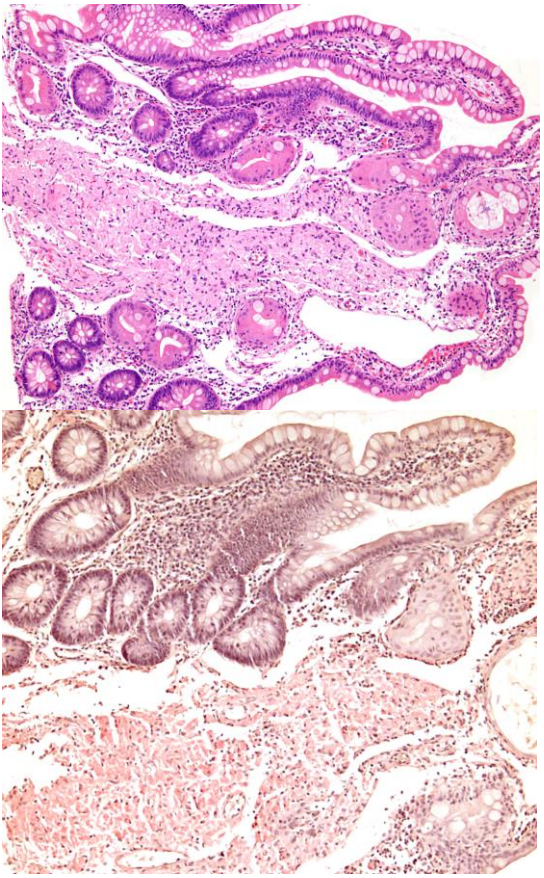
- Pathology
  - Amyloid is deposited in
    - Blood vessel walls (ischemia, infarction)
    - Muscle layers (dysmotility)
    - Mucosa, muscularis mucosa (↓ absorption)
    - Intrinsic nervous system



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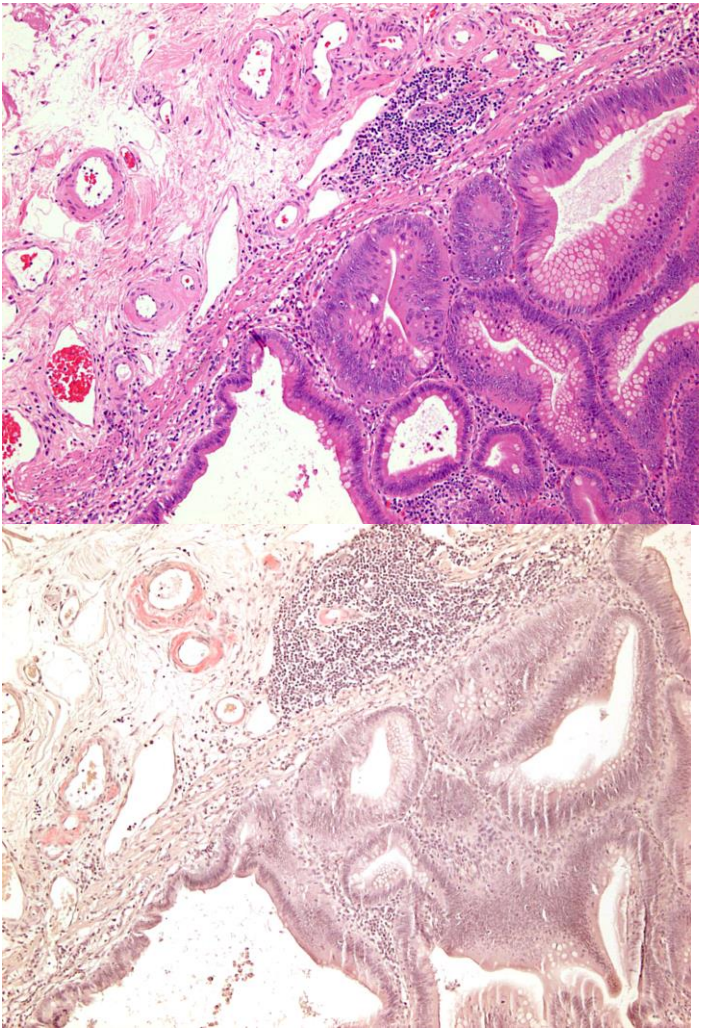

Kindly provided by Dr. Jeremy Parfitt, MD, FRCP, Department of pathology, Western University, London, Canada.

- Clinical
  - Causes GI symptoms from “top to bottom”
  - Systemic Manifestations
    - General
      - Fatigue
      - Weakness
      - Weight loss
    - Head / neck
      - Purpura
      - “racoon eyes”
    - MSK
      - Athralgias
      - “shoulder pad sign” (buffalo lump)
    - Neurological
      - Carpal tunnel
      - Autonomic dysfunction
    - Cardiac
      - Heart failure
      - Cardiomyopathy
    - Renal
      - Nephrotic syndrome
    - Hematology
      - Bleeding diathesis (e.g. factor X deficiency)
  - Syndromes
    - Bleeding (30%)
      - Ulcers, polypoid lesions, erosions, submucosal hematomas
    - Malabsorption (5%)
      - Weight loss, diarrhea, steatorrhea
    - Chronic intestinal dysmotility (stasis syndromes)
      - Dysphagia
      - Gastroparesis
      - Constipation
      - Chronic pseudo-obstruction
      - Small intestinal bacterial overgrowth (SIBO)

- Diagnosis
  - Made on tissue specimen
    - Biopsy rectum or subcutaneous fat if no infiltrated tissue easily accessible
  - Homogenous and amorphous under light microscopy
  - Congo red (the most specific stain) →
    - Red appearance in normal light
    - Green birefringence in polarized light
  - Determine protein type by immunohistochemistry
  - If AL amyloidosis SPEP/UPEP, multiple myeloma w/u indicated
  - Can determine total body amyloid deposits by injecting radiolabelled protein (serum amyloid P component) that binds fibrils

Abbreviations: SPEP, Serum protein electrophoresis; UPEP, urine protein electrophoresis

Mouth & Esophagus

- 10 – 20 % of patients with AL amyloidosis
- Most common oral manifestation is macroglossia
- Other oral manifestations:
  - Sleep apnea
  - Chewing / speech difficulties
  - Airway obstruction
  - Hardening of perioral tissue → Loss of facial expression, difficulty opening mouth, xerostomia (if glands involved)

Esophageal disease

- ~ 10 – 20 % of patients
- Dilated, atonic esophagus with ↓ peristalsis
- Less commonly
  - Ulcerations
  - Masses
- Symptoms include
  - Heartburn
  - Chest pain
  - Dysphagia

Stomach

- 8 % of patients with amyloid
- May find thickened irregular gastric folds or loss of rugal folds
- Gastric ulcers with clean bases or irregular edges
- Hematomas (amyloid in submucosal vessels)
- Bleeding due to weakness of vessel walls

Duodenum

- Scalloped edges
- Duodenitis
- Ulcers
- Masses
- Mucosal friability

Small Intestine

- Most common site of involvement (1/3 of pts)
- Amyloid deposits in
  - Adventitia → luminal narrowing and ischemia
  - Muscle fibers → dysmotility
  - Mucosa (when massive depositsdestroy all mucosal tissue) → malabsorption → bleeding (30%)
- Pathogenesis of malabsorptive diarrhea
  - Autonomic dysfunction due to infiltration of autonomic ganglia can cause ↑ transit
  - ↓ orocecal transit cause small intestinal bacterial overgrowth (SIBO) → malabsorption
  - Exocrine pancreatic insufficiency due to acinar cell infiltration
  - Mucosal infiltration impairs absorption
  - If this is the predominant manifestation may manifest with severe weight loss

Colon

- Motility disorders:
  - Amyloid deposits in myenteric plexus or smooth muscle → ↓ colonic postprandial response → ↑ colonic transit time → constipation
  - Pseudo-obstruction sometimes from
  - Cisparide may be helpful
  - Promotility agents are of limited benefit
- Vascular endothelial deposition of amyloid → Ulceration and ischemic → bleeding

AA Amyloidosis and IBD

- Occurs in ~ 1% of CD and 0.1% of UC patients
- Develops ~ 15 yr after onset of IBD
- Most commonly affects the kidneys
- In ~ 80% of IBD-amyloid patients
  - ~ 80% develop proteinuria
  - ~ 40% died of renal-related disease

Amyloid in the liver

- Amyloid deposition begins periportally
- ↑ ALP most common manifestation
- Liver involved in approximately half of amyloid cases
- Usually mild disease, with hepatomegaly
- Hepatomegaly and other abnormalities do not correlate with extent of liver infiltration with amyloid
- Stigmata of chronic liver disease and portal hypertension RARE
- Liver biopsies less safe because factor X binds amyloid fibrils and is cleared from circulation

➢ Treatment

- Depends on type of amyloidosis
- Goal in AL
  - ↓ synthesis of light chain production
    - By treating plasma cell disorder with chemotherapy
  - Bortezemib, melphalan dexamethasone

- Similar therapies to multiple myeloma including
  - High dose chemotherapy
  - Stem cell transplant if
    - Good ECOG
    - Not many organ systems affected
- Goal in AA is
  - To control primary disease, e.g.
    - Anti-TNF-α for inflammatory arthritis → regression of AA deposits
  - IBD patients with renal transplants may do better due to heavy immunosuppression
- In inherited amyloidosis due to transthyretin (protein produced in liver)
  - Liver transplant is curative
- Symptomatic control
- For pseudo-obstruction:
  - Restoration of hydration/nutrition +- TPN
  - Suppression of bacterial overgrowth
  - Prokinetic agents (uncertain response)
- For diarrhea:
  - Octreotide (uncertain response)
  - Opiates (uncertain response)

➢ Prognosis

- Death is usually from cardiac or renal involvement
- AL amyloidosis:
  - Median survival is one year from diagnosis
  - High dose chemotherapy (melphalan/prednisone) → median survival is < 2 years
  - HSCT → 5 year survival rate is ~ 60 %

- AA amyloidosis:
  - Treating underlying disease can cause regression of amyloid deposits

Abbreviations: HSCT, hematopoietic stem cell transplantation

References and Suggested Reading

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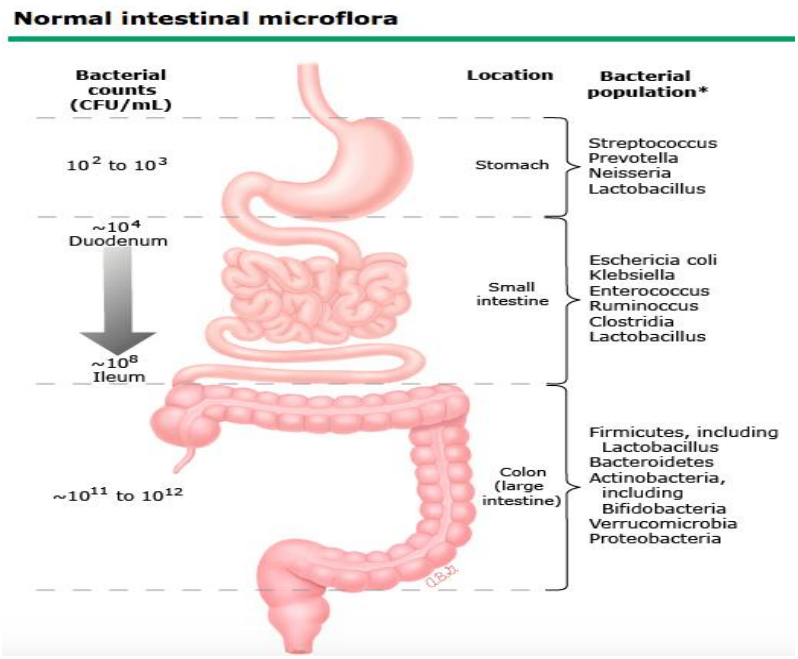
SMALL BOWEL

Small Intestinal Bacterial Overgrowth

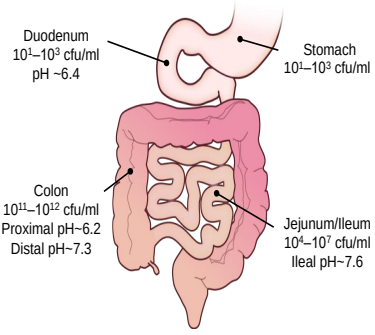
Almotasembillah Rammal

- Definition
  - A condition in which non-native bacteria and/or native bacteria are present in increased numbers resulting in excessive fermentation, inflammation or malabsorption.

- Microbiology
  - At birth the intestine is sterile
    - Within hours maternal coliforms and streptococci begin to populate the alimentary tract and are later followed by lactobacilli and enterococci.
  - Within three weeks
    - The number of coliforms decreases and *Bacteroides* organisms begin to establish themselves as the predominant microorganisms in the colon.
  - Stomach and proximal small bowel
    - Have few bacteria due to the presence of gastric acidity and the effects of peristalsis. 10”4/ml
  - Terminal ileum
    - The concentration of organisms may be as high as 10”9/mL
    - If the ileocecal valve is dysfunctional or surgically absent, the microbiology of the terminal ileum resembles that of the colon.
  - Colon
    - Microorganisms reaches as high as 10”12/mL.



Normal Intestinal Microflora & pH



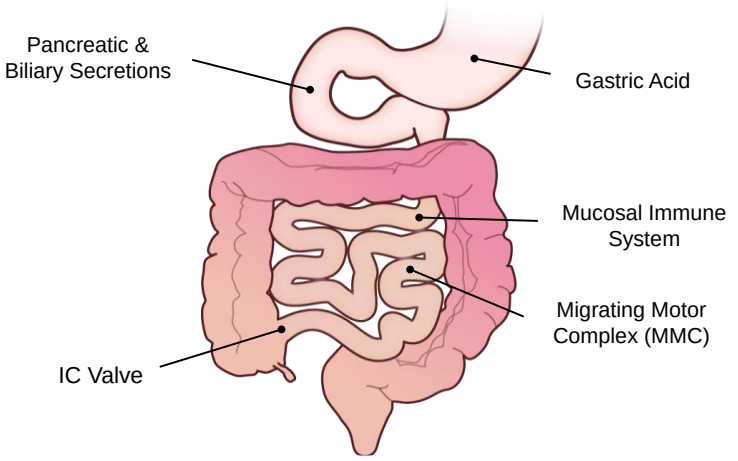
Most Common Bacteria

Anaerobic Genera	Aerobic Genera
Bifidobacterium	*Escherichia*
Clostridium	*Enterococcus*
Bacteroides	*Streptococcus*
Eubacterium	*Klebsiella*

O'Hara AM, Shanahan F. EMBO Rep. 2006;7:688-693; *Kloetzer et al. Gastroenterol 2007;132 (suppl 2):A461*

Mechanisms protecting against SIBO

- Antegrade peristalsis prevents attachment of ingested microorganisms.
- Gastric acid and bile destroy many microorganisms before they leave the stomach.
- Digestion by proteolytic enzymes helps destroy bacteria in the small intestine.
- The intestinal mucus layer traps bacteria.
- An intact ileocecal valve as well as the antegrade motility pattern of the ileum itself inhibits retrograde translocation of bacteria from the colon to the small bowel
- The immune system plays a role as evidenced by the high prevalence of SIBO in patients who have immunodeficiency.



O'Hara AM, Shanahan F. EMBO Rep. 2006;7:688-693; Kloetzer et al. Gastroenterol 2007;132 (suppl 2):A461.

Disorders Commonly Associated with SIBO

Gastric acid secretion	Pancreatic enzymes	Motility Disorder	Immune Deficiency	GI Structural Defect
○ Potent acid suppressive drugs ○ Atrophic gastritis ○ Vagotomy	Chronic pancreatitis Cirrhosis Cystic fibrosis	Aging Celiac sprue Cirrhosis Crohn's disease DM with AN Pseudo-obstruction Renal failure Radiation enteritis Scleroderma	Immuno-suppressive Rx CVID IgA deficiency	Fistula IC valve resection Bariatric surgery JI bypass Small bowel tics Surgical blind loop

Abbreviations: AN, autonomic neuropathy; CVID, common variable immune deficiency; DM, diabetes mellitus; IC, ileocecal; JI, jejunoileal; Rx, drugs

Maneeratanaporn, Chey. SIBO, 2009

Disorders associated with bacterial overgrowth

- Small intestinal stasis
  - Small intestinal diverticulosis
  - Surgically created blind loops (end-to-side anastomosis)
  - Strictures (Crohn disease, radiation, surgery)

- Abnormal small intestinal motility
  - Diabetes mellitus
  - Scleroderma
  - Idiopathic intestinal pseudo-obstruction
  - Radiation enteritis
  - Crohn disease
- Abnormal communication between the proximal and distal gastrointestinal tract
  - Gastrocolic or jejunocolic fistula
  - Resection of the ileocecal valve
- Association usually with multifactorial causes
  - Hypochlorhydria due to atrophic gastritis or medications. There are usually not clinically significant unless they coexist with concomitant motility disturbances of the small bowel
  - Immunodeficiency states (common variable immunodeficiency, AIDs, severe malnutrition)
  - Chronic pancreatitis
  - Cirrhosis
  - Alcoholism
  - End-stage renal disease
  - Advance age
  - Total parental nutrition (TPN) in children

- Clinical
  - Bloating
  - Abdominal discomfort
  - Diarrhea
  - Weight loss
  - Weakness
  - Neuropathy

- Complications

Findings	Consequence
○ Cobalamin (vitamin B12) deficiency	Peripheral neuropathy, megaloblastic anemia
○ Fat-soluble vitamin deficiency	
– Vitamin A	Night blindness, xeropthmia
– Vitamin D	Osteomalacia, hypocalcemia tetany
– Vitamin E	Neuropathy, hemolysis
– Vitamin K	Coagulopathy
○ Hypoproteinemia and hypoalbuminemia	Edema
○ Fat malabsorption	Weight loss, steatorrhea, diarrhea
○ Carbohydrate malabsorption	Weight loss, diarrhea
○ Iron deficiency	Microcytic anemia

- Laboratory
  - Most patients with small intestinal bacterial overgrowth (SIBO) have no laboratory abnormalities.
  - Macrocytic anemia, B12 deficiency, and the presence of fecal fat,
  - Serum folate and vitamin K levels are normal or may be increased.
  - Stool evaluation may reveal an increase in fecal fat

- Diagnosis
  - Jejunal aspirate/culture
    - Are considered the reference-standard for the diagnosis of SIBO.
  - Bacterial counts on quantitative jejunal aspirate cultures that exceed 105 organisms/mL were previously considered positive for SIBO, this was based on studies in Billroth II patients.
    - Studies in healthy controls suggest that the presence of >103 organisms/mL is suggestive of the presence of SIBO

- Breath test for SIBO
  - Carbohydrate breath tests
    - Lactulose and glucose, the most common substrates administered during the breath test, are nontoxic and therefore can be performed in children and women of childbearing age
    - Protocol
    - Specific foods (bread, pasta, fiber) should be avoided for 12 hours prior to testing because they cause prolonged hydrogen secretion and elevate basal hydrogen levels.
    - Cigarette smoking or physical exercise sufficient to produce hyperventilation should be avoided for two hours prior to testing.
    - Pretest mouth washing with an antiseptic should be performed.

- Lactulose is a non-absorbable substance that is normally metabolized by gut bacteria in the colon with the production of hydrogen and/or methane.
  - In individuals without SIBO, the administration of lactulose results in a single peak in breath hydrogen/methane within two to three hours due to the metabolism of lactulose by colonic flora.
  - The lactulose breath test is considered positive in the presence of any one of the following
    - An absolute increase in hydrogen by ≥20 ppm above baseline within 90 minutes.
    - A double peak pattern consisting of an early rise in hydrogen production, within one hour of ingestion, followed by the later colonic peak within two to three hours.
    - Methane ≥ 3 ppm regardless of the time during the breath test.

- Glucose is rapidly absorbed from the proximal small bowel.
  - When used as a substrate in the presence of SIBO, it is metabolized to hydrogen in the small bowel lumen prior to absorption.
  - We administer glucose orally in a dose of 50 g dissolved in 8 ounces of water.
  - We sample breath hydrogen at baseline and every 20 minutes after glucose ingestion for three hours. A glucose breath test is considered positive for SIBO in the presence of an increase in breath hydrogen by ≥12 ppm above the baseline value within two hours

- [14C]-d-xylose is a pentose sugar that is catabolized by gram-negative aerobes.
  - Bacterial action on xylose releases the radioactive isotope 14CO2, which, after absorption, is detectable in breath samples.
  - In normal individuals, 14CO2 levels peak with catabolism of xylose in the colon.
  - In patients with SIBO, 14CO2 is released in the small bowel. A positive 14C-d-xylose test is defined as an accumulated 14C dose of 4.5 percent in four hours
  - The sensitivity and specificity of the 14C-d-xylose breath test and the glucose breath test are comparable
  - However, as the administration of 14C is associated with a small exposure to radiation, its use in clinical practice is limited. The 14C-d-xylose breath test is contraindicated in children and women of childbearing age.

- Performance characteristics
  - The lactulose breath test has a sensitivity of 17 to 68% and specificity of 44 to 86%
  - The glucose breath test has a sensitivity of 20 to 93% and specificity of 45 to 86%
  - The 14C-d-xylose breath test has a sensitivity of 30 to 95%, and specificity of 40 to 94% for SIBO
  - Disorders associated with impaired gastric emptying may lead to false-negative results, while rapid intestinal emptying may lead to false-positive results

- Treatment
  - The mainstay of treatment of small intestinal bacterial overgrowth (SIBO) is antibiotic therapy
  - Treatment of the underlying disease
  - Prokinetic agents including metoclopramide, domperidone and erythromycin may have benefit but large studies are lacking. Prokinetics may be a useful adjunct for SIBO in patients who do not respond to or are intolerant of antibiotics provided that they have documented dysmotility. Dietary manipulation
    - The primary goal is to provide a diet that have fewer calories for bacterial metabolism.
    - As carbohydrates are the primary nutritional source for bacteria diets should be modified to reduce nonabsorbed carbohydrates.
    - A high fat, low carbohydrate, low fiber diet is helpful, as fat is not significantly metabolized by the bacteria and supplies a good calorie source in those requiring supplemental nutrition
  - Antibiotic therapy
    - Most patients with SIBO require treatment with antibiotics.
    - The goal of therapy is to reduce (rather than eradicate) the flora
    - Rifaximin (1650 mg/day), a nonabsorbable antibiotic for 7- to 10-dayIn a randomized controlled trial in which 142 patients with SIBO were randomized to seven days of rifaximin (1200 mg/day) or metronidazole (750 mg/day), glucose breath test normalization rates at one month were significantly higher in patients treated with rifaximin compared with metronidazole (63.4

versus 43.7 percent). Amoxicillin-clavulanate (30 mg/kg/day)
- Metronidazole (20 mg/kg/day) combined with a cephalosporin (30 mg/kg/day), such as cephalexin or trimethoprim-sulfamethoxazole (10 to 12 mg/kg/day), or oral gentamicin (10 mg/kg/day)Norfloxacin (800 mg/day).

- Probiotics, prebiotics
  - Probiotics are defined as live microorganisms, which when administered in adequate amounts confer a health benefit on the host

- Summary
  - The microbiome plays a critical role in normal development and function of the human GI tract
  - Gastric acid, pancreaticobiliary secretions, gut immune system, permeability, and IC valve protect against the development of SIBO
  - SIBO presents a clinical spectrum of disease
  - Differences in the distribution & composition of gut bacteria make diagnosis difficult
  - The mainstay of treatment of small intestinal bacterial overgrowth (SIBO) is antibiotic therapy

"The pain you feel today is the strength you feel tomorrow. For every challenge encountered there is opportunity for growth."

Unknown

Diagnostic Imaging of Small Intestine

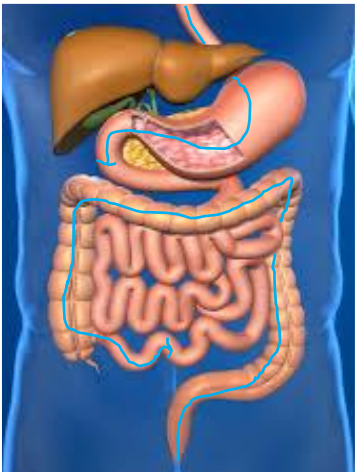
Michael Sey

HISTORICAL PERSPECTIVE

1960s

- ‘Black box’ of the GI tract
- Only the top and bottom 10-20 cm of the small bowel can be seen with an EGD and colonoscopy
- Little development because of
  - Rarity of small bowel diseases
  - Equipment limitation
  - Training requirement

EGD



1970s

- Abandoned due to
  - Trauma to the GI tract
  - Need for general anesthesia
  - Prolonged nature of procedure
- 1st successful complete enteroscopy (Ropeway)
  - Ingestion of weighted string
  - Await passage through the anus
  - Exchange string for stiffer Teflon tube
  - Advance enteroscope over Teflon tube
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Gastroenterological Endoscopy 2nd ed. pg 119.
http://www.ics-japan.org/museum/museum.html

- Sonde Enteroscopy
  - Usage of peristalsis to deliver enteroscope through the small intestine
- Abandoned due to
  - Need for general anesthesia
  - Prolonged nature of procedure
  - Sporadic visualization on withdrawal only
  - No instrument channel

Tada M, et al. Endoscopy 1977;9:33-8.

1980s

- Push Enteroscopy
  - Passage of a pediatric colonoscope or long enteroscope (2-3 m) into the small bowel

Advantages	Disadvantages
▪ Readily available equipment ▪ Simple to perform ▪ No additional training required ▪ Short procedure ▪ Well tolerated ▪ Requires only conscious sedation ▪ Potential for biopsy and therapeutics	▪ Very limited examination of the small bowel ▪ Rarely able to insert further than proximal jejunum

The Second Millennium

- Video Capsule Endoscopy (VCE)
  - Technological Advances
    - CMOS sensor
    - LED
    - ASIC

Iddan G, et al. Nature 2000:405(6785);417.

Given Imaging SB3

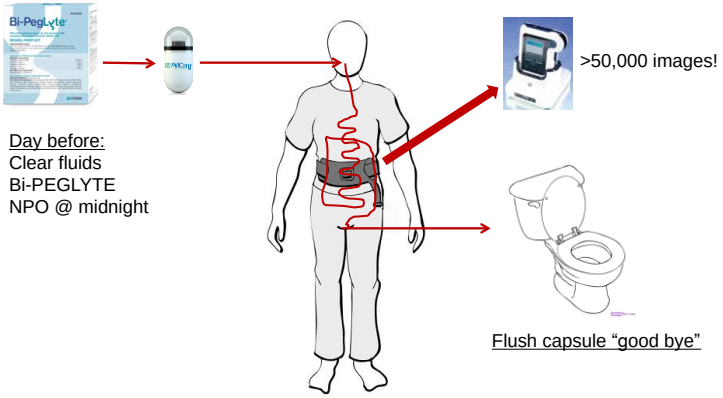
- Camera:
  - Resolution: 0.07 mm
  - Field of view: 156º
  - Adaptive frame rate: 2-6 fps
- Flash
  - 4 LED
- Battery (silver oxide):
  - Duration: ≥8 hr

3 gm
$ 1,000 per pill

- Indications
  - Obscure GI Bleeding
    - Bleeding of unknown origin after EGD & colonoscopy (some authorities suggest these endoscopic procedures be down twice, by different endoscopists)
    - *Overt:* melena, hematochezia
    - *Occult:* iron deficiency anemia, ± FOBT

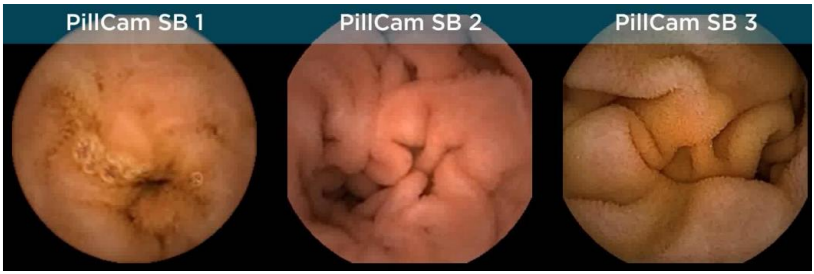
Fisher L, et al. Gastrointest Endosc 2010;72-471-79.

- Procedure



http://www.youtube.com/watch?v=K6DAjjYjBng

Technology Improvement



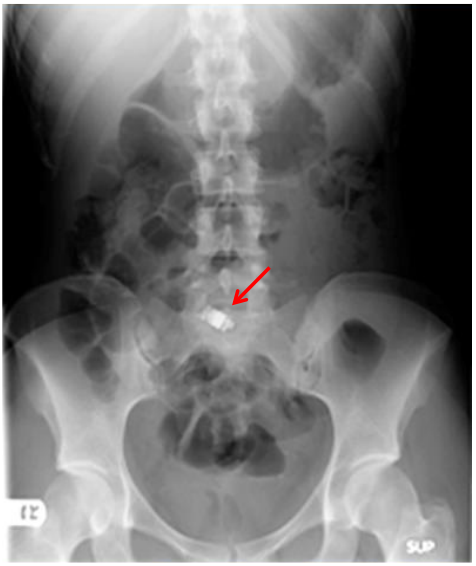
2001 2007 2013

The Problem: capsule retention

- Causes
  - Esophagus
    - Stricture
    - Eosinophilic esophagitis
  - Gastric
    - Outlet obstruction

- Small bowel
  - Crohn disease
    - Established 13% retention risk
    - Suspected 1.6% retention risk
  - Prior intestinal surgery
  - Prior radiation
  - NSAID usage
  - Suspected adhesions
  - Clinical suspicion of SI stricture
- Colon
  - Stricture
  - Diverticulosis

Capsule retention: Small bowel causes

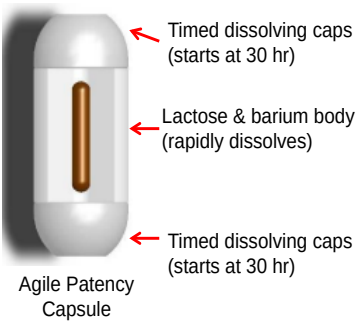


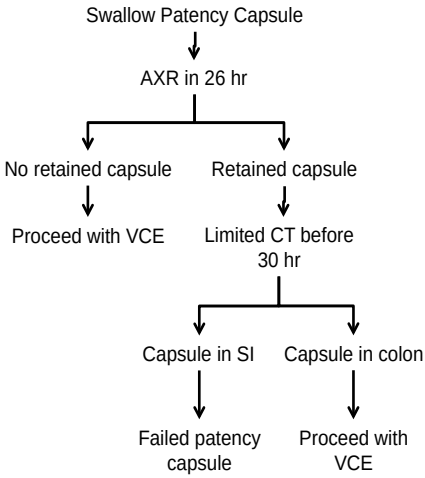
- Contraindications to VCE
  - Patient is not a surgical candidate
    - Patients who are not surgical candidates should not get VCE due to a
      - Lack of exit strategy in case of capsule retention that cannot be retrieve with deep enteroscopy

Management of Pill Retention

- Baseline abdominal x-ray to confirm retention
- Repeat in 4 weeks
- Medical Therapy
  - Purgative
  - Treat the underlying cause (e.g. Remicade, steroids, chemotherapy)
- Deep enteroscopy
- Surgical extraction

Design of capsule to ↓ risk of retention





Factors associated with a positive VCE

Factor	OR (95% CI)
○ Overt bleeding	3.8 (1.4-6.6)
○ Age > 60	1.4 (1.2-1.6)
○ Male	1.4 (1.1-2.0)
○ Inpatient	1.3 (1.1-2.3)

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

Causes of obscure GI bleeding found on VCE

Etiology	% of cases (n=2751)
○ Angioectasia	50
○ Inflammatory/ulcer	27
○ Tumors	9
○ Miscellaneous	8

○ Diagnostic rate of SI tumors
- 2.4% of ~7000 VCEs

Liao Z, et al. Gastrointest Endosc 2010;71:280-6.

Benign	Malignant
Inflammatory polyps	Adenocarcinoma
Hyperplastic polyps/Brunner's gland	NET
Ectopic gastric/pancreatic tissue	GIST
Adenomas	Lymphoma
Hamartoma (PJS, JP)	Sarcoma
Mesenchymal Hemangioma Lipoma Fibrolipoma Leiomyoma Neurofibroma Lymphangioma	Metastasis

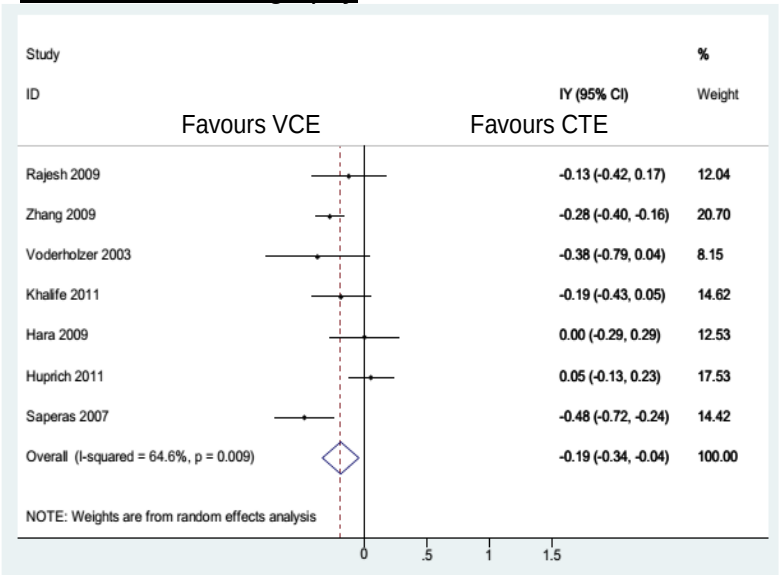
Islam RS, et al. Gastrointest Endosc 2014;79:732-40.

How does VCE compare against other modalities

VCE	Other modality methods vs.
67%	Barium, 8%
63%	Push enterostomy, 28%
53%	CTE,34% MRI, 47% Intra-op' enteroscopy, 75%

Golder SK, et al. Int J Colorectal Dis 2006;21:97-104.
Hartmann D, et al. Gastrointest Endosc 2005;61:826-32.

VCE vs. CT Enterography



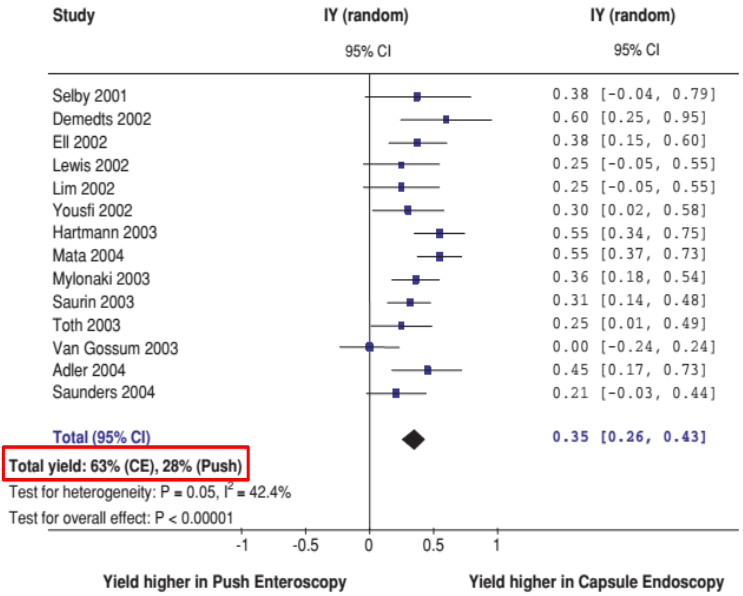
Diagnostic yield: 34% CTE vs 53% VCE (IY 19%, 95% CI 4% to 34%)

Printed with permission: Wang Z, et al. J Med Imaging Radiat Oncol 2013;57:263-73.

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

Grandad

VCE vs Push Enteroscopy

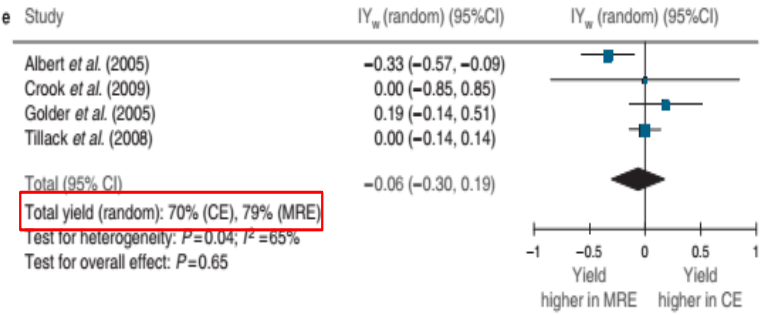


Printed with permission: Triester SL, et al. Am J Gastroenterol 2005;100:2407-18.

How does VCE compare with other modalities in Crohn Disease (CD)

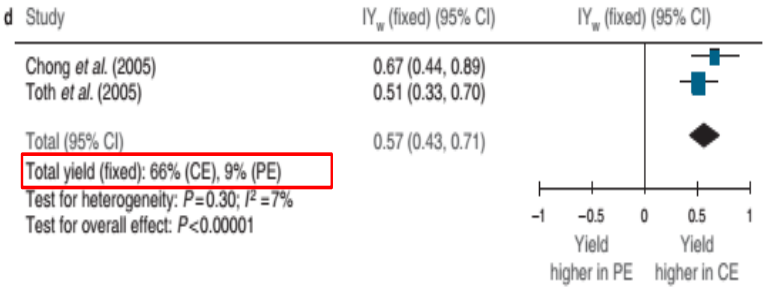
VCE	Other Modalities
70%	MRE, 79%
71%	CFE, 39%
71%	Barium, 36%
66%	PE, 9%

VCE vs. MR Enterography in CD



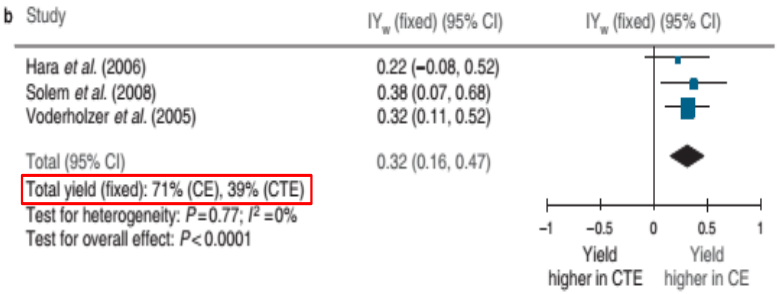
Printed with permission: Dionisio PM, et al. Am J Gastroenterol 2010;105:1240-8.

VCE vs Push Enteroscopy in CD



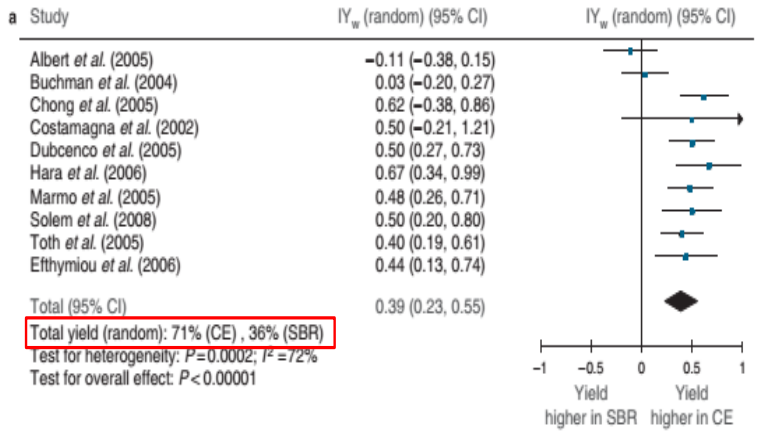
Printed with permission: Dionisio PM, et al. Am J Gastroenterol 2010;105:1240-8.

VCE vs CT Enterography in CD



Printed with permission: Dionisio PM, et al. Am J Gastroenterol 2010;105:1240-8.

VCE vs Barium Radiology in CD



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Lewis Score

Parameters	Number	Longitudinal extent	Descriptors
First tertile			
Villous appearance	Normal – 0	Short segment – 8	Single – 1
	Oedematous – 1	Long segment – 12	Patchy – 14
		Whole tertile – 20	Diffuse – 17
Ulcer	None – 0	Short segment – 5	<1/4 – 9
	Single – 3	Long segment – 10	1/4–1/2 – 12
	Few – 5	Whole tertile – 15	>1/2 – 18
	Multiple – 10		
Second tertile			
Villous appearance	Normal – 0	Short segment – 8	Single – 1
	Oedematous – 1	Long segment – 12	Patchy – 14
Ulcer		Whole tertile – 20	Diffuse – 17
	None – 0	Short segment – 5	<1/4 – 9
	Single – 3	Long segment – 10	1/4–1/2 – 12
	Few – 5	Whole tertile – 15	>1/2 – 18
	Multiple – 10		
Third tertile			
Villous appearance	Normal – 0	Short segment – 8	Single – 1
	Oedematous – 1	Long segment – 12	Patchy – 14
		Whole tertile – 20	Diffuse – 17
Ulcer	None – 0	Short segment – 5	<1/4 – 9
	Single – 3	Long segment – 10	1/4–1/2 – 12
	Few – 5	Whole tertile – 15	>1/2 – 18
	Multiple – 10		
Stenosis – rated for whole study			
Stenosis	None – 0	Ulcerated – 24	Traversed – 7
	Single – 14	Non-ulcerated - 2	Not traversed – 10
	Multiple – 20		

Printed with permission: Gralnek IM, et al. Aliment Pharmacol Ther 2008:27;146-54.

The Bottom Line: Think before referring for VCE

- Is this actually an iron deficiency anemia?
- Are there other obvious causes of iron deficiency (menses, diet restrictions, RYGB, achlorhydria, alcohol abuse)?
- Did I have an adequate look at EGD & colonoscopy (adequacy of prep, was procedure rushed)?
- Will finding more angioectasias change management?
- Should the endoscopic procedure (EGD / Colon') be repeated?
- Is there pretest probability of tumor?
- For the future: Does "spicing" up the Lewis score enhance the diagnostic use of VCE?

Fisher L, et al. Gastrointest Endosc 2010;72-471-79.

"A pessimist sees the difficulty in every opportunity;
An optimist sees the opportunity in every difficulty."

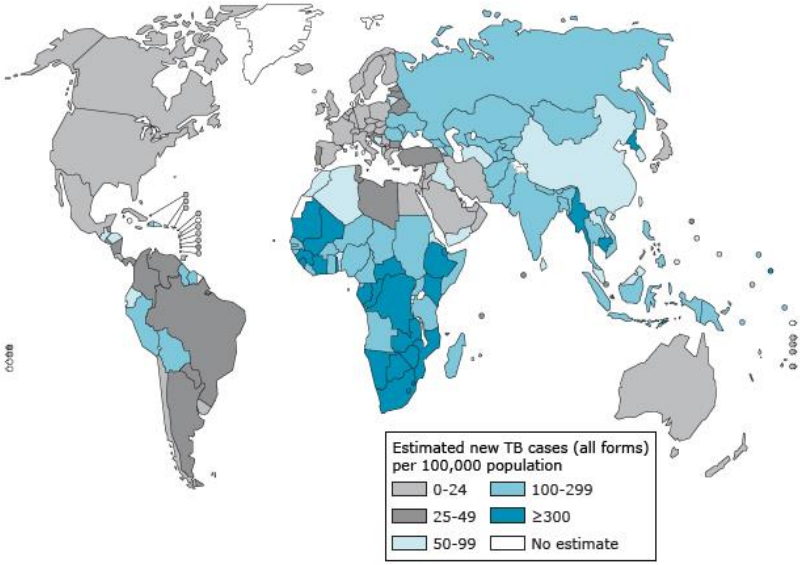
Sir Winston Churchill

Tuberculosis Enteritis

Amindeep Sandhu

- Demography
  - Member of Mycobacterium TB complex
  - 2 billion people (that's 1/3 of Earth) are infected
  - Global incidence peaked in 2003 and is now declining
  - Transmission via inhalation of droplet nuclei
  - Active untreated pulmonary/laryngeal disease is most contagious form
  - Transmission much higher if cavitary disease present or if sputum AFB +
  - TB Enteritis can affect any part of GI tract
    - 6^{th} most frequent form of active TB
    - Lymphatic > GU > Bone > Miliary > Meningeal > GI
    - Higher incidence in
      - Pakistan, Turkey, West Africa
      - Especially among young females
    - Prior to anti-TB Rx → GI involvement seen in 55-90%
  - Extra-pulmonary TB → affects 20% of immunocompetent, 80% immunosuppressed
  - Affects 50% of HIV +

Abbreviation: AFB, acid fast bacillus

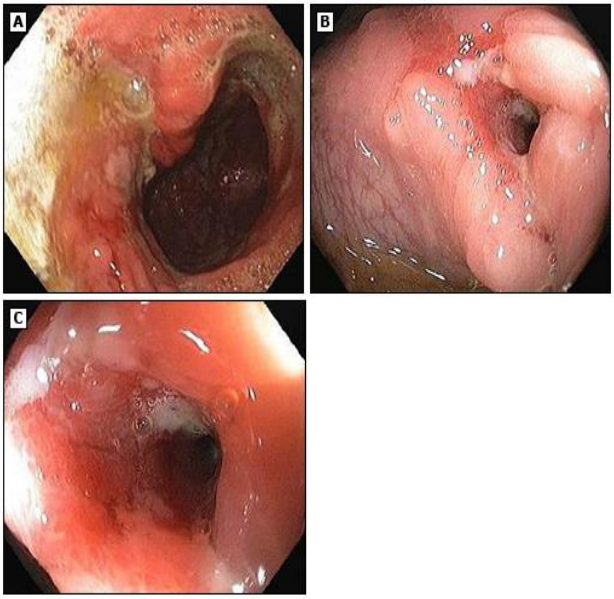


Source: http://www.who.int/tdr/news/documents/tb_child.pdf

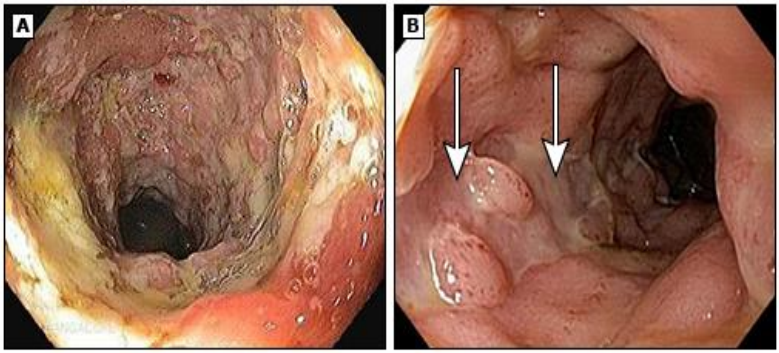
- Pathogenesis
  - 4 mechanisms:
    - Swallowing infected sputum (most common)
    - Hematogenous spread from active pulmonary or miliary TB
    - Ingestion of contaminated milk or food
    - Contiguous spread from adjacent organs
  - IC valve most common site (75%)
    - Likely due to relative stasis and abundant lymphoid tissue
    - Penetrates mucosa → localizes in submucosal lymphoid tissue → inflammatory reaction → lymphangitis, endarteritis, granuloma, mucosal ulceration, caseation necrosis
    - Often leads to IC valve incompetence (unlike CD)

➢ Pathology

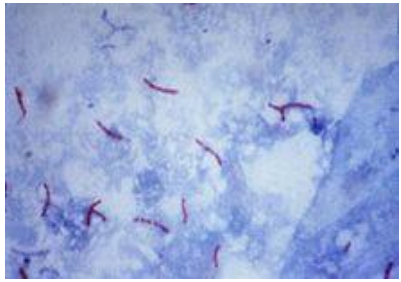
- Endoscopy
  - Ulcerative (60%)
    - Multiple superficial ulcers
    - Circumferential; highly virulent, high mortality
  - Ulcerohypertrophic (30%)
    - Mucosal ulcerations + Scar formation
    - Inflammatory mass around IC valve
    - Thickened and ulcerated walls
    - Predominant appearance at IC valve
  - Hypertrophic (10%)
    - Scarring
    - Fibrosis
    - “pseudotumors”/mass
    - Mimics cancer



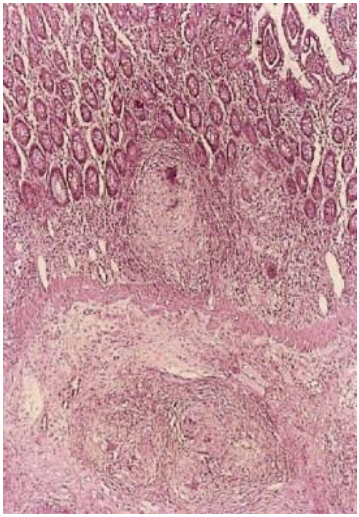
Ascending colon TB enteritis



- Histopathology
  - Large, numerous, confluent granulomas (>400um)
  - + AFB stain → Ziehl-Neelsen stain
  - Above 2 = classic = 33%



  - Disproportionate submucosal inflammation
  - Submucosal granulomas are
    - Characteristic of TB
    - Mucosa, submucosal
      - Confluent
    - Caseating (central necrosis)



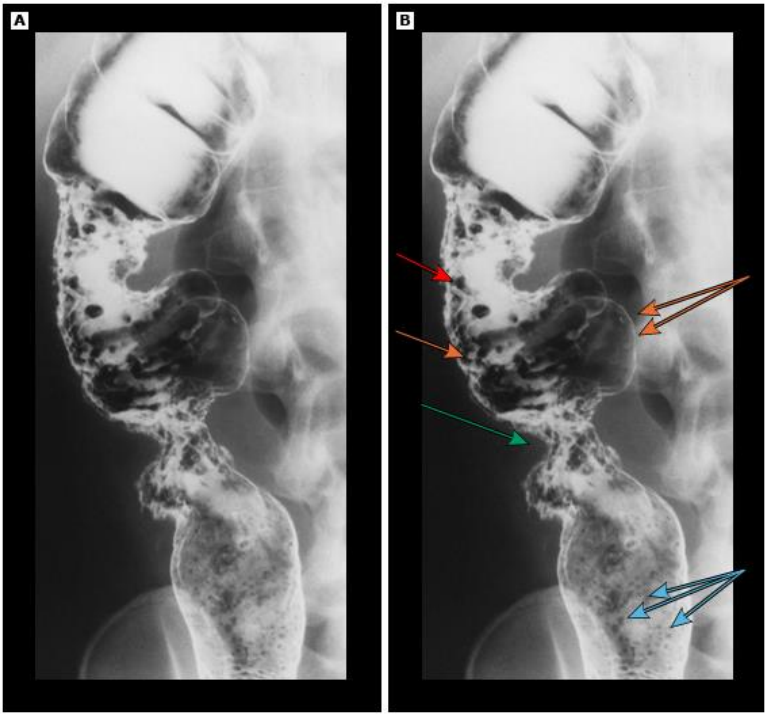
- Colonic TB →
  - Granulomas seen in both mucosa and submucosa
  - Note: Central necrosis = caseating

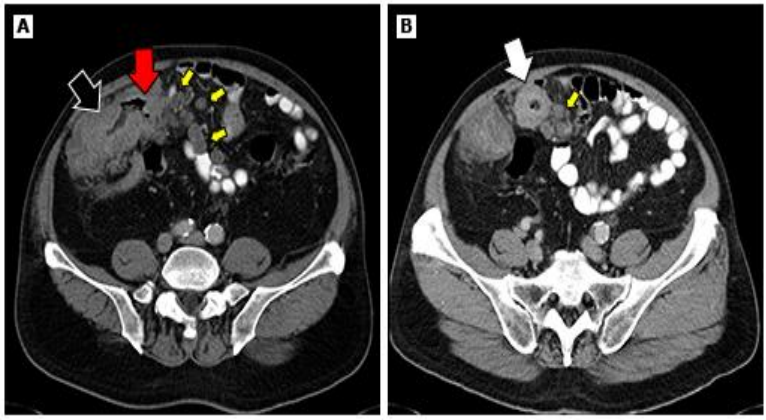
- Diagnosis
  - Presumptive
    - In setting of active pulmonary TB + clinical/endoscopic/radiographic findings
  - Definitive
    - Histology and culture of biopsy material
    - Ulcers
    - Strictures
    - Nodules
    - Pseudopolyps
    - Fibrous bands
    - Deformed IC valves
    - Apthous ulcers with normal surrounding mucosa
    - Linear ulcers
    - Cobblestoning
    - Ulcers circumferential, surrounding inflammation = TB
    - Destroyed IC valve with fish mouth opening = TB

- Laboratory
  - PCR of mucosal biopsy
    - ↑ sensitivity vs. routine culture
  - CBC
    - Normocytic anemia
    - ↑ ESR (80%)
  - TST & IGRA positive in 90% with intestinal TB
    - No differentiation between active vs. previous sensitization by contact or vaccine
  - Stool for AFB – useless, rarely positive, even in active Dz

- Clinical
  - Acute, Chronic, Acute-on-Chronic
  - Chronic – symptoms over weeks to months – most common
  - Non-specific abdominal pain – 90%
  - Palpable RLQ abdominal mass in 25-50%
  - Ascites in 15%
  - Diarrhea or Constipation
  - Constitutional symptoms
  - Fistula, structuring
  - Bowel obstruction is common (progressive stricture or adhesions)

- Diagnostic imaging
  - Contrast-enhanced CT
    - Helpful to assess intraluminal and extraluminal pathology
    - Concentric mural thickening of IC region
    - May not have proximal dilatation
    - Lymphadenoapthy with hypodense centres
      - Classic
        - Caseous liquefaction
    - Peripheral enhancement in mesentery and retroperitoneum helps to differentiate it from CD





- Differential (of terminal ileal / cecal)
  - Infection
    - Actinomycosis
    - Histoplasmosis
    - Amebiasis
    - Yersiniosis
  - Typhilitis
  - Infiltration
    - Lymphoma
    - CRC
  - Drug-induced
    - NSAIDs also causes “cecal coning”
  - Immune
    - CD – can give virtually all the changes of TB

Distinguishing CD versus intestinal TB

	Crohn disease	Intestinal tuberculosis
○ Clinical	– Perianal disease	▪ High-swinging fever (> 38.5°C) in absence of intra-abdominal abscess ▪ Evidence of pulmonary TB on chest x-ray
○ Diagnostic imaging (CT, MRI)	– Symmetrical bowel wall thickening – Mesenteric fibrofatty proliferation (creeping fat) – Mesenteric vascular engorgement (comb sign) – Small homogenous pericecal lymph nodes	▪ Asymmetrical bowel wall thickening ▪ Inflammatory mass centered around the cecum and enveloping the terminal ileum ▪ Large mesenteric nodes with necrotic centers ▪ Ascites
○ Endoscopy	– Longitudinal ulcers – Aphthous ulcers – Cobblestoned mucosa – Preservation of ileocecal valve – Multiple skip lesions – Anorectal lesions	▪ Transverse ulcers ▪ Hypertrophic mucosa ▪ Scars / fibrous bands / inflammatory polyps ▪ Gaping / destruction of ileocecal valve ▪ Hyperemic nodules ▪ Ulcers circumferential surrounding inflammation
○ Histo-pathology	– Single granulomas – Non-caseating – Small – Non-confluent	▪ Caseating granulomas or positive and fast bacilli straining ▪ Confluent (≥ 5 / biopsy) and large (diameter > 200 µm) granulomas; submucosal

- Management
  - Stable patient
    - Anti-TB therapy
      - RIPE MWF x 2 months then RI MWF x 4 months vs. daily regimen, RIPE x 2 then RI x 7 months
        - High cure rate
        - Equally effective at healing ileocecal and colonic TB
        - 79 vs. 75%
      - Anti-TB Rx can result in fairly prompt clinical response
      - Often within 2 weeks
  - Unstable / complication
    - Surgery
    - Obstruction
    - Closed loop BO
    - Perforation
    - Massive bleed
  - Stricturing Disease
    - Often due to active-TB lesion or scarring from healing
    - Mass lesions associated with hypertrophic form often do not respond well to MM = need surgery for luminal compromise
    - Surgical resection should be conservative
      - Reserved for complications – high grade obstruction, perforation
    - Multiple strictures – stricturoplasty vs. balloon dilation
  - Fistulas
    - Most fistulas and ulcerations respond to RIPE treatment
    - Rarely is surgery ever indicated

COLON


Western
UNIVERSITY · CANADA

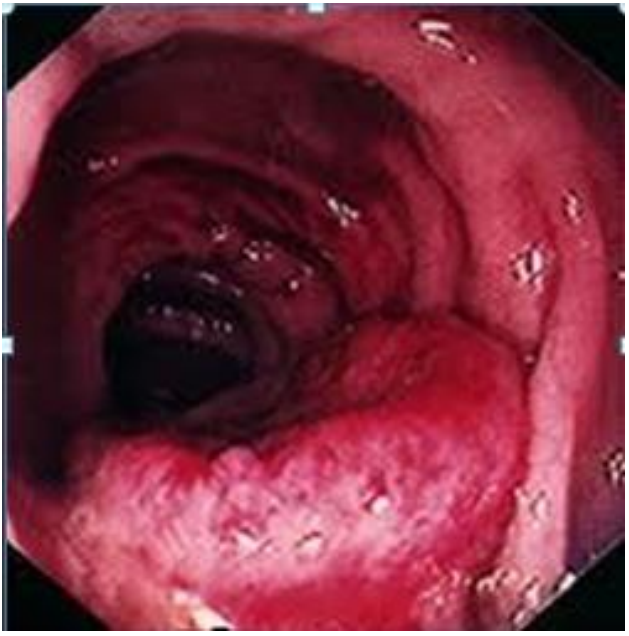
Colorectal Cancer

Amindeep Sandhu

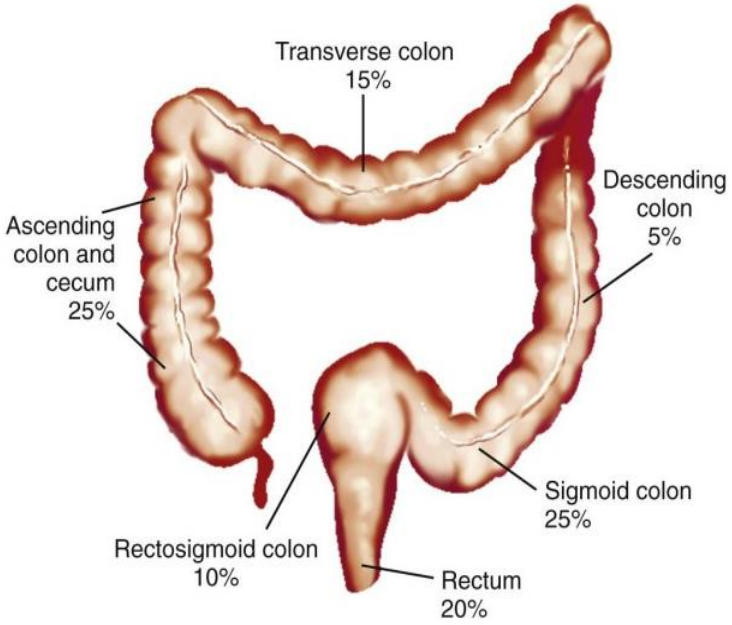
- Epidemiology
  - Constitutes 10% of new cancers in men and women
  - Men = women
  - Lifetime risk of developing CRC is 6%
  - Lifetime risk of dying from CRC is 2.5%

- Pathology

- Gross / endoscopy



- Distribution of CRC within the colon

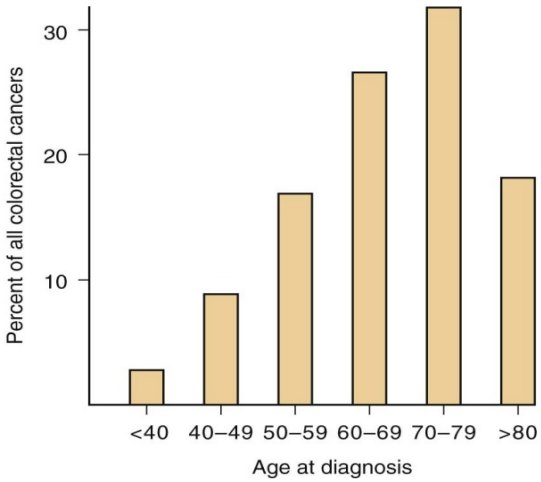


Note: ½ of all CRCs are on left side of colon, within reach of flexible sigmoidoscopy

- Histology
  - Types
    - Average risk ~75%
    - Family history ~20%
    - HNPCC 5%
    - FAP 1%

Abbreviations: FAP, familial adenomatous; HNPCC, hereditary non-polyposis colorectal cancer (aka Lynch syndrome)

- Risk factors
  - Age ≥50 years



  - High-fat, low-fibre diet
  - Personal history of
    - Colorectal adenomas (synchronous or metachronous)
    - ↑ risk of CRC
      - Number of adenomas
      - Size of adenoma (> 1 cm = Conversion Rate = CR, 3%)
      - Villous histology (CR, 17%)
      - Nuclear atypia or dysplasia (CR, 37%)
  - Synchronous carcinomas
    - 0.7% to 7.6%
  - Metachronous carcinomas
    - 1.1% to 4.7%
    - 50% of metachronous cancers arise within 5-7 years of the index lesion

- Family history
  - First-degree relative with colorectal cancer
  - Inflammatory bowel disease
  - Polyposis syndrome

Family Hx	RR
– One fist degree relative with CRC	2.3
▪ < 45 yr	3.9
▪ 45-59 yr	2.3
▪ > 59 yr	1.8
– Two first degree relatives	3.8
– More than Two first degree relatives	4.3
– One second degree or third degree relative	1.5
– Two second degree relatives	2.3
– One first degree relative < 60 yr with an adenoma	2.0

Winawer SJ. Best Pract Res Clin Gastroenterol. 2007;21(6):1031-48.

- African Americans
  - Highest CRC rates and mortality of all ethnic groups
  - Occurs younger
  - More proximally
  - ACG and ASGE recommend screening starts at 45
- Acromegaly
- Transplantation – associated with long-term immunosuppression

- Possibly causative
  - EtOH (2-3 drinks/d RR=1.21, >/4 drinks/d RR= 1.52)
  - Cigarette smoking → RR 1.18
  - Diabetes mellitus → RR 1.38
  - Environmental carcinogens and mutagens
  - Heterocyclic amines (from charbroiled and fried meat and fish)
  - Low dietary selenium

- Genetics
  - Major abnormalities
  - Alterations
    - Proto-oncogenes
    - Abnormalities in genes involved in DNA mismatch repair (MMR)
  - ↓ tumor suppressor gene activity

Gene	Chromo-some	Frequency of Tumors with Gene Alterations (%)	Gene Class
K-ras	12	50	Proto-oncogene
TGF-β1 RII	3	[‡]	Tumor suppressor
APC	5	70	Tumor suppressor
TP53	17	75	Tumor suppressor
DCC	18	70	Tumor suppressor?
SMAD4 (DPC4, MADH4)	18	?	Tumor suppressor
hMSH2	2	[†]	DNA mismatch repair
hMLH1	3	[†]	DNA mismatch repair
hMSH6	2	[†]	DNA mismatch repair

IBD – Associated CRC

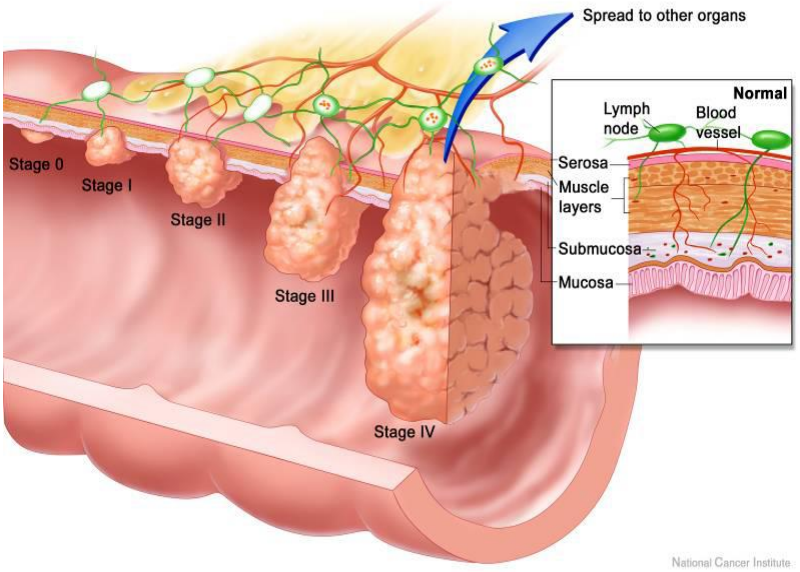
- Pancolitis (ulcerative colitis, Crohn colitis) confers a 5- to 15x ↑ risk (RR) of CRC.
  - Risk begins 8-10 years
  - IBD diagnosis
  - Risk up to 30% after 35 years of disease
- Limited left sided disease
  - 3x ↑ risk (RR)
  - Risk begins 15-20 years after IBD diagnosis
- Proctitis or proctosigmoiditis
  - No ↑ risk
- Risk with
  - Primary sclerosing cholangitis (PSC)
  - Dysplasia-associated lesion or mass (DALM)

Protective factors

- Probable Protective
  - Aspirin, NSAIDs, and cyclooxygenase-2 inhibitors
  - Calcium
  - Hormone replacement therapy (estrogen)
  - Low body mass
  - Physical activity
- Possibly Protective
  - High-fibre diet
  - Vitamins A (carotene-rich foods), D and E
  - Yellow-green cruciferous vegetables

- Clinical features
  - Abdominal pain
  - Weight loss
  - Asymptomatic
  - Proximal colon tumors grow larger than left colon ones
  - Frequency of clinical features
    - R > L
      - Microcytic iron deficiency
    - L > r
      - Altered bowel habit
      - Rectal bleeding
      - Obstruction

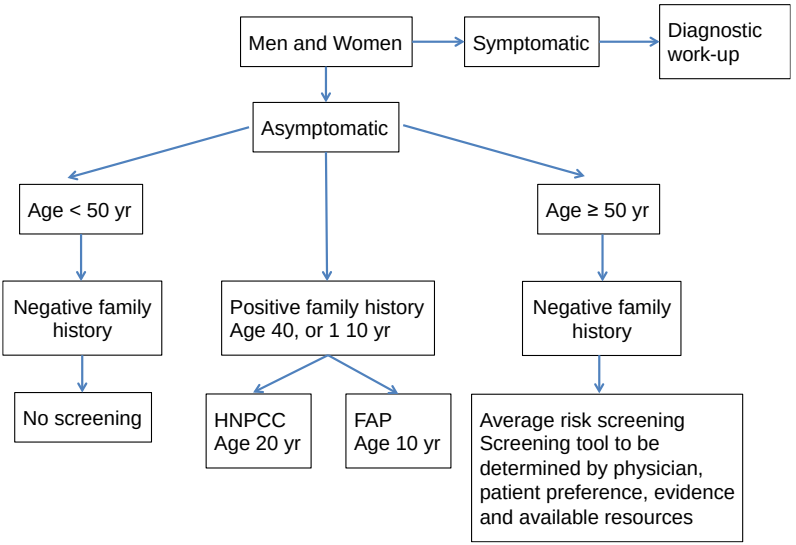
- Staging



AJCC TNM Staging of Colorectal Cancer

Stage	Criteria
0	Carcinoma in situ: intraepithelial or invasion of lamina propria[‡] (Tis N0 M0)
I	Tumor invades submucosa (T1 N0 M0) [Dukes A]
	Tumor invades muscularis propria (T2 N0 M0)
II	Tumor invades through the muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissues (T3 N0 M0) [Dukes B]
	Tumor perforates the visceral peritoneum or directly invades other organs or structures and/or perforates visceral peritoneum[?] (T4 N0 M0)
III	Any degree of bowel wall perforation with regional lymph node metastasis
	N1: metastasis in 1-3 regional lymph nodes
	N2: metastasis in ≥4 regional lymph nodes
	Any T N1 M0 [Dukes C]
	Any T N2 M0
IV	Any invasion of bowel wall with or without lymph node metastasis, but with evidence of distant metastasis
	Any T Any N M1

- Prognosis
  - Poor Prognostic Factors
    - Patient
      - Age < 30 yrs at Dx
    - Tumor
      - Poorly differentiated
      - Mucinous or signet ring cell histology
      - Colonic obstruction or perforation
    - Spread
      - Depth of colon wall penetration
      - > 4 mesenteric lymph nodes
      - Lymphatic or venous invasion
    - Laboratory
      - High preoperative CEA level
    - Grading
      - ECOG 2+, 2+ metastatic sites, peritoneal mets
  - Screening



CAG 2004 Guidelines on CRC screening

Screening for Average risk: CAG Guidelines (2004)

- FOBT q 2 ye
- Flexible sigmoidoscopy ± FOBT q 5 yr
- Flexible sigmoidoscopy combined with FOBT every five years
- Double contrast barium enema q 5 yr
- Colonoscopy q 10 yr, starting 50 yr

USPSTF and ACS Guidelines – Average Risk

Screening Tool	U.S. Preventive Services Task Force*	American Cancer Society (ACS)
○ High sensitivity FOBT (guaiac-based or immunochemical)	q 1 yr	q 1 yr
○ Flexible sigmoidoscopy	q 5 yr + FOBT q 3 yr	q 5 yr
○ Colonoscopy	q 10 yr	q 10 yr
○ Double-contrast barium enema	Not recommended	q 5 yr
○ Computed tomographic colonography	Not recommended	q 5 yr
○ Stool DNA testing	Not recommended	Recommended (interval uncertain)

- Screening with positive: Family History CAG 2004 Guidelines

Group	Age	Colonoscopy
First-degree relative before age 60 yr with CRC or adenomatous polyps	At 40 yr or 10 yrs before the age of Dx	q 5 yr
≥ 2 first-degree relatives at any age		
First-degree relative ≥age 60 yr	40 yr	q 10 yr
In 2 second-degree relatives with CRC		
One second-degree or third-degree relative	50 yr	q 10 yr

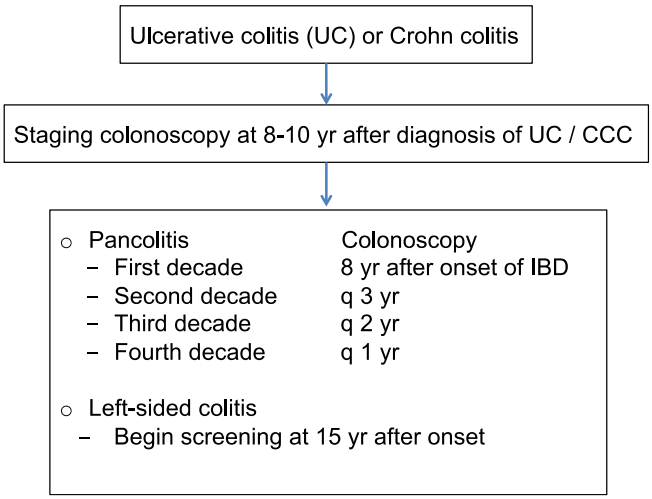
Surveillance of Polyps: CAG 2004 Guidelines

Risk category	Colonoscopy
1-2 tubular adenoma < 1 cm in size	5 years
More than 2 adenomas	3 yr
Incomplete examination	After short interval, based on clinical judgment
Advanced adenoma	
Numerous polyps	
Malignant or large sessile adenoma	

2008 ACS-Multi-Society-ACR Guidelines

Risk category	Recommendation after initial polypectomy
○ Patients with 1 or 2 small tubular adenomas with low-grade dysplasia	5-10 yr
○ Patients with 3 to 10 adenomas or 1 adenoma >1 cm or any adenoma with villous features or high-grade dysplasia	3 yr
○ Patients with >10 adenomas on a single examination	<3 yr
○ Patients with sessile adenomas after piecemeal removal	2 to 6 months (to verify complete removal)

Screening : IBD CAG 2004 Guidelines



Sensitivity of Screening Tests

Test	Sensitivity (%)			
	Adenomas ≤5 mm	Adenomas 6-9 mm	Adenomas ≥10 mm	Cancer
○ Hemoccult II (guaic-based)	2.0	5.0	12.0	40.0
○ Hemoccult Sensa	7.5	12.4	23.9	70.0
○ Fecal immunochemical test (FIT)	5.0	10.0	22.0	70.0
○ Flexible sigmoidoscopy*	75.0	85.0	95.0	95.0
○ Colonoscopy	75.0	85.0	95.0	95.0

- ○ Note
  - Flexible sigmoidoscopy has equivalent sensitivity to colonoscopy for polyps within reach (i.e. left-side of colon)
  - Fecal DNA testing is not yet ready for widespread use for CRC / polyp screeening

Zauber AG, et al. Ann Intern Med 2008;149:659-69.

Guaiac FOBT

Trial	Minnesota (46,000)	Notting-ham (152,850)	Funen (61,933)	New York (22,000)
○ ↓ CRC mortality	33% for the annual group (18 yr) 21% for biennial group (18 yr)	15% (7-8 yr)	18% (10 yr)	43% (10 yr)
○ Compliance	Annual 75%; Biennial 78%	50%	56%	-

- Summary: ~2% ↓ MR rate per yr from CRC mortality, despite compliance of only ~75%

False –ve FOBT (guaiac-based)

- Prolonged storage of slides
  - Degradation of hemoglobin by colonic bacteria
- Ascorbic acid (vitamin C) ingestion
- Improper sampling
- Lesion not bleeding at the time of stool sample

False +ve gFOBT

- Red meat
- Uncooked fruits and vegetables
  - Vegetable peroxidase
    - Broccoli
    - Cantaloupe
    - Cauliflower
    - Radish
    - Turnip
- Medications
  - Iron supplements
  - Aspirin
  - NSAIDs
- Any source of GI blood loss

* Note
  - A positive FOBT may be false-positive from the prospective of finding colonic polyp / cancer as part of a screening program, but is a true positive for there being blood in stool

Fecal immunochemical tests (FIT)

- Specific for
  - Human blood
  - Lower GI bleed (does not detect UGIB because hemoglobin is digested in small bowel)
- Not affected by diet or drugs
- Requires fewer stool samples
- About 2x ↑ sensitivity
- More expensive than gFOBT
- Note
  - Annual stool testing has been shown to ↓ mortality from CRC by ~2% per yr, but misses ~75% of clinically dangerous adenomatous polyps (≥10 mm)
  - Take home message, better than doing nothing

Flexible Sigmoidoscopy

- PROS
  - May be done in the office
  - Easier bowel preparation, usually done without sedation
  - Inexpensive, cost-effective, may be done by trained family physician, nurses, nurse practitioners
  - ↓ MR from rectal cancer by 60-70%

- CONS
  - Detects only one-half of adenomas
  - 40% of cancers arise proximal to splenic flexure → missed
  - 75% of proximal cancers have no synchronous adenomas distal to splenic flexure, to warn for nee for colonoscopy
  - Often limited by discomfort, poor bowel preparation
  - Bottom line
    - Fle' sig' does only half the job

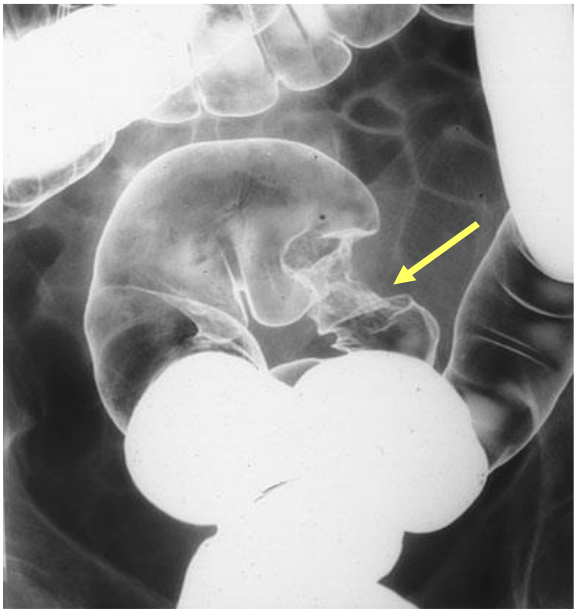
Newcomb PA, et al. J Natl Canc Inst 1992;84:1572-5.
Rex DX, et al. Gastrointest Endosc 1999;99:727-30.
Selby JV, et al. N Engl J Med 1992;326:653-7.
Stewart BT, et a. Aust N Z J Surg 1999;69:2.

Double-Contrast Barium Enema (DCBE)

- PROS
  - Low cost, widely available examines whole colon

- CONS
  - Never studied as a screening test
  - Misses 50% of adenomas < 1 cm (National Polyp Study)
  - Sensitivity for CRC in patients with positive FOBT: 50-75%
  - Poor specificity
  - Best interval unknown

Winawer SJ, et al. Gastroenterol 1997;112:594-642.
Rex DX. Endoscopy 1995;27:200-202.
Lieberman D. N Engl J Med 2000;343:163.

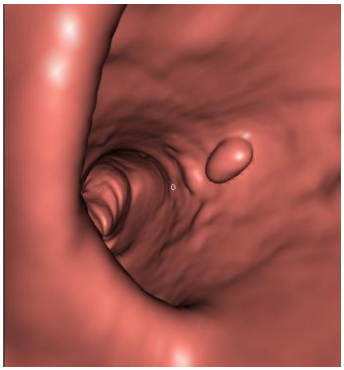


Colonoscopy

- PROS
  - Examine entire colon
  - Therapeutic – polyps removed at time of procedure
- CONS
  - Risk of complications
  - Requires bowel prep, missed work, escort home
  - Incomplete procedures ~5%
  - Miss rate ~10 % (significant lesions), including flat polyps

Virtual Colonoscopy

- 2531 asymptomatic patients were screened



Size	Sensitivity	Specificity
> 1 cm	90%	86%
6-9 mm	84 %	86-89 %

Johnson CD, et al. N Engl J Med. 2008;359(12):1207-17.

Virtual Colonoscopy: PROS

- No sedation necessary
- Low risk
- Fast
  - 20 min vs. 25 min for colonoscopy (plus 60-min recovery)
- Detection of extra-colonic lesions
- Useful for
  - Failed colonoscopy
  - Unsuitable patients
  - Patients with obstruction preventing completion of full colonoscopy

- CONS
  - Preparation still needed
  - Stool and fluid can simulate/obscure polyps
  - Flat polyps can be missed (same with colonoscopy)
  - Steep learning curve for radiologist
  - Radiation dose
  - Not interventional
  - Bottom line
    - ~5% less sensitive than standard white light colonoscopy, but the technology is improving rapidly

➢ Treatment

- Pre-operative evaluation
  - Colonoscopy (if not done already)
  - Staging CT
  - CEA level
- EUS or MRI (for rectal lesion)
- Surgery
  - Wide resection of the involved segment
    - Removal of lymphatic drainage
  - Resection performed even in the presence of distant metastases
    - Prevent obstruction or bleeding
  - Patient not fit for surgery
    - Palliation
      - Laser photo-ablation
      - APC
      - Stent placement

Rectal Carcinoma

- Rectosigmoid and Upper Rectum
  - Transabdominal low anterior resection with primary anastomosis
- Lower Rectal Lesions
  - Distal margin ≥ 2 cm normal bowel
    - Sphincter-saving resection can be performed if a distal margin of at least 2 cm of normal bowel can be resected below the lesion
  - < 2 cm normal bowel
    - Abdominoperineal resection (APR) of distal sigmoid, rectum, and anus
    - A permanent sigmoid colostomy is performed otherwise

Post-resection Surveillance Guidelines: American Society of Clinical Oncology 2005

- History and physical

Post-op' Yr	
1-3	q 3-6 mon
4-5	q 6 mon
> 5	q 1 yr

- CEA
  - Stage II / III
    - q 3 mon x 36 mon if

Candidates for surgery or systemic therapy.

- Since adjuvant 5-FU-based therapy can falsely ↑ serum CEA
- Wait until adjuvant therapy is finished to initiate surveillance is advised.

○ CT chest	– Stage II high risk III ▪ Q 1 yr x 3 yr – Pelvis CT q 1 yr x 3 yr for rectal cancer surveillance
○ FOBT	– The data are sufficient to recommend against periodic FOBTs in surveillance for colorectal cancer recurrence
○ Colonoscopy	– Full colonoscopy in the preoperative or perioperative setting to document a cancer-free and polyp-free colon. Patients who present with an obstructing cancer should undergo full colonoscopy within six months of surgery. Repeat colonoscopy is recommended at three years, and if normal, every 5 yrs thereafter
○ Flexible procto-sigmoido-scopy(rectal cancer)	– For patients who have not received pelvic radiation therapy, flexible sigmoidoscopy is recommended every six months for five years.

Adjuvant Chemotherapy

- Colon Cancer
  - ○ High risk stage II (controversial)
    - – Not recommended routinely
  - ○ Stage III
    - – Recurrence ↓ 42%
    - – Death rate ↓ 33%
  - ○ Post complete resection of liver or pulmonary metastases

- Rectal Cancer
  - Neoaduvant chemoradiotherapy
    - Locally advanced (T3/4) rectal cancer
  - Adjuvant chemoradiotherapy ↓ recurrence and ↓ mortality
    - Stage II
    - Stage III
  - Radiation
    - Never indicated for colon cancer not affecting rectum

Metastatic CRC

  - Liver is the most common site of distant metastases from CRC
  - 10% - 25% of patients have liver metastases at initial presentation

- Operable disease
  - Survival rate after liver resection is 40%
  - Resection is recommended if
    - ≤ 4 metastases
    - No extrahepatic metastases
    - Intent is curative

- Non-operable disease
  - Chemotherapy is mainly palliative
    - Overall survival ~ 1½ yr
      - Median survival
        - 2 years with chemo'
        - 5-6 mon with best supportive care
    - Maintain quality of life (QoL)
  - Palliative treatment (to ↓ obstructive symptoms)
    - Stent
    - Photoablation
    - APC


Western
UNIVERSITY · CANADA

Microscopic Colitis: Lymphocytic and Microscopic Colitis

Nilesh Chande

- History
  - First described in 1976
- Demography
  - ~20 / 10^5
- Clinical
  - Chronic watery diarrhea – near 100%
  - Abdominal pain
  - Weight loss
  - Fecal urgency
  - Nocturnal stools
  - Fecal incontinence
  - Bloating
  - Note
    - Often mislabeled as irritable bowel syndrome (IBS)
- Causes, associations, risk factors
  - ↑ age
  - Female gender
  - Autoimmune disease
    - Thyroid disease
    - Celiac disease
    - Diabetes
    - Smoking
    - Medications
  - Past / current history of malignancy
  - Solid organ transplantation

- Likelihood that a drug causes Microscopic Colitis
  - High Likelihood
    - Aspirin
    - Acarbose
    - Lansoprazole
    - Cyclo3 Fort*, Cirkan*
    - NSAIDs
    - Ranitidine
    - Sertraline
    - Ticlopidine
  - Intermediate Likelihood
    - Carbamazepine
    - Flutamide
    - Lisinopril
    - Modopar (levodopa and benserazide).
    - Oxetorone
    - Paroxetine
    - Simvastatin
    - Tardyferon (iron and ascorbic acid)
    - Vinburnine

*extract from Ruscus aculeatus, hesperidine methylchalcone and ascorbic acid)

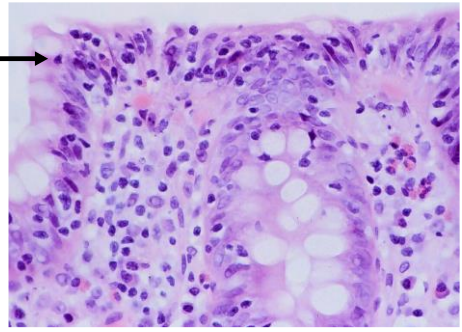
Beaugerie & Pardi Aliment Pharmacol Ther 2005; 22: 277–284.

- Type
  - Collagenous colitis
    - ↑ thickness of subepithelial collagen band
  - Lymphocytic colitis
    - ↑↑ intraepithelial lymphocytes
  - A mixed form also occurs

- Diagnostic imaging
  - Colonoscopy
    - Normal
- Pathology
  - A biopsy diagnosis
  - Changes most prominent at R colon
    - Take biopsies 3 from right, 3 from transverse, 3 from left colon (normal appearing mucosa on colonoscopy

Lymphocytic colitis

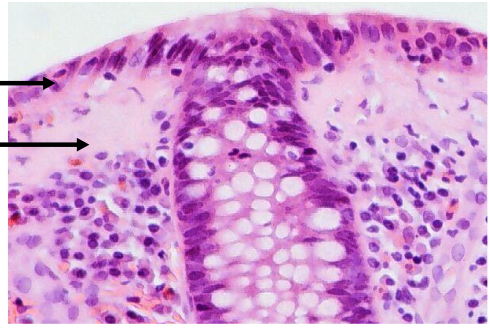
↑↑ intraepithelial lymphocytes (> 20 / 100 epithelial cell)



Collagenous colitis

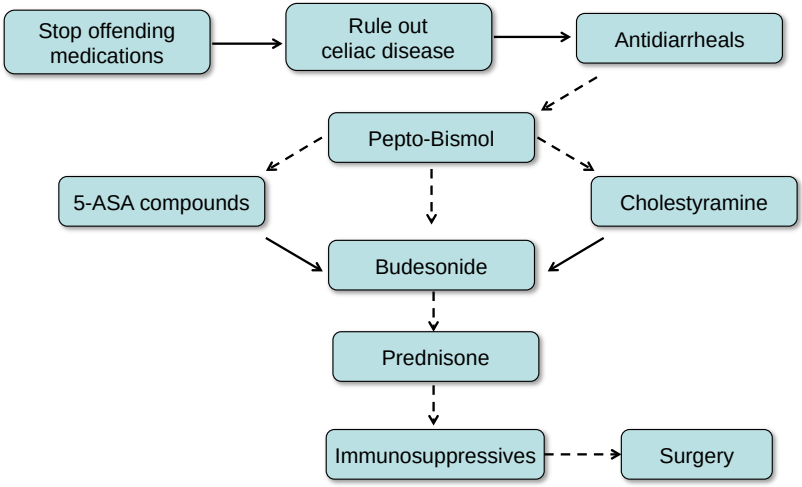
↑ Intraepithelial lymphocytes

Thickened subepithelial collagen band (> 10 µm)



- Treatment

Management Algorithm



- - - > Limited data only

- Stop offending meds
  - Acarbose
  - ASA
  - Lansoprazole (Omeprazole, esomeprazole)
  - NSAIDs
  - Ranitidine
  - Sertraline
  - Ticlopidine

- Acute
  - R/O celiac disease
    - 7-25% of microscopic colitis (MC) patients also have celiac disease
    - Screen all MC patients with anti-TTG Ab and IgA level
    - Treating celiac disease (gluten-free diet) may improve symptoms attributed to microscopic colitis

  - Anti-diarrheal
    - No RCT evidence
    - Many patients will have self-treated with OTC Imodium
      - Most will not have maximized dosing
    - Still likely to benefit from high-dose treatment
      - Imodium (loperamide) 2 mg tabs up to 8/day
      - Lomotil (diphenoxylate-atropine) 5 mg tabs up to 4/day
      - Codeine in increasing doses
    - Can be used as adjunct with other therapies

  - Bismuth subsalicylate (Pepto-Bismol)
    - 1 RCT, abstract only
    - Nine 262 mg tabs daily x 8 weeks
    - Patients
      - 9 with collagenous colitis
      - 5 with lymphocytic colitis
    - Clinical response rate 100% (0% with placebo)
    - Histological response in most patients

- Cholestyramine
  - Cholestyramine 4 g po od may have benefit when added to 5-ASA (at least for patients with collagenous colitis)
  - No RCT involving cholestyramine only
  - Case reports of benefit with this therapy alone
  - May be useful for certain patients or as an adjunct with other treatments
- 5-ASA
  - 1 RCT, unblended, and no placebo group
  - 2 groups:
    - 5-ASA 800 mg po tid
    - 5-ASA 800 mg po tid + cholestyramine
  - 6 months duration
  - Clinical response rates:
    - 23 patients with collagenous colitis
      - 5-ASA alone: 73%
      - 5-ASA/cholestyramine: 100%
    - 41 patients with lymphocytic colitis
      - 5-ASA alone: 85%
      - 5-ASA/cholestyramine: 86%
  - Histological response seen as well

Calabrese C, et al. J Gastroenterol Hepatol. 2007;22(6):809-14.

  - 1 RCT in collagenous colitis
    - Salofalk 3 g po od
    - Budesonide 9 mg po od
    - Placebo po od
    - No difference between 5-ASA inferior to budesonide

Miehlke S, et al. Gastroenterology 2014; 146: 1222-30.

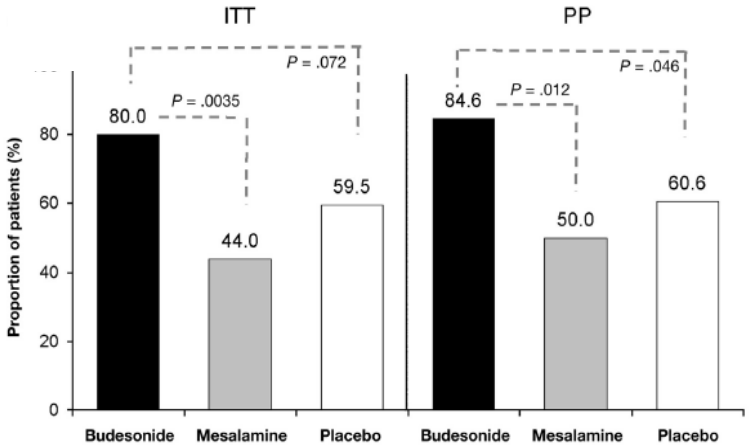
- Budesonide
  - 3 RCTs including 94 patients with active collagenous colitis
  - 9 mg po od (or tapering) x 6-8 weeks
  - Overall clinical response rate 81% (placebo 17%)
  - Pet
    - Odds ratio 12.32
    - 95% CI 5.53 – 27.46
      p < 0.00001
  - Histological response also found

Miehlke S, et al. Gastroenterology 2002;123:978-84; Baert F, et al. Gastroenterology 2002;122:20-25; Bonderup OK, et al. Gut 2003;53:248-51

- RCT in collagenous colitis
- 92 patients randomized to 1 of 3 groups:
  - Budesonide 9 mg po od
  - Salofalk 3 g po od
  - Placebo po od

} Each for 8 weeks

Clinical remission ≤ 3 BM der day)



- 1 RCT, 42 patients with active lymphocytic colitis

- Budesonide 9 mg/day vs. placebo x 6 weeks
- Results:
  - 86% vs. 48% clinical response (P=0.01)
  - 73% vs. 31% histological response (P=0.03)

Miehlke S, et al. Gastroenterology 2014; 146: 1222-30.

- Maintenance: Budesonide
  - 2 RCTs including 80 patients with collagenous colitis who responded to budesonide
  - 6 mg po od x 6 months
  - Clinical response rate 75% (placebo 25%)
  - Histological response 48% (placebo, 15%)
    - OR 5.88
    - 95% CI 1.90 – 18.17
      p < 0.002
  - Option use budesonide as maintenance therapy for frequent relapsers
  - Prednisolone
    - 1 RCT
    - Only 11 patients with collagenous colitis
    - 50 mg po od x 2 weeks
    - Trend towards clinical improvement
    - Study may have been too short and under powered

Munck LK, et al. Scan J Gastroenterol 2003;38:606-10

  - Immunosuppressives
    - Used for severe steroid-dependent / refractory disease
    - No RCT data
      - Azathioprine 2.0-2.5 mg/kg/day or 6-mercaptopurine 1-1.5 mg/kg/day
      - Methotrexate 10-25 mg po weekly
      - Cyclosporine also reported

Surgery

- Rarely required
- Diverting ostomy without colectomy
- Proctocolectomy with IPAA if permanent ostomy not wanted

Numerous Case Reports Other Pharmaceutical Treatments

- Antibiotics
- Antidiarrheals
- Bulking agents
- Ketotifen
- Octreotide
- Pentoxifylline
- Spasmolytics
- Topical steroids
- Verapamil

Medication Summary

Medication	Suggested dosing	Notes
○ Loperamide (or other antidiarrheals)	2 mg po prn (up to 8 tabs daily)	– Can be used intermittently or regularly. – Effective for breakthrough symptoms when on other treatments.

	Medication	Suggested dosing	Notes
○	Bismuth subsalicylate	3 x 262 mg tabs po tid x 8 weeks	– Possible bismuth neurotoxicity with long-term use. – If regular use required should be taken in 8 weeks on, 8 weeks off regimen.
○	Mesalamine	800 mg po tid x 6 months or longer	– Maybe effective for inducing and maintaining response if used continuously. – Addition of cholestyramine may have additional benefit for collagenous colitis.
○	Cholestyramine	4 g po od x 6 months or longer	– Can be used alone or with mesalamine to induce and maintain response.
○	Budesonide	9 mg po od (or in a tapering course) x 6-8 weeks to induce response. 6 mg po od x 6 months or more to maintain response.	– Patients that relapse after induction dosing should be considered for maintenance therapy.

	Medication	Suggested dosing	Notes
○	Prednisone	50 mg po od x 2 weeks, then tapered	– Optimal duration of therapy not clear. – Used for cases of budesonide failure.
○	Azathioprine / 6-mercaptopurine	AZA 2-2.5 mg/kg/day or 6-MP 1-1.5 mg/kg/day indefinitely	– Used only for severe steroid dependent – Refractory disease
○	Methotrexate	10-25 mg po weekly indefinitely	– Used only for severe steroid dependent or refractory disease

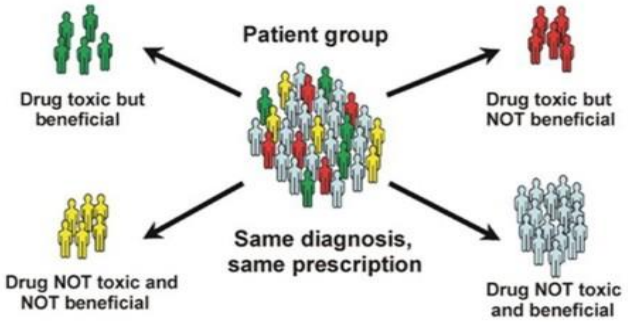
- Summary
  - Collagenous and lymphocytic colitis are an important cause of chronic watery diarrhea
  - Take multiple colonic biopsies even if endoscopically normal in patients with chronic diarrhea
  - Budesonide use for acute and maintenance therapy is evidence-based
  - Various other therapies reported, but few randomized controlled trials
  - Minimize exposure to more toxic medications

Pharmacogenomics in IBD

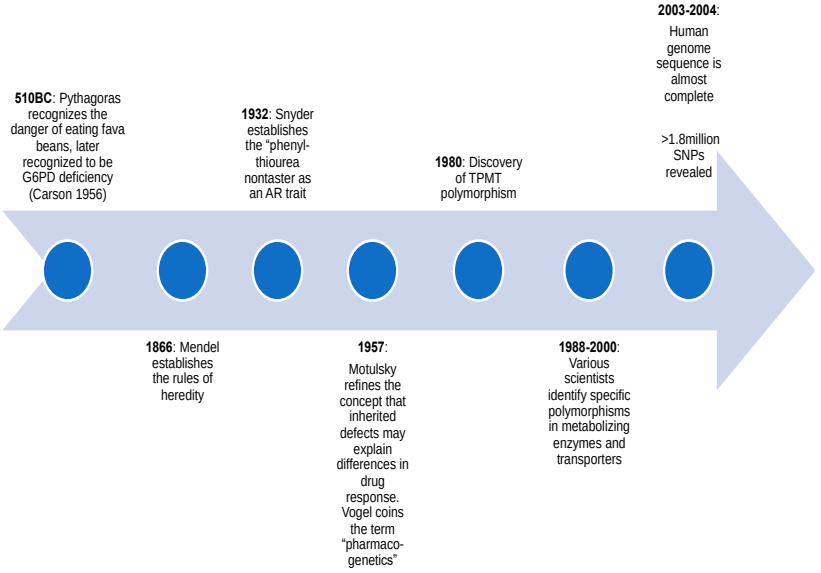
Aze Wilson

Pharmacogenomics

"The study of how genes affect a person's response to drugs."



Condensed History of Pharmacogenomics



Definitions

- Single nucleotide polymorphism (SNP)
  - DNA sequence variation occurring commonly within a population (e.g. 1%) in which a single nucleotide — A, T, C or G — in the genome (or other shared sequence) differs between members of a biological species
- Pharmacokinetics (PK)
  - What the body does to a drug, referring to the movement of drug into, through, and out of the body
- Pharmacodynamics (PD)
  - The study of the biochemical and physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect
- Area under the concentration-time curve (AUC)
  - The total body exposure to a drug after the administration of a dose

How this relates to IBD: The therapeutic dilemma

- IBD is incurable
- Patients are on treatment long term
- Rates of resistance and loss of response are high
  - IFX (55%)[1]
  - Prednisone (30%)[2]
  - Budesonide (50%)[3]
- ↑ resistance and ↓ response to
  - ↑ risk of toxicity
  - ↑ costs
- Our understanding of the *factors* affecting drug metabolism in IBD is limited

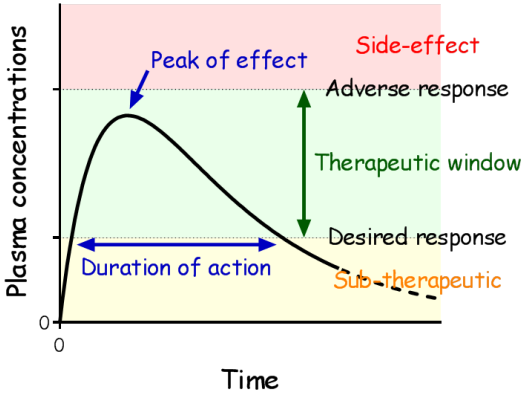
[1] Hanauer SB, et. al. Lancet. 2002; 359(9317):1541-9.
[2] Rutgeerts P, et al. N Engl J Med. 1994; 331(13):842-5.
[3] Greenberg GR, et al. N Engl J Med. 1994; 331(13):836-41.

One size may not fit all….

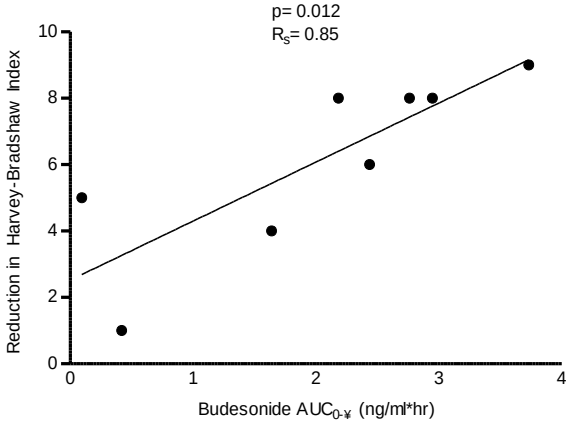
- Patients enrolled in RCTs may not represent the typical IBD population (new generalizability)
  - Retrospective cohort study of referral centre patients (n= 206)[1]
  - Inclusion and exclusion criteria of published biologic trials were applied
  - 34% CD patients and 26% UC patients would actually be eligible for a trial
  - Trial ineligible CD patients had lower response rates than trial eligible patients (60% vs 89%; p= 0.03)

Ha C, et al. Clin Gastroenterol Hepatol. 2012;10(9):1002-7.

The Therapeutic Window



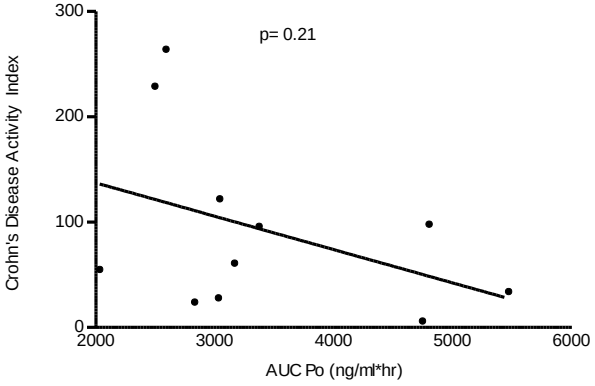
Budesonide plasma concentrations correlate with efficacy



- A greater reduction in Harvey-Bradshaw Index seen with higher drug AUC of budesonide

Wilson et.al., unpublished, 2016

Methotrexate plasma concentrations correlate with efficacy



Adapted from: Wilson et.al. Aliment Pharmacol Ther. 2013; 37(3):340-5.

- In CD and RA, low-dose plasma MTX correlates with drug efficacy in Crohn disease and in rheumatoid arthritis
- Infliximab [plasma] concentrations greater in responders than in non-responders
- Cumulative probability of sustaining initial clinical response to infliximab is greater for higher than lower plasma concentrations of infliximab (> 3 μg/mL vs. ≤ 3 μg/mL)

Azahioprine plasma concentrations based on method of dosing do not correlate with efficacy

Clinical remission rates at week 16 in the intention-to-treat and pre-protocol analyses of 50 patients with Crohn disease

	Intention to treat	Per protocol
○ Weight-based dosing	4/25 (16%)*	3/12 (25%)**
○ Personalized dosing	1//25 (40%)	9/15 (60%)

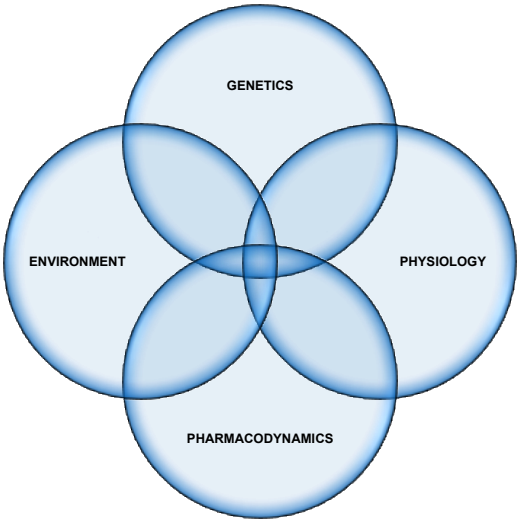
* p = 0.11; ** p = 0.12

Printed with permission: Dassopoulos T, et al. Aliment Pharmacol Ther. 2014;39(2):163-75.

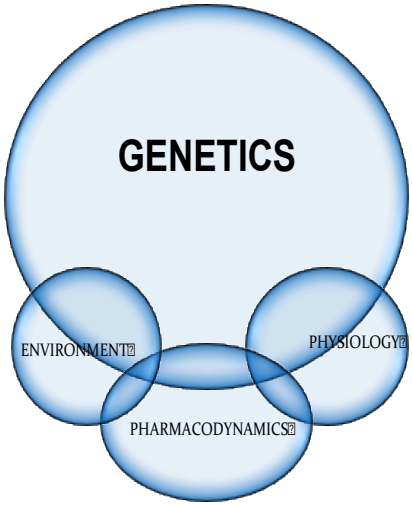
- Methods
  - Personalized vs Weight-based dosing of azathioprine in Crohn disease (n=50)
    - Randomization to either
    - Personalized dosing based on TPMT testing and then targeting 6-TGN levels of 250-400 pmol/8x10 RBC)
    - Weight-based dosing of 2.5 mg/kg/day

- Message
  - Method of dosing azathiopurine to achieve targeted 6-TGN plasma concentrations based on personalized dosing based on TPMT testing is not statistically superior to weight-based dosing in achieving clinical remission at 16 weeks in Crohn disease

- There are several factors which affect plasma concentrations of drug/drug metabolites



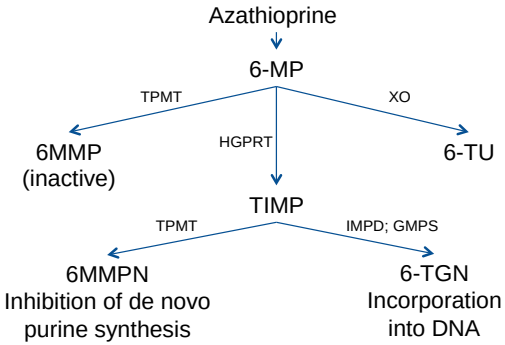
- There are several predictors of clinical outcomes



- Metabolizing enzyme expression/ activity
- Transporter (uptake, efflux) expression/ activity
- Interaction with signal transduction pathways

Thiopurine methyltransferase (TPMT): from bench to bedside

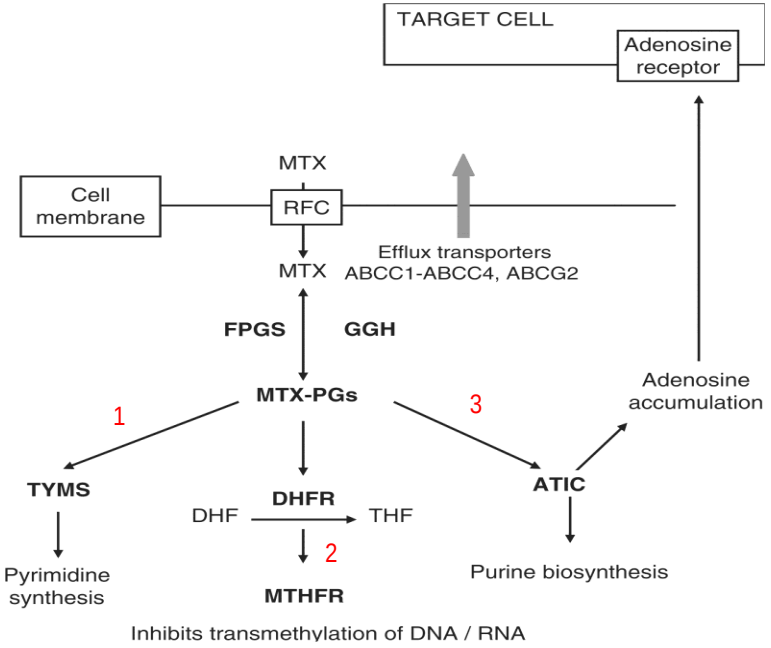
- TPMT: only inherited determinant of drug response used in IBD clinical practice



- SNPs in *TPMT* gene play a key role in:
  - Myelosuppression
  - Bone marrow toxicity
- Plasma 6-TGN concentration positively correlates with clinical response
  - Cellular accumulation of 6-TGN is *inversely* proportional to TPMT activity
- *TPMT* gene is found on chromosome 6p22.3
- *TPMT* SNPs are associated with changes in protein expression and function
  - There is a trimodal distribution of activity
- Caucasians:
  - 90% have high activity of TPMT
  - 11% have intermediate activity
  - 0.3% have low or no activity
- Effects of different TPMT activity levels
- TPMT low/absent activity
  - ↑ risk of developing severe, life-threatening side-effects (bone-marrow suppression) if prescribed a standard dose
- TPMT intermediate (reduced) activity
  - May be at ↑ risk of toxicity at a standard dose of thiopurine drug
- TPMT typical activity
  - Expected to respond to standard dose of a thiopurine drug
  - No increased risk of side effects due to gene status
- **Three SNPs** account for 80-95% of **low or intermediate** TPMT activity in caucasians:
  - *TPMT**2, *TPMT**3A, *TPMT**3C

- *TPMT**2: single nucleotide transversion leading to an AA substitution = 100x reduction in TPMT activity
- *TPMT**3A: double nucleotide transition leading to two AA substitutions
- *TPMT**3C: A719G mutation = 1.4x reduction in activity

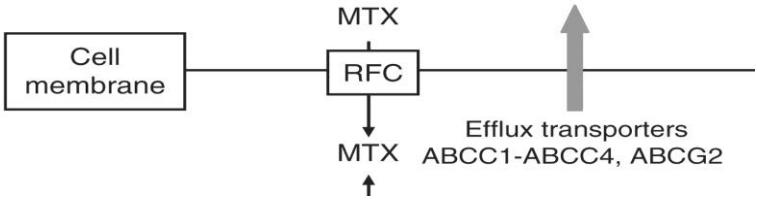
Methotrexate



Printed with permission: Hider SL, et al. Rheumatology (Oxford) 2007;46(10):1520-4.

- Pharmacogenetics

  - SNP in the RFC protein has been identified
    - Polymorphism G80A associated with higher plasma levels (Dervieux et al. 2004)
    - Toxicity vs. efficacy – no PCT show an association (Wesser et al. 2006)



  - Multiple SNPs have been identified
    - None studied with respect to the outcome of methotrexate therapy

  - GGH SNPs influence MTX-PG levels
    - 401TT = ↓ MTX-PGs
    - C452T = ↓ GGH activity (no association with toxicity or efficacy, Stratten et al. 2007)

  - MTHFR gene is the best studied gene in MTX metabolism
  - MTHFR is a central regulatory enzyme in the folate pathway
  - 15 SNPs identified: C677T and A1298C

- Thymidylate synthase (TYMS) – key enzyme in cellular proliferation via complex pathway
- Homozygous tandem repeat in TYMS genes = better MTX response (Dervieux et al 2004)

Methotrexate: MTHFR SNPs

Study	Patients	MTX toxicity	MTX efficacy
Van Ed et al	236 RA patients (48% variant allele)	C677T 2 x risk for stopping MTX (LE)	No association
Urano et al	106 RA patients	C677T Increased risk for toxicity	No association
Berkun et al	93 RA patients	C677T: no difference 1298C: toxicity	No association
Wessels et al	205 RA patients	No association	A1298: ↑ efficacy C677T: ↑ efficacy
Herlinger et al	102 IBD patients	MTHFR 1298C: more toxicity	No association

5-ASA Compounds

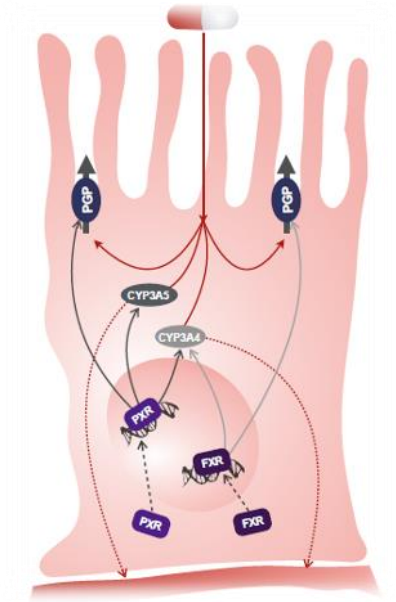
- 5-ASA compounds are acetylated via N-acetyltransferase (NAT) in the liver and gut
- The acetylated metabolite is excreted in the urine
- SNPs in *NAT* genes are associated with rapid vs slow acetylators[1]
- 50% of Caucasians are slow acetylators[2]
- There is inadequate data on the ability to predict 5-ASA response based on NAT SNPs in IBD

[1] Sim E, et al. Toxicology 2008;254(3):170-83.
[2] Wang Y, et.al. Mol Biol Rep 2014;41(3):1849-55.

Biologics

- Gene variants that have been associated with IFX response in IBD include
  - TNF
  - TNFAIP3
  - Cell surface receptors: TNFRSF1A and 1B
  - FasL (apoptosis ligand)
  - FCGR3A receptor
- No studies have been consistently replicated
- No SNP predicted to influence TNF expression, metabolism or signalling has been consistently associated with IFX response

OTHER COMMON DRUG DISPOSITION REGULATORS



- FXR regulates
  - P-gp
  - PXR
  - CYP3A4 and 3A5
- PXR regulates
  - P-gp
  - CYP3A4 and 3A5

Courtesy of Cheynne McLean 2015

Intestinal Drug Metabolism

- P-gp is a transmembrane efflux protein encoded by *MDR1* gene[1]
- P-gp is involved in exporting endogenous compounds and xenobiotics from specific tissues, including drugs used in IBD
- CYP3A4 is a key metabolizing enzyme that serves to deactivate many commonly used drugs[2]
- Together, intestinal PGP and CYP3A4 may act in a coordinated manner and play a key role in 1st pass metabolism

Proteins and Genes which influence IBD Drug Transporters and Metabolizers

Drug	Protein (gene)	Effect	Reference
○ Anti-TNF	FXR *(NR1H4)*	Suppression of NFκB pathway	Gadaleta 2011
	PXR *(NR1/2)*	Suppression of NFκB pathway	Shah 2007
○ Azathioprine	P-gp *(MDR1)*	Efflux from intracellular space	Wojtal 2009; Mendoza 2007
	P-gp *(MDR1)*	Efflux from intracellular space	Farrell 2000; Dilger 2004
○ Budesonide	CYP3A4 (*CYP3A4)*	Conversion to inactive metabolite via oxidation	Ufer 2008
	P-gp *(MDR1)*	Efflux from intracellular space	Dilger 2004
	CYP3A5 *(CYP3A5)*	Conversion to inactive metabolite via oxidation	Ufer 2008
○ Methotrexate	P-gp *(MDR1)*	Efflux from intracellular space	Takatori 2006; Norris 1996; Gifford 1998

- The presence or absence of specific SNPs in *MDR1*, *PXR* and *FXR* may allow for the identification of IBD patients at risk for drug resistance and drug adverse reactions.

Genetics Can Predict Drug Response

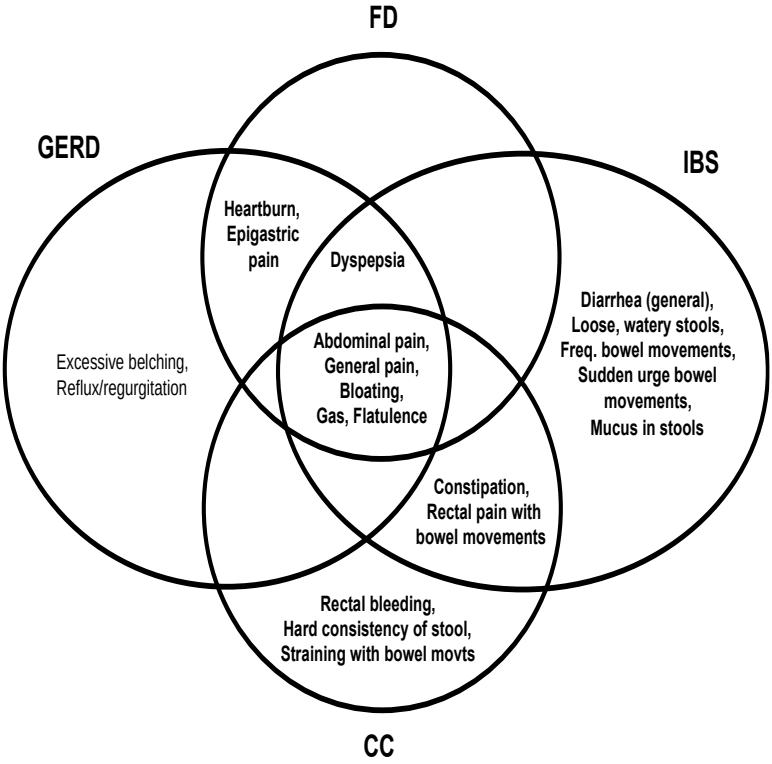
AIM: to evaluate the relationship between drug response in IBD and SNPs in the following genes encoding key drug disposition regulators: *MDR1, FXR, PXR, CYP3A4,* and *CYP3A5*

- **Summary**
  - Pharmacogenomics and the ability to personalize medical therapy is here!
  - TPMT deficiency remains the only genetic test to be used in IBD clinical practice.
  - The clinical relevance of other genetic variants found in the pathways regulating drug disposition, purine biosynthesis, folate and anti-TNF-α therapies remain to be established.
  - Clinical validation of newly identified biomarkers is necessary before implementation into routine clinical practice.

Evidence Based Treatment of Chronic Constipation and Constipation-Predominant IBS

Brian Yan and Waleed Alghamdi

- Definition
  - Symptomatic Overlap in GI Disorders



Abbreviations: CC, chronic constipation; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome;

ROME III

IBS	CIC
○ Recurrent pain or discomfort 3d/month for last 3 months PLUS 2 or more of: – Improve with BM – Onset with change of frequency of BM – Onset with change in consistency of BM	○ Must in include 2 of in 25% of BM: – Straining – Lumpy, hard stools – Sensation of incomplete evacuation – Sensation of anorectal blockage – Manual maneuvers ○ < 3 BM/week ○ Loose stools rare without laxative ○ Insufficient criteria for IBS

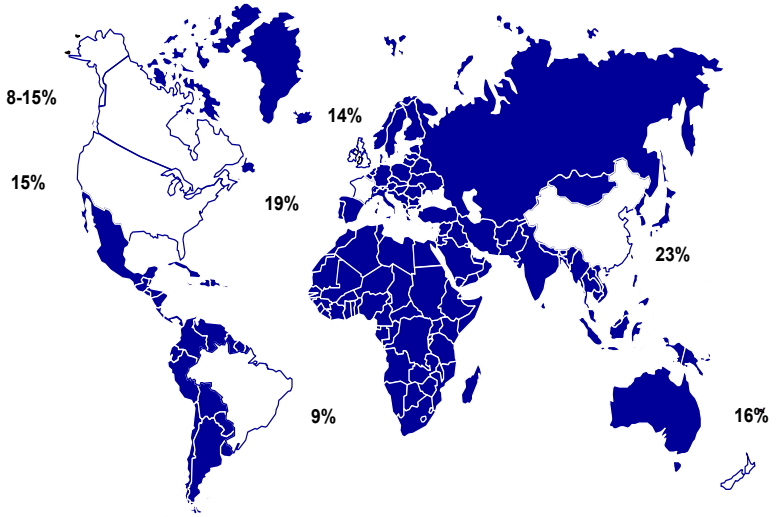
Abbreviations: CIC, chronic idiopathic constipation; IBS, irritable bowel syndrome

Adapted from: Lonseth G, et al. Gastroenterol 2006; 130: 1480 – 1491.

- Demography
  - Affects up to 12-13% of the population[1]
    - 33% are IBS-C
  - More common in women[2]
  - Prevalence decreases with age[3]
  - 2/3 of IBS sufferers do not seek a physician's help[4]
  - Accounts for 12% of primary care and 28% of gastroenterology practices[5]
  - Annual cost of disease: ~$10.5 billion[6]
  - Can be a considerable health burden[7]
  - > 3 times frequency of work loss[8]

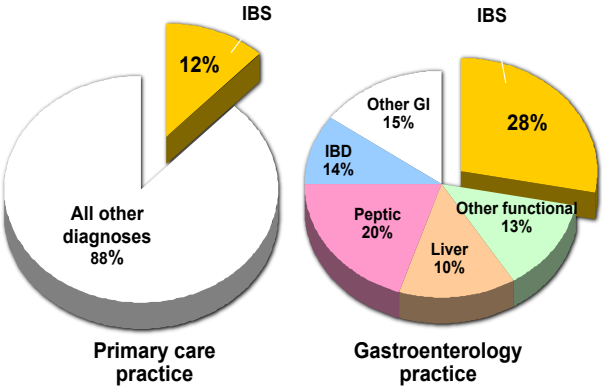
[1] Thompson WG, et al. *Dig Dis Sci 2002;* 47(1):225-35.
[2] Sandler RS. *Gastroenterology.* 1990;99: 409-15.
[3] Kay L, et al. *J Intern Med.* 1994;236:23-30.
[4] Drossman DA, et al. *Gastroenterology.* 1998;95: 701-708.
[5] Jailwala J, et al. *Ann Intern Med.* 2000;133:136-147.
[6] Talley NJ, et al. *Gastroenterology.* 1995;109:1736-1741.
[7] Drossman DA. *Aliment Pharmacol Ther.* 1999;13:3-14.
[8] Drossman DA, et al. *Dig Dis Sci.* 1993;38:1569-1580.

- World Prevalence of IBS



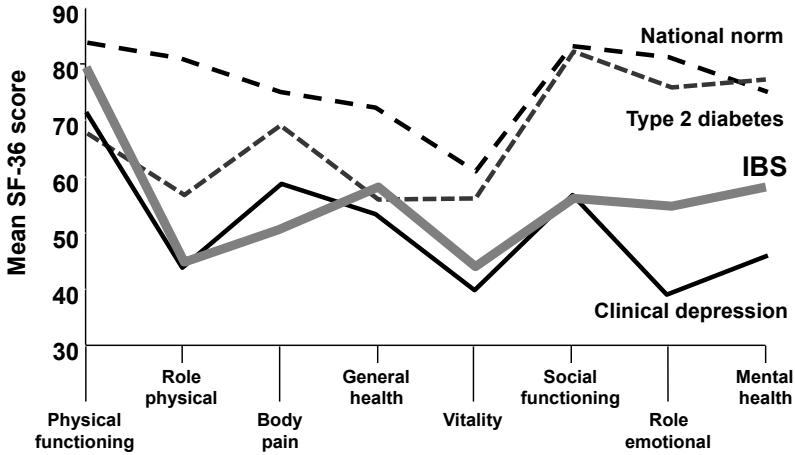
Drossman et al., DPS 1993; Sandler et al. GE 1984; Jones et al., MJ 1992; Thompson et al. DDS 2002.

- Prevalence of IBS Diagnosis in Primary Care and Gastroenterology



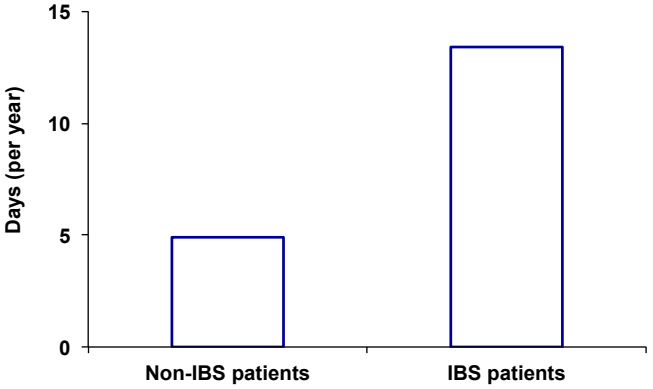
Mitchell CM, et al: *Gastroenterology*. 1987; 92:1282-84.

- IBS and Quality of Life



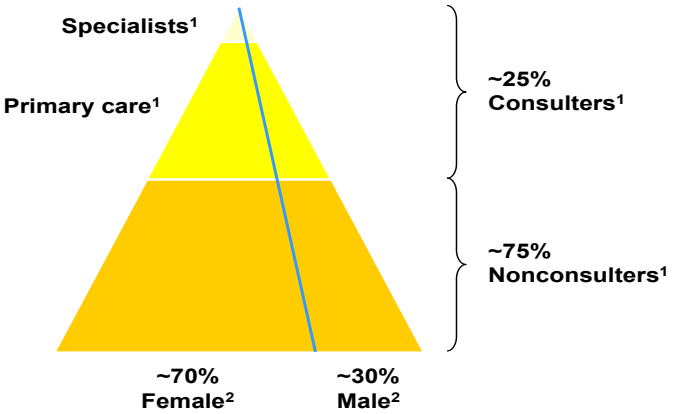
Wells, et al: *Aliment Pharmacol Ther.* 1997;11:1019-30.

- Reported IBS-Related Missed Work/School Days



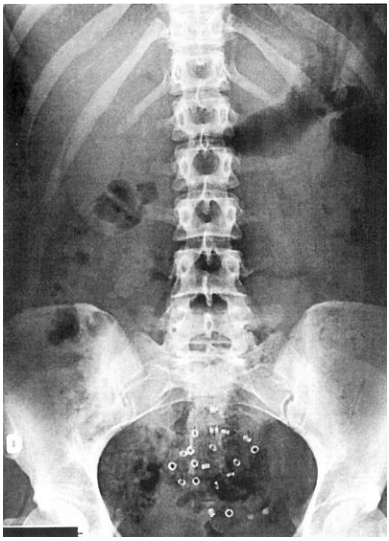
Drossman DA, et al: *Dig Dis Sci*. 1993;38:1569-80.

- IBS Consultation Pattern



[1] Drossman D: *Ann Intern Med.* 1992;116(pt 1):1009-16.
[2] Sandler RS: *Gastroenterology*. 1990;99:409-15.

➢ Investigating



- Choose Wisely
  - Avoid performing a colonoscopy for constipation in those under the age of 50 years without family history of colon cancer or alarm features.
    - Constipation is a common problem and systematic review data suggests this is not an accurate symptom in diagnosing organic disease. If the patient is also under the age of 50 and does not have a family history of colon cancer and there are no alarm features such as anemia or weight loss, then the risk of colorectal cancer is very low and the risks of colonoscopy usually outweigh the benefits in these patients.

- ASGE Recommendations
  - No scope for initial evaluation if no alarm features
  - Perform colonoscopy
    - Rectal bleeding, FOB+ stool, Fe def anemia, weight loss, obstructive symptoms
    - > 50 and no prior screening colonoscopy
    - Need for dilatation of benign strictures or insertion of cecostomy tube if clinically indicated

ASGE Standards Committee. Gastrointest Endsoc 2014; 80: 563 - 565

Colonic Transit Study

A. If 5 or fewer markers remain, patient has grossly normal colonic transit.

B. Most rings are scattered about the colon. Patient most likely has hypomotility or colonic inertia.

C. Most rings are gathered in the rectosigmoid. Patient has functional outlet obstruction.

- Treatment
  - Lifestyle
    - Diet
    - Stress Management
  - Psychological Issues
  - Pharmacotherapy

- OTC Treatments
  - Bulking agents
    - Metamucil (Psyllium)
    - Wheat Bran (insoluble fibre)
    - Benefibre (wheat dextrin)
    - Citrucel (Methylcellulose)
    - Inulin
  - Stimulants
    - Senna
    - Sodium Picosulfate
    - Ex-Lax
    - Bisacodyl
    - Castor Oil
    - Glycerine
    - Cascara, rhubarb, aloe
  - Softeners/Surfactants
    - Docusate
  - Lubricants
    - Mineral Oil
  - Osmotics
    - PEG
    - Lactulose
    - Milk of magnesia, Mg Citrate
    - Sodium Phosphate
    - Glycerine

- Note: High Placebo Response Rate in GI Clinical Trials

Author	Drug	Placebo Response (%)
Piai	Prifinium	50
Milo	Domperidone	34
Page	Dicyclomine	54
Heefner	Desipramine	60
Myren	Trimipramine	67
Longstreth	Psyllium	40
Fielding	Timolol	59
Fielding	Trimebutine	58

- ACG Guidelines on Treatment of Chronic Constipation

Summary of results of monograph on interventions for CIC.

Statement	No. of trials	No. of pts	RR symptoms (95% CI)	NNT (95%CI)	Recom-menda-tion	Quality of evidence
Some fiber supplements increase stool frequency in patients with CIC.	3	293	0.25 (0.16–0.37)	2 (1.6–3)	Strong	Low
PEG effective in increasing stool frequency and improving stool consistency in CIC.	4	573	0.52 (0.41–0.65)	3 (2–4)	Strong	High

Statement	No. of trials	No. of pts	RR symptoms (95% CI)	NNT (95%CI)	Recom-menda-tion	Quality of evidence
○ Lactulose effective in increasing stool frequency and improving stool consistency in CIC.	2	148	0.48 (0.27–0.86)	4 (2–7)	Strong	Low
○ Sodium picosulfate and bisacodyl effective in CIC.	2	735	0.54 (0.42–0.69)	3 (2–3.5)	Strong	Moderate
○ Prucalopride more effective than placebo at improving symptoms of CIC.	8	3,140	0.81 (0.75–0.86)	5 (4–8)	Strong	Moderate
○ Linaclotide effective in CIC.	3	1,582	0.84 (0.80–0.87)	6 (5–8)	Strong	High
○ Lubiprostone effective in the treatment of CIC.	4	651	0.67 (0.58–0.77)	4 (3–6)	Strong	High
○ Biofeedback effective in CIC patients with demonstrated evidence of pelvic floor dyssynergia.	3	216	0.33 (0.22–0.50)	2 (1.6–4)	Weak	Low

Abbreviations: CI, confidence interval; CIC, chronic idiopathic constipation; NNT, number needed to treat; PEG, polyethylene glycol; RR, relative risk

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- ACG Guidelines on Treatment of IBS-C

Summary of results of monograph on interventions for IBS

Statement	No. of trials	No. of pts	RR symptoms (95% CI)	NNT (95%CI)	Recom-menda-tion	Quality of evidence
○ Specialized diets may improve symptoms in individual IBS patients.	3	230	NA	NA	Weak	Very low
○ Fiber provides overall symptom relief in IBS.	14	906	0.86 (0.80–0.94)	10 (6–33)	Weak	Moderate
○ Psyllium, but not bran, provides overall symptom relief in IBS (data presented for psyllium).	7	499	0.83 (0.73–0.94)	7 (4–25)	Weak	Moderate
○ There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	2	198	NA	NA	Weak	Very low

Statement	No. of trials	No. of pts	RR symptoms (95% CI)	NNT (95%CI)	Recommendation	Quality of evidence
○ Probiotics improve global symptoms, bloating, and flatulence in IBS.	23	2,575	0.79 (0.70–0.89)	7 (4–12.5)	Weak	Low
○ Rifaximin effective in reducing total IBS symptoms and bloating in IBS-D.	5	1,805	0.84 (0.78–0.90)	9 (6–12.5)	Weak	Moderate
○ Certain anti-spasmodics provide symptomatic short-term relief in IBS.	23	2,154	0.69 (0.59–0.81)	5 (4–9)	Weak	Low
○ Peppermint oil superior to placebo in improving IBS symptoms.	5	482	0.51 (0.33–0.79)	3 (2–4)	Weak	Moderate
○ There insufficient evidence to recommend loperamide for use in IBS.	2	42	0.44 (0.14–1.42)	NA	Strong	Very low
○ As a class, antidepressant effective in symptom relief in IBS.	17	1,084	0.67 (0.58–0.77)	4 (3–6)	Weak	High

Statement	No. of trials	No. of pts	RR symptoms (95% CI)	NNT (95%CI)	Recommendation	Quality of evidence
○ A variety of psychological interventions are effective in improving IBS symptoms.	32	2,189	0.68 (0.61–0.76)	4 (3–5)	Weak	Very low
○ Alosteron is effective in females with IBS-D.	8	4,987	0.79 (0.69–0.90)	8 (5–17)	Weak	Moderate
○ Mixed 5-HT4 agonists/5-HT3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	9	2,905	0.96 (0.83–1.11)	NA	Strong	Low
○ Linaclotide is superior to placebo for the treatment of IBS-C.	3	2,028	0.80 (0.75–0.85)	6 (5–8)	Strong	High
○ Lubiprostone is superior to placebo for the treatment of IBS-C.	3	1,366	0.91 (0.87–0.95)	12.5 (8–25)	Strong	Moderate
○ There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	2	166	NA	NA	Weak	Very low

Abbreviations: CI, confidence interval; 5-HT3, serotonin subtype 3; 5-HT4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; NA, not available; NNT, number needed to treat; RR, relative risk.

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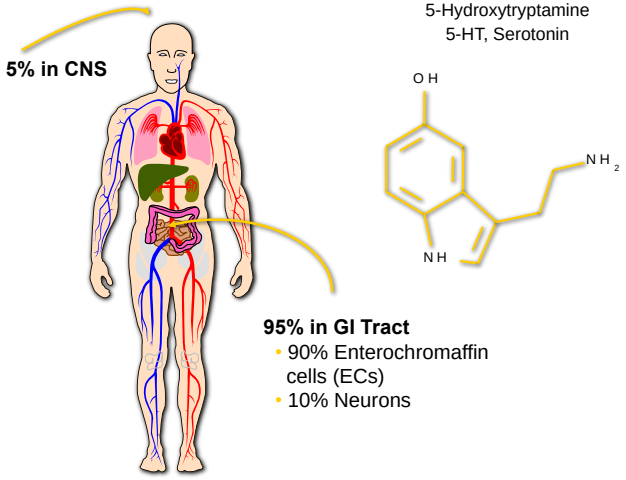
NEWER DRUGS FOR CONSTIPATION

Physiological Distribution of Serotonin



Wood JD: Gastroenterol Endosc News 2000;(suppl):S1-S8.

- Several 5-HT receptor subtypes identified in the human GI tract: 5-$HT_{1,2,3,4}$
- Diverse effects due to different receptor subtypes
- 5-HT_3 and 5-HT_4 receptors involved in multiple GI functions
  - Motor
  - Sensory
  - Secretory

Prucalopride (Resotran™)

- Selective, high affinity 5-HT4 agonist
- Enhances peristalsis and propulsive motor patterns in the GI tract
- Studies: 8 phase III trials
- Pivotal Trial

Treatment Associated Adverse Events Reported by At Least 10% of Patients Receiving the Trial Medication in Any Group

Variable	Prucalopride, 2 mg (N = 207, %)	Prucalopride, 4 mg (N = 204, %)	Placebo (N = 209, %)
Patients with adverse events – no. (%)	80.2	79	71
Nausea	22	22	8
Diarrhea	14	19	15
Headache	27	29	12

Adapted from: Camelleri, M et al. N Engl J Med 2008;358:2344-54.

- Special Considerations: Caution
  - Reduced efficacy of oral contraceptive pill (OCP)
  - Spontaneous abortions in females <35 higher in prucalopride vs. placebo
  - 26 unintended pregnancies in open label study
  - 4 fetal deaths
  - 8 fetal malformations

- Adverse events
  - CNS
    - Anxiety / depression
  - Heart
    - Ischemic heart disease
    - Palpitations
    - Atrial dysrhythmia
  - GI
    - Diarrhea
    - Ischemic colitis
  - GU
    - Urinary incontinence
  - Endocrine
    - Prolactin related events

- Prucalopride: Health Canada 2008
  - Based on the Health Canada review of data on quality, safety and efficacy, Health Canada considers that the benefit/risk profile of Resotran™ is favourable in the treatment of chronic idiopathic constipation in adult female patients in whom laxatives failed to provide adequate relief.
  - Note: Similar results in men (Yiannakou Y et al, Am J Gastro 2015; 110:741–748)

Linaclotide (Constella™)

- Phamacology
  - 14 amino acid molecule
  - Minimally absorbed
    - Acts locally at the mucosal surface of the bowel
    - Effects are limited to the GI tract
  - Guanylate cyclase – C agonist
    - Related to guanylin and uro-guanylin (naturally occuring peptide hormones)

  - Regulates intestinal fluid and electrolyte homeostasis via GCC mediated production of cGMP
  - Abundant GC-C expression in intestinal epithelial cells
- Pharmacodynamics
  - ↑ fluid secretion
  - ↑ rate of intestinal transient
  - visceral nociception

- Pivotal Studies: Chronic Constipation
  - Lembo et al. NEJM 2011; 365: 527 – 536
    - 2 Randomized placebo controlled trials
    - 12 weeks, dual dose
    - 1276 pts with chronic constipation
  - Rao S, et al. Am J Gastroenterol 2012; 107:1714-1724
    - Double blinded, placebo controlled RCT
    - 800 pts CIC, 26 weeks
  - Outcomes CSBMs/wk
    - Linacotide
      - 145 mcg 16-21 %
      - 290 mcg 19-21 %
    - Placebo 4-6 %

Abbreviations: CSBMs, complete spontaneous bowel movements

  - Benefits of linaclotide
    - Percent of patients with abdominal pain improvement ≥ 30% by week
    - ≥ BM / week and an increase of ≥ 1 complete spontaneous BM (CSBMs) from baseline for at least 9/12 weeks

IBS-C

- Phase 3, DB-RCT
- 290 mcg linaclotide vs. placebo
- 26 week study
- Primary endpoints:
  - Improvement of ≥30% from baseline in average daily worst abdominal pain score
  - Increase of ≥1 spontaneous complete BM from baseline, both in the same week for ≥6/12 weeks
  - >30% improvement in the weekly average of abdo pain score
  - ≥3 CSBM and increase ≥1 from baseline
  - Combination of above

FDA Primary End Point:

	Linaclotide 290 mcg	Placebo	P value
– CSBMs	48	23	< 0.0001
– Pain*	49	35	< 0.0001

* pain, > 30% improvement in pain for > 6 / 12 wks

- CSBMs and pain improvement continued for 26 wk treatment

Abbreviation: CSBMs, complete spontaneous bowel movements

Chey W, et al. Am J Gastroenterol 2012; 107:1702–1712.

- Dose recommendation of linaclotide
  - Chronic constipation 145 mcg/d
  - IBS-C 290 mcg/d

- Summary
  - Chronic Constipation: 145ug/d
  - IBS-C: 290 ug/day
  - Adverse events: Diarrhea
    - No severe side effects or deaths in studies out to 78 weeks
  - Notice of Compliance by Health Canada: December 2013
  - Many prior options for treatment of CIC and IBS-C
    - Lack proven efficacy from rigorous clinical trials
    - Unfavourable side effect profile
    - Only treat single symptom
  - Prucalopride
    - Selective 5-HT4 agonist approved for CIC, good efficacy data and acceptable side effect profile
  - Linaclotide
    - First in class GCCA approved for CIC and IBS-C
    - Novel dual action of mechanism
    - “Gut specific”
  - Naloxegol
    - First oral PAMORA approved for OIC when conventional laxatives fail

Opioid-Induced Bowel Dysfunction

Waleed Alghamdi and Brian Yan

- Demography
  - Opioids, a mainstay of the treatment for acute and chronic pain, are the most commonly prescribed class of drugs in US
  - More than 240 million prescriptions per year
  - Canada and United States have the highest levels of prescription opioids consumption in the world, and the use of these medications continues o increase dramatically across North America.
  - The rate of dispensing high-dose opioid formulations increased 23%, from 781 units per 1000 population in 2006 to 961 units per 1000 population in 2011.
  - Although these rates remained relatively stable in Alberta (6.3% increase) and British Columbia (8.4% increase), rates in Newfoundland and Labrador (84.7% increase) and Saskatchewan (5% increase) rose substantially.
  - Ontario exhibited the highest annual rate of high-dose oxycodone and fentanyl dispensing (756 tablets and 112 patches per 1000 population, respectively).
  - Alberta's rate of high dose morphine dispensing was the highest in Canada (347 units per 1000 population)
  - Two of the highest rates of high-dose hydromorphones dispensing were found in Saskatchewan and Nova Scotia (258 and 369 units per 1000 population, respectively).
  - Conversely, Quebec had the lowest rate of high-dose oxycodone and morphine dispensing (98 and 53 units per 1000 population, respectively).

- Unfortunately, tolerance to GI side effects does not typically develop and several studies have confirmed a high prevalence of OIBD in patients taking opioid pain medication.
- The most common manifestation of OIBD is opioid-induced constipation (OIC).
- 60% and 90% of subjects with cancer-related opioid use.
- 40% and 60% of patients taking opioids for non-malignant pain.
- Opioid-induced constipation (OIC) is one of the mist debilitating side effects of opioid therapy.
- 54% of patients on both medications fail to symptomatically improve greater than half the time.
- 2011 Cochrane Collaboration review failed to demonstrate the superiority of one laxative over any other.
- A newer class of agents are called peripheral acting mu-opioid receptor antagonists (PAMORAs).
- PAMORAs reverse or prevent the peripheral side effect of OIC while preserving the centrally mediated opioid analgesic effects.

➢ Pathogenesis

- Opioid-induced constipation (OIC) is due to effects on mu-opioid receptors present in the GI tract.
- ↓ muscular contraction
- ↓ water and electrolyte secretion
- Increased rectal sphincter tone
- ↓ rectal contractility

- Clinical
  - Dry Mouth
  - GERD
  - N/V
  - Bloating
  - Abdominal pain
  - Anorexia
  - Hard stools
  - Constipation
  - Incomplete evacuation

Abbreviation: OIBD, opioid-induced bowel dysfunction

Tack J, et al. Exper Rev Gastroenterol 2014; 8(8): 855-861; Chey WD, et al. N Engl J Med 2014: 370(25): 2387-2396.

- Adverse effects
  - ↓ activities of daily livings
  - Missed work, reduced work productivity
  - ↓ levels of overall health, health related QoL, well being
  - Hospitalization in 16% of cancer pts
  - Estimated 30% require reduction or stop opioids due to OIC

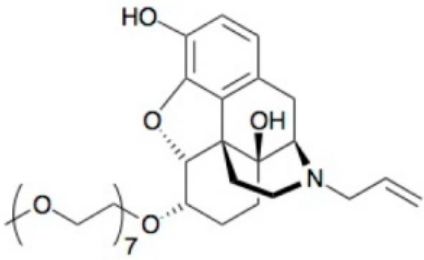
Tara G, et al. Canadian Family Physician 2014; 60(9): 826-832; Tack, J et al. Expert Rev Gastronterol Hepatol 2014; 8: 855 -861; Candy B, et al. Cochrane Database Sys Rev 2011;1: CD003448; Meissner W, et al. Eur J Pain 2009;13:56-64; Kumar L, et al. Gastroenterol Res Pract 2014;2014:141737

Available PAMORAs

- Methylnaltrexone (Relistor®)
  - Approved in 2008
  - Limited due to SC administration
  - Indicated in advanced illness
  - May have increased risk of GI perforation
- Alvimopam (Entereg®)
  - For postop ileus
  - Increased risk of MI
  - Not approved in Canada
- Naloxegol (Movantik®)

Naloxegol (Movantik®)

- Pegylated naloxone
- Peripheral mu-opioid antagonist
- Low affinity
  - Delta (brain, peripheral sensory)
  - Kappa (brain, spinal cord, peripheral sensory)
- Pegylation reduces passive permeability (i.e. through Blood Brain Barrier)
- Substrate for P-glycoprotein transporter (ie: increase efflux across blood brain barrier)



- Pharmacology
  - Dose
    - 25 mg in the morning on empty stomach
    - Requires adjustment if CrCl < 60 ml/min >>> 12.5 mg daily
  - Metabolism
    - Mainly hepatic via CYP3A4 (primarily)
  - Half-life elimination
    - 6-11 hrs
  - Time of peak
    - < 2 hrs
  - Excretion
    - Feces 68%, urine 16%
  - Mechanism
    - Mu receptor antagonist
    - Naloxone conjugated with PEG polymer (to limit BBB crossing ability)
  - Pricing in US
    - 12.5 mg/ 25 mg ($ 299.52)
    - Pregnancy class C, unknown if it is excreted in breast milk
- Efficacy Studies
  - KODIAC-1 – Phase 1
  - KODIAC-2
  - KODIAC-3 – Phase 2
  - KODIAC-4 – Phase 3
  - KODIAC-5
  - KODIAC-6 – Discontinued
  - KODIAC-7 – Safety extension trial
  - KODIAC-8 – 52w, Open label, randomised, parallel group

- **Critical Review:** Naloxegol for Opioid-induced Constipation in Patients with Non-cancer Pain

William D, et al. N Engl J Med 2014; 370:2387-2396.
(The Study: KODIAC-4/5)

- In a phase 2b trial, naloxegol at a daily dose of 25 or 50 mg increased in frequency of spontaneous bowel movements in patients with opioid-induced constipation, whereas 5 mg had no significant effect.
- The 25 mg dose was selected for phase 3 development on the basis of the safety and efficacy profile in the phase 2b trial. They included a 12.5 mg dose to continue exploring the threshold for the minimally effective dose.
- RR were 60% and 35% with active treatment and placebo, respectively.

Webster L, et al. Pain 2013;154: 1542-1550.

Methods

A. Patients and Study Design

- Two identical, multicenter, randomized
- Double-blind, parallel-group, placebo controlled
- Phase 3 studies in USA and Europe

KODIAC-04 [STUDY 04]	KODIAC-05 [STUDY 05]
○ 115 centers	– 142 centers
○ Start: March 14, 2011	– March 28, 2011
○ End: August 16, 2012	– September 20, 2012
○ 652 patients randomized	– 700 randomized
○ 524 ITT patients (80.4%) completed	– 537 ITT patients (76.7%) completed

- 15 patients were excluded from ITT set (study, n = 3; naloxegol 12.5 mg, n = 4; naloxegol 25 mg, n = 4; study 05, placebo, n = 1; naloxegol 12.5 mg, n = 1; naloxegol 25 mg, n = 2).
- These patients were found, prior to database lock and unblinding, to have participated in the program multiple times at different centers.

KODIAC-4/5

- Combined 1352 patients
- Non-cancer pain and opioid-induced constipation
- Placebo vs. 12.5mg vs. 25mg oral Naloxegol
- Primary end point: 12 week response rate
  - ≥ 3 BMS/week and Increase from baseline of ≥ 1 spontaneous BM for ≥9/12 weeks, and ≥3 of last 4 weeks

- Patient Disposition (All Randomized Patients)

	STUDY 04				STUDY 05			
		Placebo	Naloxegol 12.5 mg/d	Naloxegol 25 mg/d		Placebo	Naloxegol 12.5 mg/d	Naloxegol 25 mg/d
○ Enrolled	1750				1969			
○ Non-randomized	1098				1269			
○ Randomized	652	217	217	218	700	233	233	234
○ Study discontinuations		36	37	41		44	53	59
○ Completed study		177	174	173		187	177	173

- Most common maintenance opioid medications used
  - Hydrocodone + acetaminophen
  - Oxycodone
  - Morphine
- OIC defined as
  - Documented < 3 SBMs/ week on average over the 2-week OIC confirmation period. (patients with uneven distribution of SBMs across the 2-week OIC confirmation period 0 SBM in 1 week with ≥ 4 SBMs in the other week, were excluded)

Plus

- Patients must report ≥ 1 of the following symptoms in at least 25% of the BMs recorded in the electronic diary (eDiary) during the OIC confirmation period:
  - Bristol Stool Scale (BSS) stool type 1 or 2
  - Moderate, severe, or severe straining
  - Incomplete BM (patients who have 0 BMs over the 2-week OIC confirmation period will not be randomized)
  - A minimum of 50% of patients are to meet criteria for being laxative inadequate responders (LIR).

- Target population
  - Inclusion criteria
    - Adult patients who are receiving a stable maintenance opioid regimen (total daily dose of 30 to 1000 mg of oral morphine, or equianalgesic amount[s])
    - 1 or more other opioid therapies
    - For a minimum of 4 weeks
    - Non-cancer-related pain
    - > 3 spontaneous bowel movements (SBMs) / week and at least 1 OIC associated symptoms at screening and have a confirmed diagnosis of OIC.
  - Exclusion criteria
    - Uncontrolled pain despite opioid analgesic therapy (patients in the study were required to be receiving a stable maintenance regimen for pain with no anticipated change for the duration of the study)
    - Cancer within 5 yr before enrollment

- Conditions or use of medications associated with diarrhea or constipation (other than opioid-induced constipation)
- Evidence of gastrointestinal obstruction
- Conditions that confer an increase risk of bowel perforation

- Stratification and randomization
  - Stratification was on the basis of prescreening laxative-response status
  - Randomization was in a 1:1:1
  - Three study groups (25 mg group), (12.5 mg group), (placebo group)
  - Once daily for 12 weeks
  - 50% or more of patients randomly assigned to a group were patients with an inadequate response to laxative (ILR)

- Definition of inadequate response to laxatives
  - Taking medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and whose symptoms were rated as moderate, severe, or very severe in at least one of the four stool-symptom domains on the baseline laxative-response questionnaire.
  - Laxatives and other bowel-treatment regimens (e.g. prune juiceor herbal products) are not allowed.
  - If a bowel movement had not occurred within 72 hr after the last recorded bowel movement, the use of bisacodyl as a recue medication was permitted.

- Only bisacodyl (10 to 15 mg; maximum 3 daose per episode) followed by one-time use of an enema (if necessary) was allowed as rescue treatment.
- Opioid antagonists, mixed antagonists, and strong inhibitors of cytochrome P-450 3A4 and P-glycoprotein were prohibited.
- All patients provided written informed consent at screening, before any study procedure were performed.
- Study protocol were design by AstraZeneca with input from the academic authors, who served as consultants to the sponsor.
- Study conduct, monitoring and data analysis were performed by Quintiles, a contract research organization, under supervision of the sponsor.
- All authors had full access to the study data and attest to the completeness and accuracy of the data and statistical analysis.
- The first author wrote the first draft of the Introduction and Discussion without any written assistance, revise the first draft of the Methods and Results (as prepared by the medical writer contracted by the sponsor), and reviewed and revised all subsequent version of the manuscript.
- Editorial support was provided by Complete Healthcare Communications, and was paid for by the sponsor.

- Primary end point
  - Response rate (response to treatment) during the 12-week treatment period.

- Response defined as (≥ SBM (bowel movements without the use of rescue laxative treatment in the previous 24 hr) per week and an increase of ≥ SBM over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks.
- Note
  - If patients did not record electronic diary entries for at least 4 of 7 days in a given week, they are classified as not having a treatment response during those weeks.
  - Patients who discontinued the study prematurely were classified as not having a response during the weeks after discontinuation.

- Key secondary efficacy variables
  - The response rate in the subpopulation of patients with an inadequate response to laxatives before study enrollment.
  - The time to the first dose spontaneous bowel movement
  - The mean number of days per week with one or more spontaneous bowel movements

- Additional secondary efficacy end points
  - The mean number of spontaneous bowel movements per week
  - Severity of straining (measured on a 5-point scale, with 1 denoting no straining and 5 denoting an extreme amount of straining)
  - Stool consistency (assessed on the Bristol stool scale)
  - Rescue laxative use

- Safety-related variables
  - Adverse events
  - Changes in mean daily opioid dose (morphine-equivalent dose in mg/d)
  - Changes in pain score 9on a numeric rating scale, with 0 denoting no pain, and 10 denoting the worst imaginable pain). Adverse events of special interest:
    - Major cardiovascular events and serious GI events related to bowel perforation
    - Withdrawal symptoms (Opioid-withdrawal signs were assessed with the use of the modified Himmelsbach scale)

Farrar JT, et al. Pain 2001;94:149-58; Culpepper-Morgan JA, et al. Clin Pharmacol Ther 1992;52:90-5; Himmelsbach CK. Ann Intern Med 1941;15:829-39

  - Major cardiovascular events and serious GI events related to bowel perforation were evaluated by independent external adjudication committees whose members were unaware of the study-group assignments.
  - Changes in vital signs and electrocardiographic characteristics were also monitored.

- Statistical Analysis
  - Efficacy analyses were performed in the intention-to-treat population.
  - Bonferroni-Holm procedure was used to control for multiple comparison.
  - Adjusted p-value used was 0.025 in 25 mg group.

- Adjusted p-value used was 0.05 in 12.5 mg group compared to placebo.

- Key secondary variables analysis
  - The response rate in the subpopulation of patients with an inadequate response to laxatives before study enrollment (analyzed using chi-square test)
  - The time to first post dose spontaneous bowel movement (analyzed using log-rank test)
  - The mean number of days per week with one or more spontaneous bowel movements (analyzed using mixed-model repeated-measures approach)

- Safety analysis
  - Safety analyses were conducted for patients in the intention-to-treat population who had received one or more doses of the study drug.

- Results
  - Baseline characteristics
    - Balanced across the study groups and were similar between the two studies. Please see Chey WD, et al. N Engl J Med 2014;370:2396-2396.
    - Back pain was the most common reason for opioids use (in 56% and 56.8% of the participants in studies 04 and 05, respectively)
    - Other reasons were arthritis, joint pain, or fibromyalgia pain (in 18.1% and 21.6% of the participants in studies 04 and 05, respectively)

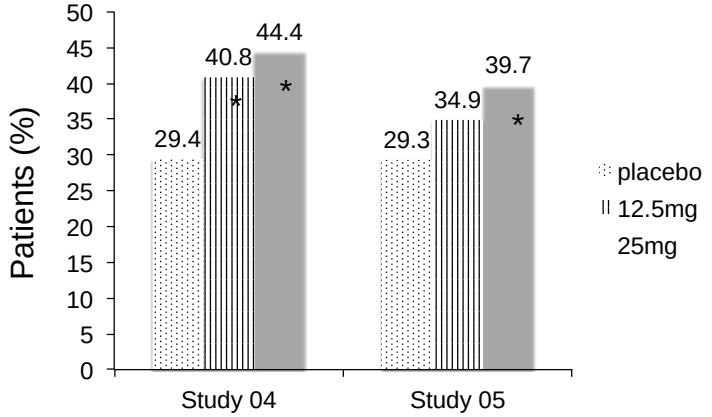
- Headache, migraine, neuralgia, or other pain syndrome (5.9% and 4.5%)
- Other conditions causing pain (primarily musculoskeletal disorders) (19.7& and 17.1%)
- The mean duration of opioid use at baseline was 3.6 yr in Study 04 and 3.7 yr in Study 05
- 71% pf patients had taken a laxative in the 2 weeks before enrollment in both studies
- Most of these patients had used laxatives from one drug class (68.3% and 66.9% in Studies 04 and 05, respectively) or two drug classes (25.8% and 26.9%)
- Most commonly stimulants (61.9% and 52.9%) and stool softeners (28.9% and 31.9%)
- More than 50% of patients in Studies 04 and 05 (54.6% and 53.2%, respectively) were classified as having an inadequate laxative response.

- Response rates over the 12-week treatment period in studies 04 and 05

	STUDY 04 / 05	RR	NNT
- Naloxegol			
▪ 12.5 mg	35 – 41	1.2 – 1.4	9 – 18
▪ 25 mg	40 – 44	1.4 – 1.5	7 – 10
- Placebo	29	-	-

Abbreviations: NNT, number needed to treat; RR, relative risk

Results: Primary Outcome, ITT



* = p<0.05 for comparison with placebo

Abbreviation: ITT, intention-to-treat population

- For the primary end point in both studies, there was no significant interaction between treatment and baseline daily opioid dose with either dose of naloxegol versus placebo (P ≥ 0.11)
- In study 05, because the primary end point did not differ significantly between the 12.5 mg group and the placebo group, significance could not be claimed for any of the key secondary end points in the comparison of the 12.5 mg dose with placebo, according to the multiple-testing procedure.
- The time to the first post-spontaneous bowel movement was significantly shorter with either naloxegol dose than with placebo in study 04 and was significantly shorter with the 25 mg dose than with placebo in study 05 (P < 0.001 for all comparisons).

- The studies 04 and 05, the median time to the first spontaneous bowel movement was 5.9 and 12.0 hr, respectively, in the 25 mg group, as compared with 35.8 and 37.2 hr in the placebo group.
- There was a significant increase in the mean number of days per week with one or more spontaneous bowel movements from week 1 to week 12 with both doses of naloxegol in study 04 and with the 25 mg dose in study 05 ($P < 0.001$ for all comparisons) [this effect remained consistent during the 12 weeks period]
- Over the 12-week period, the proportions of patients who used bisacodyl at least once as a rescue laxative in the placebo group, 12.5 mg group, and 25 mg group were 72.0. 63.4 and 54.7%, respectively, in study 04 and 70.7, 57.3 and 57.3% in study 05.

Kaplan-Meier analysis of the time to first post-dose SBM in studies 04 and 05 (intention-to-treat population)

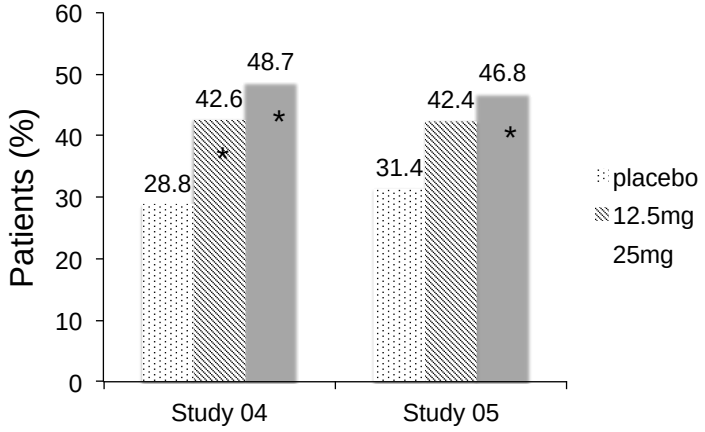
Cumulative % of patients with SBM		Time to first post-dose SBM, hr
25%	PL	8 – 16
	N 12.5 mg	4 – 8
	N 25 mg	2 – 3
50%	PL	35 – 38
	N 12.5 mg	18
	N 25 mg	6 – 18
75%	PL	55 – > 72
	N 12.5 mg	50
	N 25 mg	24 – 50

Time to first post-dose SBM, h		Cumulation % of patients with SBM
○ 24 hr	– PL	25% – 35%
	– N 12.5 mg	50% – 75%
	– N 25 mg	50%
○ 48 hr	– PL	50% – 55%
	– N 12.5 mg	75% – 85%
	– N 25 mg	70% – 75%

- Pooled data from KODIAC 4/5
  - 42% in Naloxegol vs 29% placebo
  - Only 13% difference = unclear clinical relevance
    - Efficacy endpoint of SBM is softer than CSBM
    - Pre-specified study difference was estimated at 25%
  - For CSBM, difference is only 6.2%, NNT = 16

Health Canada Response Not Good Enough !

Results: Laxative Inadequate Subgroup



* = p< 0.05 for comparison with placebo
    - Pooled response rate 48% Naloxegol vs 30% placebo
        - 18% difference = NNT 5.7
    - CSBM
        - 21% Naloxegol vs 10% placebo
        - 11% difference = NNT 9
        - Moderate response but felt to be clinically significant
    - Approved by Health Canada as second line therapy June 2015

- Safety
    - The mean duration of exposure to the study drug was similar in all group in both studies (range, 72.4 to 77.5 days)
    - There were two deaths in study, both in the 12.5 mg group (one from advanced-stage-non-small-cell lung cancer diagnosed during the study, and the other from complications of heart-valve replacement).
    - Only one major cardiovascular event was considered by the investigator to be related to the study drug, and it occurred in the placebo group. No serious gastrointestinal events were adjudicated as probable bowel perforation.

- Conclusion
    - In both studies, naloxegol at a dose of 25 mg was associated with an increased rate of response (10 to 15 percentage points higher than the response with placebo) over a period of 12 weeks.

- Naloxegol at a dose of 12.5 mg was also associated with a significantly higher response rate than placebo (in study 04).
- In addition, other constipation-related end points were improved in the patients who received naloxegol, as compared with those who receive placebo.
- In clinical practice, osmotic and stimulant laxatives are likely to be used before more expensive prescription medication. Thus, the findings that naloxegrol prove beneficial in patients who had persistent symptoms of opioid-induced constipation despite using standard laxative therapies is of potential importance.
- The most commonly reported adverse effects with naloxegol were gastrointestinal and appeared to be dose-ordered in frequency, occurring more commonly in 25 mg group.
- A/E were mild-moderate / shortly after initiation.
- A/E leading to study discontinuation.
- Major cardiovascular events were rare.
- There was no significant changes in opioid dosing or pain score during the study.
- Generally, there was no reduction in opioid-mediated analgesia.

Critical Appraisal

Q: Are the results of the trial valid?

A: Internal validity

Q: What did the study ask?

- The study answers a specific question about efficacy of naloxegol in patients with opioid-induced constipation (OIC) in non-cancer pain population in 12 weeks duration.
- Patients: non-cancer pain population
- Intervention and comparison: 25 mg daily dosing group vs. 12.5 mg vs. placebo
- Primary outcomes: RR during 12 weeks treatment period
  - ≥ 3 spontaneous BM per week
  - Increase in spontaneous BM ≥ 1 over baseline for at least 9 – 12 treatment weeks and at least 3 of the final 4 treatment weeks
- Secondary outcomes
  - RR in the subpopulation of patients with an adequate response to laxatives before study enrollment
  - The time to the first post spontaneous BM
  - The mean no. of days per week with ≥ 1 spontaneous BM
  - The mean no. of spontaneous BM per week
  - Severity of straining (5-point scale)
  - Stool consistency (Bristol stool form scale)
  - Rescue laxative use
- Timing: the study was for the duration of 12 weeks

Q: Was the assignment of patients to treatment randomized?

- Eligible patients who continue to meet study inclusion criteria were randomized in a 1:1 ratio to all groups.

Q: Were the groups similar at the start of the trial?

- Baseline characteristics were balanced across the study groups and similar between the studies.

Q: Aside from the allocated treatment, were the groups treated equally?

- All patients entered the trial were accounted for. Losses to follow up was minimal. All patient were analyzed in groups to which they were randomized using ITT analysis.

Q: Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?

- They used objective measures when it comes to outcomes. It is a double study.

B. External Validity

Q: Will the results help me in caring for my patients?

- This drug is an important development as opioid-induced constipation is a common problem in chronic pain patient
- 15% (2 – 40%) of adult population are suffering from chronic pain
- One third of people with chronic low back pain in one study included 100,000 patients were prescribed opioids.
- Add to that around 3% of adults in US are receiving long term opioids therapy for chronic non-cancer pain

Verhaak PF, et al. Pain 1998;77:231-239; Blyth FM, et al. Pain 2001;89:127-134; Breivik H, et al. Eur J Pain 2006;10:287-333; Clark JD. J Pain Symptoms Manage 2002;23:131-137.

C. Final Consideration

- Dose Adjustments
  - Metabolism via CYP3A4
    - Contraindicated with strong CYP3A4 inhibitors or inducers
    - Dose adjustment if moderate CYP3A4 inhibitors; only use if necessary
    - Weak inhibitors: dose adjustment
  - Mild-Moderate liver dz: no dose adjustment
  - Renal
    - Minor route of elimination but start with lower dose if creatinine clearance < 60mL/min
    - Not effectively removed during hemodialysis

- Prucalopride:
  - $3.20 / 2 mg
- Linaclotide:
  - $5.30/ 290 ug capsule
  - $3.30/ 145 ug capsule
- Naloxegol:
  - $10 USD / 25 mg tablet

- Summary
  - Around 250 million opioids prescription are filed annually
  - Percentage of patients receiveing opioids prescriptions for pain related visits increased from 23% to 37% from 1993 to 2005 (1-2% per year) and described as “opioids epidemic”
  - Use other laxatives first
  - Consider naloxegroll in laxative inadequate patients
  - Doesn’t reverse the systemic effect of opioids
  - Naloxegol is generally a safe medications
    - Side effects were mainly GI
    - No withdrawal symptoms
    - No associated increase in opioid use in the low percentage of people who had S/E

Manchikanti L, et al. Pain Physician 2012;15:ES9-E38; Chou R, et al. J Pain 2009;10:113-130; Dunn KM, et al. Ann Intern Med 2010;152:85-92.

Western
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Familial and Hereditary Colon Cancer

Amindeep Sandhu

Not All CRC's Created Equal

- Increasingly clear that genetic predisposition plays a role in many CRC's
- Familial vs. Sporadic distinctions for convenience only, until basis for all CRCs better defined
- Better to assume that all CRC's have genetic components that may be acquired with variable penetrance
- Environmental risk factors may augment the ↑ genetic predisposition → malignant phenotype

Familial CRC

- Common Familial Risk CRC
  - Individuals with first degree relative of CRC
  - 2 – 3x ↑ risk of CRC if diagnosis > 50, 3-6x if < 45-50
  - Arise from a number of different, lower-penetrance susceptibility genes than the inherited syndromes
- High –Risk Familial, Non-Syndromic – "Type X"
  - Fit Amsterdam I or II
  - Do NOT have DNA mismatch repair deficiency nor do they have microsatellite instability
  - CRC Risk lower than Lynch Syndrome

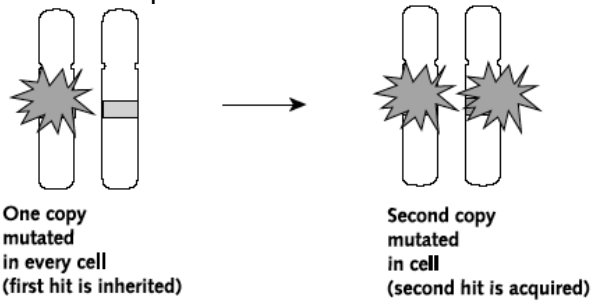
Hereditary CRC

- ~ 5 % of all CRC's
- Adenomatous polyps
  - Lynch Syndrome
  - Familial Adenomatous Polyposis (FAP)
  - MUTYH-associated polyposis (MAP)

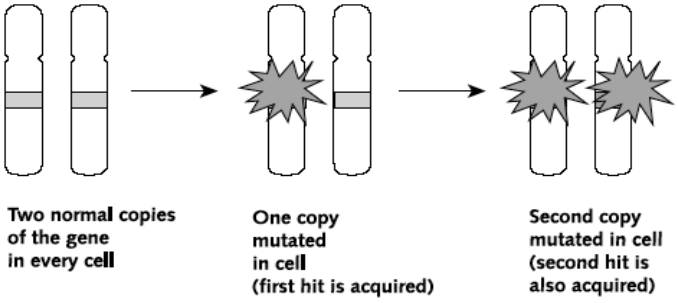
- Also includes some Hemartomatous Polyps
  - Peutz-Jeghers Syndrome (PJS)
  - Juvenile Polyposis Syndrome (JPS)
- Hyperplastic Polyposis (HPP)
  - Rarely inherited, but substantial CRC risk

➢ Genetics

- Types of mutation
  - Germline mutations
    - Mutations in sperm, ova, zygote
      - Inherited from previous generation, or
      - Spontaneous



  - Somatic mutations
    - Mutation during growth/development of tissues
      - Spontaneous



Mutation Types	Genes Involved	Type of Disease Caused
○ Germline	– APC	▪ Familial adenomatous polyposis ▪ HNPCC (Lynch syndrome) ▪ Sporadic disease
○ Somatic	– Oncogenes ▪ myc ▪ ras ▪ src ▪ erbB2 – Tumor suppressors ▪ p53 ▪ DCC ▪ APC – MMR genes ▪ hMSH2 ▪ hMLH1 ▪ hPMS1 ▪ hPMS2 ▪ hMSH6 ▪ hMSH3	
○ Genetic poly-morphism	– APC	▪ Familial colon cancer in – Ashkenazi Jewish persons

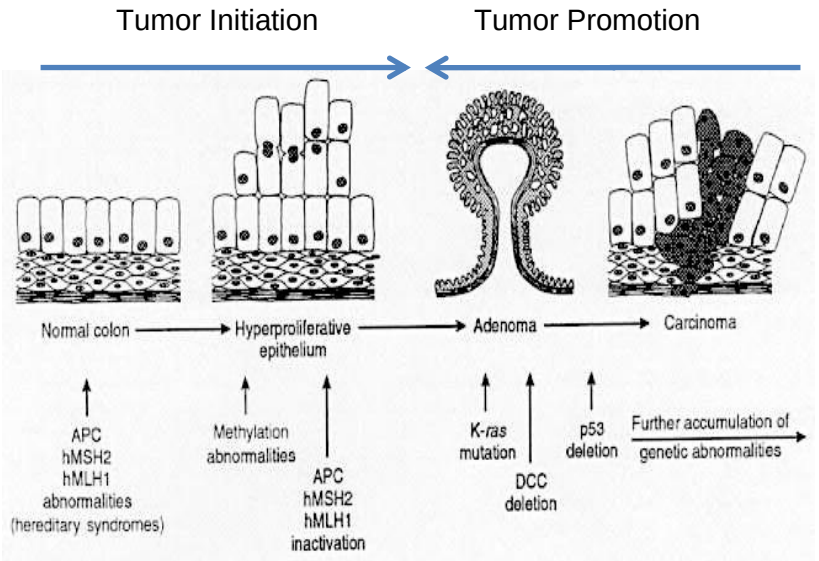
Abbreviations: DCC, deleted in colorectal carcinoma; HNPCC, hereditary non-polyposis colorectal cancer; MMR, mismatch repair

Calvert and Frucht. Ann Intern Med 2002

- Types of genes
  - Oncogenes
    - Makes cells grow
    - Mutated oncogene → constitutive activation → uncontrolled proliferation
      - E.g. ras (K-ras), c-myc
  - Suppressor genes
    - Inhibit growth
    - Promote apoptosis
    - Function lost when both alleles are lost - 2-hit hypothesis
      - E.g. APC, DCC, p53
  - Mismatch Repair (MMR) genes
    - Correct DNA replication errors
      - E.g. hMSH2, hMLH1 in HNPCC
  - Modifier genes
    - influence cell function
      - E.g. COX-2, PPAR

- Types of abnormalities
  - Point mutations
  - Altered DNA methylation
  - Gene rearrangements
  - DNA Amplification
  - Deletions

Adenoma → Carcinoma Sequence



HNPCC/ Lynch Syndrome

- Epidemiology
  - 2-4% of all CRCs
  - Polyposis is rare
  - Develop colonic adenomas with > frequency than general population
  - CRC in 50-80%
    - Younger age
    - Proximal (R-sided) tumors

- Genetics
  - Germline mutation in DNA mismatch repair genes → 80% penetrance
  - Maintain genomic stability
    - Repair single base pair mismatches
    - Repair insertion or deletion loops/mismatches
    - These are generated during DNA replication
  - Mismatch repair (MMR) requires synchrony between many repair genes:
    - MSH2 - mutation in 39%
    - MLH1 – mutation in 32%
    - PMS1/2 – 14%
    - MSH6 – 15%
    - MLH3
  - Inactivation of any one gene, two alleles → MMR deficiency

Differences in Cancer Risk with Mutations

	Mutation	Frequency	CRC risk	Other cancer risk
○	hMSH2 hMLH1	90%	50 – 80%	40 – 60% endometrial cancer
○	hMSH6	10%	< hMSH2 / hMLH1	> hMSH2 / hMLH1
○	hPMS2	Rare	15 – 20%	15% endometrial cancer 25 – 30% any other Lynch cancer
○	EpCAM	6%		

➢ Diagnosis

- Clinical “Diagnosis” (suspicion)
  - Amsterdam 1 and 2 criteria – lack specificity for Lynch syndrome diagnosis
    - 50% of families meet Amsterdam 2 criteria but do **not** have Lynch
    - No identified MSI/MMR mutation
  - Bethesda criteria
    - More sensitivity than Amsterdam criteria
      - Useful to identify persons at risk who require further testing
      - Genetic testing for individuals at risk can miss 28% of HNPCC cases
        -4 MMR genes and EpCAM

Clinical Guidelines for the Diagnosis of Lynch Syndrome

Amsterdam I Criteria

At least three relatives with colorectal cancer including all of the following

1. One should be first degree relative of the other two
2. At least two successive generations be involved
3. FAP should be excluded in any cases of colorectal cancer
4. Tumors should be verified by pathological examination

Amsterdam II Criteria

Three relatives with a Lynch-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis) including all of the following:

1. One should be a first relative of the two
2. At least two successive generations should be involved
3. Cancer in one of the affected individuals should be diagnosed before the age of 50 years
4. FAP should be excluded in any cases of colorectal cancer
5. Tumors should be verified by pathological examination

Revised Bethesda guidelines

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age
2. Synchronous, metachronous colorectal cancer, or other Lynch-related cancer* regardless of age
3. Colorectal cancer with MSI-H histology (presence of tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous / signet-ring differentiation, or medullary growth pattern) diagnosed in a patient less than 60 years of age.
4. Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumor*, with one of the cancers being diagnosed under age 50 years

5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch-related tumors*, regardless of age

* includes endometrial, ovarian, gastric, small bowel, urinary tract, biliary tract, pancreas, brain and sebaceous gland

Gala et al, Sem Oncol 2011

- Test Tumor for MMR mutations (MSI analysis or IHC)
  - 90% of HNPCC tumors will be positive by MSI analtsis or IHC testing
  - 15% of sporadic CRC will be MSI-positive from somatic hypermethylation of hMLH1

Abbreviation: IHC, immunohistochemistry

- Extraintestinal manifestations
  - Non-malignant
    - Eye
      - CHRPE
        - Congenital hypertrophy of the retinal pigment epithelium → Darkly pigmented round lesion – retina
    - ENT
      - Nasopharyngeal angiofibromas
    - Bone, connective tissue
      - Osteomas
      - Radiopaque jaw lesions
      - Supernumerary teeth
      - Lipomas
      - Fibromas

        - Epidermiod tumors
        - Desmoid tumors

    - Cancers / polyps
        - Brains
            - Meduloblastoma (FAP)
            - Gliobastoma (HNPCC)
        - Thyroid
        - GI
            - Pancreas
            - Periampullary
            - Hepatoblastoma
            - Biliary tree
            - Gastric adenomas / fundic gland polyps
            - Duodenal (90%), jejunal, ileal adenomas

- Management
    - If meets Bethesda or Amsterdam II or has known disease
        - Obtain 3 generation FHx of all cancers + any pathology reports
        - MSI and IHC testing on CRC or Endometrial cancer pathology
            - Stable Microsatellites = excludes Lynch
            - Unstable = full genetic counselling and MMR gene testing

Condition: Inheritance	Gene	Lifetime Cancer Risks		Non-Malignant Features
		Non-polyposis		
Lynch syndrome: Autosomal dominant	hMLH1	Colon	50 – 80%	Physical or non-malignant features, besides keratoacanthomas and sebaceous adenomas / carcinomas, are rare
	hMLH2	Endometrium	40 – 60%	
	hMSH6	Stomach	11 – 19%	
	hPMS2	Ovary	9 – 12%	
	EpCAM	Hepatobilary tract	2 – 7%	
		Upper urinary tract	4 – 5%	
		Pancreatic	3 – 4%	
		Small bowel	1 – 4%	
		ANC (glioblastoma)	1 – 3%	

NCCN Guidelines for Extracolonic Cancer Surveillance in Lynch Syndrome

- Gastric and duodenal cancer
  - Upper gastrointestinal endoscopy with side-viewing examination at age 25 -30 years with repeat examination in 1 – 3 years
- Urothelial cancer
  - Annual urinalysis

- CNS cancer
  - Annual physical examination. No recommendations have been made
- Pancreatic cancer
  - Annual physical examination. No recommendations have been made
- Endometrial and ovarian cancer
  - Patient education and response to endometrial cancer symptoms
  - Referral to gynecologic oncologist for surveillance (annual endometrial sampling, transvaginal ultrasound, and serial CA-125 measurements starting by age 30 -35 years or 5 – 10 years before the earliest age in the family)
  - Consider prophylactic total abdominal hysterectomy and salpingo-oophrectomy after completion of children of childbearing or during colectomy

Gala et al. Sem Oncol 2011

Once MMR-positive (Lynch Syndrome)

- Annual colonoscopy
  - Starting age 20, or
  - 10 years before earliest age of CRC patient in family
- Annual endometrial and ovarian cancer screening
  - With Endometrial biopsy plus CA-125 / Transvaginal ultrasound
  - Start at
    - Age 30, or
    - 5-10 years before earliest diagnosis
  - Discuss TAH/BSO once childbearing age ends

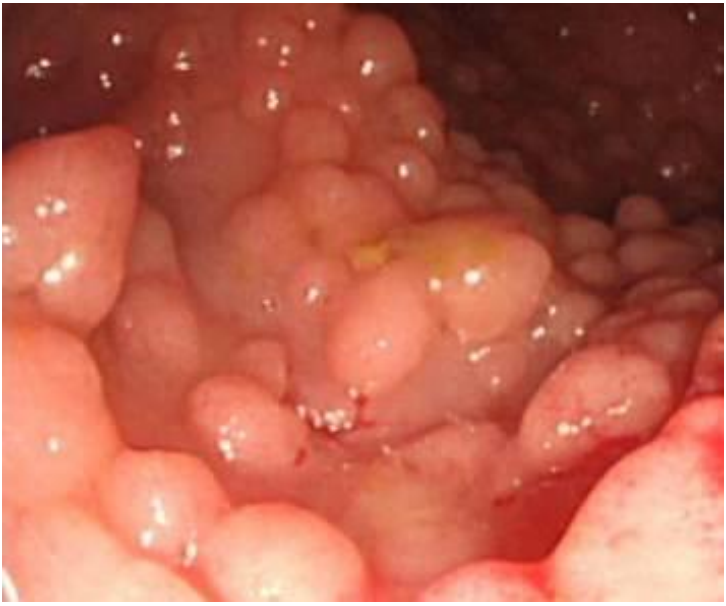
- Annual urinalysis
  - 25 years
- Annual Skin surveillance
- Periodic EGD

Abbreviations: BSAO, Bilateral Salpingo-oophorectomy; EGD, Esophagogastro-duodenoscopy; EGD, esophagogastroduodenoscopy; TAH, total abdominal hysterectomy

Polyposis Syndromes

- Characterized by
  - Distinct clinical manifestations
    - Multiple polypoid lesions of the GI tract
  - Most are inherited
  - Varying degrees of ↑ risk of CRC

- Non-Hereditary GI Polyposis
  - Hyperplastic
  - Lymphoid
    - Reactive lymphoid hyperplasia
    - Lymphoma
  - Lipomatosis
  - Angiomatosis
  - Leiomyomatosis
  - Pneumatosis cystoides intestinalis
  - Cronkhite-Canada syndrome



- Hereditary GI Polyposes
  - Adenomatous polyposes syndromes:
    - Familial adenomatous polyposis (APC)
    - Gardner, Turcot
    - Attenuated (APC)
    - MUTYH Associated Polyposis (MAP)
  - Hamartomatous polyposes syndromes:
    - Peutz Jeghers syndrome (STK11)
    - Familial juvenile polyposis (SMAD4 or BMPR1A)
    - Cowden disease (PTEN)
    - Intestinal ganglioneuromatosis (varying syndrome genes)
    - Ruvalcaba-Myrhe-Smith syndrome (PTEN)
    - Tuberous sclerosis (TSC1)

Familial Adenomatous Polyposis (FAP)

- Demography
  - Most common polyposis syndrome, <1%
  - Autosomal dominant inheritance
    - 80-100% penetrance
    - 1:8300 - 1:14,025 live births

- Genetics
  - Germline mutations of APC gene
    - 80% will demonstrate mutation
    - One mutated APC allele inherited → subsequent loss/mutation of normal allele → polyposis (2-hit hypothesis)
    - 15-25% of patients do not have family history
      - Suggesting spontaneous germline mutation
  - APC gene
    - 15-exon gene
    - Large protein - 2843 amino acids; 310 kDa
    - Cell adhesion, signal transduction, transcriptional activation
    - > 300 different mutations identified
      - Insertions, deletions, nosense mutations → premature stop codons
      - Truncated APC gene product

- Pathology
  - ≥ 100 adenomas throughout the colon
  - 50% have adenomas by age 15
  - 95% have adenomas by age 35
  - Colon cancer risk 80 – 100%
  - Mean age colon cancer 39 yr

Lifetime Cancer Risk in FAP

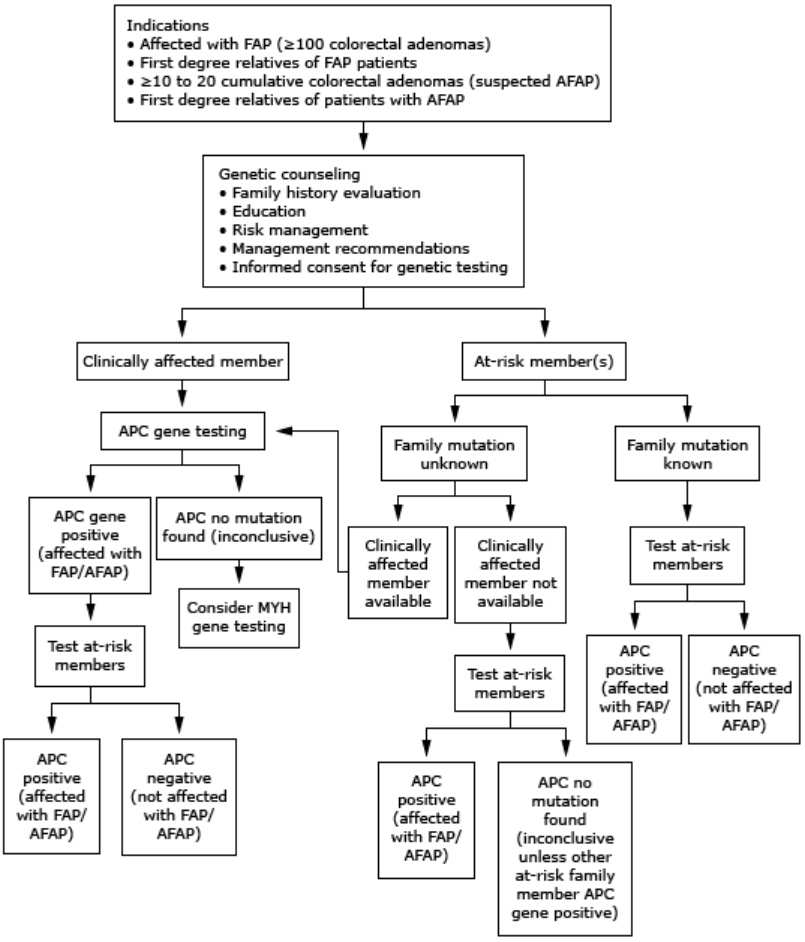
Cancer	Risk
Colon	~100%
Duodenal/periampullary	5-12%
Gastric	~0.5%
Pancreatic	~2%
Thyroid	~2%
CNS	<1%
Hepatoblastoma (age < 5)	1.6%

- Variants of FAP
  - Gardner syndrome = FAP + extracolonic manifestations
  - Turcot = FAP + primary CNS tumors
    - Medulloblastomas (APC mutations) – FAP / Turcot
    - Glioblastomas (HNPCC mutations) – HNPCC / Turcot
  - Attenuated adnomatous polyposis coli (AAPC)
    - Fewer adenomas (<100)
      - Polyps by median age 35-45
      - Cancer by median age 55
    - Often R-sided (like HNPCC)
    - Flat adenomas
    - Germline APC mutations
      - Proximal and distal ends of gene
    - Lifetime risk of CRC ~ 70%

➢ Diagnosis

- Suspect in any patient with >10 colorectal adenomas or family history of CRC
- Genetic testing for germline mutation in APC gene required for definitive diagnosis

- Genetic test if 10-20 adenomas in lifetime
- Genetic counseling always before testing
- If mutation found, mutation-specific testing should be offered to at-risk relatives (all first degree of index patient
  - All subsequent cases



- Treatment
  - Once FAP-associated colonic polyposis diagnosed
    - Full colonoscopy to evaluate extent
    - Colectomy at diagnosis if:
      - Profuse polyposis
      - Multiple > 1 cm adenomas
      - Any adenomas with villous histology/HGD
    - Colectomy in near future if:
      - Polyposis, < 5 mm
    - Once total proctocolectomy complete with pouch
      - Regular surveillance of Ileal Pouch

- Screening guidelines
  - Colonoscopy
    - Mutation screening of at risk individuals age 10+
      - At risk = 1st degree relatives of FAP patients
    - If no mutation → annual flexible sigmoidoscopy age 12-50 yr
  - Upper endoscopy q1-3 yr starting at time of colonic polyps or age 20, whichever first
    - Upper GI polyps rare prior to onset of colonic disease
    - Side-viewing scope should be used for periampullary lesions
  - Annual thyroid exam
    - Starting at age 10-12 yr
  - Periodic abdominal ultrasound after age 20 (pancreatic CA)
  - Periodic CT head in families with CNS neoplasms

- Surveillance – UGI
  - Routine biopsy of papilla
    - If any abnormality noted or if history of pancreatitis, biliary obstruction
  - Proximal gastric polyps
    - Biopsy for dysplasia
  - Antral gastric polyps
    - Remove (usually adenomas)

MUTYH Associated Polyposis (MAP)

- M(UT)YH gene mutations
  - High frequency of MYH gene mutations in a subset of patients with familial adenomatous polyposis
  - Autosomal recessive
    - Siblings of affected patients have 25% of having MUTYH mutation
    - Unlike FAP, parents and children are rarely affected
  - Genetic testing warranted in individuals with 10 adenomatous polyps without identifiable mutations in APC
  - Germline mutations in MYH base excision repair gene
  - Role of MUTYH
    - Base excision repair glycosylase involved in the repair of oxidative damage to guanine
    - Prevents G/C to T/A transversions
      - Frequently occurs in APC coding regions
      - Transversions seen for k-RAS in 70% of individuals with MUTYH

- MUTYH Polyposis Genetics
  - Bi-allelic mutation in MUTYH
    - 25-30% of AFAP patients with >10-15 adenomas have MYH biallelic mutations
    - Mutations in two hotspots, Y165C or G382D mutations in 1/165 C or G382D account for 70% of all Caucasian mutations
    - Full gene sequencing if these are negative
    - Significant polyposis similar to AFAP/FAP with (-) mutations in APC should be tested for MUYTH mutations

- MUTYH Phenotype
  - Phenotype mimics attenuated FAP (AFAP)
    - CRC penetrance
      - 19% at 50
      - 43% at 60
      - 80% lifetime
  - Polyposis typically by 40's
    - Adenomatous, Hyperplastic, SSAs
  - UGI polyps in 11-17%
    - Duodenal Cancer in 4%
  - Possible ↑ risk of other cancers
    - Ovarian
    - Bladder
    - Skin
    - Sebaceous glands
    - Breast
  - Clinical diagnostic criteria **not** established

- Management
  - Colonoscopy q 2 – 3 yr
    - Start mid 20s in at-risk individuals
  - Subtotal colectomy if
    - CRC
    - Multiple adenomatous polyps
    - Large polyps
    - High grade dysplasia (HGD)
  - UGI tract screening as per FAP
    - EGD q1-3y starting age 25

Peutz-Jegher Syndrome (PJS)

- Autosomal Dominant
- Multiple Hamartomatous polyps
- Mucocutaneous Hyperpigmentation
- GI, Non-GI Cancers

- Epidemiology
  - 1:8000 – 1:200,0000
  - M = F

- Genetics
  - Due to germline STK11 (LKB1) gene mutation
  - Tumor Suppressor Gene → 2-hit (Germline + Acquired = PJS)
  - Encodes a serine threonine kinase on Chrm. 19

- Regulates cell polarity – defect causes mucosal prolapse/hamartomas by unknown mechanism
- Defect in TSG increases cancer risk
- Defect in STK 11 seen in ~ 60% of PJS, suggesting another locus

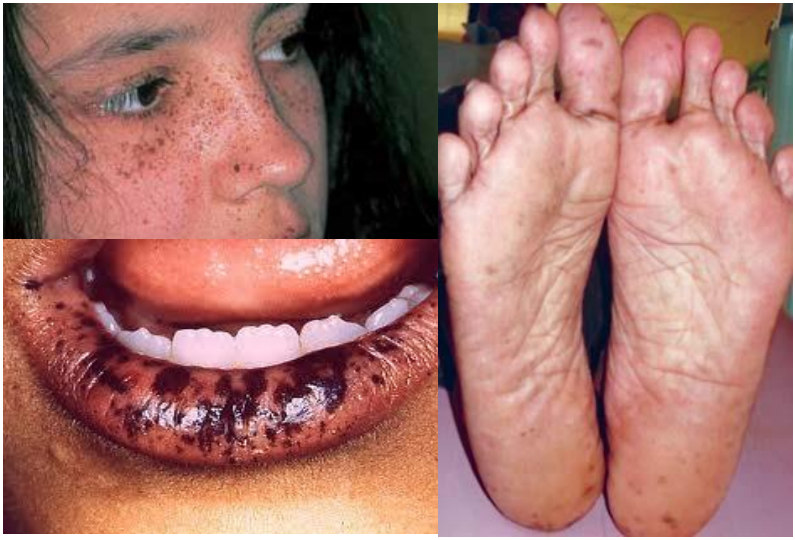
➢ Clinical

- Mucocutaneous Pigmentation
  - Macules (Melanin spots)
  - Seen in > 95%
  - Pigment-laden macrophages
  - Flat, blue-gray or brown spots, 1-5mm
- Timing
  - Usually appear in first year of life
  - Increase in size / number over the years
  - Fades after puberty, buccal mucosa remain
  - Lips/peri-oral (94%)
  - Palms of hands (74%)
  - Buccal mucosa (66%)
  - Soles (62%)
- Extra-intestinal polyps
  - Renal Pelvis
  - Urinary bladder
  - Lungs
  - Nasopharynx
- GI tract
  - 50% asymptomatic at diagnosis
  - Often symptomatic between ages of 10-30

- Complications
  - Abdominal pain
  - Acute/chronic rectal bleeding (ulceration)
  - Obstruction via occlusion
  - Extrusion of polyp into rectum
  - Intussusception (70% lifetime risk)

- Cancer Risk
  - ↑ risk for GI and non-GI Malignancies
  - Lifetime cancer risk
    - 37 – 93%
  - Average age of developing malignancy 42 years of age
    - Cumulative cancer risk
      - 40 yr = 20%
      - 70 yr = 76%
  - Most common sites (in order):
    - GI
      - Colon (39%)
      - Stomach (29%)
      - Pancreas (20%)
      - Small bowel (13%)
    - Non-GI
      - Gynecological (15%)
      - Testicular (9%)

PIGMNETATION IN PJS



➢ Pathology

- Gross / endoscopy
  - Sessile, pedunculated, lobulated
  - Sizes up to 5 cm
  - Small Bowel
    - 90% (Jejunum vastly more common)
  - Colon
    - 60%,
  - Stomach
    - 25%

- Histopathology
  - Hamartomas
    - Proliferation of smooth muscle extends into lamina propria
    - Normal overlying epithelium

- Diagnosis – any one of:
  - ≥ 2 histologically confirmed PJ polyps
  - 1 PJ polyp plus family history (first degree relative with PJS)
  - Mucocutaneous pigmentation, plus
    - Family history
    - 1 RJ polyp
  - Once criteria met
    - Genetic test for STK11 to confirm diagnosis
  - If genetics negative and no one in family positive for STK11 defect
    - Difficult, still require frequent endoscopic surveillance
  - Genetics tests if positive
    - Test at-risk relatives
    - Provides true positive and true negative results

- Screening Guidelines (expert consensus)
  - Annual CBC, LFTs, clinical examination

- GI
  - GI: baseline EGD plus colonoscopy plus VCE at diagnosis (or age 8 yr)
    - If polyps → Repeat both q3yrs until 50
    - If no polyps → Repeat at age 18 or if symptoms, then q 3 yr
    - After age 50 → colonoscopy q 2 yr
    - Alternatives to CE
      - MRE
      - SBFT (problem of radiation in children, not recommended for children if MRE available)

Abbreviations: CE, capsule endoscopy; MRE, MR enterography; SBFT, small bowel follow through

- Genital tract
  - Male
    - Annual testicular exam from birth to age 12 yr
    - Testicular ultrasound if physical examination is positive
  - Female
    - Pap smear at 21 yr
    - Then q 2 yr
  - No routine surveillance for ovarian or endometrial cancer
    - Some groups say annual CA-125 + transvaginal U/S
  - Monthly breast self-examinations at 18yr
    - Annual breast MRI's 25-50 yr, mammography yearly after 50 yr
  - No pancreatic imaging recommendations

➢ Treatment
  - Polypectomy
    - If > 1cm
  - Surgery
    - If very large (obstructing lumen, sessile, difficult resection)

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LIVER

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Disease of Excess Fat in the Liver: Alcoholic Liver Disease

Melanie Beaton

- Overview
  - Alcoholic Liver Disease (ALD) and Non-alcoholic Fatty Liver Diseases (NAFLD) are disease of excess fat
    - Both conditions due to consumption
    - Abstinence is key to treatment of both

- Demography
  - Alcoholism
    - 15-20 million Americans
    - 100,000 deaths/y
  - Responsible for 40% of liver-related deaths
  - #3 Cause of preventable mortality
    - Cigarettes & Obesity #1 & 2
  - #2 Cause of mortality from GI diseases
  - Affects up to 20% of heavy drinkers
    - 1 in 10 Americans report “heavy drinking” (≥ 3/d)
  - ≈1% of all hospital admissions in US
  - Average LOS 6.5 d
  - In-hospital mortality 7%[1]
  - Severe AH
    - 1 month mortality 30-60% in untreated patients

Abbreviations: AH, alcoholic hepatitis; d, days; LOS, length of hospital stay

- Statistics

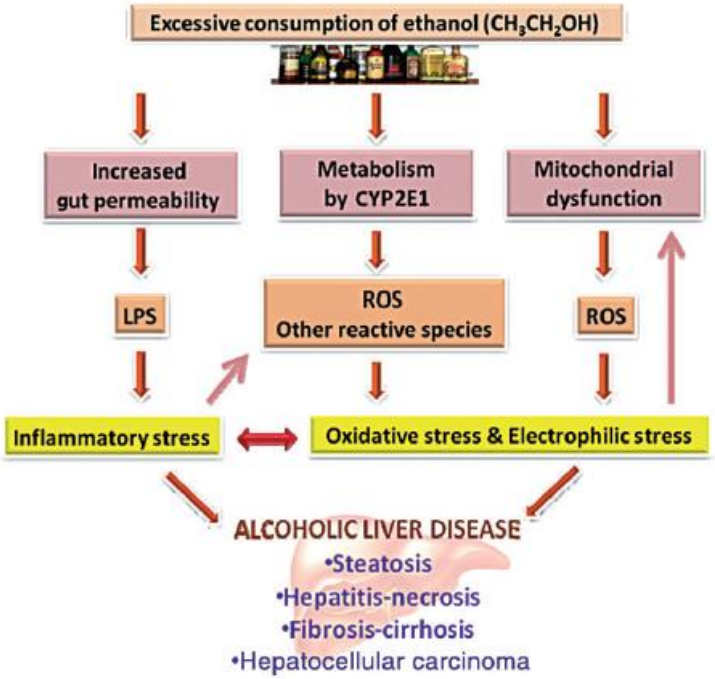
- Alcohol intakes
  - Relative risk of liver disease rises at >30 g/d
    - Small absolute risk

- Even at > 60-80 g/d, only 5-15% develop liver disease
- *"Safe"* levels of ingestion
  - Women 10 g/d, Men 20g/d
  - 1 drink ≈ 12 g EtOH
    - Beer-12 oz, Wine-6oz, Liquor-1 oz

- Give the reasons why do only a small % of heavy drinkers develop ALD.
  - Genetic variation in EtOH metabolizing enzymes
    - ADH
    - PNPLA3 polymorphism
  - Genetic variation in response to damage
    - Pro-inflammatory genes (TNF)
    - Autoimmune predisposition
  - Female gender and younger age
    - 2-4x risk at similar intake
  - Nutritional Status
    - Under and "Over" nutrition
  - Co-factors
    - Binge drinking (≥ 5 "drinks" at a time)
    - Drugs/Toxins, Iron, α1AT deficient
    - Hepatotropic viral infection (HBV, HCV, HIV)
    - Ethnicity – African-American and Hispanic higher risk than Caucasian

➢ Pathophysiology

- Overview



Printed with permission: Zhu H, et al. J Dig Dis. 2012;13(3):133-42.

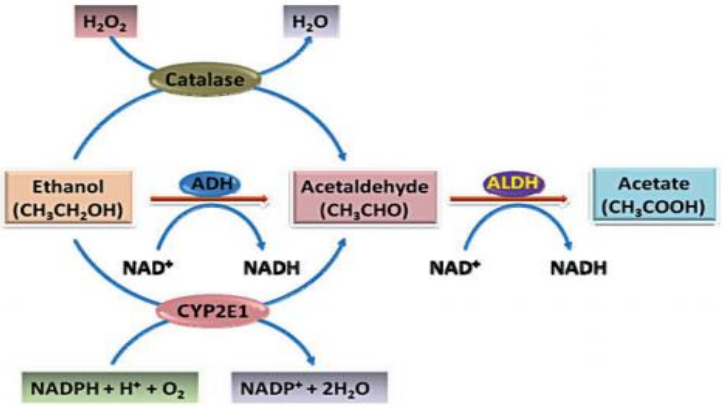
- GI
  - Absorbed
    - Stomach (70%)
    - Duodenum (25%)
    - Peak serum 30-90 min post ingestion

Gut Endotoxins

- Liver
  - Catabolized by:
    - ADH
      - Metabolism of acetaldehyde to acetate is slowed
      - Acetaldehyde accumulates → damage to intestinal tight junctions
        → ↑ gut permeability to endotoxins
        → ↑ ROS
        → ↑ NADH:NAD ratio
    - CYP2E1
      - With chronic ingestion, microsomal enzyme oxidation system (MEOS) is induced → generates O_2 free-radicals → oxidative / electrophilic stress → mitochondrial dysfunction

➢ Pathogenesis

- Hepatic Fat Accumulation
  - ↑ FA oxidation →↓ fat export from liver
  - ↑ peripheral lipolysis /TG synthesis → ↑ influx of lipid into liver
- Gut Endotoxins
  - EtOH → Aldehyde → tight junction damage → ↑ gut permeability/barrier → ↑ bacterial endotoxin (LPS) absorption / interacts with Kupffer cells
- Kupffer cells
  - LPS activated Kupffer cells
  - ↑ cytokine production (TNFα), IL-1β, IL-12, IL-8 → inflammatory stress → fibrosis



Printed with permission: Zhu H, et al. J Dig Dis. 2012;13(3):133-42.

- Oxidative Damage
  - Free radicals → lipid peroxidative damage
  - ↓ Antioxidants (Glutathione, Vit A & E)
  - Neoantigens
    - Acetaldehyde-Protein adducts' (APA)
    - Antibodies form against these APA→ immune-mediated damage
  - PMNs accumulate
  - Attracted by lipid peroxidative damage & neoantigens → release inflammatory cytokines
- Resultant Inflammation, Cell Death & Fibrosis
  - Proliferation of stellate cells, transformation into myofibroblasts → collagen deposition & fibrosis

➢ Laboratory

- Alcohol – Non-alcohol Index
  - http://www.mayoclinic.org/girst/mayomodel10.html
  - Uses BMI, MCV, AST/ALT ratio & gender to determine if EtOH is the etiology of liver disease

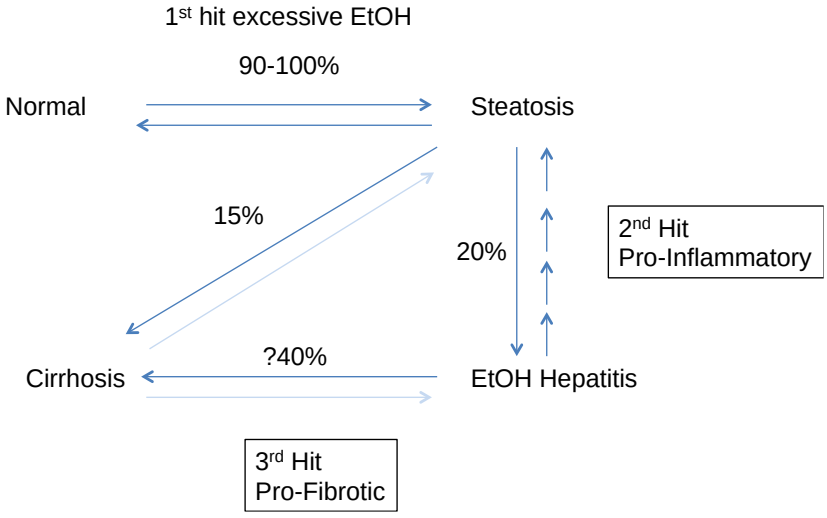
- Helpful when patients are skeptical that the "minimal amount" of alcohol they drink is actually excessive/harmful

Dunn W, et al. Gastroenterology. 2006;131(4):1057-63.

- AST: ALT > 2
  - Reduced ALT activity (ALT rarely > 200 IU/L)
  - Alcohol-induced depletion of hepatic pyridoxal 5'-phosphate
  - Increased hepatic mitochondrial aspartate
- ↑ WBC (PMN)
- ↑ Bilirubin
- ↑ INR

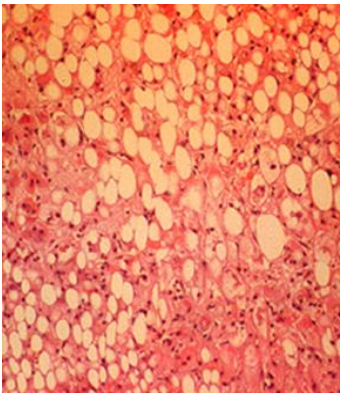
➢ Pathology

Spectrum of Alcoholic Liver Disease (ALD)

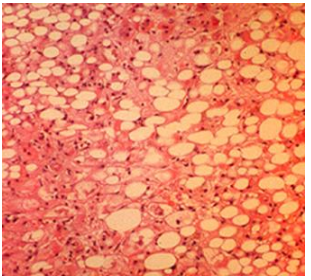


- Histology

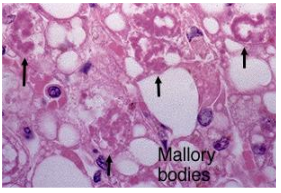
Alcoholic Steatosis

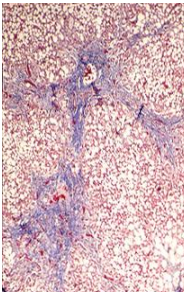


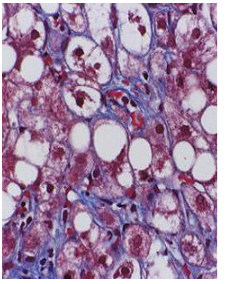
Alcoholic Hepatitis (AH)



- Steatosis (Macro / Microvesicular)
- Mallory Bodies
- PMN Infiltration
- Perivenular (Zone 3) Inflammation
- Pericellular Fibrosis







- Prognosis
  - Risk Factors for Mortality
    - Patient
      - Older age
      - Continued drinking*
      - EtOH Consumption > 120 g/d
    - Laboratory
      - Acute renal injury
      - ↑ serum creatinine (Cr_s)
        - Ominous, often portends onset of hepatorenal syndrome (HRS)
      - ↑ bilirubin, INR, WBC
    - Complications (↓ 1 yr mortality)
      - Hepatic Encephalopathy (RR 4.0)
      - Spider Nevi (RR 3.3)
      - Ascites (RR 4.0)
      - Visible Veins across anterior abdominal wall (RR 2.2)
      - Weakness (RR 2.1)
      - Infection
      - HE
      - UGI Bleed
    - Histopathology
      - Inflammation on liver biopsy
      - Inflammation on liver biopsy showing alcoholic hepatitis – worse prognosis

* Most Important Factors for Overall Prognosis

  - Prognostic Scores
    - Maddrey Discriminant Function (DF)
      - DF > 32, high short-term mortality (50% at 1 mon)
      - DF < 32 spontaneous survival ≈ 90%
      - Used to determine need for CS Rx
      - DF = 4.6(PT- Control PT) + Total Bili/17

- Presence of ascites and bilirubin > 176
- MELD Score
  - Poor Prognosis if > 18
  - Change of ≥ 2 points during 1st week independently predicts in-hospital mortality
  - Shown to predict 30 & 90d mortality
  - www.mayoclinic.org/meld/mayomodel7.html
- Others
  - Glasgow AH Score
  - Lille Model
  - Child-Pugh Score

Srikureja W, et al. J Hepatol. 2005;42(5):700-6.
Dunn W, et al. Hepatology. 2005 Feb;41(2):353-8.
Sheth M, et al. BMC Gastroenterology. 2002;2:2.

- Use of different scoring systems
  - Overall risk
    - ABIC
    - MELD
  - Who needs corticosteroids
    - Maddrey
    - GANS
  - Who needs ‘steroids non-responsive (stop the ‘steroids)
    - Lille

Abbreviations: ABIC, age, serum bilirubin, INR, and serum creatinine; GAHS, Glasgon alcoholic hepatitis score; Lille, a city in Northeastern France; LT, liver transplantation; MELD, model for end-stage like disease

	5 yr Mortality	
	Abstinent	Drinking
– All Patients	35%	60%
– No complications	10%	30%
– Complications	40%	70%

- Treatment
  - The first step in treating the person with ALD is abstinence
    - Intervention
      - Discussion with patient and assessment of readiness to change, non-judgmental, empathic approach
    - Baclofen
      - 10 mg tid or 30 mg od x 12wk
      - ↓ withdrawl symptoms / ↓ alcohol craving
        - 2 of 3 studies improved achieving (70% vs. 20-30%) and maintaining (63d vs. 31d) abstinence
      - $GABA_B$ receptor-agonist
      - Safe in cirrhosis
      - 5 yr mortality rate

Garbutt JC, et al. Alcohol Clin Exp Res. 2010;34(11):1849-57.
Addolorato G, et al. Lancet. 2007;370(9603):1915-22.
Addolorato G, et al. Alcohol Alcohol. 2002;37(5):504-8.

- Monitor for and treat withdrawal
- GI bleed prognosis
- Investigate for possible infections
  - Aspiration pneumonia
  - Spontaneous bacterial peritonitis (SBP)
  - Urinary tract infection (UTI)
- Note:
  - No data that empiric antibiotics improve outcome

Clinical Caution

- Alcoholic hepatitis as a cause of fever
  - A diagnosis of exclusion!

- Nutrition/Hydration
- Malnutrition
  - Risk factor for infection[1]
  - Correction of malnutrition
    - Possible Mortality Benefit[2]
  - Enteral replacement (NG/NJ) preferred
    - 5 RCTs
    - Improved nutritional status vs. standard po diet
  - Also add
    - Vitamins
      - Thiamine
      - Vitamin B6
      - Vitamin K
      - Folate
    - Minerals
      - Phosphate
      - Mg

- Do not routinely restrict protein
  - Branched-chain amino acids (BCAA) may be helpful if HE develops during feeding

[1] Singal AK, et al. Clin Liver Dis 2012;16(4):805-26.
[2] Cabre E, et al. Hepatology. 2000;32(1):36-42.

- Renal Function
  - Hemodynamic consequences of portal HTN +/-SIRS
  - Nephrotoxic meds/contrast = ↑ risk for renal failure
  - N-acetylcysteine (NAC)
    - IV, given days 1-5 in Severe AH (+ Prednisone)
    - Improves renal function
    - Mortality benefit at 1 mon (not at 6 mon)[1]
  - Possible benefit from pentoxifylline

[1] Nguyen-Khac E, et al. N Engl J Med. 2011;365(19):1781-9.

- Corticosteroids (CS)
  - Prednisolone 40 mg po for 28 d
  - Multiple trials, mixed results
  - Meta-analyses:
    - Short-term mortality reduced if HE present (NNT = 5) (Imperiale, Annals IM 1990 & Reynolds, Gastro Intl 1989)
    - ↓ mortality if DF ≥ 32 or HE present (Cochrane Review, Rambaldi, APT 2008)
    - > 28 d survival with CS vs. non-CS (80% vs. 66%)
  - Earlier / greater improvement in LFTs and response to therapy, as per Lille model (Mathurin P, Gut 2011)

Abbreviations: DF, discriminant function (Meddrey score); HE, hepatic encephalopathy; LFT, liver function tests; NNT, number-needed-to-treat

- Infection in severe AH-effects of CS
  - 25% Severe AH are infected at presentation
  - 25% develop infection after starting CS
- Lille Score > 0.45 after 7d prednisolone predicts poor outcome → stop CS

- Lille model to assess CS response at 7d
  - Complete responders (≤ 0.16)
    - 90% survival
  - Partial responders (0.16-0.56)
    - 79% survival
  - Null-responders (≥ 0.56)
    - 53% survival
    - Recommend d/c CS

Mathurin P, et al. Gut. 2011;60(2):255-60.

A Most Important Paper: the STOPAH Trial

- "The STOPAH trial will be different from previous studies as it will attempt to provide a definitive answer as to whether steroids or pentoxifylline (or both) are beneficial in patients with severe alcoholic hepatitis."
- Double-blind placebo controlled RCT
- 1103 AH patients (DF >32)
  - 1^0 Endpoint – 28 d Mortality
  - 2^0 - 1 yr mortality
- 4 Groups
  - Prednisolone (Pred)/ Pentoxyphylline (PTX), Pred/Pbo, PTX/Pbo, Pbo/Pbo

- Factors Significantly Associated with 28 d Mortality

Factor	Odds Ratio	*P* Value
– Prednisolone use	0.609	.015
– PTT ratio	1.380	.002
– Bilirubin	1.002	.003
– Age	1.050	<.001
– WBC	1.030	.037
– Urea	1.065	.037
– Creatinine	1.564	.028
– HE	3.073	<.001

Abbreviations: HE, hepatic encephalopathy; WBC, white blood cell count

- Prednisolone improves 28 d mortality

Treatment Group	Patients (N)	Percent (%)
– Pred/PTX	274	13.5
– Pred/Pbo	277	14.3
– PTX/Pbo	276	19.4
– Pbo/Pbo	276	16.7

- Absolute ↓ 28 d mortality with prednisolone ~4%
- At 1 yr, no difference between Pred and PTX
  - Possibly d/t increased infections in Pred group (double), which even occur after stopping the corticorticosteroid
    - Abstinence from alcohol major determinant of 1 yr survival
    - 3x ↑ mortality if no reduction/increase EtOH
    - STOPAH Trial

- Pentoxifylline (PTX)
  - Inhibitor of TNF synthesis
  - Alternative to Prednisolone (CS) for severe AH (SAH)
    - Especially if corticosteroids (CS) contraindicated
    - No benefit if non-responder to CS[1]
    - No benefit to combination of PTX + CS[2]
  - Child's C Cirrhotic patients[3]
    - N = 335, 6 mon PTX vs. Placebo
    - ↓ hepatorenal syndrome (HRS), hepatic encephalopathy (HE), Infection
    - No ↓ 3 mon mortality

[1] Parker R, et al. Aliment Pharmacol Ther. 2013;37(9):845-54.
[2] Thiele M, et al. Alim Pharmacol Ther 2012;35(10); 1155-65.
[3] Lebrec D, et al. Gastroenterology 2010;138(5):1755-62.

  - Meta-analysis (10 trials, N=884)
    - "PTX appears superior to placebo in prevention of fatal HRS and thus may be effective treatment for SAH when steroids are contraindicated. However, multiple trials have failed to show conclusive superiority of either PTX or CS"

Abbreviations: CS, corticosteroids; HRS, hepatorenal syndrome; PTX, pentoxifylline; SAH, severe alcoholic hepatitis

Lebrec D, et al., Gastroenterology 2010;138(5):1755-62.

- Antioxidant
  - RCT, N = 174[1]
    - NAC alone vs. NAC + CS days 1 to 5
    - ↓ 30 d mortality in combination group (NAC + CS)
    - No difference in 6 mon mortality (primary outcome)
    - Caution
      - More study needed as CS group had higher than expected mortality rate

Abbreviations: CS, corticosteroids; NAC, N-acetylcysteine

Nguyen-Khac E, et al. N Engl J Med. 2011;365(19):1781-9.

- Combination therapy
  - Meta-analysis network
    - Network meta-analysis methodology incorporates both conventional (direct) meta-analysis as well as indirect comparisons based on transitive properties (if A=B & B=C, then A=C) to compare & rank interventions for a common outcome.
    - Provides methodological tool to evaluate comparative effectiveness in area where there exist clinical equipoise and major research gaps.
  - 30 d mortality
    - CS alone, CS + NAC & PTX alone superior to placebo
    - CS & PTX similar benefit
      - CI for PTX low & quality of evidence low, so authors suggest PTX if CS contraindicated
      - CS + NAC had highest probability of benefit
        - Better than CS alone
        - Combination also best for reducing acute kidney injury (AKI)
    - No impact on Medium (3-12 mon) or longterm mortality (> 12 mon)

Singh S, et al. Gastroenterology 2015; 149: 958-70.

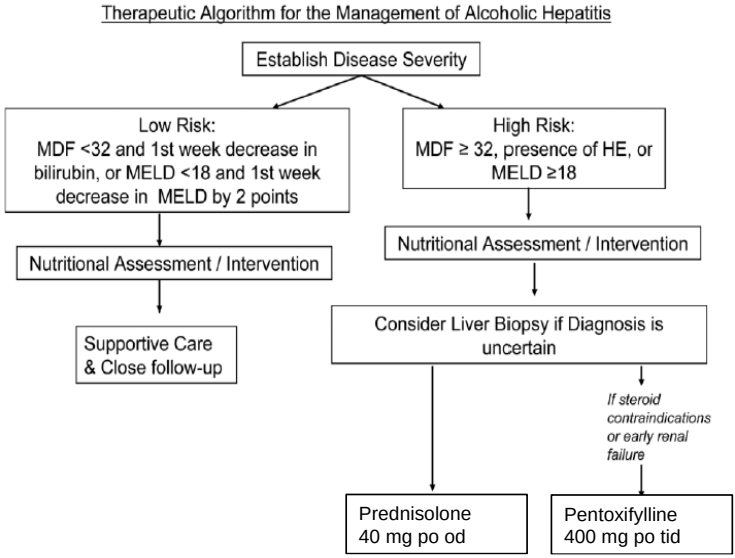
- GCSF
  - Mechanisms of action
    - Mobilize bone-marrow derived stem cells
    - ↑ hepatic regeneration
  - RCT
    - N = 64
    - Standard care (PTX) + GCSF vs. standard alone[1]
    - ↑ 90 d survival with PTX + GCSF

Singh V, et al. Am J Gastroenterol. 2014;109(9):1417-23.

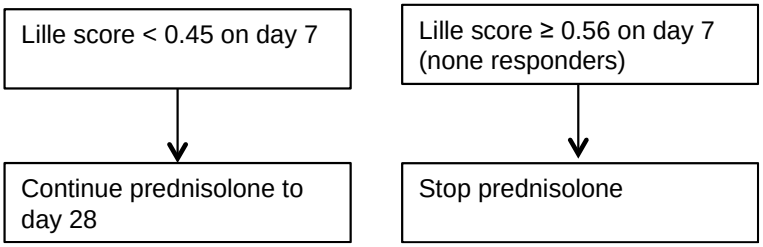
- Other pharmaceuticals Investigated
  - Anabolic steriods
  - Colchicine
  - Etanercep
  - Infliximab
  - Insulin + Glucagon (+/-)
  - PTU
  - SaME (based on systematic review 8 trials)
  - Silymarin/Milk Thistle
- Liver transplantation
  - Survival similar as non-EtOH indications
  - Recidivism
    - 1 yr 10-15%
    - 5 yr 25-50-%

- Strategies to ↓ recidivism
  - Family Supports
  - New Social Circle
  - Social worker / Psychologist
  - AA/Addiction Rehabilitation Program
  - No other substance abuses
  - Treat psychiatric problems, including depression
  - MD-Patient relationship

AASLD Practice Guidelines: Therapeutic algorithm of the management of alcoholic hepatitis



Printed with permission: O'Shea RS, et al. Hepatology. 2010;51(1):307-28.



Adapted from: Mathurin P and Lucey MR. J Hepatol. 2012;56 Suppl 1:S39-45.

Algorithm for severe AH

- Candidates for treatment (corticosteroids or pentoxifylline) need to fulfill the following criteria:
  - History of long-standing alcoholism
  - Recent onset of jaundice (< 3 mon)
  - Absence of recent gastrointestinal hemorrhage (i.e. < 15 d)
  - Liver chemistry suggestive of severe AH
  - Maddrey function ≥ 32 (alternative score such as Glasgow or MELD scores may be used to identify disease severity)
  - For patients who will be included in studies evaluating new molecules or therapeutic strategies, transjugular liver biopsy is required
- Before starting corticosteroids or pentoxifylline, clinicians need to perform:
  - Abdominal ultrasound to exclude other causes of jaundice
  - Systemic infectious screenings consisting of chest X-ray, blood urine and ascites cultures
- In patients cured of bacterial infection, corticosteroids may be used
  - Screening of hepatitis B, C and HIV virus

Hepatitis B in Organ Transplantation

Paul Marotta

Hepatitis B Virus (HBV) and SOT

- HBV can cause liver-related morbidity and mortality in non-liver transplant recipients.
- Post Transplant HBV occurs:
  - Secondary to the procedure
    - Infected donor organs
    - Blood products
  - Reactivation induced by immunosuppression

Hepatitis B in Transplantation

- Donors
  - HBsAg (+)
  - HBcAg -) and HbsAb (+)
  - HbcAb (+) and HBsAb (+/-)
- Recipients

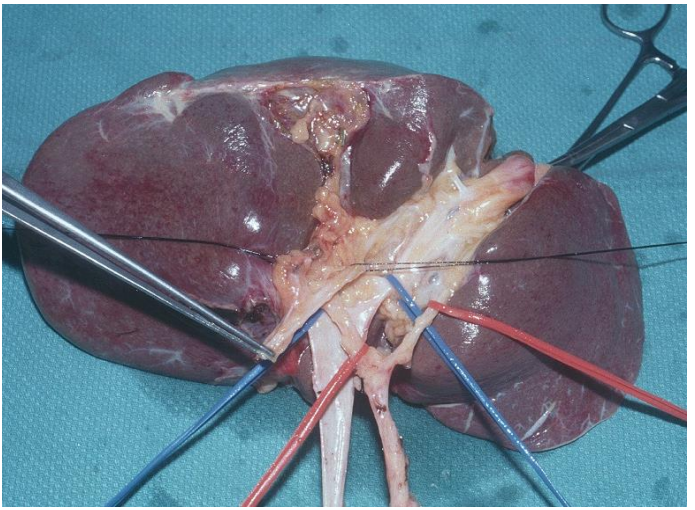
Hepatitis Serology

	HBsAg	HBsAb	HBcAb
Active HBV	+	-	+
Immunity	-	+	+/-
False=, low level	-	-	+

Donor: HBsAg +

- Organs from HBsAg + donors universally transmit HBV → HBV liver-related morbidity and mortality.
- Use of these donor organs remains a **relative contraindication**.
  - Occasional HBsAg+ donors have been transplanted into naïve heart and kidney recipients and also into HBsAg+ liver recipients with minimal morbidity.
  - These organs can be used with the utilization of HBV prophylaxis (Lamivudine +/- HBIG).

Hepatitis B in Donor Organs... Can we use them ?



- Is there an organ specific risk ?
- Is the recipient HBV status important ?
- Is recipient therapy/prophylaxis required ?

QUESTION

A donor's kidneys, heart, lungs, and liver are offered. The donor is found to have HBsAg(-), HBsAb(+), and HBcAb(+). At our center we would:

a) Transplant the kidneys, heart and lungs into any suitable recipient because the risk of transmission of HBV is very low but if possible select a HBsAb+ recipient .

b) Not use any organs from this donor as I never did understand any of that HBV serology.

c) Transplant the liver only into HBV immune recipients, a high status HBsAg+ or a HBV non-immune recipient, with lamivudine and HBIG coverage.

d) Use all organs from this donor since the risk of HBV transmission in this setting has not been described.

Answer:

Donor HBcAb (+)

- Donors with HBcAb(+) status are not uncommon.
  - Canada (79/1656) 4.7%
  - US Population 5.4%
  - UNOS 3.8%
- Isolated HBcAb(+) donors:
  - Potentially infectious (low level active infection)
  - Immunity (low titre sAb)
  - False positive (low level)

* Low HBV endemic areas (US, Canada) : 1-5%

What Can We Learn From Other Organ Donation?

- HBcAb+ donors to RENAL Allograft Recipients
  - Wachs *(Transplantation, 1995)*
    - 42 cAb+ donors
    - 1/42 became sAg+ at 3 months, (2.4%)
    - F/U 4yrs, asymptomatic, all naïve preRtx
    - 2 acquired new antibody (HBsAb)
  - Madayag *(Transplantation, 1997)*
    - 45 cAb+ donors
    - 0/45 became sAg+, F/U 2yrs
    - No difference in graft/pt survival
    - 12 acquired new antibody sAb+ or cAb+
    - All vaccinated pre-transplant
  - Satterthwaite *(Transplantation, 1997)*
    - 38 cAb+ donors
    - 0/38 became sAg+
    - 27 naïve, 5 acquired new antibody sAb+
    - F/U 4yrs

- HBcAb+ donors to CARDIAC Allograft Recipients
  - Wachs *(Transplantation, 1995)*
    - 7 cAb+ donors
    - 0/7 became sAg+
    - 4 were naïve
  - Preiksaitis *(Transplantation, 1997)*
    - 7 cAb+ donors
    - 0/7 became sAg+
    - 1 gained sAb and cAb

- HBV from HBcAb + donors KIDNEY and HEART Recipients

		No. HBV Infected / No. Recipients			
Miller	1993	Heart	0/12	Renal	0/19
Cirocco	1994			Renal	0/16
Kadian	1994	Heart	0/13	Renal	0/19
Wachs	1995	Heart	0/7	Renal	1/42 (2.4%)
Radomski	1995			Renal	0/10
Paletta	1996	Heart	0/8	Renal	0/28
Madayag	1997			Renal	0/45
Satterthwaite	1997			Renal	0/38
Krieger	2001			Renal	1/26 (3.8%)

  - Bottom line: ~ 1% of kidney / heart donations result in HBV infection

- HBcAb+ donors to LIVER Allograft Recipients
  - Douglas *(Liver Transplantation and Surgery, 1997)*
    - 9 cAb+ donors
    - 3/9 became sAg+ post OLTx (33%)
    - Only 1/3 Severe disease
    - All 3 recipients naïve (sAb-, cAb-)
  - Prieto, Gomez et al *(Liver Transplant, 2001)*
    - 30 cAb+ donors from Spain
    - HBsAg+ developed in…
      - 15/26 naïve (58%)
      - 0 / 4 with sAb+ and cAb+/-

- Del Pozo *(AST, 2001, [A1147])*
  - 12 cAb+ donors to 12 sAb+ recipients
  - 0/12 HBsAg+
- Dickson *(Gastroenterology, 1997)*
  - 23 cAb+ donors
  - 18 / 23 became sAg+ post OLTx (78%)
  - 15 / 18 recipients naïve (sAb-, cAb-)
  - 3 / 18 recipients sAb+

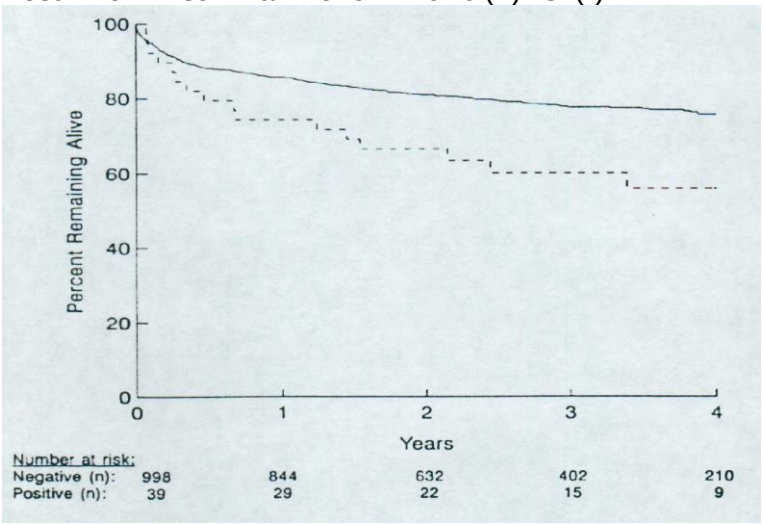
HBsAb(+) may not be protective if donor HBcAg(+)

- Dodson *(Transplantation,1997)*:118 donors

	Recip. status	%HBV
48 cAb-, sAb+	cAb+/-, sAb+/-	0%
70 cAb+. sAb+/-	cAb-, sAb-	72%
	cAb-, sAb+	0%
	cAb+, sAb-	13%

  - No restriction on sAb+ donors
  - No need to test donor sAb

Post Liver Tx survival: Donor HBcAb (+) vs. (-)



HBV from HBcAb (+) donors Liver Allograft Recipients

		n	Immune	Naïve	
Miller	1993	(12)	----	4/12 (33%)	
Kadian	1994	(11)	----	4/11 (36%)	
Wachs	1995	(6)	0/1 (0%)	3/5 (60%)	
Dodson	1997	(70)	2/29 (6.9%)	25/41 (61%)	
Douglas	1997	(9)	0/1 (0%)	3/8 (37.5%)	
Dickson	1997	(23)	3/5 (60%)	15/18 (83%)	
Dodson	2001	(50)	0/22 (0%)	1/28 (3.6%)	(LAM/HBIG)
Del Pozo	2001	(12)	0/12 (0%)	3/3 (100%)	
Kaul	2001	(27)	2/24 (8.3%)	---	
Nery	2001	(27)	0/19 (0%)	0/8 (0%)	(LAM/HBIG)
Vierling	2001	(9)	----	0/9 (0%)	(LAM)
Prieto	2001	(30)	0/4 (0%)	15/26 (58%)	

- Bottom line: ~ 6% of liver donations result in HBV infection

QUESTION

The kidneys, heart, lungs, and liver are offered. The donor is found to have HBsAg(-), HBsAb(+), and HBcAb(+). At our center we would:

a) Transplant the kidneys, heart and lungs into any suitable recipient because the risk of transmission of HBV is very low but if possible select a HBsAb+ recipient.

b) Not use any organs from this donor as I never did understand any of that HBV serology.

c) Transplant the liver only into HBV immune recipients, or high status HBsAg + or HBV non-immune patients with lamivudine and HBIG coverage.

d) Use all organs from this donor since the risk of HBV transmission in this setting has not been described.

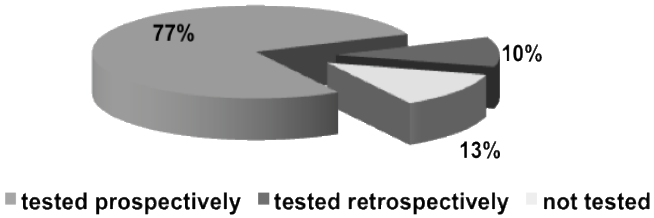
e) a and c

Answer:

Questions About HBcAb (+) **Donors**

- Is there an organ specific risk ?
- Is the recipient HBV status important ?
- Is recipient therapy/prophylaxis required ?

Canadian HBcAb Testing (1999)



HBcAb donor testing should be mandatory

Summary

- HBsAg(+) donors:
  - Remains an **absolute relative contraindication** for organ transplantation.
- HBcAb(-) and HBsAb(+) donors:
  - Use all organs, any recipient, no prophylaxis
- HBcAb(+) and HBsAb (+/-) donors:
  - Livers only into HBsAg(+) recipients
  - Critically ill, HBsAb(+) recipient or naïve recipient *with HBIG/LAM*.
  - All other organs can be used freely regardless of recipient serology, no prophylaxis.
    - Preferably sAb(+)
    - Vaccinate recipients

Recipients with Hepatitis B

- Recipients can reactivate HBV
- Non-Liver recipients can develop clinical hepatitis, or severe FCH.

➢ Recipients with HBV: HBsAg(+)

- High risk of HBV reactivation
  - Prior to effective HBV therapy --- Death
  - Currently nucleoside analogues are used
    - Lamivudine, famciclovir, adefovir, entecavir
  - If not initiated early severe reactivation (death) may occur.

Must start LAM +/- HBIG at time of (before) transplant

- RENAL
  - Huo (DDS, 2001)
    - 34 sAg+ vs. 145 sAg- (f/u 6 yrs)
    - No patient or graft survival difference in sAg+ vs neg

- HEART
  - Ko (J Heart Lung Transplant, 2001)
    - 8 / 101 hearts into sAg+ recipients
    - 6 / 8 reactivated all responded to LAM
    - 2 / 8 have not re-activated and on no treatment

- Recipients with HBV: HBsAg(-), HBcAb(+), HBsAb(+/-)
  - Isolated HBcAb (+)
    - Reactivation can occur
    - Monitor at regular intervals (serology, DNA)
  - HBcAb (+), HBsAb (+)
    - Reactivation (serologically or clinically) occurs in up to 20% likely secondary to low level viral replication in the liver, even years after loss of sAg
    - Prophylactic vs Preemptive therapy with NA
    - PreTransplant vaccine possibly helpful

Preemptive treatment with LAM monitor serology / DNA for potential HBV reactivation

- Summary
  - HBsAg(+) recipient:
    - Initiate LAM +/- HBIG at time of transplant
  - HBcAb(+) and HBsAb(-) recipient:
    - Potential for reactivated HBV disease.
    - Monitor serology/DNA, preemptive treatment with LAM
  - HBcAb(+) and HBsAb (+) recipients:
    - Low risk of reactivation.

HBV from HBcAb + donor: **KIDNEY and HEART Recipients**

		No. HBV Infected / No Recipients			
Miller	1993	Heart	0/12	Renal	0/19
Cirocco	1994			Renal	0/16
Kadian	1994	Heart	0/13	Renal	0/19
Wachs	1995	Heart	0/7	Renal	1/42 (2.4%)
Radomski	1995			Renal	0/10
Madayag	1997			Renal	0/45
Satterthwaite	1997			Renal	0/38
Preiksaitis	1998	Heart	0/7	Renal	0/17

HBcAb+ donors to LIVER Allograft Recipients

- Wachs *(Transplantation, 1995)*
  - 6 cAb+ donors
  - 3/6 became sAg+ post OLTx (50%)
  - Severe disease (death, ESLD, Re-OLTx)
  - All 3 recipients naïve (sAb-, cAb-)
- Vierling *(Liver Transplantation, 2001)*
  - 15 cAb+ donors
  - 6 into HBsAg+ recipients with HBIG/LAM
  - 9 naive recipients all given Lamivudine
    - 0/9 developed HBsAg, or HBcAb
- Dodson *(Transplantation, 2001 AST [A942])*
  - 50 cAb+ donors
  - 22 into HBsAb+ recipients
    - No treatment, No HBV
  - 28 into HBsAb- recipients
    - All Given HBIG and Lamivudine

- 1/28 developed HBV (HBIG only)

		No. HBV Infected / No. Recipients	
Miller	1993	4/12	(33%)
Kadian	1994	4/11	(36%)
Wachs	1995	3/6	(50%)
Douglas	1997	3/9	(33%)
Dickson	1997	18/23	(78%)
Dodson	1997	31/70	(45%)
Preiksaitis	1998	4/6	(66%)
Prieto	2001	15/30	(50%)

Efficacy of HBIG and Lamivudine as prophylaxis for Recipients of HBcAb+ livers (Dodson*; Transplantation,1999)*

Recipient status	Prophylaxis	HBsAG(+)
○ Naïve	HBIG	1 / 1
○ Naïve	HBIG and LAM	0 / 7
○ HBcAb (+)	HBIG and LAM	0 / 8

- Follow-up 1.5 yr

MISCELLANEOUS

Western
UNIVERSITY · CANADA

Testing of Endoscopic Pathology Recognition

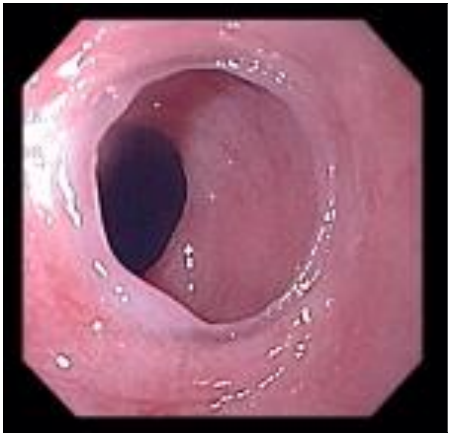
Frances Tse and Louis Liu

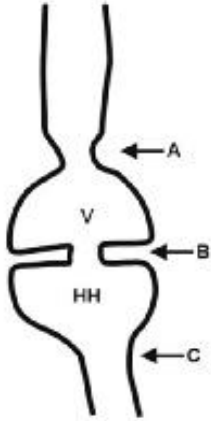
Suggested Endoscopy Report Layout

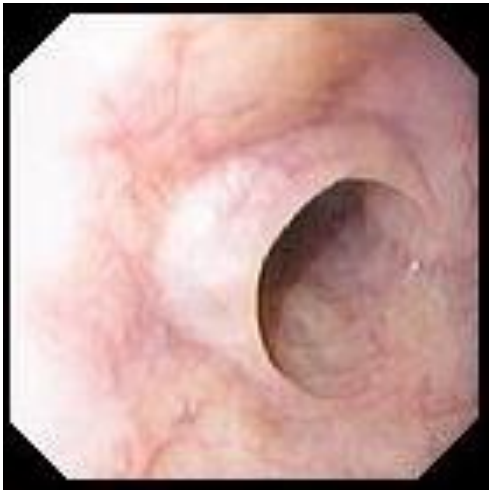
- Brief History & limited pertinent P/E
  - 3-5 sentences
- Medications
  - Antibx, sedations etc
- Procedure
  - Detail description of findings
- Impression
  - Summary of findings/diagnosis
- Plan
  - Any new therapy, additional investigations, follow up plan, etc.

ESOPHAGUS

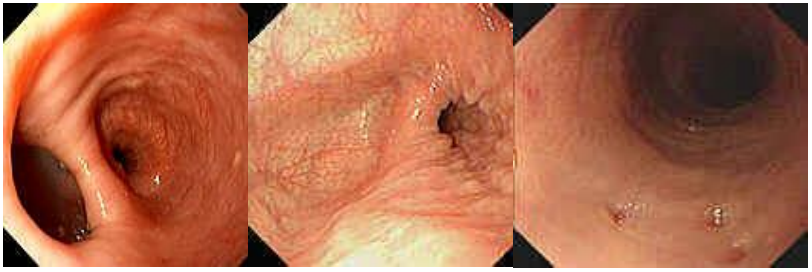
- Web vs. Ring







- Esophageal Diverticula

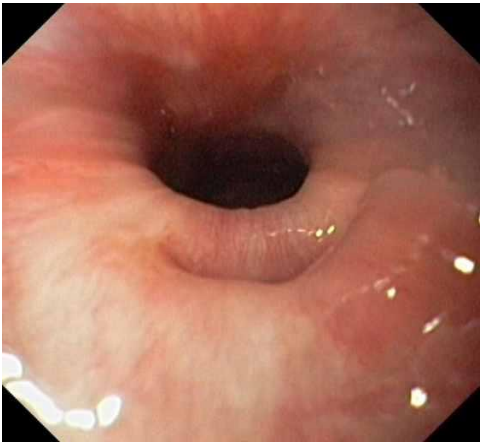


Mid-esophageal (traction)

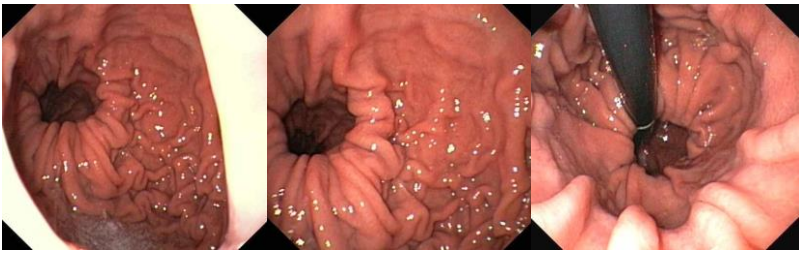
Epiphrenic (pulsion)

Intramural

- Zenker Diverticulum

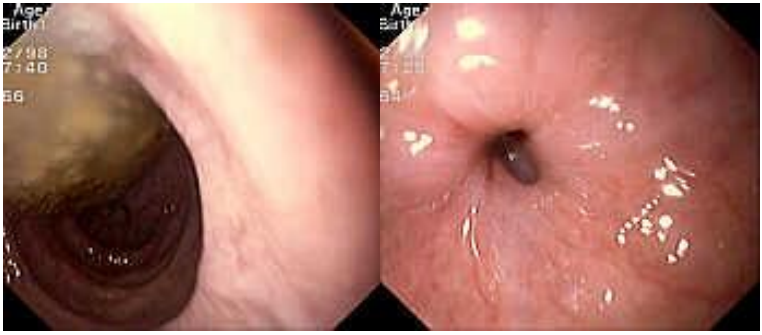


- Hiatus Hernia

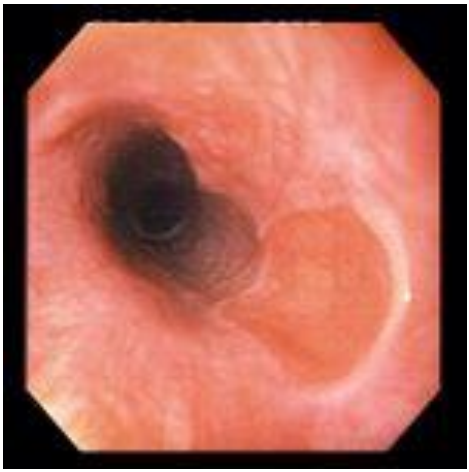


Above Inside Retroflexed

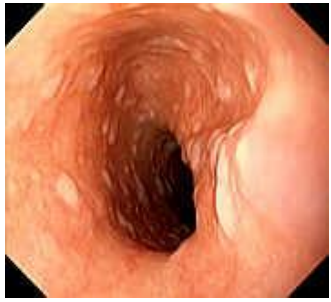
- Achalasia



- Inlet Patch



Description of White Patches in Esophagus

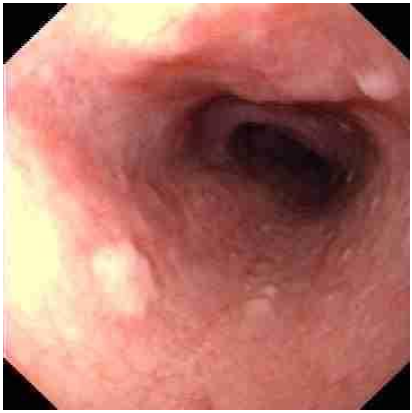


- Size: – Small vs. large
- Number – Single vs. multiple
- Shape – Nodular, irregular
- Border – Well-circumscribed, irregular, confluent
- Location – Proximal, mid, distal
- Lesion – Washed off?
- Surrounding and underlying mucosa normal?

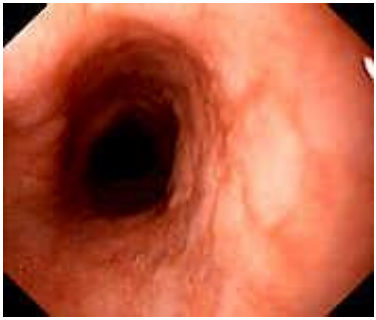
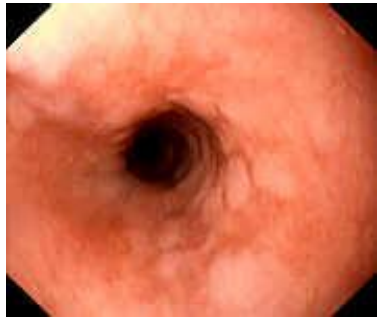
Differential diagnosis of causes of white patches in esophagus

- Acanthosis glycogen
- Basal cell hyperplasia
- Candidiasis
- Granular cell tumor
- Papilloma (squamous cell)

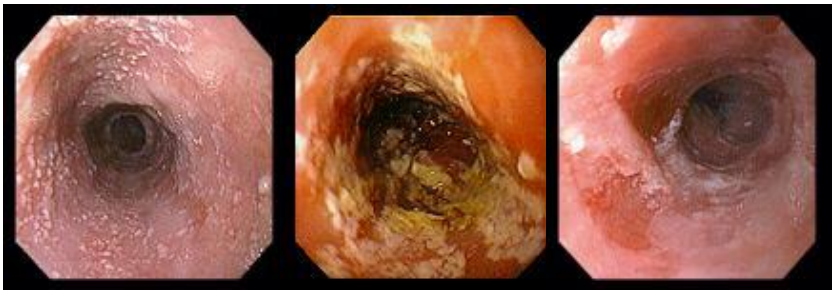
- Acanthosis Glycogen



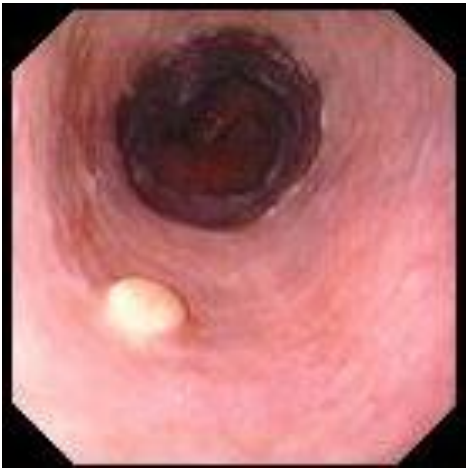
- Basal Cell Hyperplasia

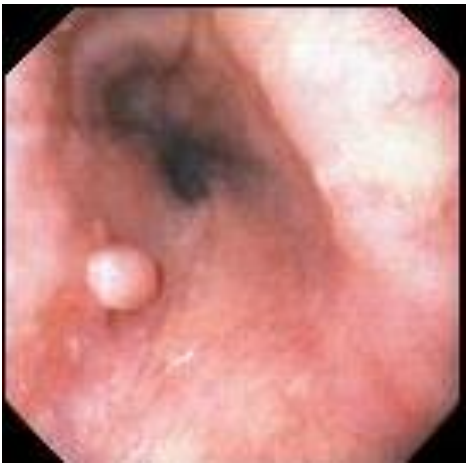
- Candidiasis



- Granular Cell Tumor



- Squamous Cell Papilloma



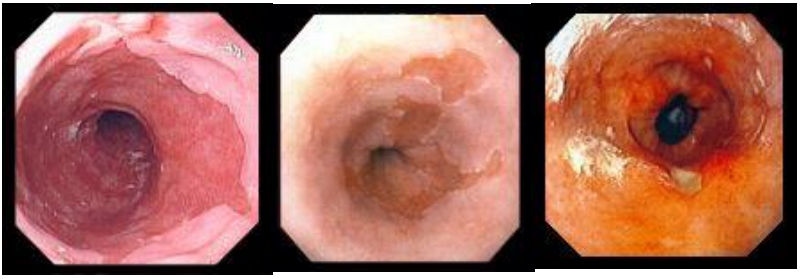
Los Angeles Esophagitis Classification System

Grade A	Mucosal break ≤ 5 mm in length
Grade B	Mucosal break > 5mm in length
Grade C	Mucosal break continuous between > 2 mucosal folds
Grade D	Mucosal break ≥75% of esophageal circumference

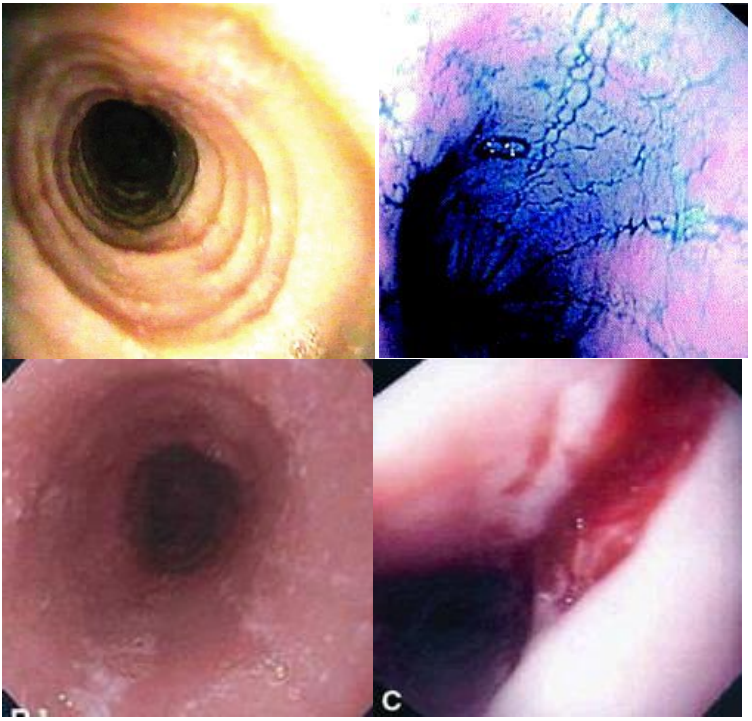
Lund ell L, et al. Gut 1999; 45:172-80.

Sample of Grade A-D GERD EE

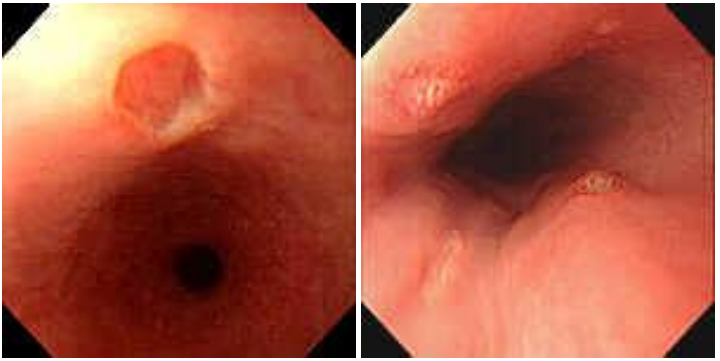
Barrett esophagus



Eosinophillic Esophagitis (EoE)

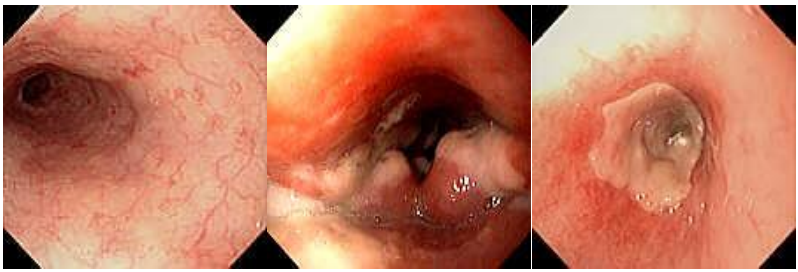


Viral Esophagitis

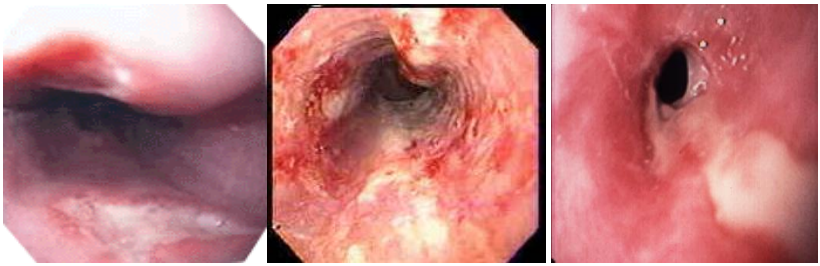


CMV HSV

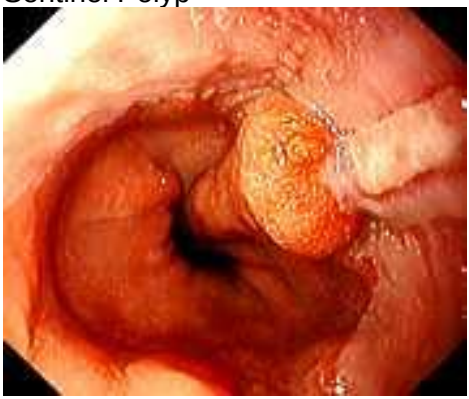
Radiology Esophagitis



Pill-induced Esophagitis Ulcer

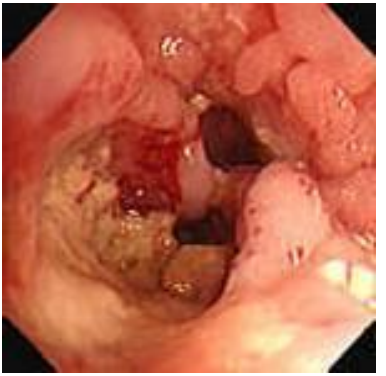


Sentinel Polyp



Esophageal Cancer

Early



Late

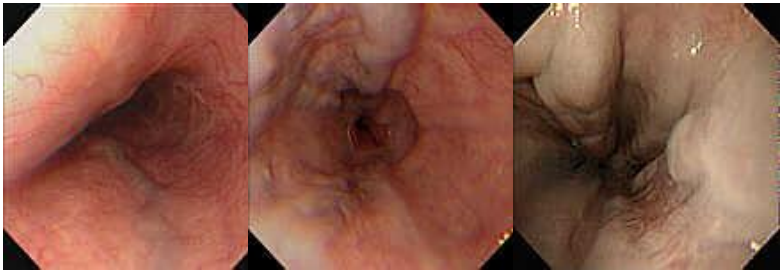
Esophageal Varices and Risk of Bleeding

- Patient
  - CTP grade
- Varices
  - Large
  - Stigmata

Abbreviation: CTP, Child-Turcotte Pugh grading

The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. NEJM 1988;319:983-989.

Esophageal Varices – Grading

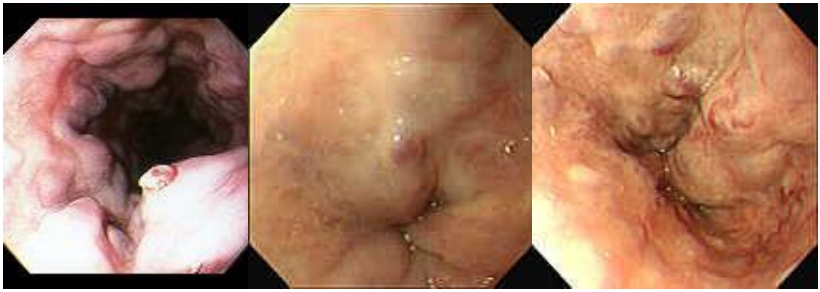


G1: small, straight varices

G2: enlarged, tortuous varices, < 1/3 of lumen

G3: large, coil shaped varices, > 1/3 of lumen

Esophageal Varices – Stigmata



Visible vessel

Cherry Red Spots

Red Wale Signs

STOMACH

Type	Cause	Site
○ Non-atrophic	HP	Antral
○ Atrophic		
– AI	AI	Corporal
– Multiple	HP	Pangastritis
– Chemical	Bile NSAIDs	Antral, corporal
– Radiation	Radiation	
○ Lymphocytic	Celiac	
○ Granulomatous	CD, Sarcoid, Wegners, Churg-Straus	
○ Eosinophilic infection	Bacteria, virus, fungi, parasites	

Examples of Gastropathy (“Gastritis”)

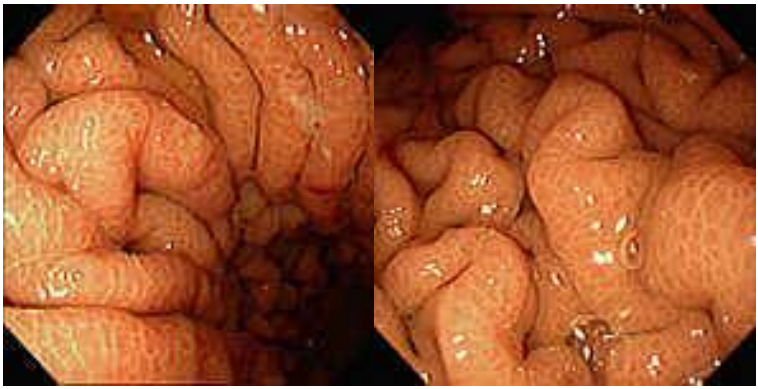
- H. pylori associated gastritis
- NSAID-associated gastropathy

Helicobacter pylori-associated Gastritis

- Non atrophic
  - Edema
- Atrophic (multifocal) gastritis; MAG)
  - Nodular
  - ↓ folds
  - ↓ submucosal versus plexus
- Gastric cancer
- Peptic ulcer

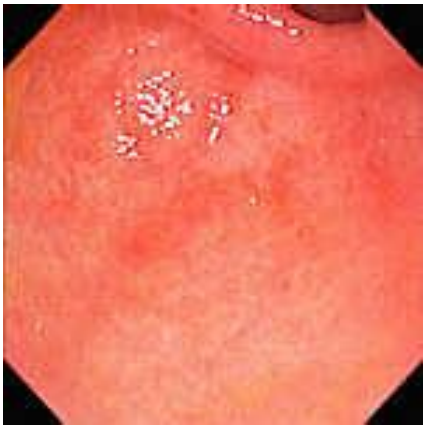
Non-atrophic Gastritis

- Edema

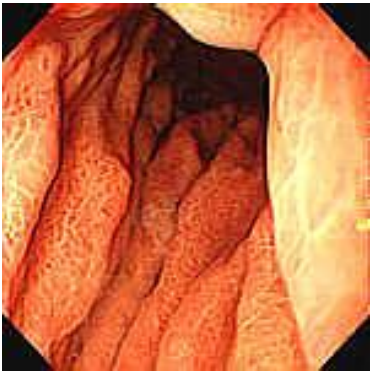


Accentuated area gastricae

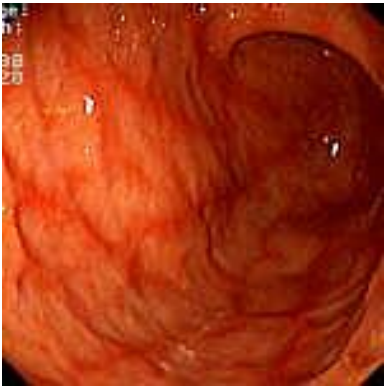
- Erythema



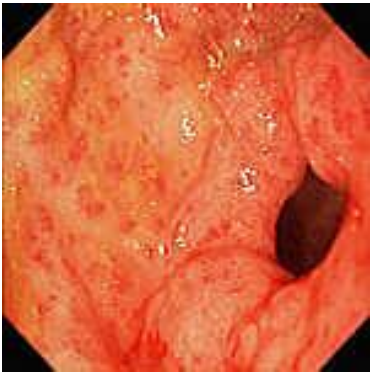
Patchy erythema



Diffuse erythema

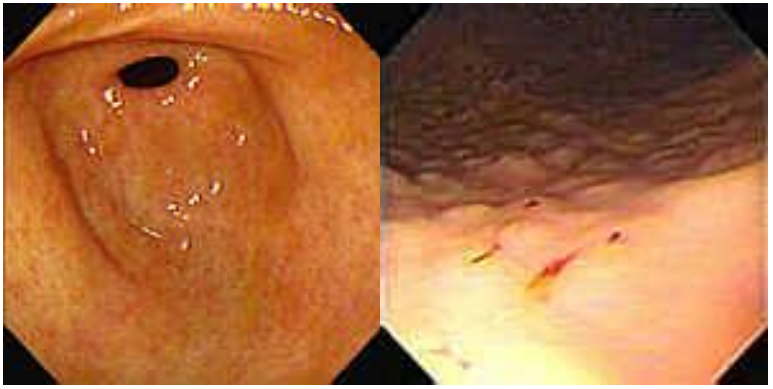


Linear erythema



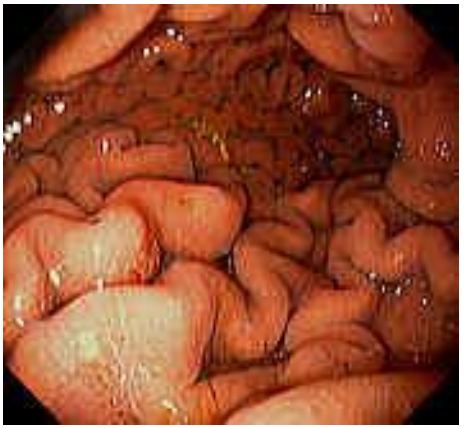
Multiple red dots

- Nodularity



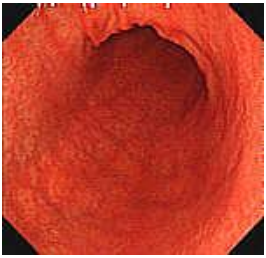
Antral predominant gastritis Nodularity at antrum

- Thickened Gastric Folds

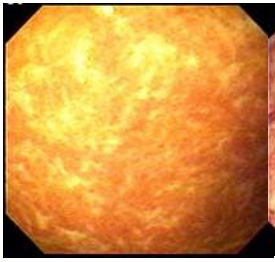


- Gastric cancer/lymphoma
- Menetrier disease
- Infectious gastritis (HP, CMV)
- ZES
- Gastric varices

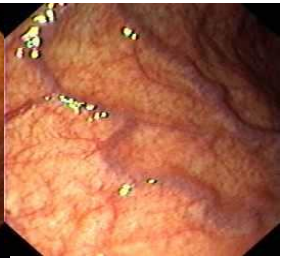
Atrophic Gastritis



Loss of gastric folds

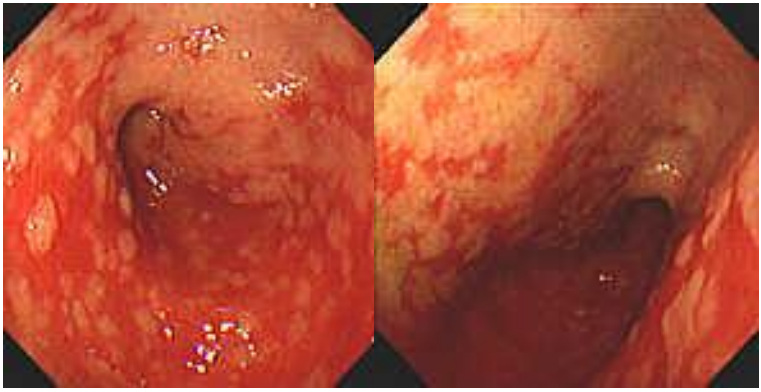


Mottling



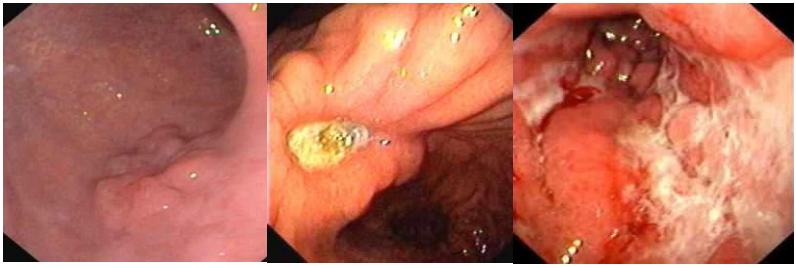
Submucosal venous plexus

Intestinal Metaplasia (IM)



Chronic gastritis → MAG → IM → GCa (gastric cancer)

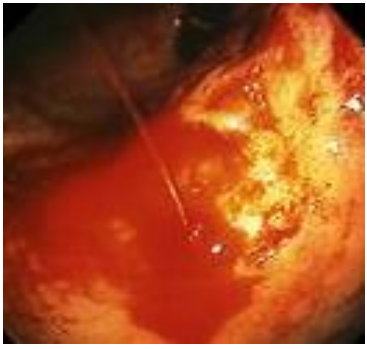
Gastric Cancer



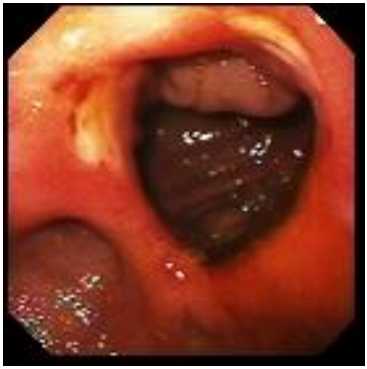
PUD

- Description:
  - Size
  - Shape
  - Depth
  - Border
  - Location
  - Number
  - Chronicity
  - Stigmata of recent bleeding

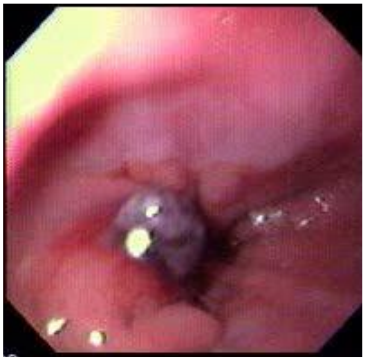
PUD Stigmata



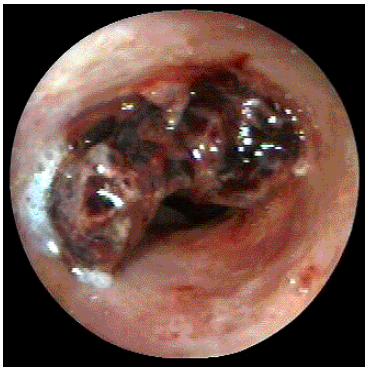
Spurter (Forrest IA)



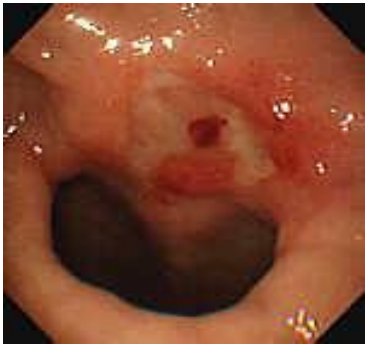
Oozer (Forrest IB)



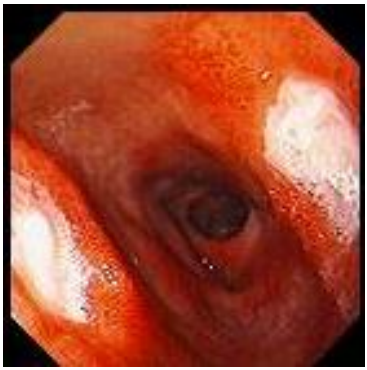
Visible Vessel (Forrest TIIA)



Adherent clot (Forrest IIB)

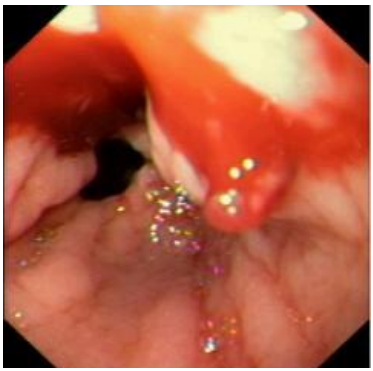


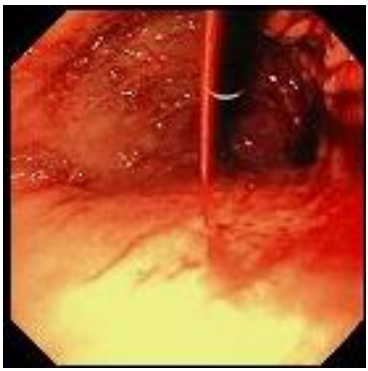
Flat pigmented spot (Forrest IIC)



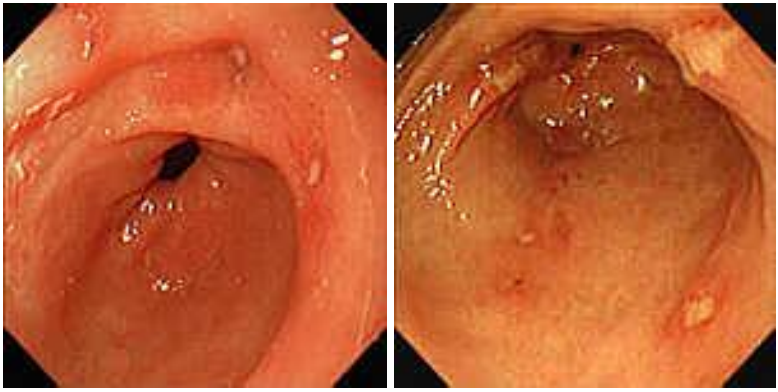
Clean Based Ulcer (Forrest III)

Look closely: Forrest A, or Dieulafoy Lesion

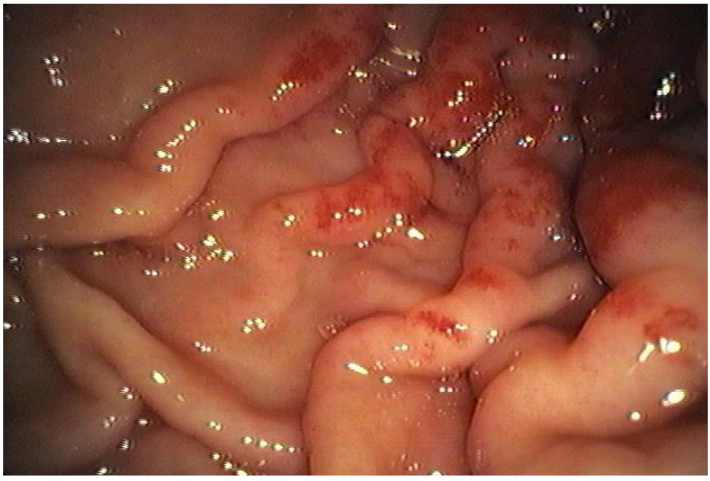




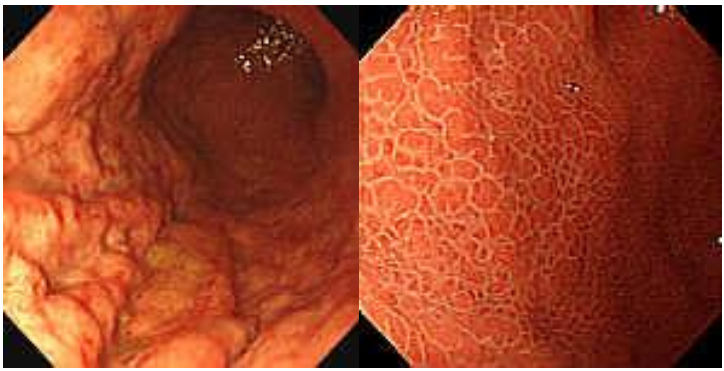
NSAID-Induced Gastropathy



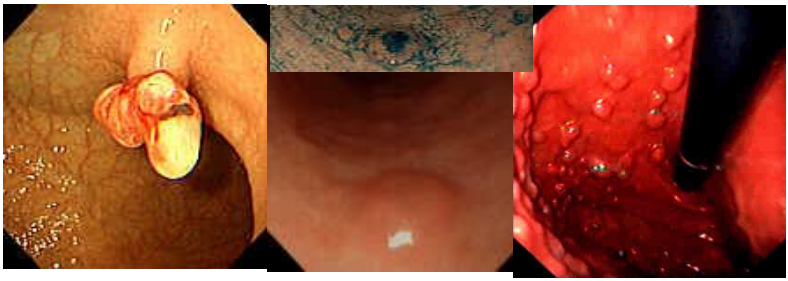
Gastric Antral Vascular (GAVE)



Portal Hypertensive Gastropathy

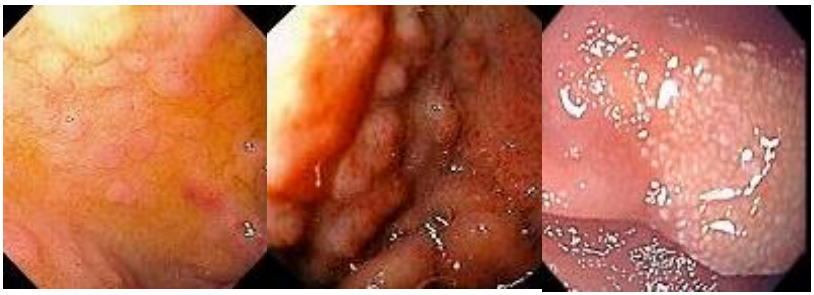


Gastric Polyps



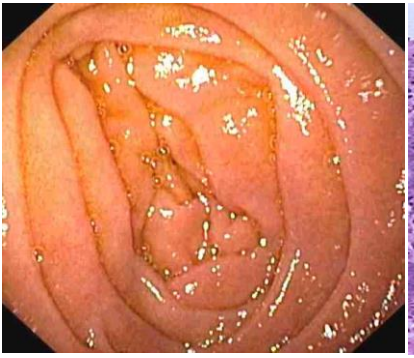
Hyperplastic Polyp Adenomatous Polyp Fundic Gland Polyps

More Gastric Neoplasia

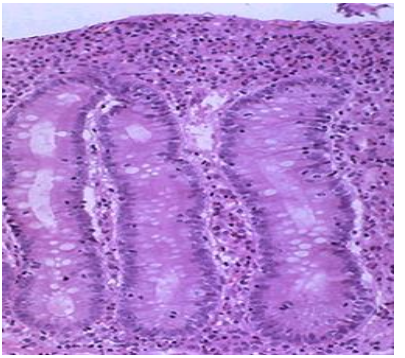


SMALL BOWEL

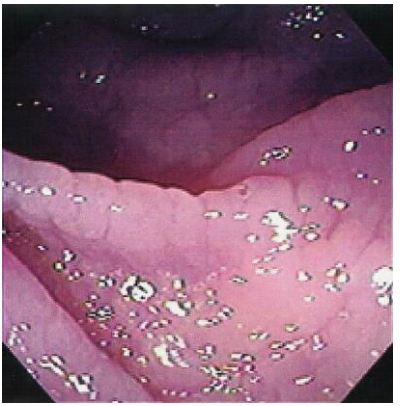
Celiac Disease



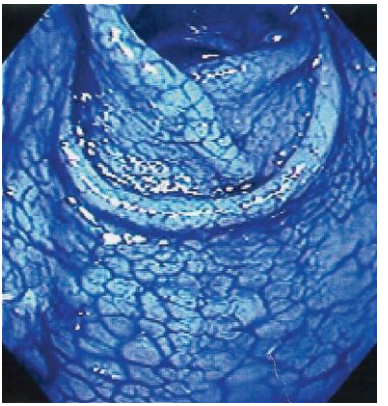
Endoscopically Normal Mucosa



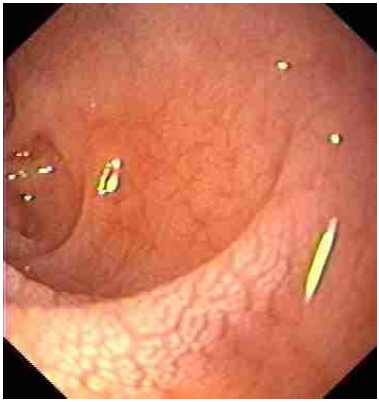
- Villous atrophy
- Crypt hyperplasia
- ↑ Intraepithelial lymphocytes (IEL)
- Lymphocytes in LP



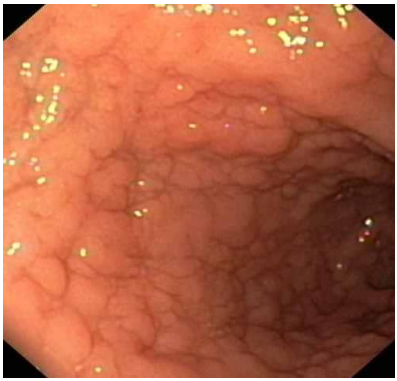
Scalloping of folds



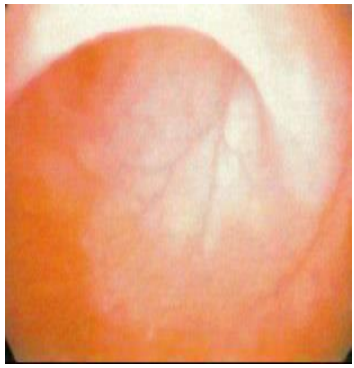
Mosaic mucosal pattern (methylene blue)



Loss of folds



Nodular pattern in bulb



Prominence of submucosal vessels

- Scalloping of folds
- Mosaic Pattern
- Loss of Folds
- Nodularity in bulb
- Submucosal vessels

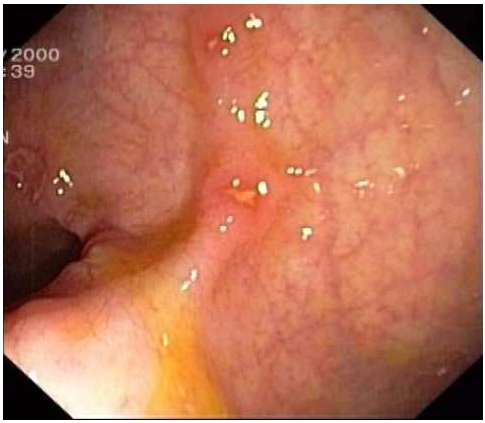
Performance characteristics
- Sensitivity 50%
- Specificity 99%

Niveloni S, et al. GI Endosc 1998;47:223-9.

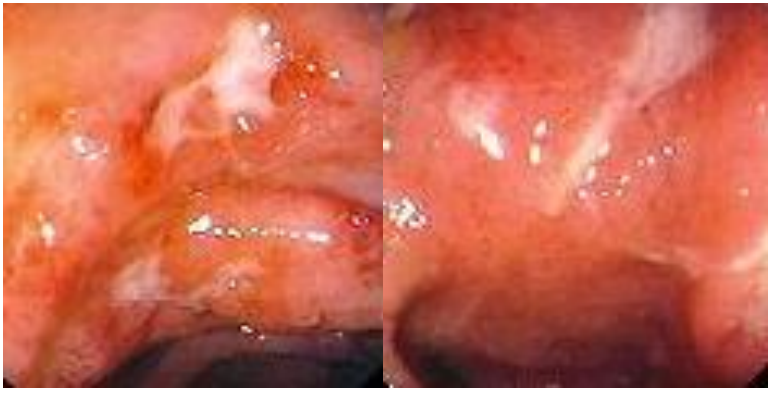
COLON

Crohn Disease

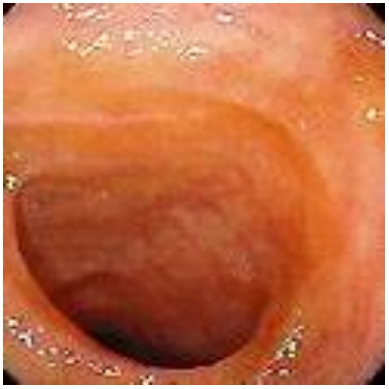
- Apthous Ulcer



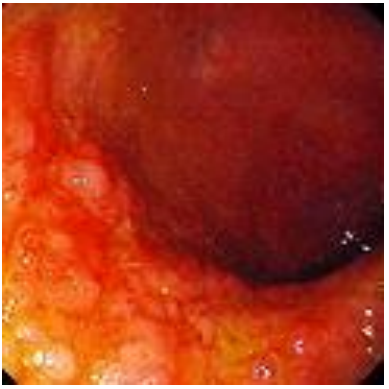
- Serpignosis Ulcers



- Terminal Ileum

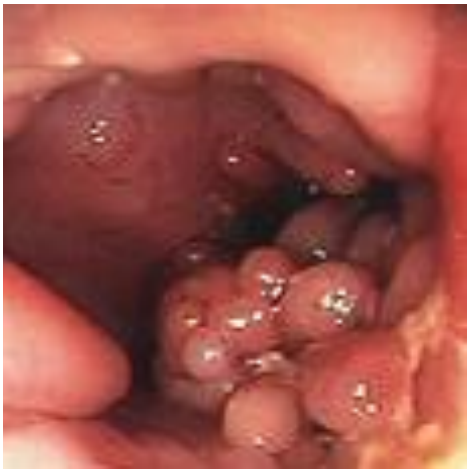


Normal

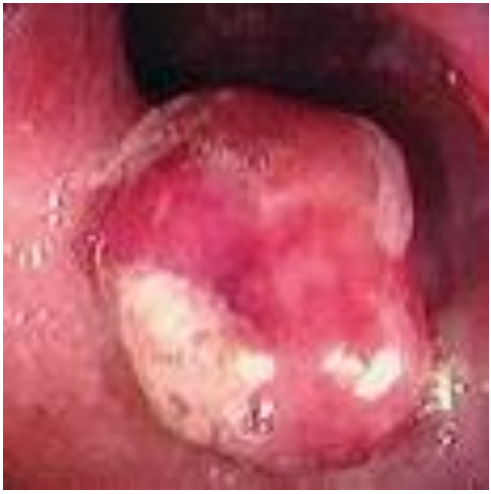


Red, friabile, edematous granular, cobblestoned

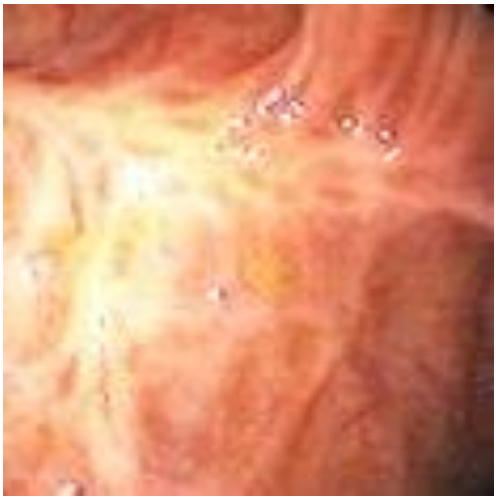
- Pseudopolyps



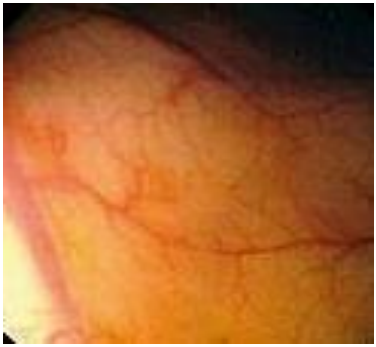
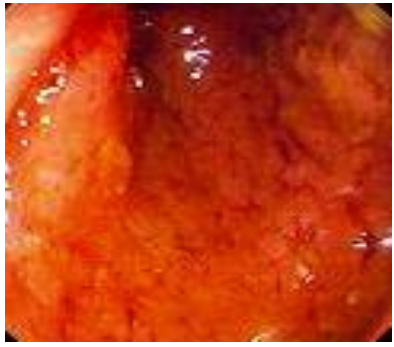
- Adenoma



- Fibrosis

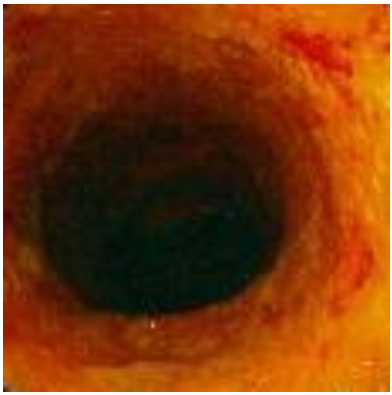


Ulcerative Colitis (UC)

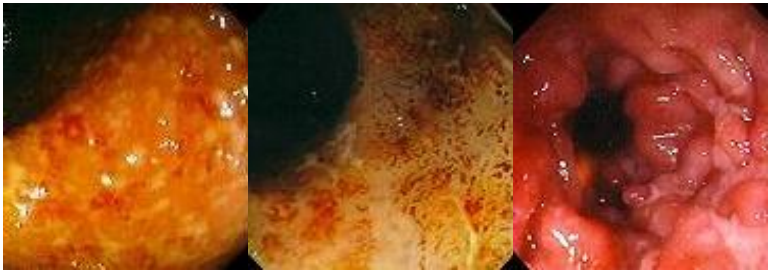
- Loss of vascular markings
- Granularity
- Friability

➢ Exudates



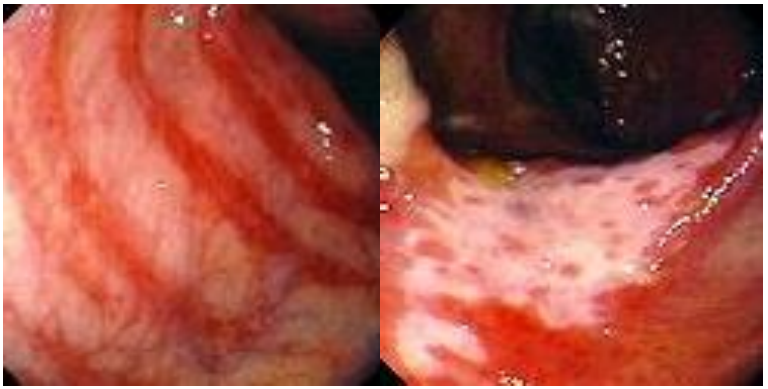
- Granularity
- Friability

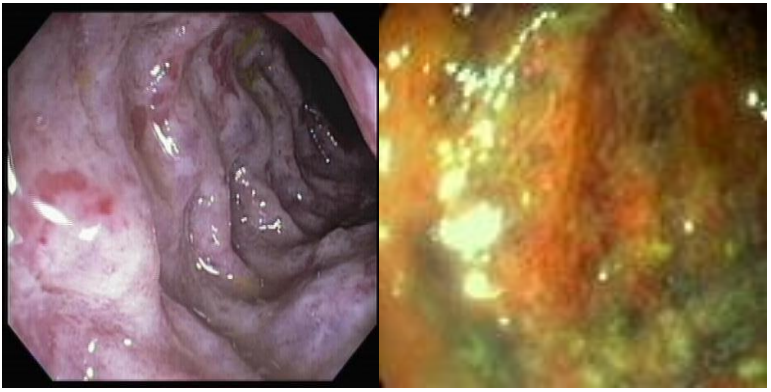
- Ulceration



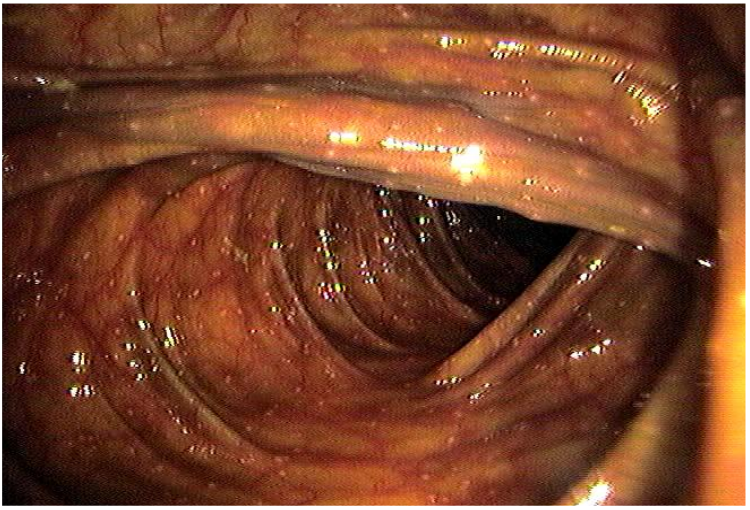
  - Punctate
  - Linear

Ischemic Colitis





Melanosis Coli




Western
UNIVERSITY · CANADA

GI Biopsy Crash Course: Normal Histology, Classical Entities and Common Issues

David Driman

Outline

- Normal histology
- Features of some selected common entities
- Requisition forms
- Common issues and scenarios to highlight endoscopist-pathologist communication

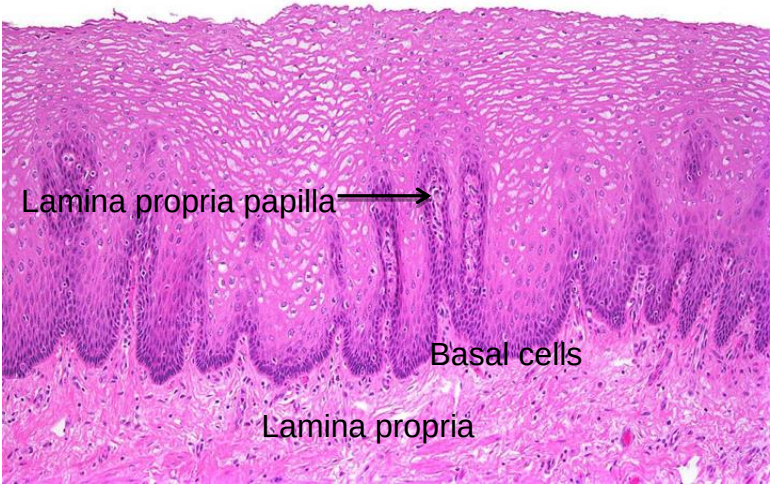
If you have a basic understanding of normal histology, you will:

- Be able to readily identify abnormalities presented to you
- Be more able to interpret pathology reports and to understand the processes behind your patients' symptoms and signs
- Be better able to communicate with your pathologist colleagues

Normal GI Mucosal Structure

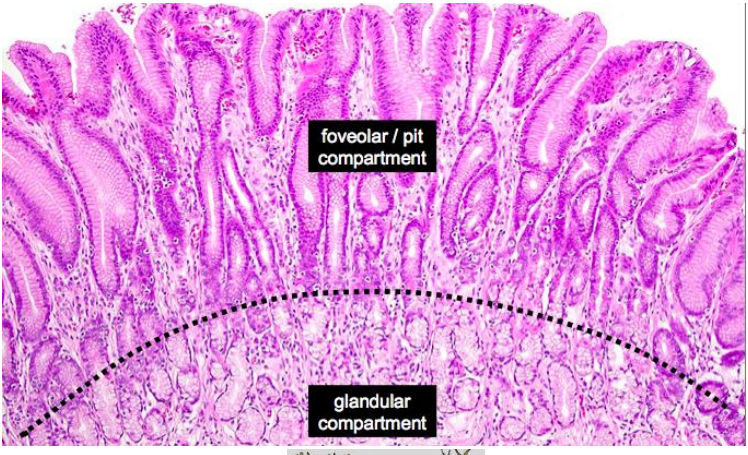
ESOPHAGUS

Normal Esophageal Squamous Mucosa

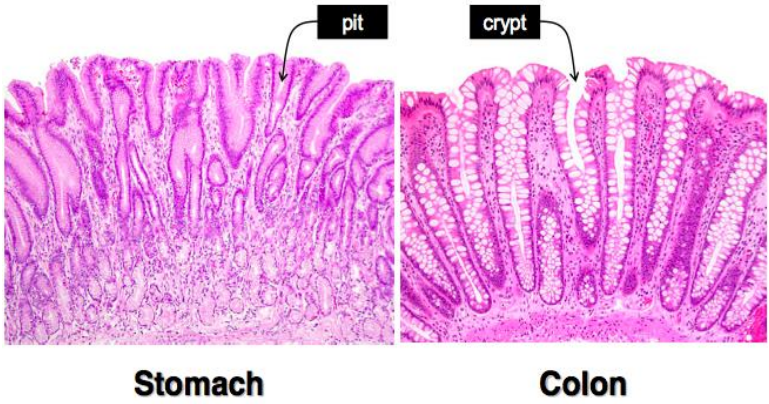


STOMACH

Normal Gastric Mucosa

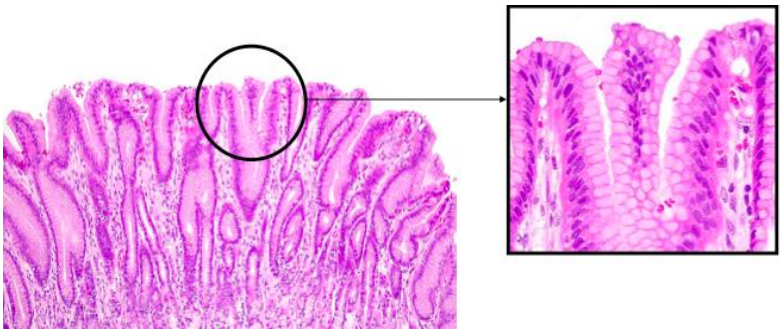


Stomach vs. Colon: Pits vs. Crypts

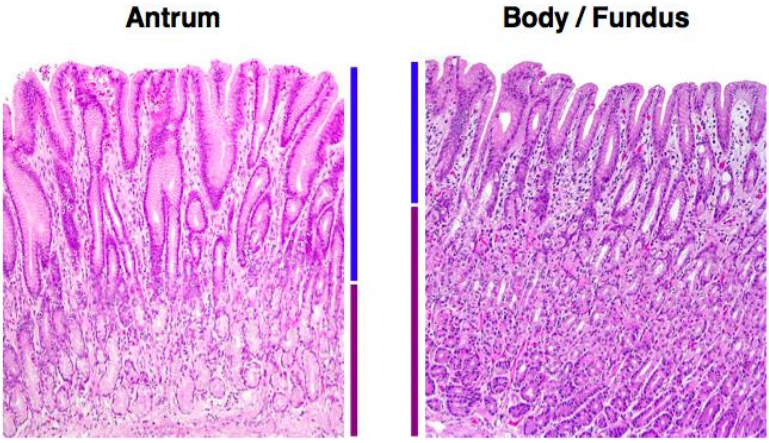


Normal Gastric Mucosa

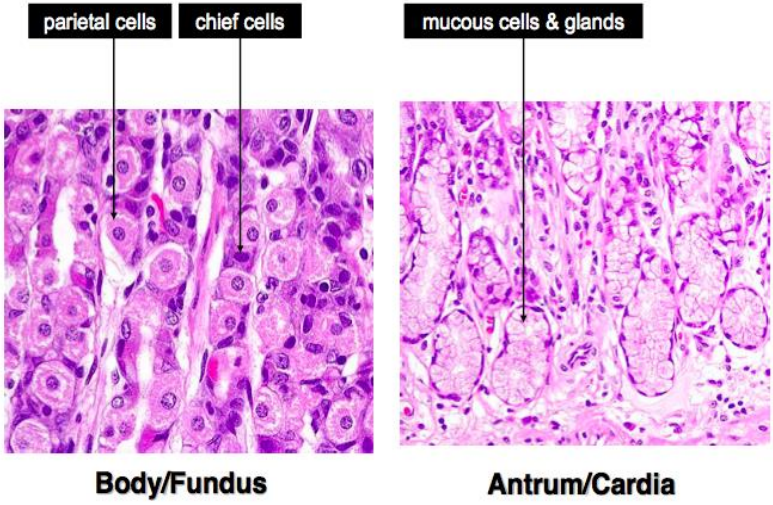
Surface epithelium columnar mucous cells only
No goblet cells
No absorptive cells



Pits and Glands

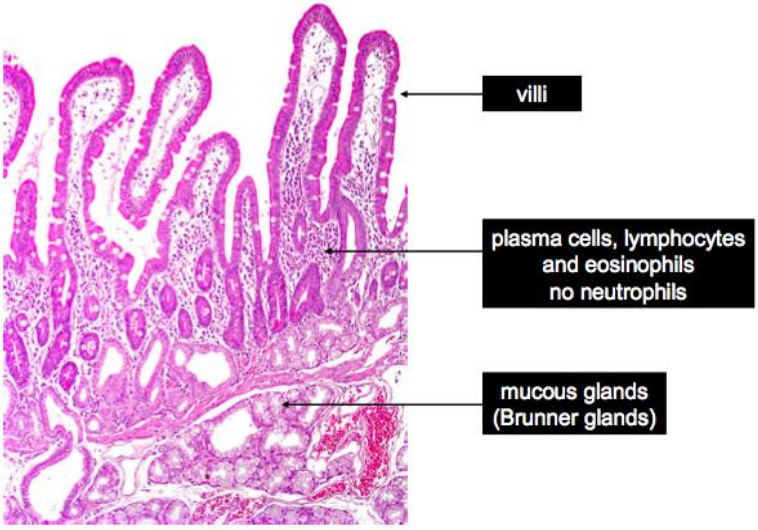


Glands of the Body / Fundus and Antrum

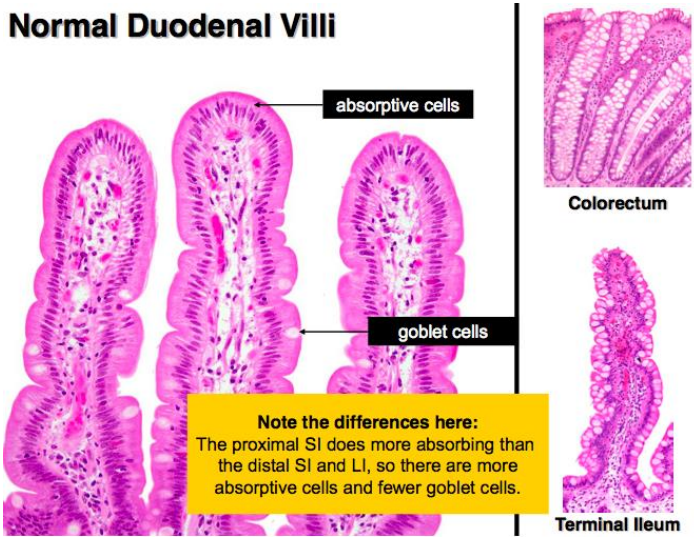


SMALL BOWEL

Normal Duodenal Mucosa

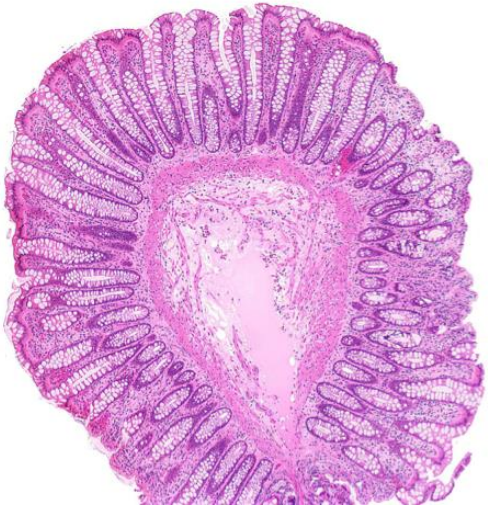


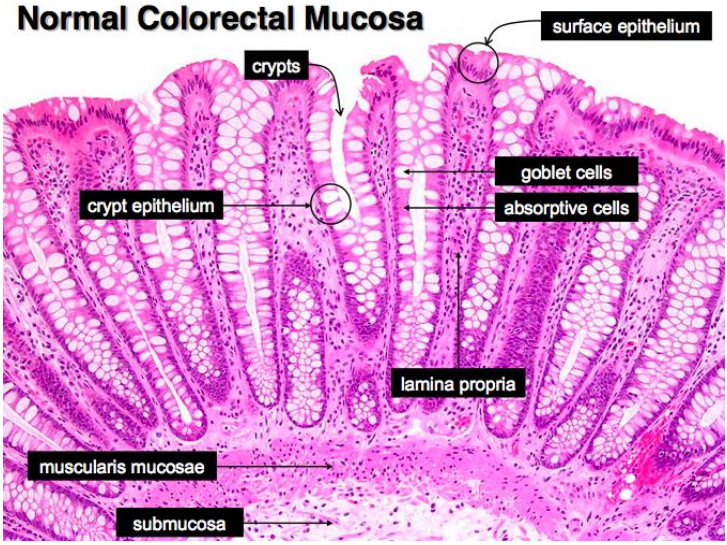
Normal Duodenal Villi



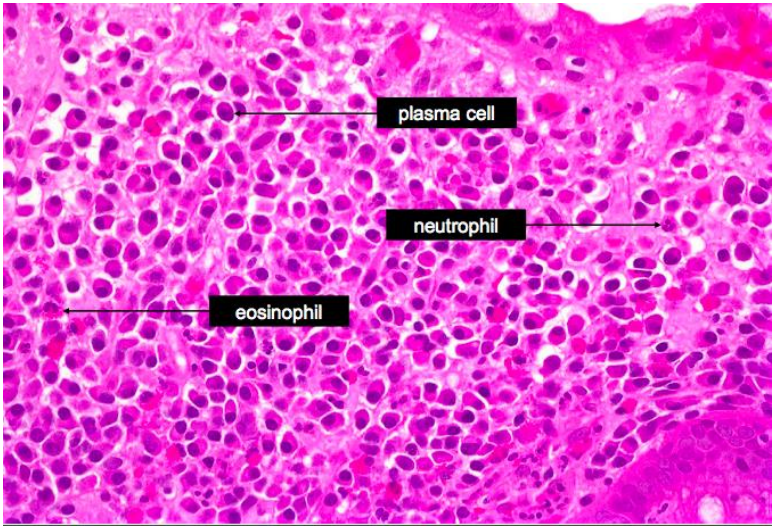
COLON

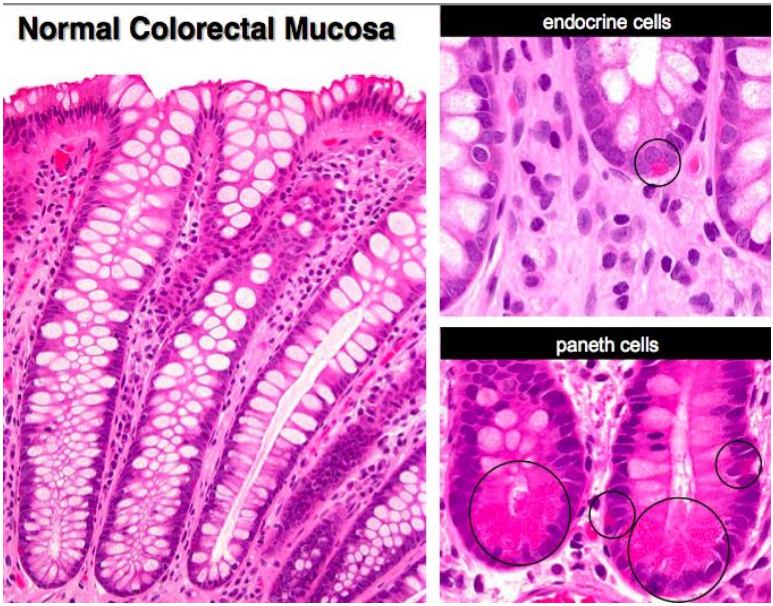
Normal Colorectal Mucosa



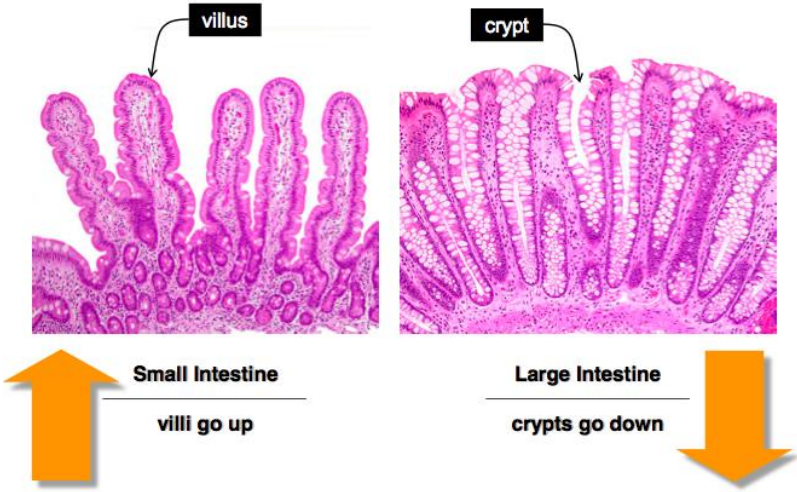


Inflammatory Cells – Lamina Propria





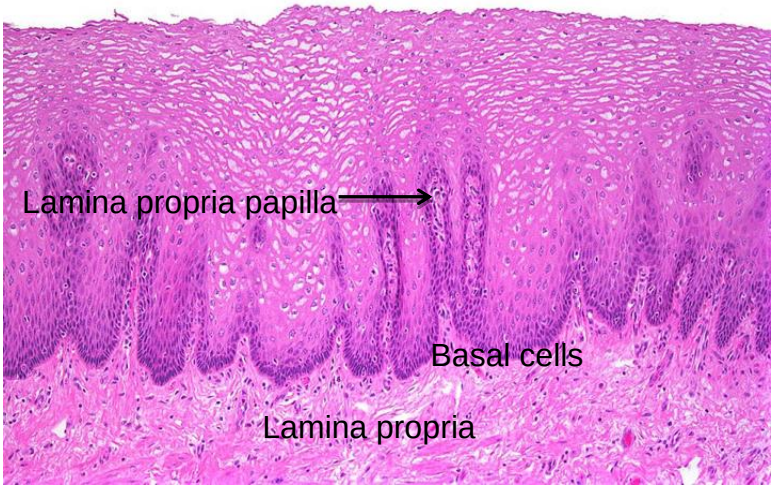
Intestinal Mucosa – Small vs. Large Intestine



Selected Common Pathological Entities Recognition Testing

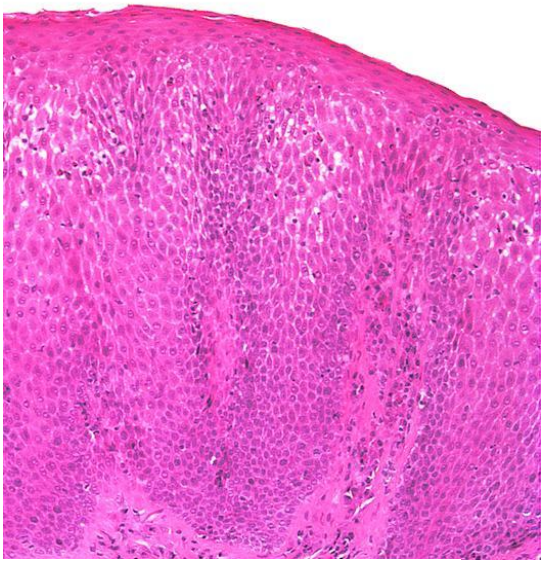
ESOPHAGUS

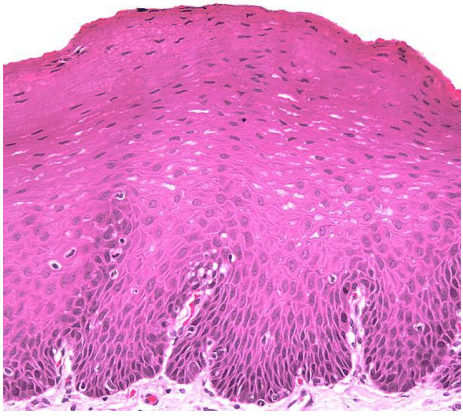
Normal Esophageal Squamous Mucosa



GERD

- increased thickness of basal layer
- Elongated lamina propria papillae
- Intraepithelial eosinophils <10/hpf

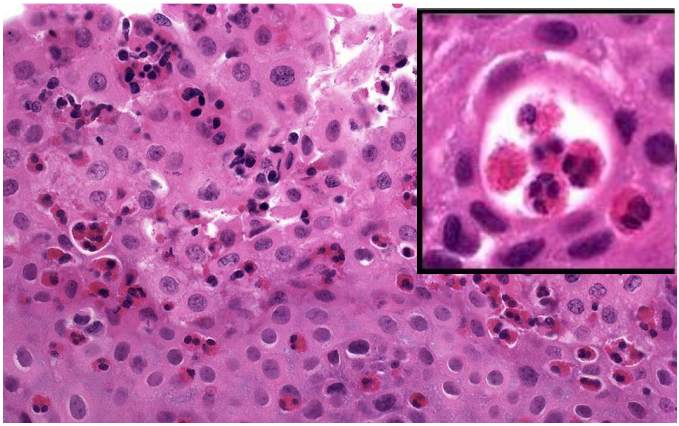




Normal

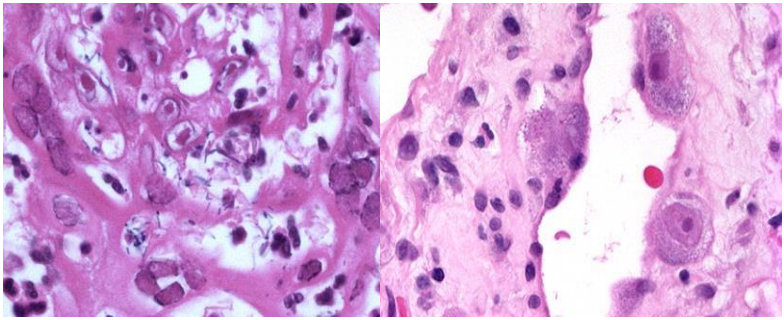
Eosinophilic Esophagitis

- Increased thickness of basal layer
- Elongated lamina propria papillae
- Intraepithelial eosinophils >15-20/hpf • eosinophilic microabscesses



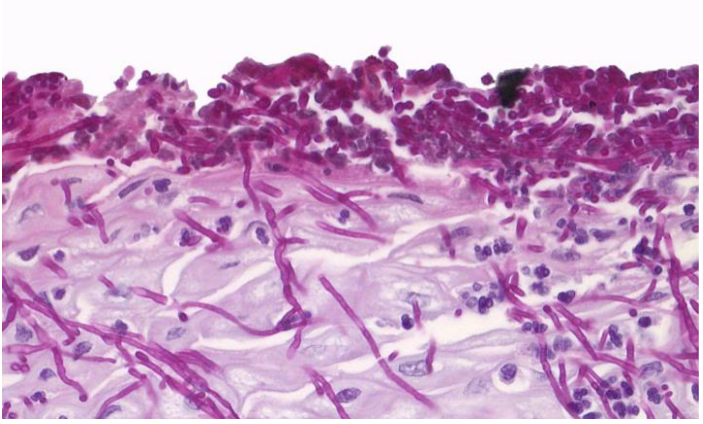
Viral Inclusions

Herpes **CMV**



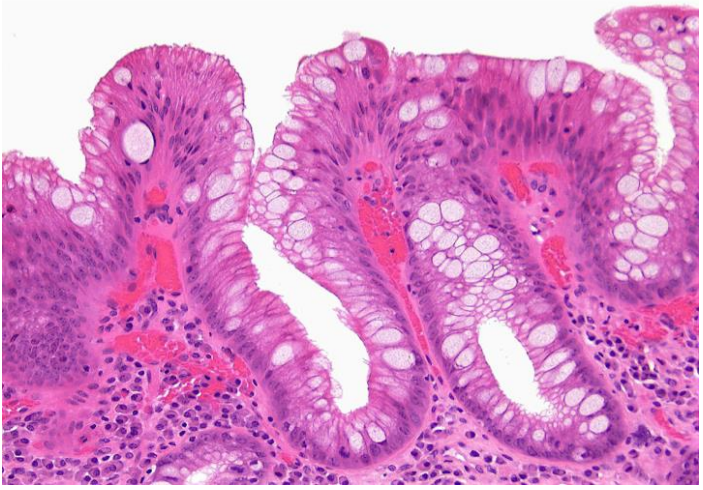
Candida

- Pseudohyphae in tissue
- Budding yeast forms



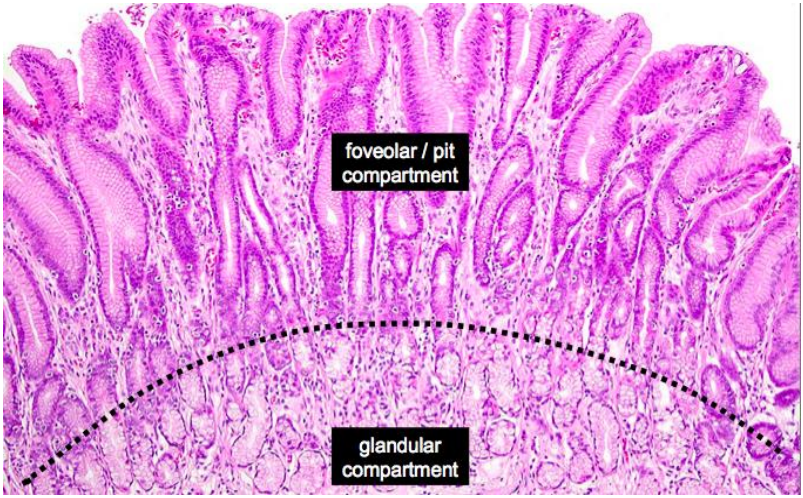
Barrett Esophagus

- intestinal metaplasia with goblet cells



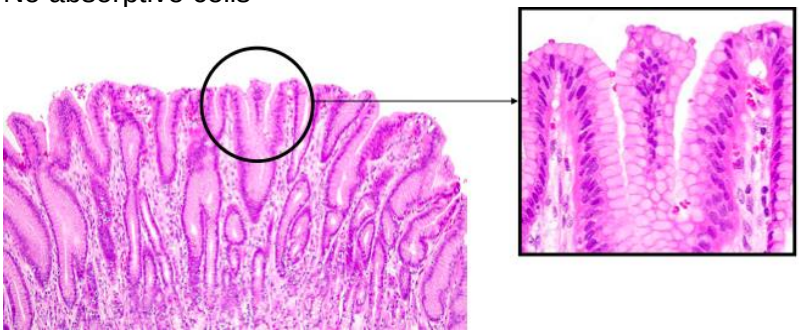
STOMACH

Normal Gastric Mucosa

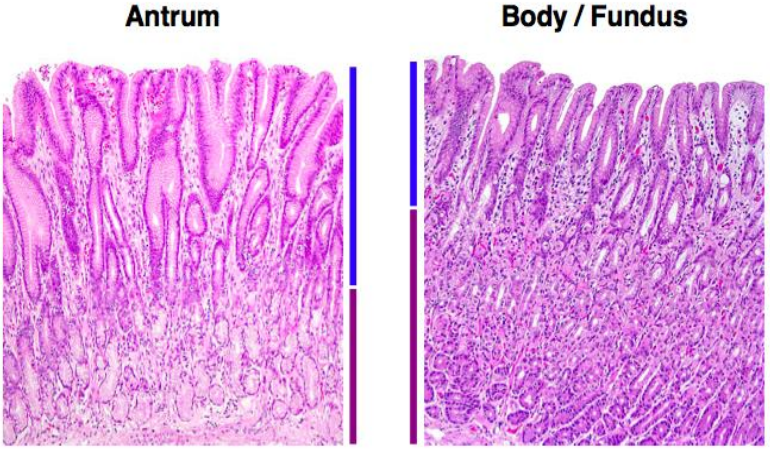


Normal Gastric Mucosa

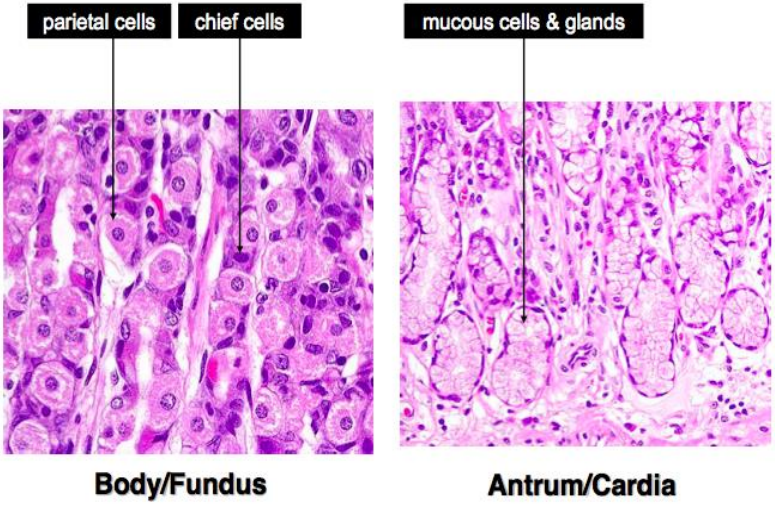
Surface epithelium columnar mucous cells only
No goblet cells
No absorptive cells



Pits and Glands

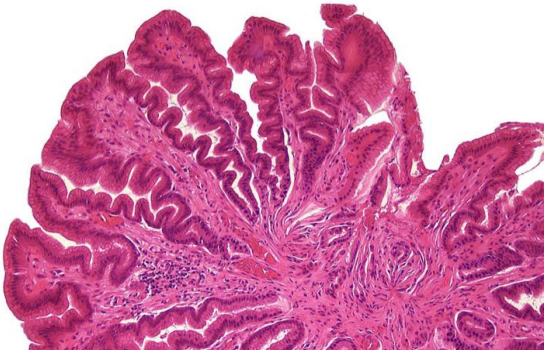


Glands of the Body / Fundus and Antrum

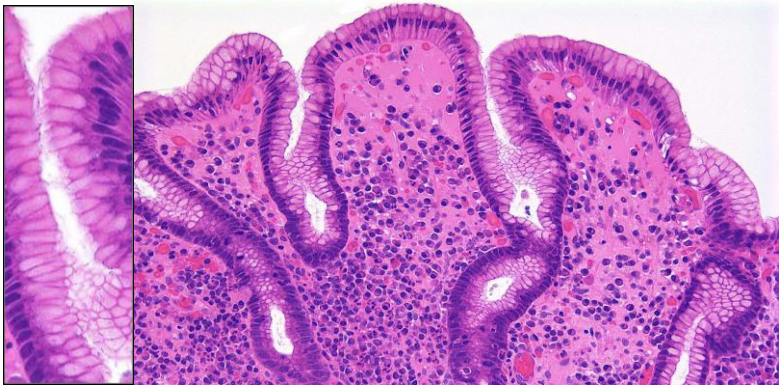


Reactive Gastropathy

- Foveolar hyperplasia (pit corkscrewing)
- Mucin depletion
- Smooth muscle bundles in lamina propria
- Little inflammation

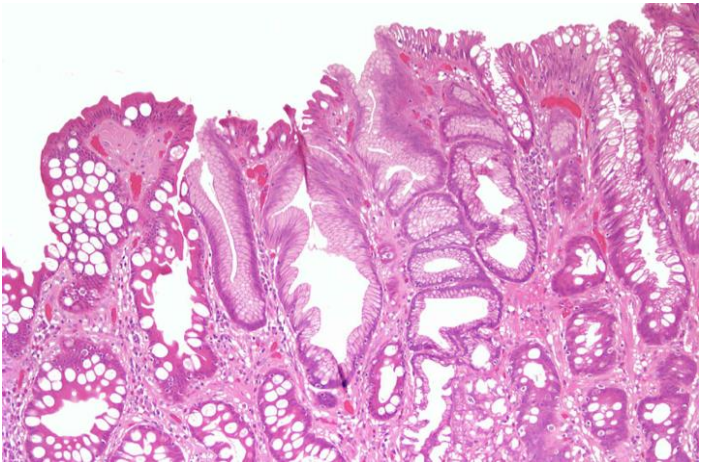


H. pylori Gastritis

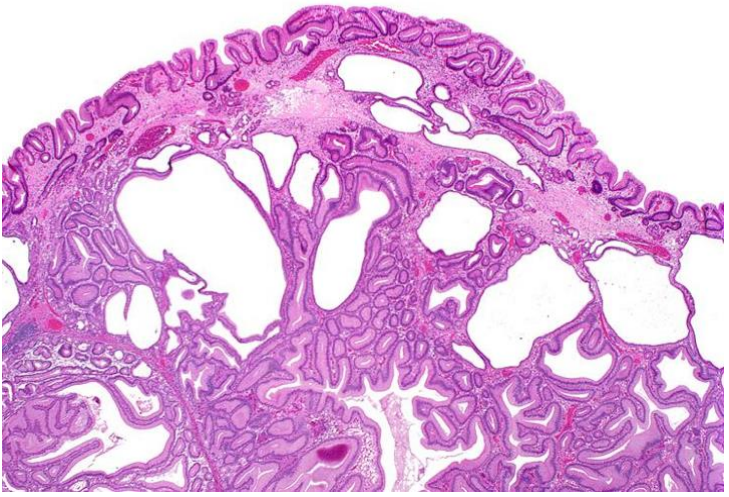


- Mixed lamina propria inflammation (plasma cells, lymphocytes, neutrophils)
- Organisms

Intestinal Metaplasia in Stomach

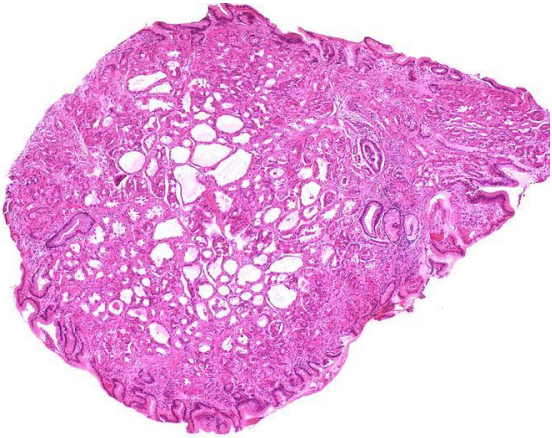


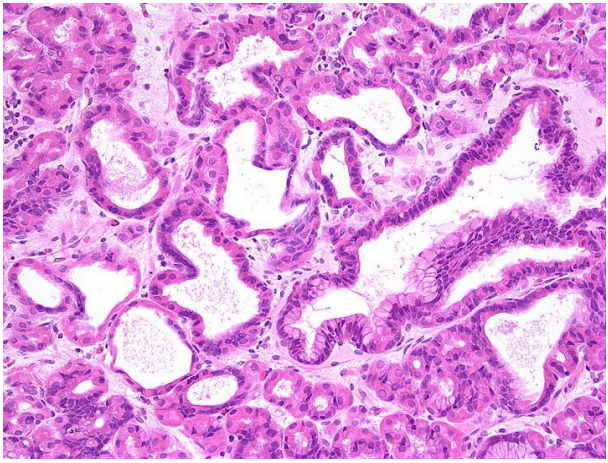
Gastric Hyperplastic Polyp



- Abnormal pit compartment with cystically dilated pits

Fundic Gland Polyp

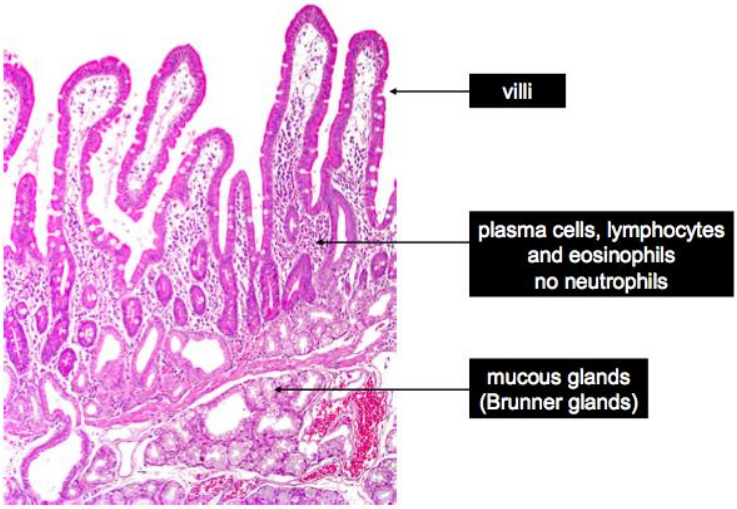


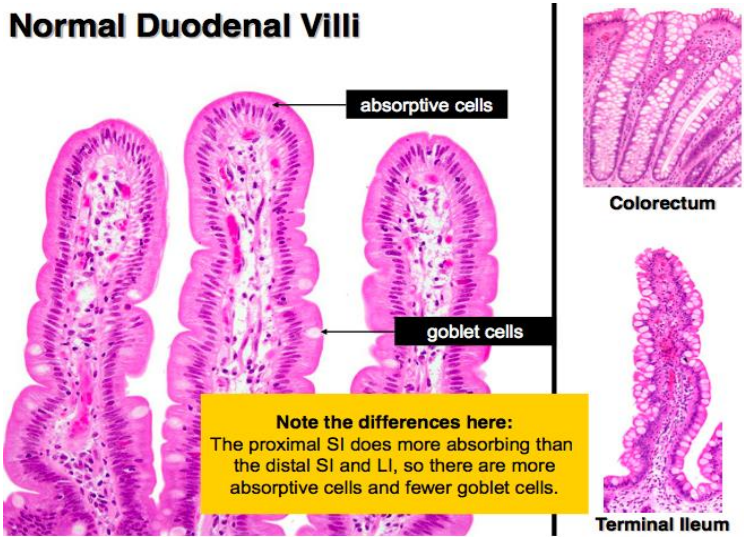


- Abnormal gland compartment
- Cystically dilated glands lined by parietal cells and chief cells

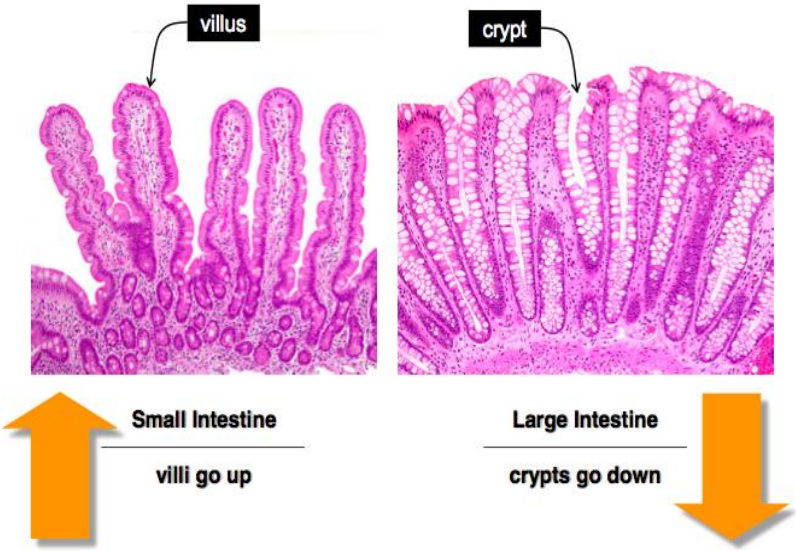
SMALL INTESTINE

Normal Duodenal Mucosa

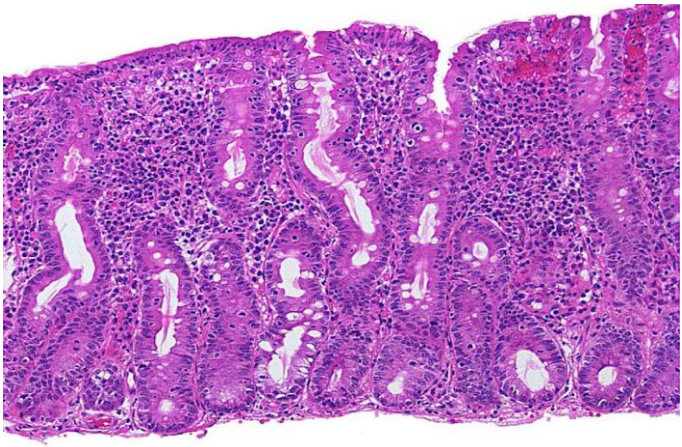


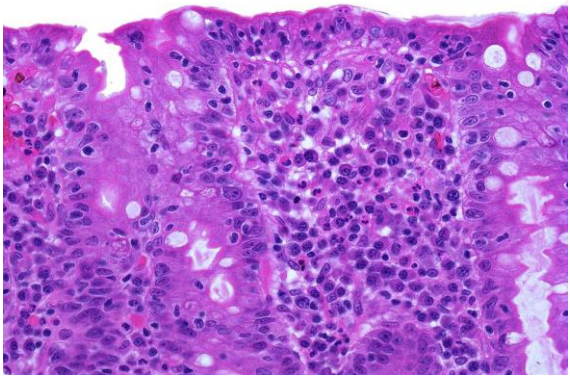


Intestinal Mucosa – Small vs. Large Intestine



Celiac Disease

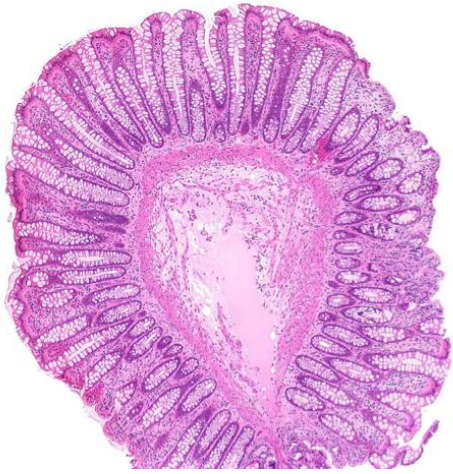


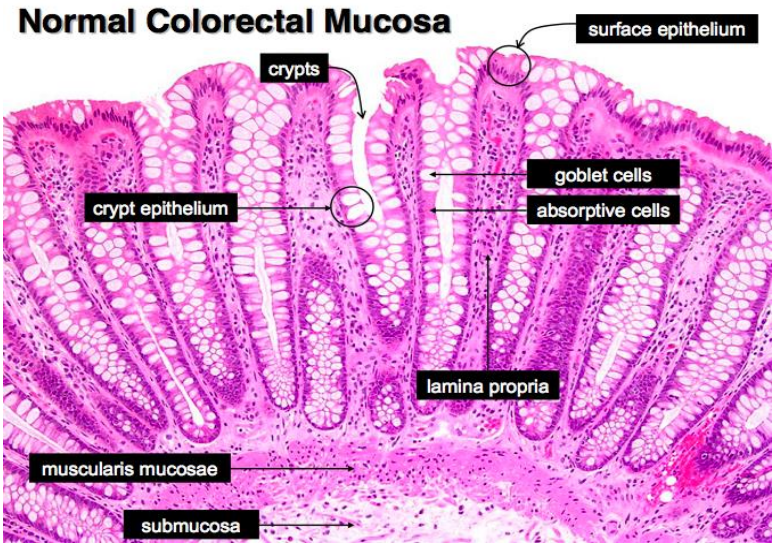


- Abnormal villi
- Increased lamina propria inflammation
- Increased intraepithelial lymphocytes

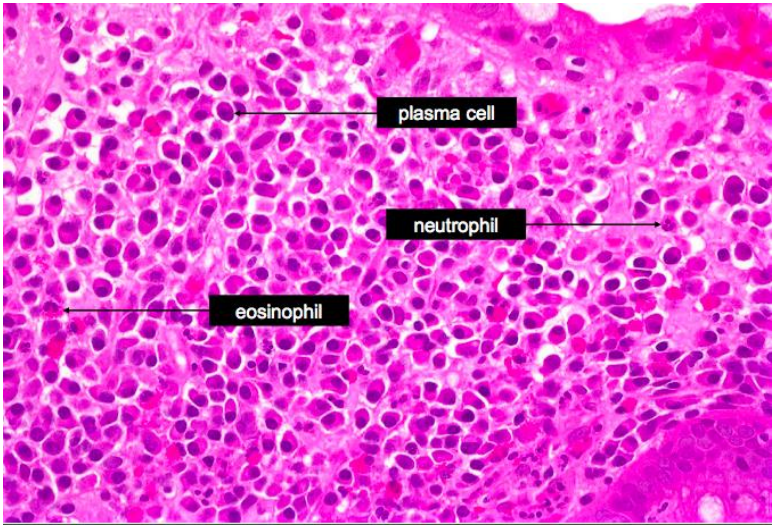
COLON

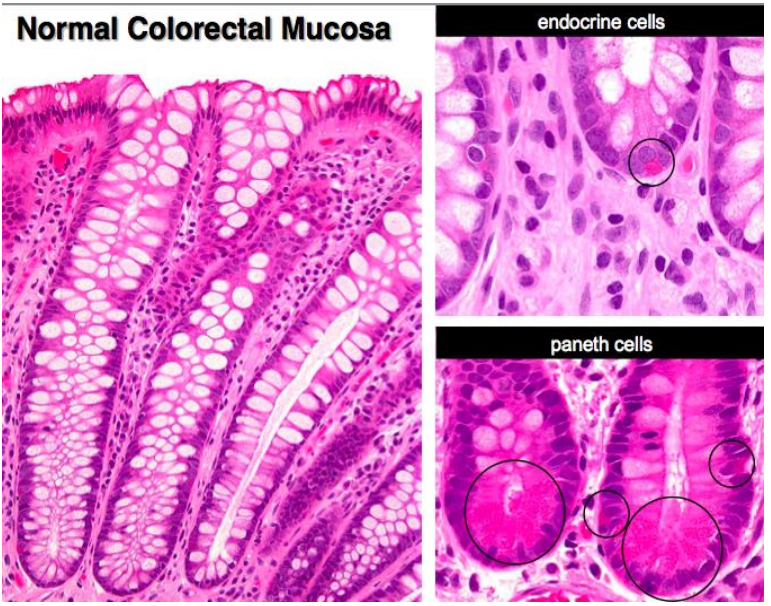
Normal Colorectal Mucosa



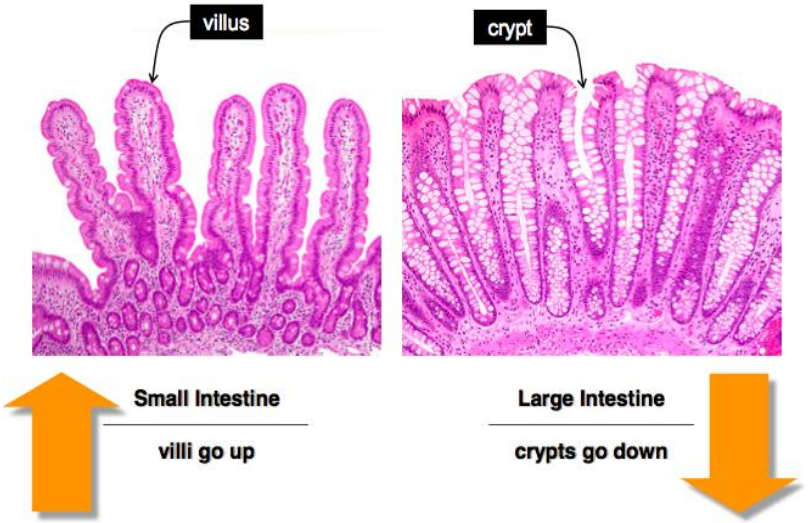


Inflammatory Cells – Lamina Propria



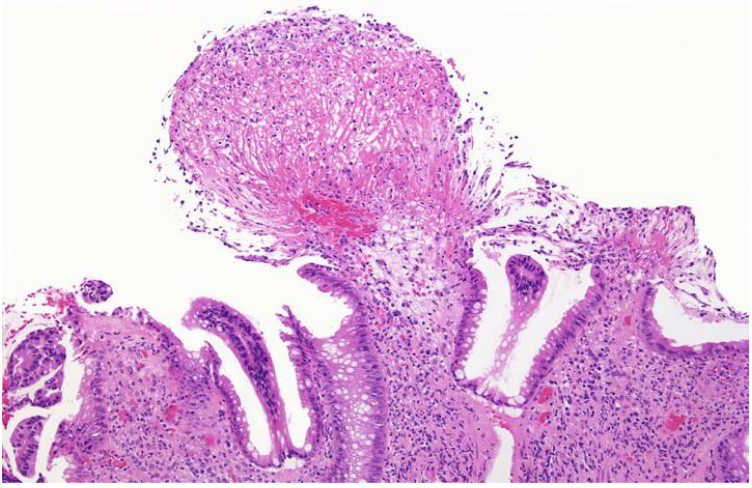


Intestinal Mucosa – Small vs. Large Intestine



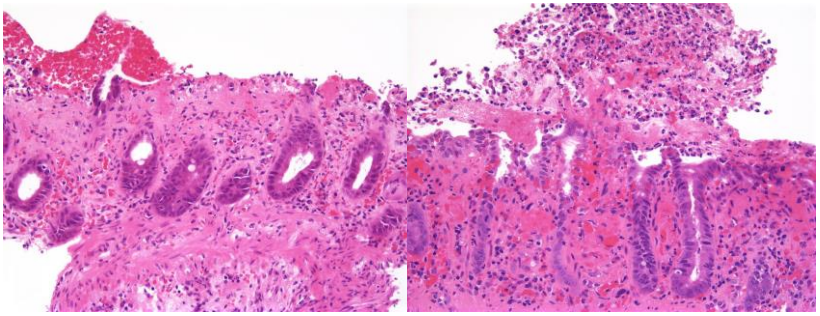
Pseudomembranous Colitis

- Erupting volcano-like exudates



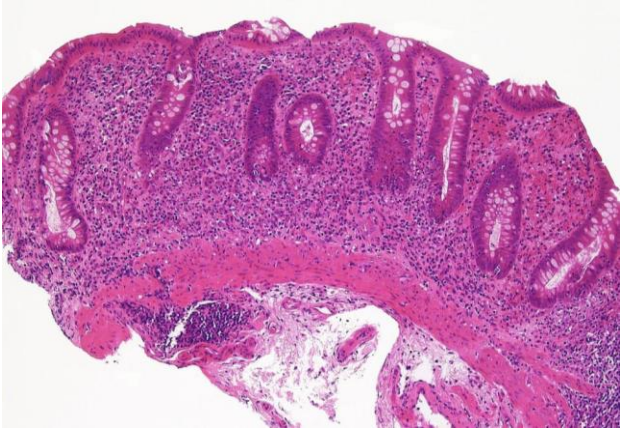
Acute Ischemic Colitis

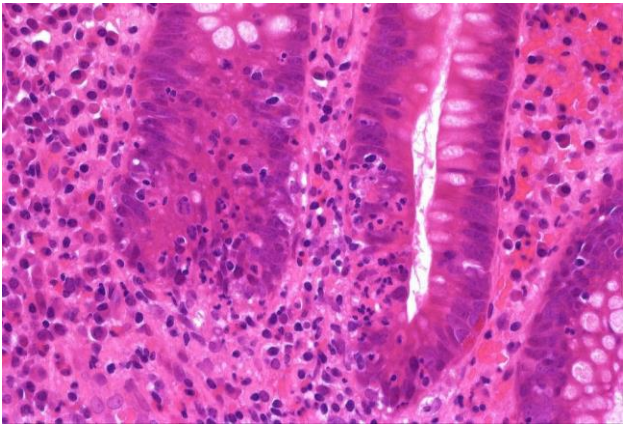
- Abundant lamina propria hemorrhage and congestion
- Erosions, exudation like PMC
- Withering crypts

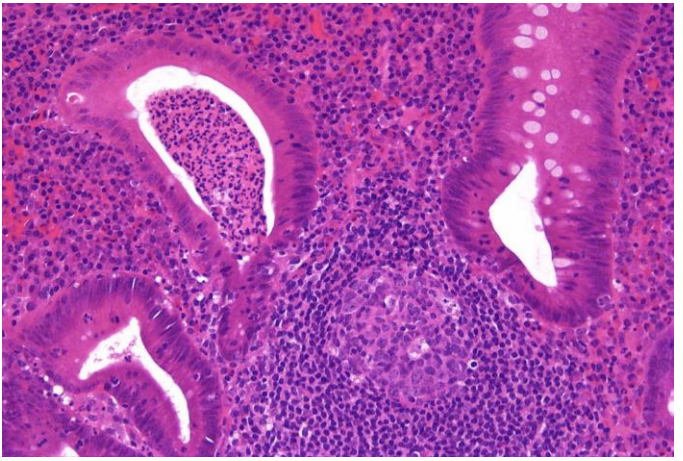


Ulcerative Colitis

- Abnormal crypts
- Increased lymphocytes and plasma cells in lamina propria
- Cryptitis
- Crypt abscesses

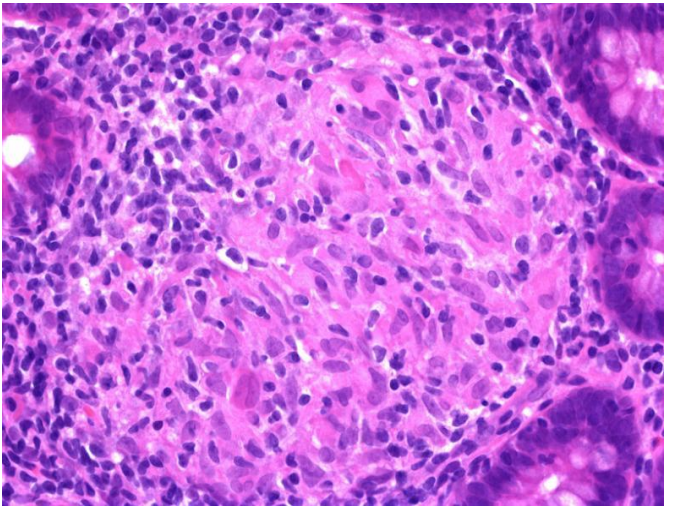


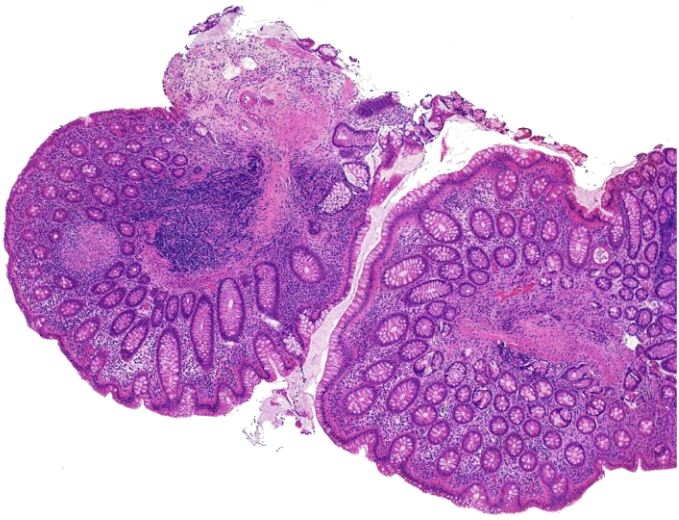




Crohn Disease

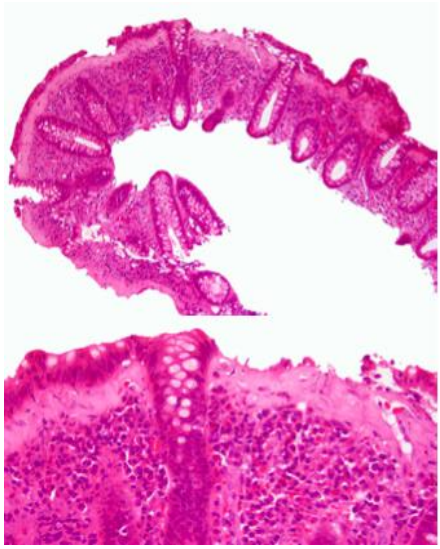
- Focal disease
- Granulomas





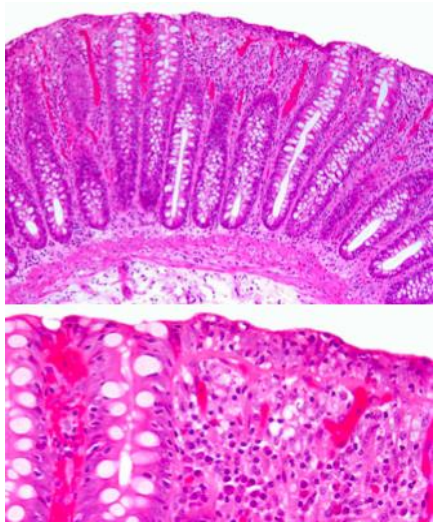
Collagenous Colitis

- Thickened sub-epithelial collagen band
- Increased lamina propria inflammation
- Stripping off of surface epithelium



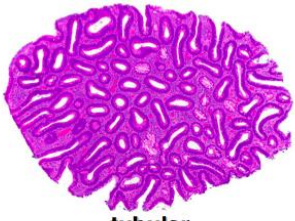
Lymphocytic Colitis

- Collagen band not thickened
- Increased lamina propria inflammation
- Increased IELs



Neoplasms

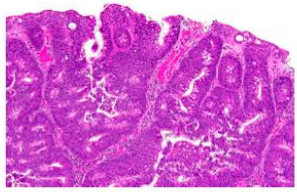
- Adenomas



tubular

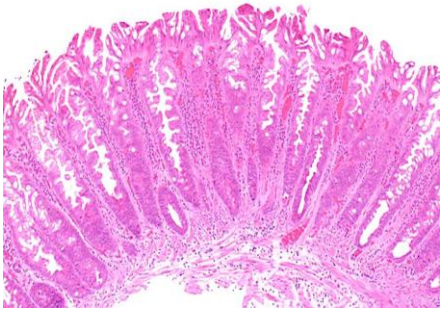
villous

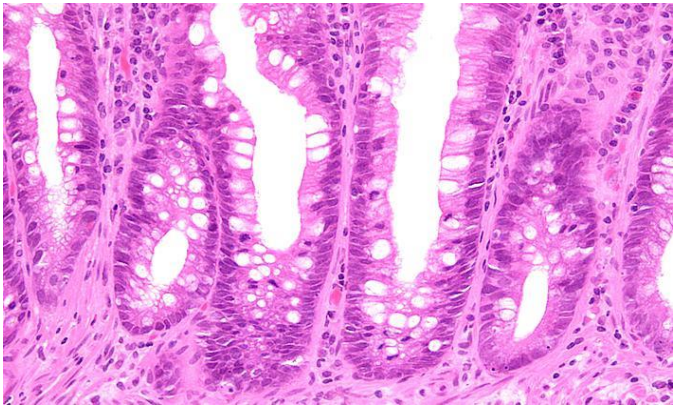
low grade dysplasia



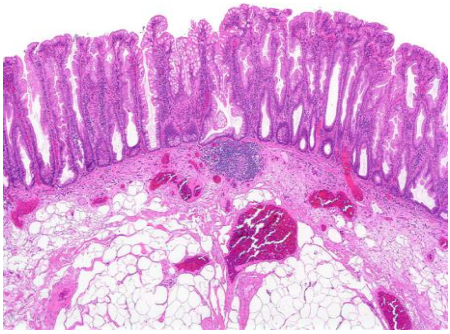
high grade dysplasia

- Hyperplastic Polyp
  - Serrations in luminal half
  - Straight crypts, narrow bases
  - Immature proliferative cells in lower crypts

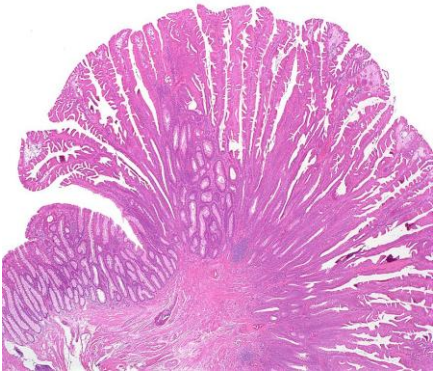


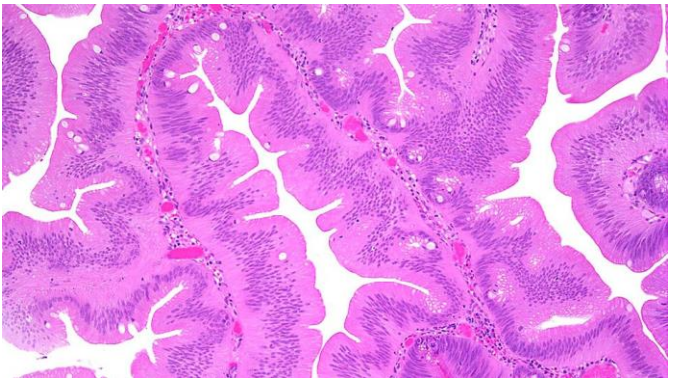


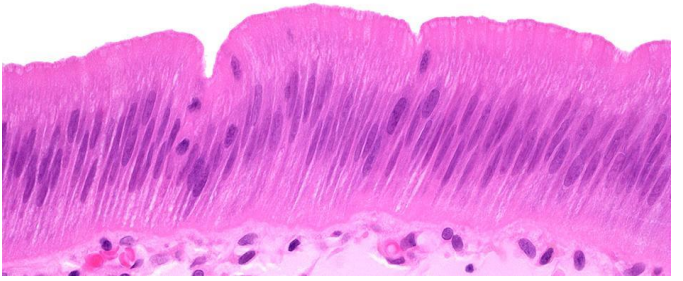
- Sessile Serrated Adenoma
  - Exaggerated deep crypt serrations
  - Dilated crypt bases
  - Funny looking crypts



- Traditional Serrated Adenoma
  - Protuberant, not sessile
  - Complex villous growth pattern
  - May be misdiagnosed as villous adenoma
  - Cytoplasmic eosinophilia
  - Pencillate nuclei







Pathology Requisition Forms

Remember

- Submission of biopsy material to a pathologist constitutes a consultation
- Accurate interpretation of pathological material and the generation of an accurate, clinically relevant report requires:
  - Knowledge of key clinical history and findings
  - Knowledge of both the microscopic findings and the macroscopic/gross findings (provided by the endoscopist)

Information Needed on Biopsy Requisition Forms

3 Items:

1. What is the relevant history?
2. What did you see?
3. What do you want to know?

What's wrong with this requisition form?

What is the relevant history?
1. What did you see?
2. What do you want to know?

Some Good Examples

- Barrette esophagus. History of LGD. Repeat EGD with jumbo forceps. R/O dysplasia
- 80 yr male. Repeat EGD shows nicely healed GU, biopsy to R/O malignancy and Hp
- CUC x 12 yr. Pseudopolyps R colon and sigmoid. Assess for dysplasia. No gross sign of malignancy
- Incidental 12 mm sessile polyp ascending colon
- 40 yr, longstanding GERD. Normal EGD. Biopsy to R/O Hp

Some Bad Examples

- Dyspepsia. (Gastric biopsies)
- 19 yr with perianal fissure. R/O Crohn. (TI biopsies)
- R/O Hp / GERD / Celiac. (Duodenal, gastric, esophageal biopsies)
- R/O IBD
- Stomach R/O dysplasia, Duodenum R/O dysplasia, Esophagus R/O dysplasia
- Long-standing diarrhea. To R/O Crohn, Celiac, microscopic colitis (TI and colon biopsies)

Some Common Scenarios & Issues: To highlight the importance of good endoscopist-pathologist communication

Scenario 1

- Information from endoscopist: Biopsies from around the GEJ/cardia.
- Pathologist: Goblet cells present.
- Diagnostic possibilities:
  - Short-segmentBarrett
  - Intestinal metaplasia of the cardia
- Resolution:
  - Did you see salmon-pink (Barrett) mucosa?
  - Did you biopsy elsewhere in the stomach?

Scenario 2

- Endoscopist: Duodenal biopsies duodenitis
- Pathologist: Duodenitis, non-specific
- Diagnostic possibilities
  - Peptic duodenitis
  - Drug (NSAID)-induced duodenitis
  - Celiac disease
- Resolution:
  - Peptic and drug duodenitis are usually associated with gastric pathology. Was the stomach biopsied?
  - Celiac disease can be potentially over-diagnosed with proximal (bulb) biopsies where the villi are shorter and where peptic injury is maximal. Was the distal duodenum biopsied?

Scenario 3

- Endoscopist: polypoid lesion in UC patient
- Pathologist: adenoma-like lesion
- Diagnostic possibilities
  - Incidental adenoma
  - IBD-related dysplastic lesion (DALM)
- Resolution
  - Depends on
    - What did it look like to the endoscopist
    - What did the mucosa around the lesion show? Was it biopsied?

(DALMs typically arise in a field of dysplasia; sporadic adenomas do not biopsies are needed of the surrounding mucosa)

Scenario 4

- Endoscopist: Sigmoid biopsies, segmental colitis? Crohn disease
- Pathologist: chronic active colitis
- Diagnostic possibilities:
  - Crohn disease
  - Diverticular colitis (affects sigmoid only)
  - Partially treated UC (affects rectum with variable proximal extension)
- Resolution:
  - Were there diverticula? (Crohn vs. diverticular colitis)
  - Is the rectum normal or not? Did it look normal? Take a biopsy as “normal” looking rectum may be histologically abnormal – (UC vs Crohn’s)

Western
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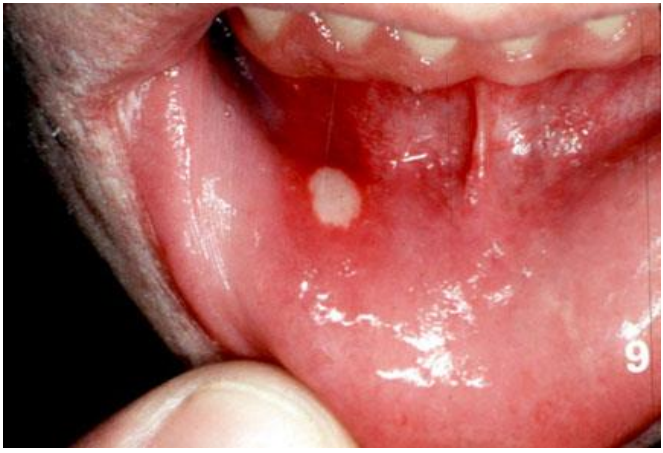
GI Endoscopy & Pathology

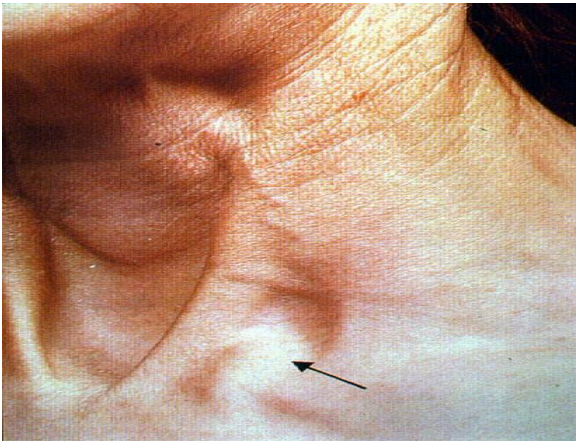
Amindeep Sandhu

- Give the differential diagnosis and causes / associations of these lesions.



- Differential diagnosis, and causes / associations of Aphthous Ulcers
  - IBD/Crohn Disease.
  - gluten-sensitive enteropathy, Celiac Disease.
  - Behçet syndrome.
  - immunodeficiency syndromes
  - HIV infection.
  - Cyclic neutropenia.
  - Nutrient Deficiencies (Iron, Folate, Vitamin B12)
  - Idiopathic.

- Give the differential diagnosis and causes / associations of this lesion.



➢ Differential diagnosis, and causes of Virchow Node

- Gastric cancer
- Pancreatic cancer
- Colon cancer
- Ovarian cancer
- RCC

- Give the complications & Indications for EGD in caustic ingestion.

➢ Complications

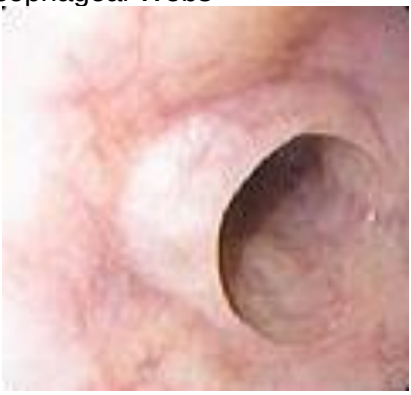
- Esophageal
  - Erosions
  - Ulcerations
  - Perforation
  - Stricture

- Indications
  - Dilation
  - Endoscopic hemostatic therapy (for bleeding)

- Give the differential diagnosis and causes / associations of this endoscopic lesion.

- Differential diagnosis of esophageal rings
  - Ulcers
  - Strictures
  - Cancer
  - Infiltration
  - Eosinophilic esophagitis

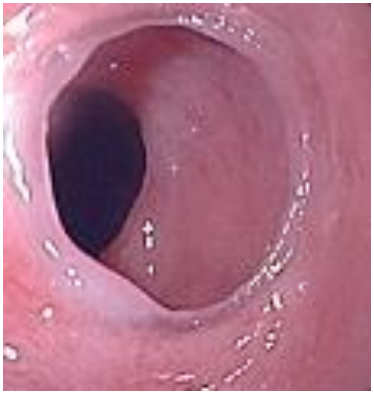
- Causes / associations of Esophageal Webs



  - Plummer-vinson syndrome
    - Cervical esophageal web
    - Dysphagia
    - Iron deficiency anemia
  - Celiac disease
  - Inlet patch (? Acid exposure)
  - Chronic GVHD
  - Skin diseases:
    - Epidermolysis bullosa
    - Pemphigoid
    - SJS
    - Psoriasis

Abbreviations: GVHD, graft-versus-host disease; SJS, Stevens Johnson syndrome

- Causes / associations of lower esophageal rings

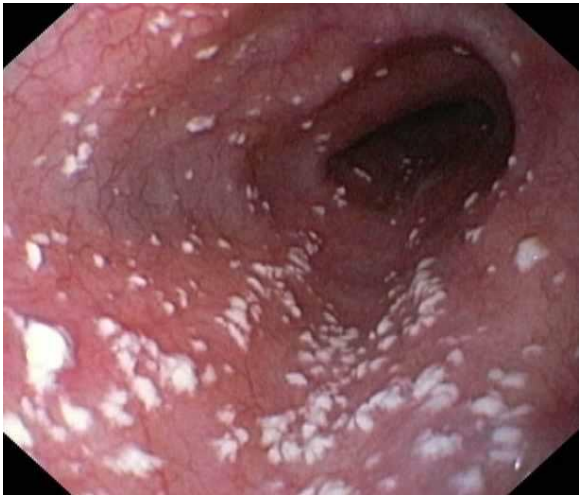


  - Esophagitis
    - GERD
    - Caustic Ingestion
    - Pill induced esophagitis
    - Mediastinal radiation

Conditions Associated with Upper Esophageal Webs

- Plummer-vinson syndrome
  - Cervical esophageal web
  - Dysphagia
  - Iron deficiency anemia
- Celiac disease
- Inlet patch (? Acid exposure)
- Chronic GVHD
- Skin diseases:
  - Epidermolysis bullosa
  - Pemphigoid
  - SJS
  - Psoriasis

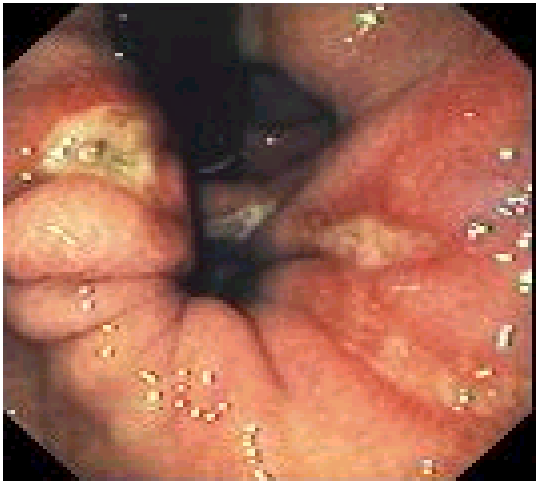
- Give the differential diagnosis and risk factors for this endoscopic lesions.



Candida Esophagitis

- Risk Factors for Candida Esophagitis
  - Patient
    - Age
    - Drugs
      - Immunosuppressants
      - Corticosteroids
      - Antibiotics
    - Infection
      - HIV
    - Alcohol excess
    - Recent surgery
  - Esophagus
    - Motility disorders
      - Achalasia
      - Scleroderma
  - Stomach
    - Hypochlorhydria
    - PPIs
    - Resection
    - Bariatric surgery
  - Endocrine
    - DM
    - Adrenal insufficiency
    - Cushing
  - Hematology
    - Leukemia / Lymphoma (especially post-chemo)

- Give the pathophysiology and treatment of this endoscopic lesion.

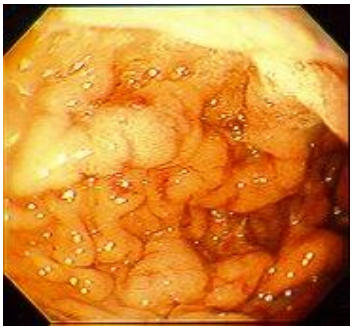
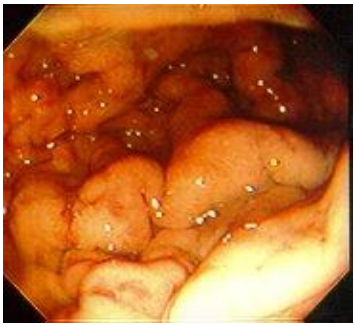


Cameron Ulcer

- Pathophysiology
  - Mechanical trauma of diaphragmatic contraction
  - Ischemia
  - Acid may extend injury
- Treatment
  - PPI
  - Prokinetics
  - Iron replacement
  - Hiatus hernia repair

GIST: Definition, types, pathology,

- Give the differential diagnosis and causes /associations of this endoscopic lesion.

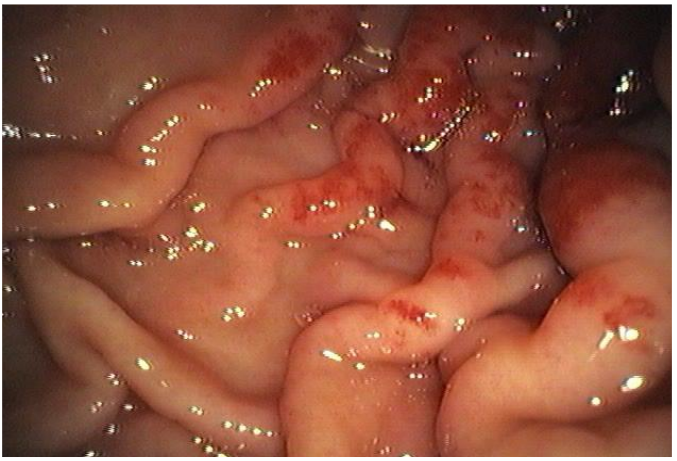
➢ Differential diagnosis of Hyperplastic Gastropathy

- Ideopathic
  - Menetrier disease
  - Hyperplastic hypersecretory gastropathy
- Infection
  - HP
  - CMV
- Infiltration
  - ZES
  - Lymphoma
  - MALT
  - Linitis plastic
  - Gastric adenocarcinoma
- Inflammation / immune
  - Lymphocytic gastritis
  - Eosinophilic gastritis
  - Granulomatous gastritis
- Ischemic / vascular
  - Gastric varices
  - GAVE

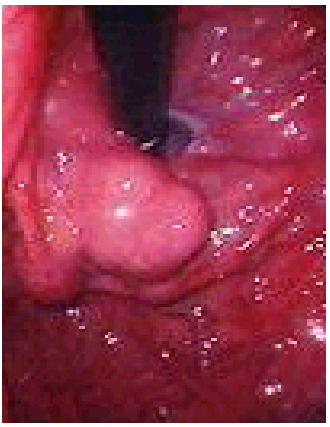
Menetrier Disease

- Clinical
  - N/V/pain/blood loss
  - Protein losing enteropahty (low albumin)
  - Hypochlorhydria

Gastric Antrial Vascular Ectasia (GAVE)

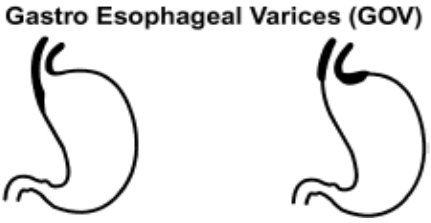


Gastric Varices

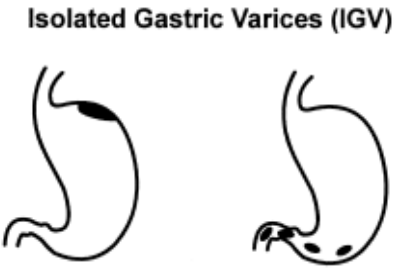


Gastroesophageal Varices (GEV)

- Classification of



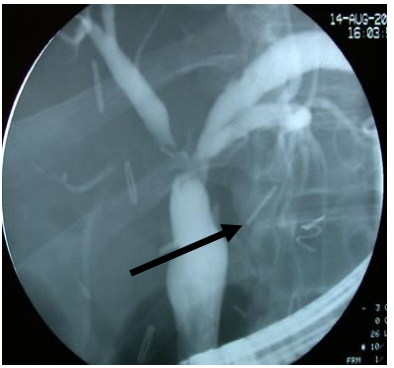
GEV1 GEV2



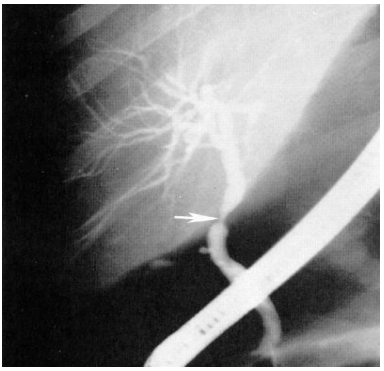
IGV1 IGV2

- Treatment
  - Short term
    - Octreotide
    - Glue/thrombin (obturation)
    - Balloon tamponade
  - Long term
    - Non-specific beta blockers (NSBB)
    - Splenorenal shunt
    - Splenectomy
    - TIPS

Post-liver Transplantation (PLT) **Stricture**



Non-anastomotic stricture



Anastomotic stricture

- Pancreatic pseudocyst

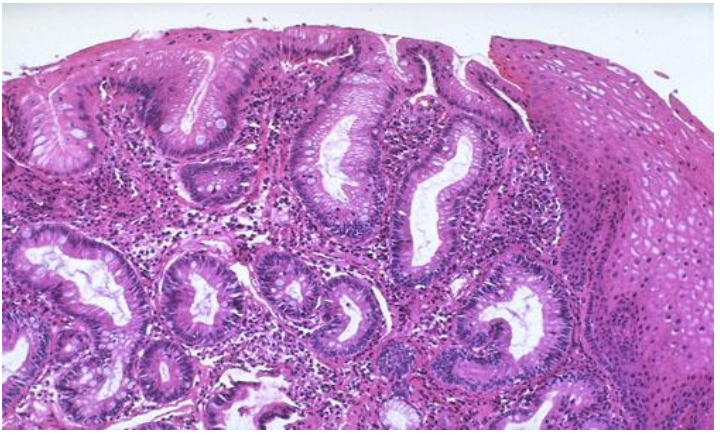
- Give the differential diagnosis of these endoscopic lesions.

- Complications
  - Duodenal obstruction
  - Biliary obstruction
  - Vascular occlusion
  - Fistula with
    - Viscera
    - Pleural space
    - Pericardium
  - Infection
  - Pseudoaneurysm
  - Rupture into peritoneal cavity
  - Pancreatic ascites

- Treatment indications
  - Symptomatic
  - Enlarging
  - Complications
  - Suspicion of cancer
  - Note
    - Size does not matter

Barrett Esophagus

55 yr male underwent EGD for dyspepsia. Bx of the esophagus 30cm from the incisors.

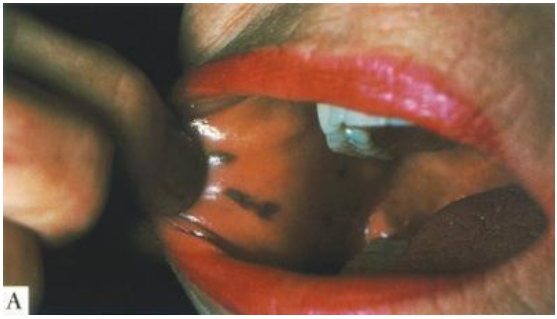


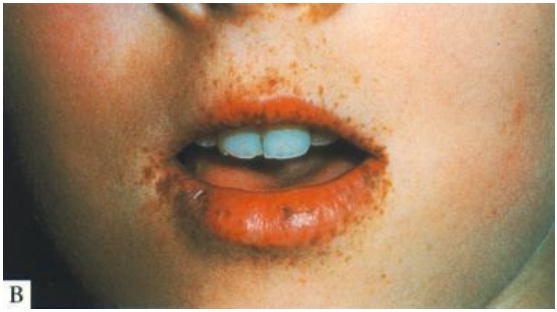
AGA Surveillance Guidelines for Barrett Esophagus

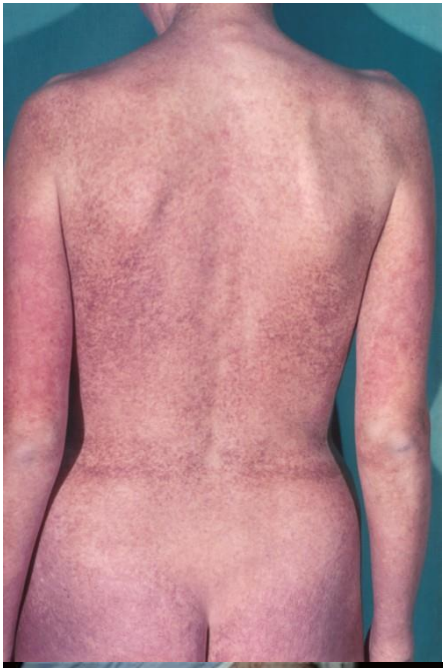
- Biopsy techniques:
  - 4 quadrant bx q 2cm entire length of Barrett mucosa
  - Biopsy any irregularity

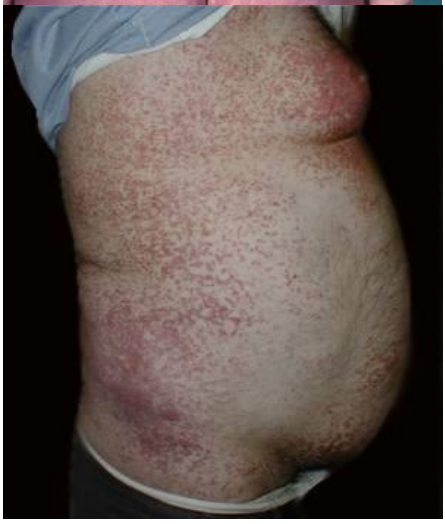
- Follow up
  - No dysplasia
    - EGD q 2 yr
  - LGD
    - EGD q 6 mon x 2, then q 1 yr
  - HGD
    - Confirm by 2 pathologists
    - Intensive EGD: 4 Q bx q 1 cm with jumbo bx and EGD q 3 mon
    - Ablation
      - EMR
      - APC
      - PDT

Extra-Intestinal Manifestations of Peutz-Jeghers Syndrome





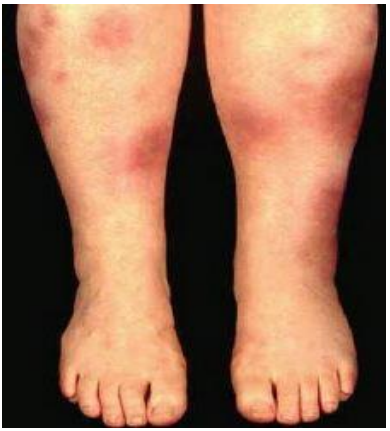




Mastocytosis

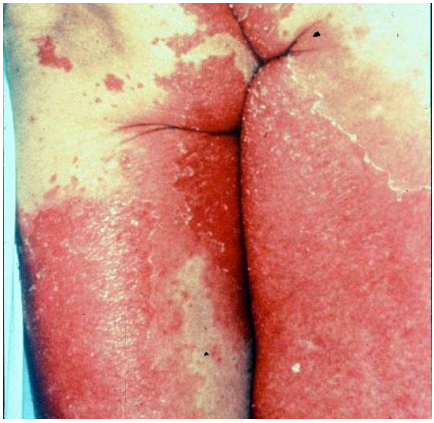
- Associated with PUD

Erythema Nodosum

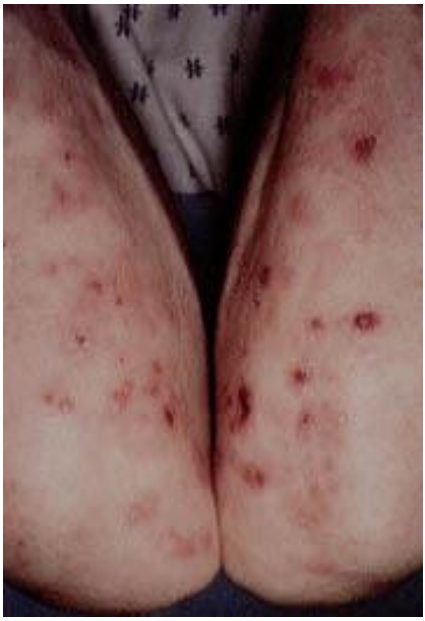


- Causes
  - Infection
    - GI
      - Campylobacter
      - Yersinia
      - Shigella
    - Non-GI
      - Streptococcus
      - Tuberculosis
      - Fungus
  - Inflammation / Immune
    - Inflammatory bowel disease IBD)
    - Sarcoidosis
  - Infiltration
    - Leukemia
  - Iatrogenic
    - Rx e.g. oral contraceptive agent (OCA)

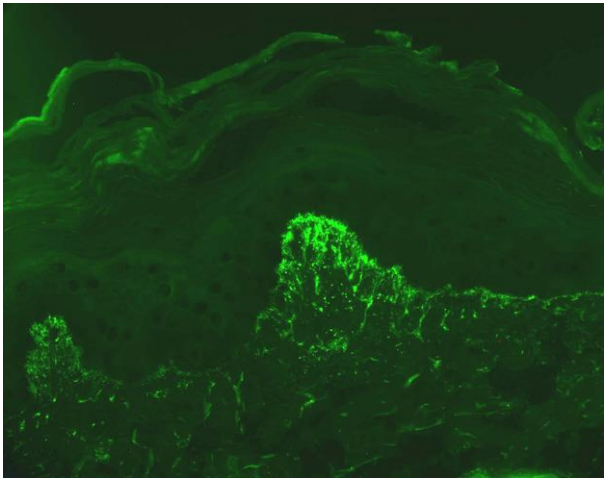
Neuroendocrine Tumor (NET)



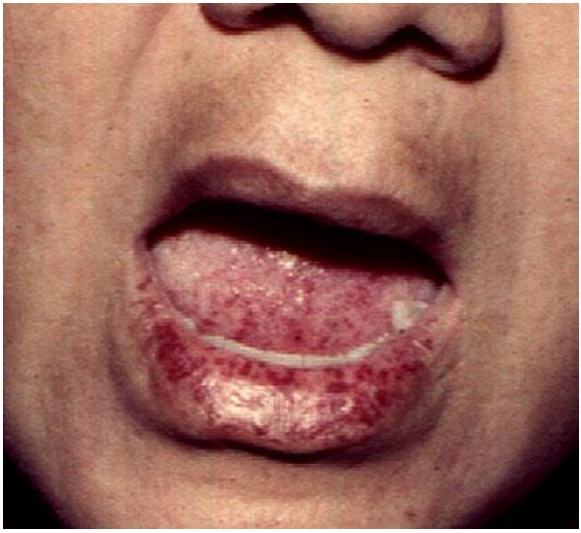
Glucagonoma



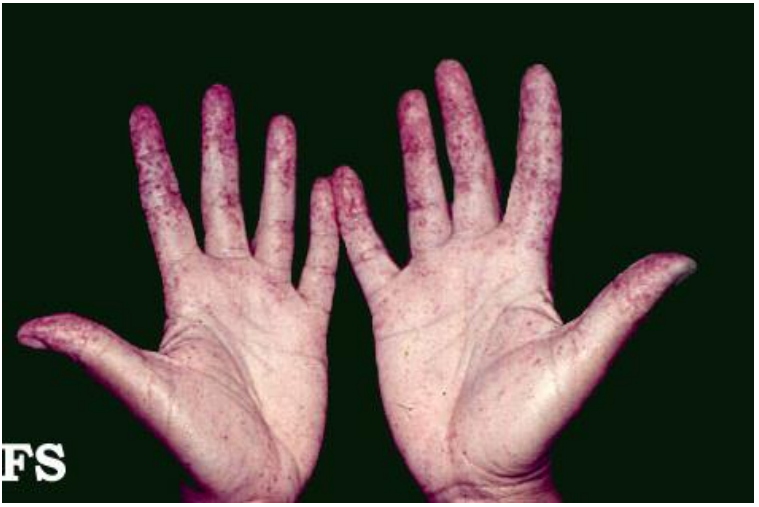
Dermatitis Herpetiformis



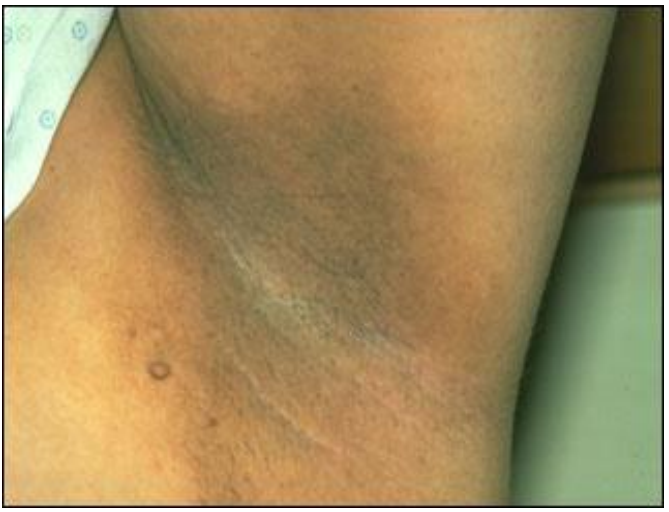
IgA on dermoepidermal junction

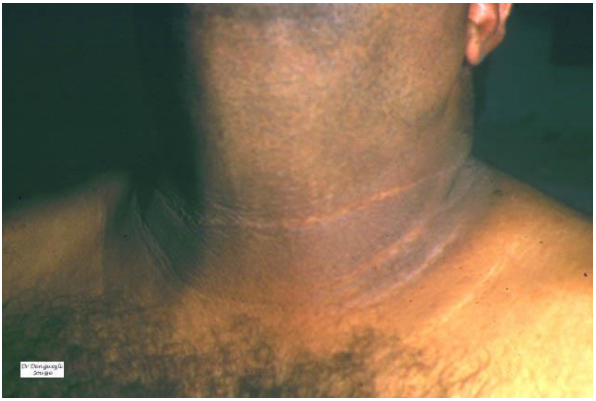


Osler Weber Rendu Syndrome



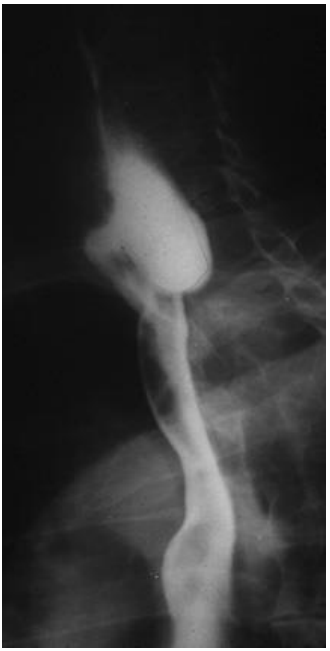
Acanthosis Nigricans

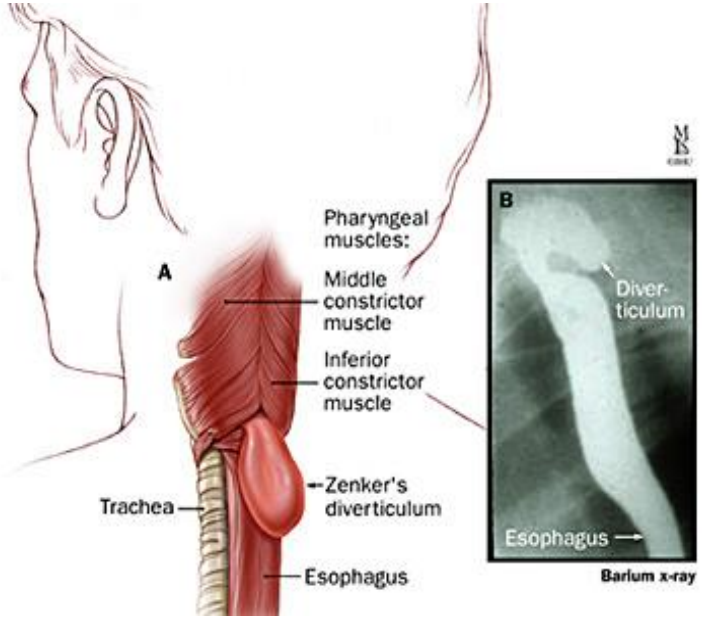




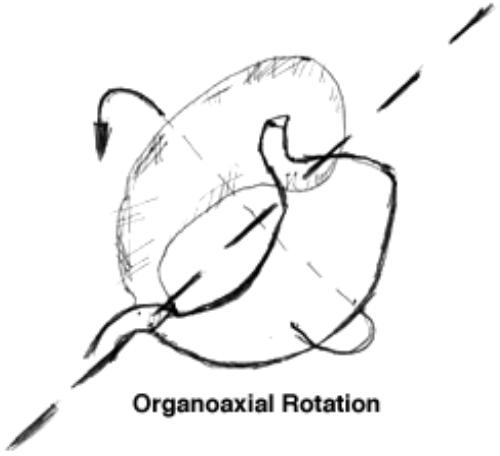
Radiology

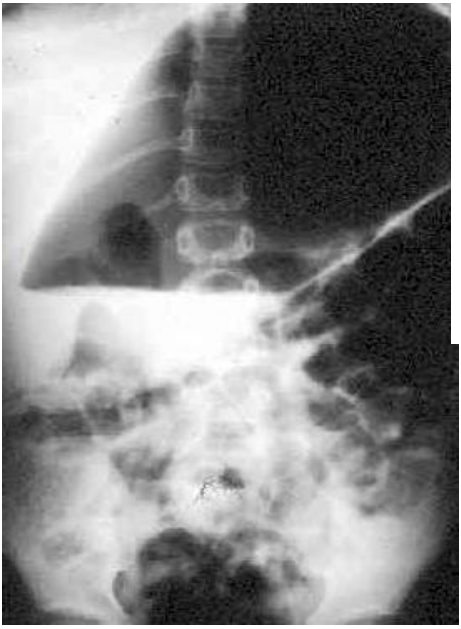
Describe the pathophysiology of this condition.

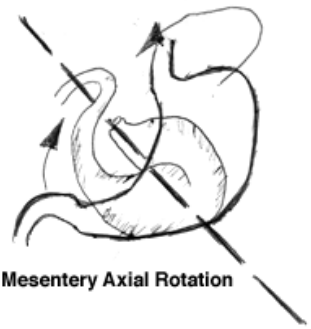




Gastric Volvulus: Borchardt triad






Mesentery Axial Rotation

Western
UNIVERSITY · CANADA

Gastrointestinal and Hepatic Complications of Solid Organ and Hematopoietic Stem Cell Transplantation

Noor Al Yatama

- Demography
  - Solid organ transplantations (SOT) recipients
    - Complications in 40%
  - Hematopoietic stem cell transplantation (HSCT) recipients
    - Non allograft related adverse outcomes

INFECTIONS

- Various presentations
- Risk depends on
  - Surgery
  - Immunosuppression
  - Use of antibiotics
  - Infectious exposures
  - Prophylactic measures used

- General principles
  - ↓ inflammatory responses by immunosuppressive therapy, → ↓ symptoms and muted clinical and radiologic findings.
  - As a result, infections are often advanced (disseminated) at the time of clinical presentation.
  - Serologic testing is not generally useful for the diagnosis of acute infection in the immunocompromised host since seroconversion is often delayed.
  - Microbiologic cultures are supplemented by antigen-based tests ELISA or PCR for diagnosis.
  - Diagnosis often requires anatomic data from imaging CT MRI.

- Biopsies with histopathology are often needed for diagnosis.
- Clinical samples must be obtained early and before the patient's illness progresses to a point where such procedures can no longer be performed.
- Complex antimicrobial regimen
  - Urgency of therapy
  - Drug toxicities/ drug interactions.
- Surgical intervention (debridement) often necessary to localize infections
- Drug levels provide only a crude means of monitoring immunosuppressive regimens.
- The central focus must be on
  - Disease prevention
  - Drug therapy and vaccination.
  - Stratification of the risk for various infections.

➢ Perioperative timing of infection

- Early
  - 1 mon
  - Previous existing pathogens in the recipient
  - Donor derive
  - Consequence of transplant operation (viral opportunistic)
- Intermediate
  - 1 to 6 mon
- Late
  - > 6 mon
  - Community acquired
  - Poor graft function
  - Hospitalization
  - Intense immunosuppression

- Challenging to establish presence and source of infection
- Management
  - Antimicrobials
  - ↓ immunosuppression
  - Debridement, if necessary

Viral Infections

- **Cytomegalovirus**

➢ Demography

- Most common viral infection in SOT / HSCT
- 1/3 affects GI
- More common in certain types of SOT
  - Liver
  - Lung
  - Pancreas
- Patients at highest risk for CMV disease
  - Patients who are seronegative for CMV (immunologically naive) and receive an allograft from a seropositive donor (D+/R-)
  - Patients with latent CMV infection who require treatment with antilymphocyte antibodies as a part of induction therapy or for graft rejection.

➢ Clinical

- Fever
- Malaise
- Anorexia
- Dysphagia

- N/V
- Abdominal pain
- Diarrhea
- GI bleeding
- Site
  - Mouth to rectum
  - Liver
  - Pancreas

- Microbiology
  - From donor to CMV
  - Superinfection in CMV
  - Reactivation
- Endoscopy
  - 1-2 round, deep ulcers
- Diagnosis
  - PCR
  - Biopsy
- Treatment
  - Ganciclovir IV plus
  - CMV immunoglobulin for severe disease
- Prophylaxis
  - Gancyclovir IV and valgancyclovir po

- **Herpes Simplex Virus**

➢ Demography
  - The second most common viral infection in SOT / HSCT

➢ Clinical
  - Ulcers in any part of GI tract / liver
  - Many GI manifestations

➢ Microbiology
  - Can be reactivated in first mon from latent phase during intense immune suppression

➢ Endoscopy
  - Patients with dysphasia or odynophgia should be evaluated with endoscopy to determine the etiology (oral infections can be treated with oral acyclovir)
    - Multiple small, round, superficial lesions
  - Disseminated infection requires intravenous treatment acyclovir

➢ Prophylaxis
  - Patients with a history of herpes simplex virus (HSV) or varicella-zoster virus (HZS) infection should receive antiviral prophylaxis
    - During 3-6 mon after transplantation
    - During periods of intensified immunosuppression (treatment of graft rejection)
    - Other "stresses" (concomitant infection or surgery).

- HSV+ and who are undergoing
  - Allogeneic HSCT
  - Induction chemotherapy for acute leukemia

- **Ebstein-Barr Virus** (EBV)
  - Affects > 90% of the human population
  - Persist in memory of B cells
  - With immunosuppression
    - Faulty T cell immunity cannot contain the growth of the EBV in B cells laden with the virus →
      - Oral hairy leukoplakia
      - PTLD

Abbreviation: PTLD, post-transplantation lymphoproliferative disorder

- **Oral Hairy Leukoplakia**

➢ Clinical
  - Affects
    - Lateral portions of the tongue
    - Floor of the mouth
    - Palate
    - Buccal mucosa
  - Fever
  - Lesions
    - Corrugated painless plaques that,
    - Cannot be scraped from the surface to which they adhere (unlike candida).
  - Not premalignant

- Prophylaxis
  - Can only be suppressed with valgancyclovir
- Treatment
  - Usually not indicated
  - If necessary
    - Zidovudine
    - Acyclovir
    - Ganciclovir
    - Foscarnet
    - Topical podophyllin
    - Topical isotretinoin

- **Viral Hepatitis: HCV and HBV**

Hepatitis B virus (HBV)

- Vaccination
  - Recommended for all individuals prior to SOT/ HSCT.
  - ↑ mortality due to SOT / HSCT
  - HBV can be reactivated after transplantation
  - Among liver transplant recipients, preventive therapy with hepatitis B immune globulin (HBIG), lamivudine, and/or other antiviral drugs are given to prevent reinfection of the graft.
  - Kidneys can be taken from anti-HBc–positive donors.
    - Transmission of HBV is uncommon in this setting
    - These donor kidney are frequently transplanted to expand the pool of available kidneys

Hepatitis C virus (HCV)

- No vaccination available
- No consensus on preventive therapy in HCV-infected liver transplant recipients
  - Eradication of HCV pretransplant may prolong the recipient's wait time for donor organs
- Conversely, the direct-acting agents (DAAs) have the potential for expanding the donor pool for all organ recipients (and reducing wait times) as hepatitis C–infected donor organs could potentially be given to hepatitis C–uninfected recipients, provided that post-transplant "prophylaxis/eradication" therapy is administered to the recipient.

Fungal Infection: Candidiasis

- **Acute Localized Candidiasis**

➢ Clinical

- Seen in first 6 mon after SOT / HSCT
- Affects mouth and esophagus
- Common GI presentations
  - Dysphagia
  - Odynophagia
  - Gastroesophageal reflux
  - Rarely GI bleed

➢ Risk

- ↑ with high dose corticosteroids or antibiotics

- Endoscopy
  - Superficial erosions / ulcers
  - White nodules or plaques
  - Easily washed away (unlike oral hairy leukoplakia [OHL])
- Diagnosis
  - Histopathology
  - Cultures
- Treatment
  - Oral nystatin
  - Fluconazole
  - In case of resistance: caspofungin, posa or voriconazole
- Microbiology
  - Chronic disseminated candidiasis (aka hepatosplenic candidiasis)
  - Patients with hematologic malignancies recovering from an episode of neutropenia
  - Organism
    - Usually *Candida albicans*
    - Sometimes *C. tropicalis*
    - Rarely *C. glabrata* and *C. krusei*
- Clinical
  - Fever
  - RUQ pain
  - Nausea / Vomiting

- Laboratory
  - ↑ alkaline phosphatase (ALP)
- Diagnostic imaging
  - CT scan during neutrophil recovery
    - Characteristic multiple lucencies in the liver, spleen, and sometimes the kidneys
- Histopathology
  - Multiple granulomas
  - With special stains, yeasts and hyphal forms
  - Cultures of hepatic tissue obtained at biopsy are usually negative (particularly if antifungal therapy has been given).
- Treatment
  - Amphotericin B
  - Echinocandin
  - Continue antifungal therapy until
    - Resolution
    - Calcification of the lesions on follow-up contrast-enhanced CT
  - Antifungal agent plus corticosteroid
    - Debilitating persistent fevers despite appropriate antifungal therapy

Parasitic Infections

- Protozoal infections
  - Microsporidium
  - Cryptosporidium
  - Isospora belli
  - Giardia lamblia
- Present with diarrhea
- Stool test for O&P x3
- Small bowel and colonic biopsy sometimes needed

- Treatment
  - Metronidazole, plus ↓ immunosuppression
  - Of interest
    - Cyclosporine has antihelmenthic properties → may suppress parasite Strongyloides stercoralis

Bacterial Infection

- Demography
  - Half of SOT / HSCT who received antibiotics develop C. difficile infection (CDI)

- Clinical
  - Diarrhea

- Microbiology
  - C. difficile
  - Yersenia enterocolitica
  - Campylobacter jejuni
  - Salmonella
  - Listeria monocytogenes

- **Neutropenic enterocolitis** (aka "typhlitis," "necrotizing enterocolitis," and "ileocecal syndrome)

➢ Demography

- Mainly with HSCT less in SOT

➢ Pathogenesis

- Incompletely understood
  - Mucosal injury by cytotoxic drugs
  - Profound neutropenia
  - Host defense to invasion by microorganisms, leads to necrosis of various layers of the bowel wall.
- Cecum is usually affected, and the process often extends into the ascending colon and terminal ileum.

➢ Presentation

- Abdominal pain
- Fever with ANC < 500 cells/μL
- Usually 3rd week of chemo

➢ Microbiology

- Gram-positive cocci
- Gram-negative bacilli

➢ Diagnostic imaging

- CT
  - Bowel wall thickening
  - Mesenteric stranding
  - Dilatation
  - Mucosal enhancement
  - Pneumatosis.

- Treatment
  - Antimicrobials
    - Broad spectrum
      - Piptazo
      - Carbapenem
      - Cefipime
      - Metronidazole
  - If fever > 72 hr add antifungal.
  - Transfuse blood products as needed
  - Surgery
    - Failed medical therapy
    - Perforation

Oncogenic infections

- EBV
  - PTLD
  - Nasopharyngeal oral cancer ↑ risk 6x in transplant patient
- HHV8
  - Kaposi sarcoma
- HCV HBV
  - Hepatocellular cancer (HCC)
- H. pylori
  - Gastric cancer
- HPV
  - Anal squamous cell cancer (10-20x ↑ risk in transplant patient

GI Malignancies

- Important cause of morbidity and mortality
- ↑ probability of GI malignancy over longer follow up
- Length of exposure to immunosuppressive agents and intensity of therapy are related to post-transplant risk of malignancy

➢ Pathogenesis
- Calcineurin inhibitors- pro oncogenic effect
- Cancer with immunosuppression → ↑ proliferation of tumor

HSCT Malignancies

➢ Time
- Early
  - < 1 year
    - Acute leukemia
    - MDS PTLD
- Late
  - > 1 year
    - Variety of solid organ tumors

Post Transplantation Lymphoproliferative Disease (PTLD)

➢ Demography
- Incidence
  - 1-3% of SOT and HSCT
  - 30-50x general population incidence
- One of most common malignancies

- Serious and potentially fatal
- Seen in SOT and HSCT
- Can involve GI as abundant
- Most common in
  - Intestinal and multiorgan transplant 11-33%
  - Lowest in renal, and liver transplants
  - Heart and lung transplants
- Intensity of immunosuppression directly associated with risk of PTLD

➢ Pathogenesis

- Usually EBV-associated
- EBV negative dx also occurs
- Majority of cases PTLD is host cell origin
- ↑ risk if SOT / HSCT recipient is given
  - T cell depleted or HLA mismatched bone marrow
  - Anti-lymphocyte antibodies
  - Have CMV
  - Gets primary EBV infection after transplantation
- If no prior EBV exposure
  - ↑ risk for PTLD

➢ Clinical

- Symptoms of infectious mononucleosis
- Localized lymphoproliferation
  - Fever
  - Weight loss
  - Fatigue
  - Lymphadenopathy
  - > 50% extranodal masses
- Dysfunction of involved organs

- Compression of surrounding structures.
- Involved organs include
  - Gastrointestinal tract
    - Stomach
    - Intestine
    - Liver
  - Lungs
  - Skin
  - Central nervous system
  - Allograft itself

- Laboratory
  - Anemia / thrombocytopenia / leukopenia
  - ↑ LDH
  - Hypercalcemia
  - Hyperuricemia
  - Monoclonal protein in the serum or urine
  - Tissue biopsy needed to confirm diagnosis

- Image
  - Diagnosis and staging: CT / PET scanning

- Treatment
  - Early detection strategy can reveal ↑ EBV DNA → ↓ immunosuppression and careful surveillance
  - Chemotherapy
    - Based on histopathological characteristic of tumor
  - Surgical removal

Adverse Drug Events

- Cyclosporine
  - Gingival hypertrophy inducing collagenolytic activity in the gums – this may necessitate substitution with Tacrolimus or Sirolimus
  - ↑ cholesterol saturation in bile
    - Potential risk for cholelithiasis

- Tacrolimus
  - GI
    - Nausea
    - Abdominal pain
    - Diarrhea
    - Anorexia
    - Weight loss
    - Cholestasis (at ↑ levels)
  - Liver
    - Cholestasis (at ↑ levels)

- Sirolimus (mTOR kinase inhibitor)
  - Liver
    - Dose dependent ↑ aminotransferases
  - GI
    - Mouth ulceration
    - Incisional hernia
    - Diarrhea
  - “Black box” warning in liver transplant setting
    - Possible hepatic artery thrombosis

- Mycophenolate mofetil (oral inosine monophosphate dehydrogenase inhibitor)

➢ Clinical
  - Ulceration
  - Nausea / vomiting
  - Diarrhea
  - Debilitating mucositis
  - ↓ dose improves symptoms

➢ Indications
  - Myeloablative conditioning therapy
    - Used in HSCT candidates
      - To prevent the recipient from rejecting donor HSC and
      - For tumor cell ablation

General GI complications

- **Oral Mucositis**
  - May be severe
    - Total parenteral nutrition (TPN)
  - Usually self limiting

➢ Treatment
  - Palifermin (recombinant human keratinocyte growth factor)
    - ↓ oral mucositis after autologous transplant

- **Upper GI**
  - Pill induced esophagitis
  - GERD
  - Peptic ulcer disease
    - 10% of renal transplants
    - ↑ risk of major upper GI bleeding
    - ↑ risk of gastric ulcers after liver transplantation

➢ Treatment
  - PPI po for dyspepsia
  - Avoid NSAIDs or use with PPI-cotherapy
  - Test and treat for H. pylori

- **Acute Biliary Tract Disease**

➢ Clinical
  - With LT concern about hepatic artery stenosis / thrombosis → ↓ blood flow
    - Severe graft dysfunction
    - Ductopenia / cholestasis
    - Strictures / cholangitis
  - Mortality ~30%
  - Early
    - Vascular compromise:
      - ↑ LE → ALF
  - Late
    - Biliary stricturing → cholangitis / intrahepatic abscess
    - Types of stricture
      - Anastomotic 2-6 mon post-LT
      - Duct-to-duct: endoscopic dilation
      - Choledochojejunostomies: percutaneous/ surgical repair

- **Colonic Perforation**

➢ Demography
  - Incidence 1-2%
  - Mortality 20-38%

➢ Causes / associations
  - Diverticular disease
  - Ischemic
  - CMV
  - Higher risk in kidney transplantation

- **Diarrhea**
  - Very common

➢ Causes / associations
  - Infection
    - Adenovirus
    - Bacterial overgrowth
    - C. difficile
    - Campylobacter
    - Cryptosporidium
    - Cyclospora
    - Cytomegalovirus
    - E. coli
    - Entamoeba histolytica
    - Giardia
    - Norwalk virus
    - Rotavirus
    - Samonella
    - Shigella
    - SIBO with stasis in Roux limb anastomosis
    - Vibrio parahemolyticus
    - Yersinia

- Inflammation
  - Exacerbation of IBD, IBS, celiac disease
- Iatrogenic
  - Drugs
  - Antibiotics
  - Narcotics → Overflow diarrhea
  - Immunosuppressants
- Ischemia
- Infiltration
  - PTLD
  - Colorectal cancer

- **Perianal Pain**
  - Common after BM transplantation
  - Originates near anus in agranulocytopenic patients
  - Bacterial infection → abcess in supralevator / intersphincteric region
  - HSV2 HPV exacerbations → herpes flare / condylomata

➢ Treatment
  - Drainage and antibiotic

Graft-versus Host Disease (GVHD)

- More often after HSCT then SOT

- Pathogenesis
  - Acute
    - Mismatches in histocompatibility between donor and recipient → activation of donor T cells → damage to various epithelial tissue through
      - Dysregulated cytokine production
      - Recruitment of effector cells.
    - Up to 50% of allogenic HSCT from HLA identical sibling despite intensive prophylaxis with immunosuppressive medication
    - Timing: 15-100 days
  - Chronic
    - Not well understood
    - Timing: after 100 days

- Clinical
  - Upper GI
    - Anorexia
    - Dyspepsia
    - Nausea / vomiting
  - Both acute and chronic predominantly affect
    - Skin
    - Liver GVHD
      - Damage to bile canaliculi
        - ↑ ALP
        - ↑ bilirubin
    - GI tract
      - GI involvement often severe
        - Diarrhea > 10 L /day (watery or bloody)

- Differential
  - Sinusoidal obstruction syndrome (SOS)
  - Infection
  - Drug adverse effects

- Causes / associations
  - Older age
  - HLA disparity
  - Donor and recipient gender discordance
  - Previous GVHD
  - Amount of radiation
  - Intensity of transplant conditioning regimen
  - Use of methotrexate, cyclosporine, tacrolimus
- Pathology of small bowel
  - Crypt cell necrosis
  - Accumulation of degenerative material in dead crypts
- Endoscopy
  - Edema of gastric antral and duodenal mucosa
  - Patchy erythema
- Prophylaxis
  - Methotrexate and cyclosporine routinely prescribed for months after HSCT
- Treatment
  - Immunosuppressive therapy
    - Response upper > lower GI

Sinusoidal Obstruction Syndrome (SOS, aka veno-occlusive syndrome)

- Demography
  - HSCT
    - 5-20%
    - Uncommon after liver transplant
    - Mortality 20-50%

- Causes / associations
  - Both after SOT and HSCT
  - Also with azathioprine (AZA) and radiation
  - Chronic liver disease
  - C282Y allele of HFE gene
  - Advanced age
  - Hepatic metastases
  - Previous radiation to liver
  - High dose conditioning regimens (busulfan, gemtuzumab, cyclophosphamide)
  - Infection
    - CMV
    - HCV

- Pathogenesis
  - Early
    - Damaged sinusoidal endothelium → sloughs off and obstructs hepatic circulation → destroying centrilobular hepatocytes → release of 5 hydroxytryptamine, prostaglandins, leukotrienes, free radicals → furhter endothelial damage, ischemia and cell death

- Late
  - Intense fibrinogenesis in sinusoids → obliteration of the venules → chronic outflow obstruction

- Clinical
  - 7-10 days post-transplantation
  - Weight gain and jaundice
  - Ascites
  - RUQ tenderness
  - Hepatomegaly
  - Conjugated hyperbilirubinemia
  - In severe cases
    - Renal
    - Cardiac
    - Respiratory failure

- Diagnostic Imaging
  - Doppler ultrasound
    - Signs of portal hypertension

- Diagnosis
  - Histopathology

- Treatment
  - Supportive care

- Prevention
  - ↓ intensity of chemotherapy
  - Ursodiol
  - Defibrotide (fibrinolytic agent)

Gastrointestinal Graft-versus Host Disease (GVHD)

Amindeep Sandhu

- Demography
  - Acute < 100 days post-transplantation

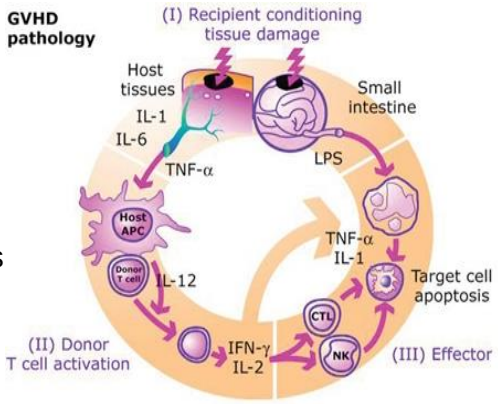
	GVHD
HLA antigen	
– None	35-45%
– One	60-80%

  - GVHD is a leading cause of morbidity and mortality after allogeneic human stem cell transplantation (HSCT)

- Pathophysiology

  - Donor HSCT immune cells
    ↓
  - Activation of
    - Antigen presenting cells
    - Donor T cells
  - Cellular and inflammatory effector phase
    ↓

Target cell apoptosis



Abbreviation: HSCT, human stem cell transplantation

Source: Reddy P. and Ferrara JLM. Mouse models of graft-versus-host disease (February 28, 2009), StemBook, ed. The Stem Cell Research Community, http://www.stembook.org/node/548

- Risk factors
  - Host
    - Age
    - Conditioning regimen intensity
    - Incomplete GVHD prophylaxis
  - Donor
    - Multiple donor pregnancies
    - Prior infections in donors
    - Graft source (Blood, BM > Umbilical cord blood)
  - Donor-host disparity
    - Degree of HLA disparity
    - Sex mismatching

- Distribution of Involvement
  - GI tract only – 17%
  - GI tract + skin – 24%
  - GI + Skin + Liver – 24%
  - Skin – 15%
  - Skin + Liver – 7%
  - Liver only – 4%
  - Neutropenia, thrombocytopenia
    - ↑ risk of infection

- Clinical

- Skin
  - First and most common symptoms of GVHD
  - Maculopapular Rash – neck, ears, shoulders, palms
  - “Sunburn”
  - Desquamation-like (erythroderma)
  - Pruritic, painful
  - Can progress to generalized erythroderma

- Gastrointestinal Tract
  - Upper gastrointestinal symptoms
    - Anorexia
    - Dyspepsia
    - Food intolerance
    - Nausea* and vomiting
  - Lower gastrointestinal symptoms
    - Diarrhea*
    - Abdominal cramps
    - Ileus

* key symptoms for grading severity grade

- Diagnosis
  - Acute GVHD often occurs closer to the 70-100 day mark post HSCT as immunosuppression is reduced
  - Acute GVHD can readily be made on clinical grounds if within 100 days:
    - Classic rash
    - Abdominal cramps + diarrhea
    - Rising Bilirubin
  - Often much less straightforward, and need biopsy
  - Skin / mucosa biopsy often needed
  - Laboratory tests or not useful to diagnose GVHD

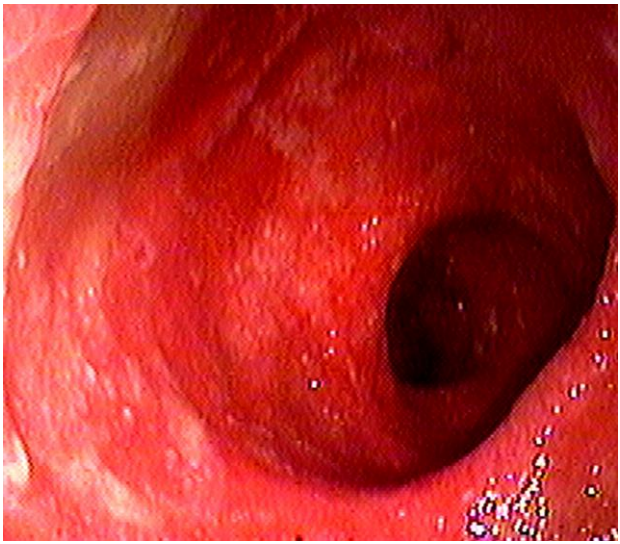
Grading System

Stg	Skin	Liver bilirubin, mmol/L	GI diarrhea, L/day
1	< 25% BSA	34 – 51	Nausea or diarrhea 0.5 – 1 L/d
2	25 – 50% BSA	51 – 103	Diarrhea 1.5 – 15
3	Erythroderma	103 – 257	Diarrhea > 15
4	Desquamation	> 257	Severe abdominal pain or ileus

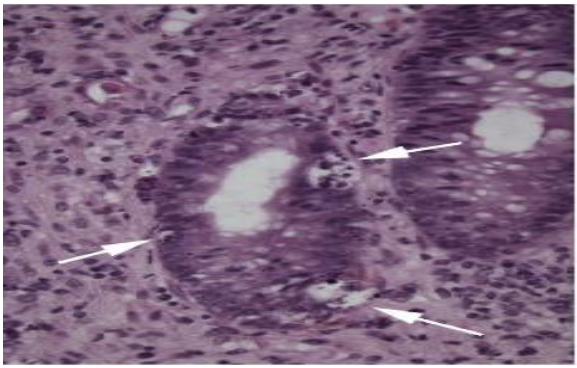
Abbreviation: BS, body surface area; Stg, severity grade / stage

➢ Pathology

- Gross / endoscopy
  - Hyperemia
  - Diffuse mucosal loss



- Histopathology
  - Apoptosis
  - Endoscopic findings do not usually correlate with histology or clinical grading of GVHD
  - Optimal site for diagnostic biopsy unclear
  - The rectum has traditionally been the preferred site of biopsy



- Differential of apoptosis
  - Infection
    - CMV infections
    - Cryptosporidium
  - Drugs
    - Cyclosporin
    - Mycophenolate mofetil
    - NSAIDs
    - Ticlodipine
  - Immune disorder
    - Immunodefieincy and related T cell defects
  - IBD
  - Malignant thymoma
- Treatment
  - Corticosteroids
  - Methotrexate, MTX
  - Tacrolimus
  - Cyclosporine

Approach to Ancillary Endoscopy Tools

Michael Sey

Purpose

- Practical introduction to some of the endoscopy devices you will encounter
- Usage and practice pattern varies widely by endoscopist and what is presented here is how the author practices
  - Speak to the consultant you are scoping with
  - See how different consultants do things and choose a style you like
  - Discuss with your local device representative regarding the availability of supplies

Devices

- UGIB tools (injection, bipolar, APC, clips, Hemospray®, variceal band ligator)
- Esophageal dilation (Savary, Maloney, TTS balloon dilator)
- PEG tube
- Endoscopic mucosal resection (saline lift, Duette®, cap assisted, under water)
- Endoscopic submucosal dissection
- Biopsy forceps (normal vs jumbo)
- Polypectomy snares (cold vs hot)
- New and exciting tools

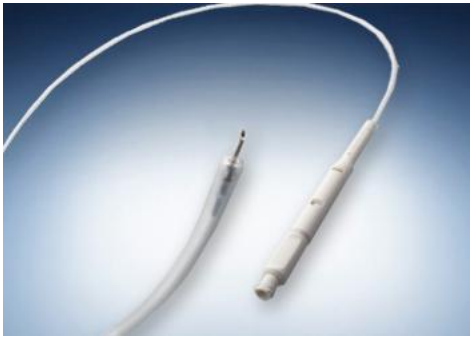
UGIB Tools

- Types of tolls for upper GI bleeding
  - Injection
    - Saline
    - Saline + epinephrine
    - Cyanoacrylate

- Cautery
  - Bipolar
  - Argon plasma coagulation (APC)
- Mechanical
  - Clips
  - Variceal band ligator
- Thrombosis
  - Hemospray ®)

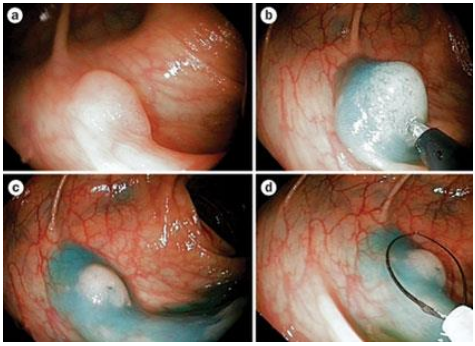
Injection Types

- Saline +/- 1:10,000 epinephrine
  - Works by tissue tamponade
  - Monotherapy generally considered inferior to combination with clip or cautery



Olympus Force Max injection needle

- Cyanoacrylate
  - Generally used to glue gastric and ectopic varices
  - Easy to use but tricky part is not fouling up the scope

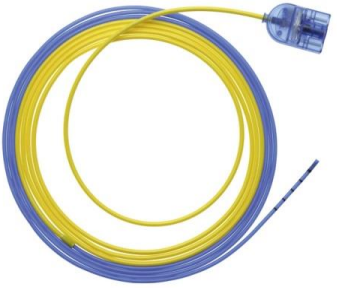


Cautery Types

- Bipolar (aka gold/silver probe)
  - The probe also contains the ground…hence no need to pad the patient
  - Monopolar used for APC, hot snare and sphincterotomy

Bipolar probe, US Endoscopy

- Argon plasma coagulation
  - Provides a more superficial burn than bipolar
  - Often used for angioectasias, GAVE, radiation proctopathy



ERBE APC catheter

Cautery Settings

- Bipolar
  - Generally 20 W (15 W in the cecum)
  - Firm pressure and hold 8-10s for vessels
- Argon Plasma Coagulation (APC)
  - Generally 30 W at 1.6-1.8 L/min (20 W at 1.4 L/min in cecum and SI)
  - Avoid perforation and intestinal explosion by exchanging air

Mechanical

- Clips
  - Mechanical means of closing two edges
  - “clip out”→”open”→”close”→”fire”
  - Can be rotated and reopened prior to fire if you don’t like position

Cook Instinct Hemoclip

- Variceal band ligator
  - Suction of varix into cap and ligate with rubber band
  - 6 bands in total (second last band is clear)

Cook 6-Shooter MBL

Hemospray® Thrombosis

- CO_2 delivery of mineral based compound that forms mechanical barrier and concentrates clotting factors
- Very easy to use
- Beware of gas perforation and embolization (NVGIB

Cook Hemospray

only)

Esophageal Dilation

- Maloney
  - Mercury or Tungsten weighted dilator
  - Softer
  - Good for straightforward dilation
- Savary
  - More rigid and requires a guidewire
  - Good for more complex dilation

Maloney Savary

Size Conversion

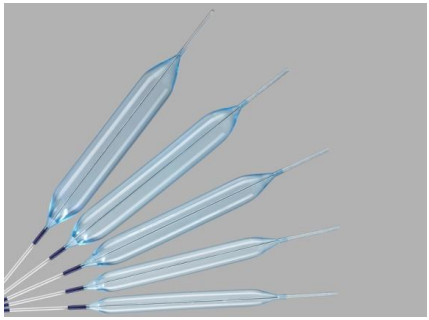
- Maloney
  - Size referred to in French (FR, i.e 48 Maloney)
- Savary
  - Size referred to in mm of diameter (ie. 16 Savary)
- Math
  - “FR” is defined as diameter x 3
  - Thus, 16 Savary x 3 = 48 Maloney

Starting Dilation: Size

- EGD ~9 mm
- Start with a size that's a little larger than the stricture
- Can sequentially dilated up a total of 3 mm per session increasing by 1 mm at a time (i.e. 12, 13, 14 Savary)
- A lot of this is based on how much resistance you feel
- For tight strictures, bring back for serial sessions q 2-4 weeks until stricture is > 15 mm

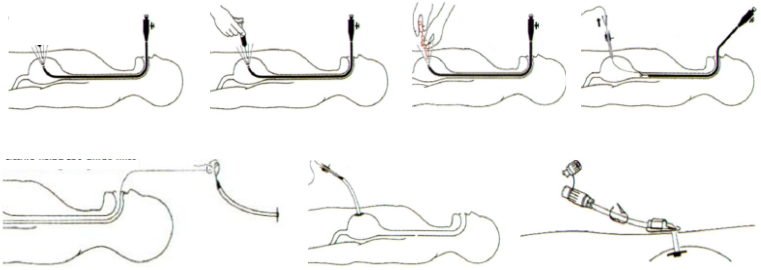
Balloon Dilator

- Uses only radial force only (no linear force)
- Good for complex strictures (in London, usually reserved for the small bowel or colon)
- Types: long (8 cm) and short (5 cm) +/- guidewire
- Sizes (mm): 8-9-10, 12-13.5-15, 15-16.5-18
- Expensive!!



Cook Hercules 3 stage dilator

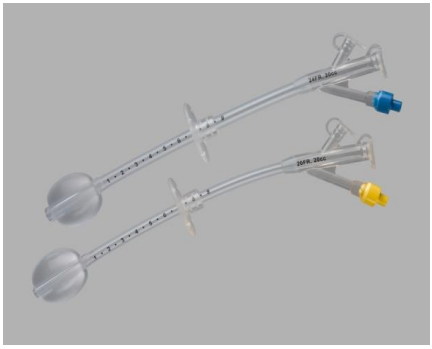
PEG Tube



Nurs Times. 2012;108:20-2

PEG Tube Replacement

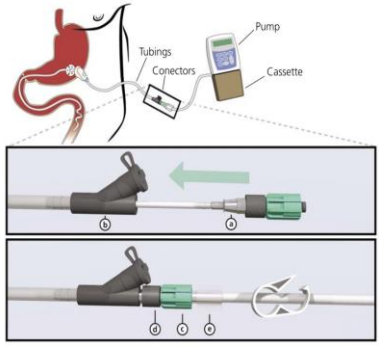
- Once the gastrocutaneous fistula tract matures in 4 weeks, PEG replacement can be done at the bedside without endoscopic guidance
- Replacement PEGs have a non-collapsible inflatable balloon that must be deflated to remove (the initial PEG inserted endoscopically can be pulled out by traction alone)



Cook Triton Balloon replacement gastrostomy tube

Freka/Abbvie Duodopa PEG-J

- Duodopa is a novel Parkinson disease treatment based on closely controlled delivery of dopamine gel directly into the small bowel
- GI involvement is placement of a specific type of PEG-J (only for Duodopa gel…not to be used with other drugs or feeds)



Abbvie Duodopa PEG-J tube

Endoscopic Mucosal Resection (EMR)

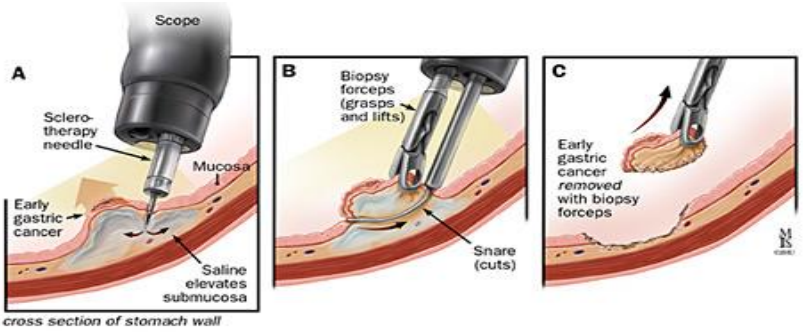
- Indication
  - Large flat/sessile polyps not suitable for simple snare polypectomy
  - Staging of dysplastic Barrett esophagus (HGD or IMC)
- Principle
  - Create a submucosal cushion safety barrier to permit more aggressive polypectomy

Abbreviations: HGD, high grade dysplasia; IMC, intramucosal cancer

Saline Cushion EMR

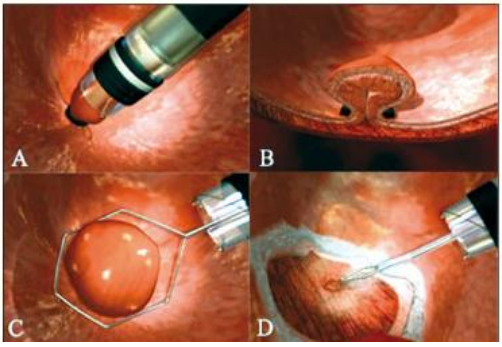
1. Raise the lesion
2. Cut
3. Seal the defect if desired

- Saline
- Methylene blue
- 1:20,000-100,000 epinephrine
- Gel and sugar based compounds
- Inject in a way to turn the polyp towards you



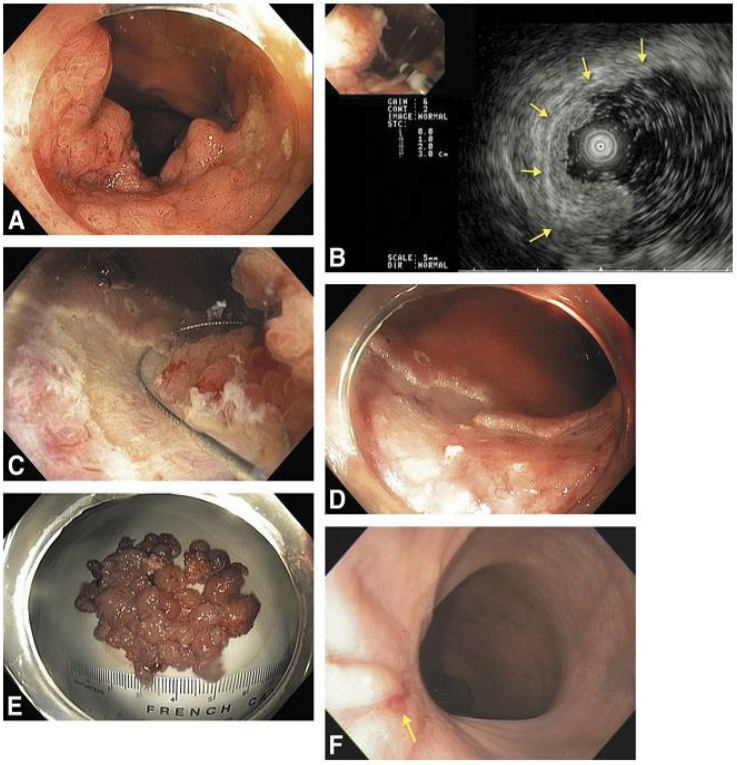
Duette® EMR

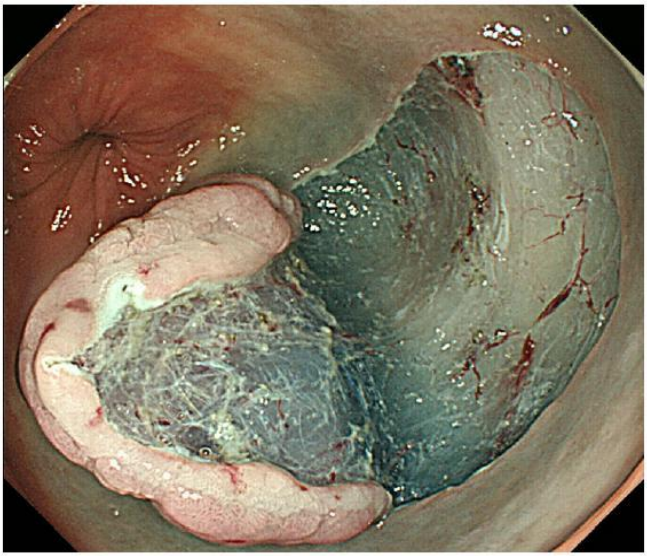
- Suck lesion into cap & deploy band to create SM cushion
- Deploy snare and affix beneath the band (or above)
- Cut with electrocautery
- Close, if desired



Cap Assisted EMR

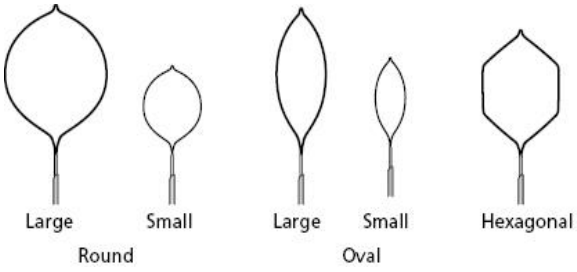
Underwater EMR





Polypectomy Snares

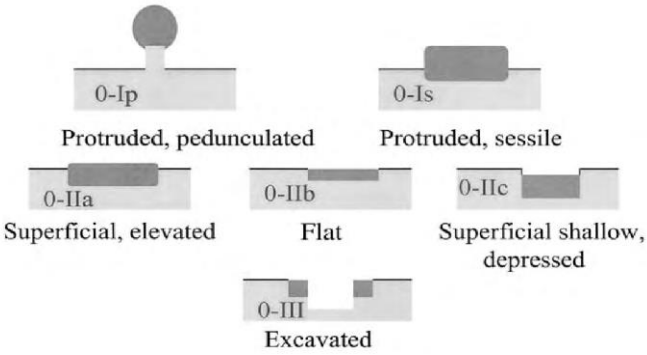
- Wide variety exists
  - Round/oval
  - Small snare (most often used)
  - Large snare (rarely needed)
  - Spiral snare (flat lesions)
- Special order
  - Hexagonal snare



This is the author's preference

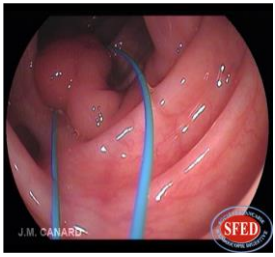
- 3-4 mm
  - Jumbo biopsy forceps
- 5-6 mm
  - Cold snare
- 7+ mm
  - Hot snare
- Very sessile/flat polyps > 1 cm, laterally spreading polyps – EMR, ESD

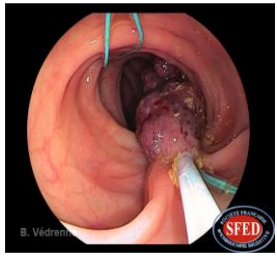
Paris Classification of Polyps

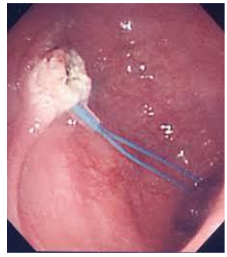


Endoloop

- Used for pedunculated polyps with a thick stalk to prophylactically ligate any vessels
- Alternative is clipping the stalk before polypectomy





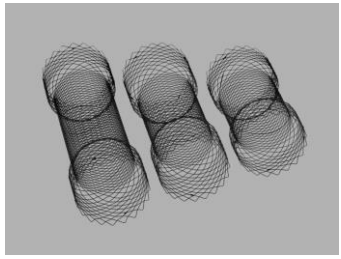


Luminal Stents

- In some institutions, the surgeons have traditionally done most of the luminal stents
- A wide variety of stents exists on the market
- General Framework for Stents
  - Esophageal stents
    - Self expanding metal stents (rare plastic exceptions)
    - Fully covered for benign diseases
    - Partially covered for malignant diseases
    - Placed endoscopically generally without the need for fluoroscopy

Boston Scientific WallFlex esophageal stent

  - Small bowel and colonic stents
    - Uncovered SEMS
    - Generally only used for malignant diseases



Cook Evolution Colonic Stent

Radiofrequency Ablation

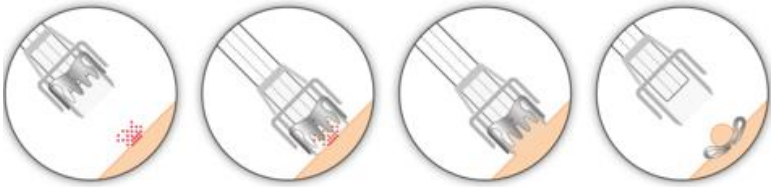
- Generally limited to use for endoscopic ablation of Barrett's with HGD or intramucosal carcinoma

Barrx 360 RFA

Barrx 90 RFA

Over-the-scope clip (OTSC)

- Provides full thickness closure (rather than mucosal closure with hemostatic clips)
- Indications: closure of perforation and fistula



Ovesco OTSC

Overstitch

- Endoluminal suturing via over-the-scope device
- Requires 2T endoscope and overtube
- Indication: closure of fistula/ EMR defect/perforation, esophageal stent anchoring, bariatric surgery revision

Apollo Endosurgery OverStitch

Managing Antiplatelet and Antithrombotic Drugs

Neel Malhotra

- Demography: The Growing Patient Population at Risk
  - The chronic cardiac patient: ACS, MI, Unstable Angina, Atrial Fibrillation +/- HF
  - In USA
    - 5 million with CHF with 1.2 million considered end stage (considerable hospitalization and death)
  - As the number of those with CV disease increase
    - Aggressive ↑ use of antiplatelet / anticoagulant for primary and secondary prevention[1]

[1] Heidenreich PA, et al. Circulation. 2011;123(8):933-44.

- The Danger: GI bleeding outcomes (one-year number needed to harm [NNH]
  - Lowest risk of UGIB, hospitalization ASA plus antiplatelets
    - 93 (34-544) vs. 65 (24-379) and
    - 67 (30-214) vs. 39 (16-214)
  - Highest risk for need for transfusions ASA plus anticoagulant
    - 16 (9-31) vs. 14-182
  - No difference for LGIB
    - 19 (9-49)

* The higher the value of NNH, the lower the likelihood of complications

Abbreviations: LGIB, lower GI bleeding; UGIB, upper GI bleeding

Adapted from: Abraham NS, et al. Circulation. 2013;128(17):1869-77.

- Causes / association
  - Growing number of agents…
  - Antithrombotic drugs
    - Antiplatelet agents
      - ASA
      - Thienopyridines/ ADP receptor inhibitors (Clopidogrel, Prasugrel, Ticagrelor)
      - PAR-1 antagonists (Vorapaxar)
  - Anticoagulants
    - Direct Thrombin Inhibitors
      - Dabigatran
    - Vitamin K Antagonists
      - Warfarin
    - Factor Xa Inhibitors
      - Rivaroxaban
      - Apixaban
      - Edoxaban

Note: In many of these, the real world GI bleeding has yet to be determined

Table 1. Pharmacodynamic characteristics of novel oral anticoagulants compared to warfarin

Characteristics	Warfarin	Novel oral anticoagulants			
		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Inhibition of vitamin K-dependent γ-carboxylation	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Metabolism	Liver	Renal	Renal	Renal/liver	Renal/liver
Time to maximum effect	90 Days for circulating drug; 5–7 days for a therapeutic INR	1.25–3 h	2–4 h	1–3 h	1–2 h
Half-life	36–42 h for circulating drug; ~5 days to normalize INR	12–14 h	9–13 h	8–15 h	6–11 h
Excretion	92% Renal	80% Renal	66% Renal	~25% Renal	50% Renal

INR, international normalized ratio.

Vorapaxar

- Protease activated receptor 1 (PAR-1)
- Inhibits thrombin related platelet aggregation
- Approved an adjunct to traditional antiplatelet therapy (2014)
  - Triple antiplatelet therapy
    - Associated with 13% reduction in MI, stroke, CV death and revascularization in patients with a previous MI or Peripheral Artery disease[1]
  - 66% increase in bleeding (overall) → black box warning in patients with a past history of stroke, TIA, intracranial hemorrhage (UpTodate: Includes PUD)
    - Moderate to severe bleeding in 4.2%

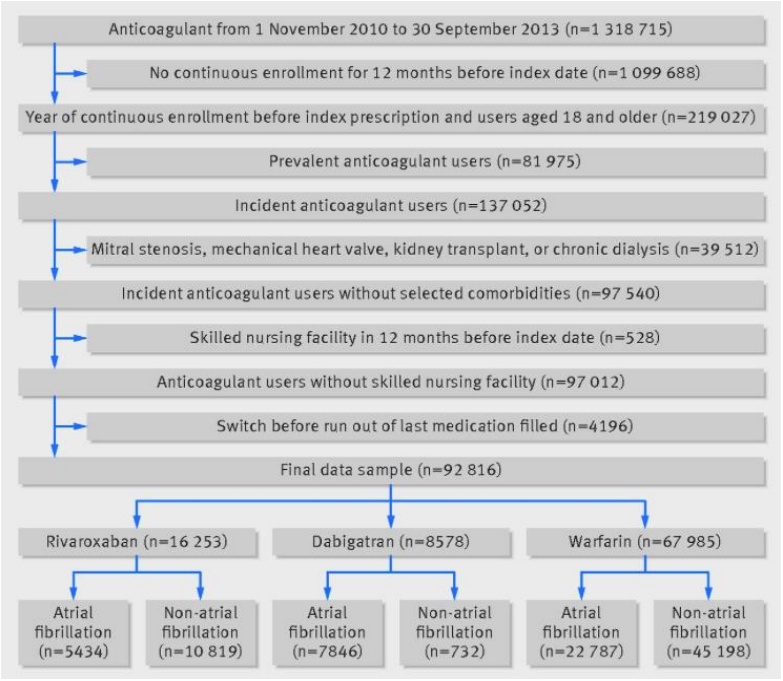
[1] Bhatt DL, et al. Circ Res. 2014; 114(12): 1929-1943.

Edoxaban

- Oral reversible Factor Xa inhibitor
- 50% renal excretion with 62% bioavailability (reaches maximal concentration 1-2 hours following administration)
- Approved for prevention of stroke in patients with Atrial Fibrillation, DVT, PE
- ENGAGE trial: inferior to warfarin, but risk of GI bleeding was 23% higher
  - Increased risk of bleeding in those < 60 kg

Novel Agent Bleeding

- Comparative risk between dabigatran, rivaroxaban and warfarin (Published 2015)
  - Adjusted and Unadjusted rates of dabigatran and rivaroxaban associated GI bleeding was similar to warfarin in AF and non-AF patients
  - Increased GI bleeding after age 65 (By age 76 → risk exceeded warfarin)
    - HR Dabigatran 2.49 (CI: 1.61 to 3.83)
    - HR Rixaroxaban 2.91 (CI: 1.65 to 4.81)



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	Events per 100 patient years (95% CI)		Hazard ratio* (95% CI) for bleeding: dabigatran *v* warfarin	Events per 100 patient years (95% CI)		Hazard ratio* (95% CI) for bleeding: rivaroxaban *v* warfarin
	Dabigatran	Warfarin		Rivaroxaban	Warfarin	
Atrial fibrillation						
Total bleeding events	2.29 (1.88 to 2.79)	2.87 (2.41 to 3.41)	0.79 (0.61 to1.03)	2.84 (2.30 to 3.52)	3.06 (2.49 to 3.77)	0.93 (0.69 to 1.25)
Upper GI bleeding events	1.42 (1.11 to 1.83)	1.81 (1.45 to 2.25)	0.78 (0.56 to 1.09)	1.83 (1.40 to 2.39)	1.74 (1.32 to 2.28)	1.05 (0.72 to 1.54)
Lower GI bleeding events	0.86 (0.63 to 1.19)	1.06 (0.80 to 1.41)	0.81 (0.53 to 1.24)	1.02 (0.97 to1.82)	1.33 (0.97 to 1.82)	0.77 (0.48, 1.24)
Non-atrial fibrillation						
Total bleeding events	4.10 (2.47 to 6.80)	3.71 (2.16 to 6.40)	1.14 (0.54 to 2.39)	1.66 (1.23 to 2.24)	1.57 (1.25 to 1.99)	0.89 (0.60 to 1.32)
Upper GI bleeding events	2.73 (1.47 to 5.08)	2.57 (1.34 to 4.94)	1.09 (0.44 to 2.69)	1.03 (0.70 to 1.51)	0.99 (0.74 to 1.33)	0.87 (0.53 to 1.44)
Lower GI bleeding events	1.37 (0.57 to 3.28)	1.14 (0.43 to 3.04)	1.23 (0.33 to 4.59)	0.63 (0.39 to 1.03)	0.58 (0.40 to 0.86)	0.91 (0.48 to 1.73)

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Note: The lack of difference in the comparative risk of GI bleeding when comparing warfarin vs. dabigatran, or warfarin vs. rivaroxaban, was not influenced by the age groups of the patients (18-64, 65-75, ≥ 76)

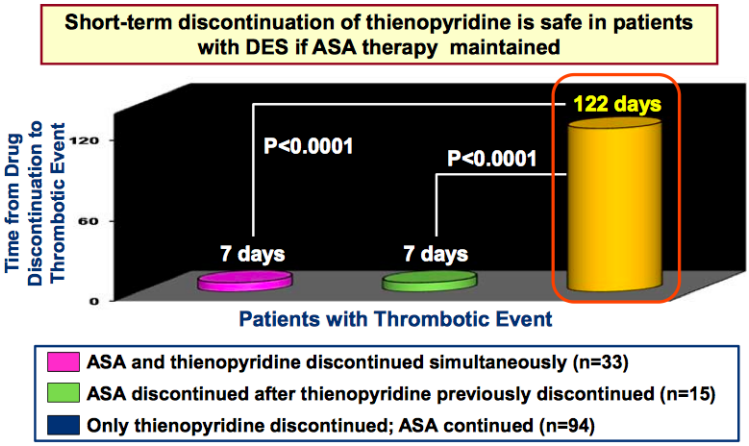
Dual Antiplatelet Agents

- Indications (as per AHA / ACC guidelines)
  - Post ACS
    - Up to 12 months following Unstable Angina or NSTEMI (medically managed)
    - At least 14 days (12 months in some) post STEMI
  - Post STENT (ASA indefinitely) Additional agent:
    - Up to 12 months after BMS placement
    - At least 12 months after DES placement

Antiplatelet Therapy

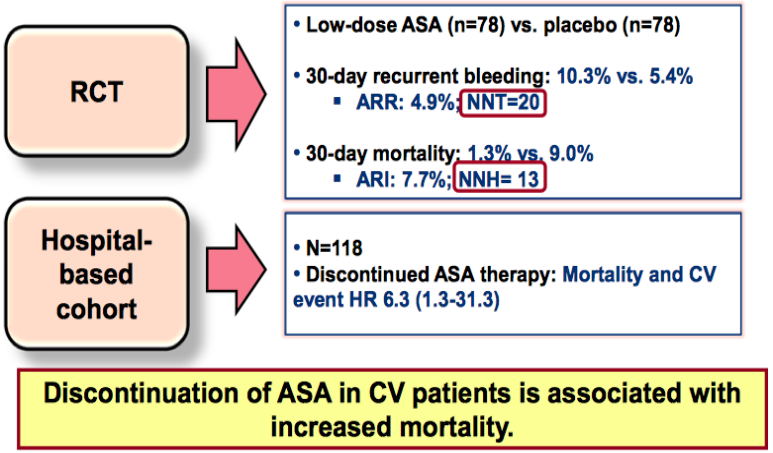
- Current Guidelines[1]
  - Bare Metal Stent: Wait ~1 month until surgery
    - Go to OR with ASA
  - Drug Eluting Stent: Wait ~ 12 months until surgery
    - Go to the OR with ASA
    - Urgent: Continue dual agent > ASA alone

Drug Eluting Stents (DES)



Adapted from: Eisenberg MJ, et al. Circulation. 2009;119(12):1634-42.

Recommendation 1

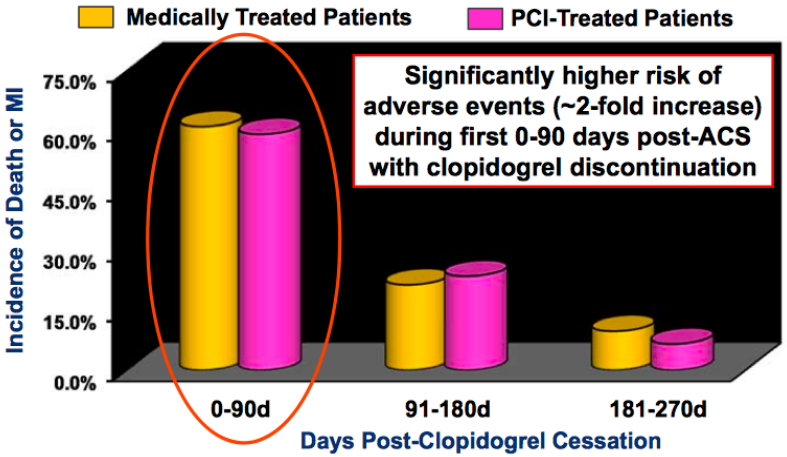


Adapted from: Sung JJ, et al. Ann Intern Med. 2010;152(1):1-9 and Derogar M, et al. Clin Gastroenterol Hepatol. 2013;11(1):38-42.

- Perform diagnostic and therapeutic endoscopic procedures in patients taking cardiac doses of aspirin[1]
  - Discontinuation of cardiac aspirin in cardiac patients is associated with increased mortality[2]

[1] Becker et al. J Am Coll Cardiol. 2009; 54(24): 2261-2276.
[2] Derogar et al. Clin Gastroenterol Hepatol. 2013; 11(1): 38-42.

Recommendation 2



Adapted from: Ho PM, et al. JAMA. 2008;299(5):532-9.

- Do not stop thienopyridine antiplatelet drugs (clopidogrel, prasugrel, ticagrelor) in
  - First 90 days post ACS
  - First 30 days following stent insertion (BMS)
  - These are the highest risk periods for cardiovascular mortality, recurrent MI and stent thrombosis
  - Defer elective exams until safe to stop thienopyridine – up to 12 months in some patients (DES)[1]

[1] Becker et al. J Am Coll Cardiol. 2009; 54(24): 2261-2276.

Recommendation 3

- With any temporary interruption in thienopyridine agent, you must continue cardiac aspirin in a patient on dual anti-platelet therapy[1]
  - Can safely perform elective endoscopic procedures 5-7 days following clopidogrel cessation / 7-9 following prasugrel cessation / 3-5 days following ticagrelor cessation
  - Restart once hemostasis achieved
  - No need to interrupt dual therapy for diagnostic procedures or procedures with low risk of post-endoscopic bleeding[2]

[1] Abraham NS, et al. BMJ 2015; 350:h1857.
[2] Becker et al. J Am Coll Cardiol. 2009; 54(24): 2261-2276.

Recommendation 4

- GI bleeding associated with Novel agents: aggressively resuscitate the patient to support drug excretion by the kidneys
  - Drug effect with completely dissipate within 24 hours if kidney function is normal.
  - With impaired glomerular filtration, higher levels of circulating drug may be present
  - Prompt endoscopic evaluation for high risk stigmata of bleeding is recommended with moderate to severe bleeding.
  - The use of coagulation factors (FFP, PCC) is more successful in reversing upstream inhibitors of coagulation (Factor Xa inhibitors) than dabigatran
  - If bleeding continues after resuscitation: FFP and urgent endoscopy to treat high risk stigmata
  - If last dose of NOAC < 3 h: consider charcoal, PPI for absorption

- Idarucizumab (IV formulation)
  - Monoclonal Antibody (humanized) with high affinity for dabigatran
  - REVERSE AD trial (Published 2015)
    - Looked at 123 patients with uncontrolled bleeding or requiring major surgery on Dabigatran
    - Reversal of effect in 89% within 4 hours
  - Accelerated approval by FDA in October 2015: For life threatening uncontrolled hemorrhage
- Andexanet Alpha
  - Phase II study in healthy volunteers
  - Decreased anti-Xa activity and plasma concentration of free apixaban
  - Future studies required in setting of major hemorrhage
- Perosphere
  - Synthetic molecule that binds heparin, LMWH and NOACs in animals
  - Whole blood clotting time (in vitro studies) show reduction of edoxaban effect within 10 minutes
  - Needs human studies / clinical trials

Abbreviation: NOAC, novel anticoagulant

Abraham NS, et al. Curr Opin Gastroenterol. 2013; 29(6): 676-683.

Temporary interruption of NOAC prior to endoscopic procedure

Drug (CrCl)	Last dose prior to low-risk endoscopic procedure*	Last dose prior to high-risk endoscopic procedure**
○ Dabigatran		
– > 50 mL/min	1 day	2 days
– 31 – 50 mL/min	2 days	4 days
– < 30 mL/min	4 days	6 days
○ Rivaroxaban / Apixaban / Edoxaban		
– > 50 mL/min	1 day	2 days
– 31 to 50 mL/min	1-2 days	3-4 days
– < 30 mL/min	2 days	4 days

* A low-risk procedure has a 48 hr risk of major bleeding of 0% to 2%; a high-risk procedure** has a 48 hr risk of major bleeding of 2% to 4%

Abbreviation: CrCl, creatinine clearance

Recommendation 5

- Non-GI Bleed
  - Resume anticoagulation or non-ASA antiplatelet agent as soon as hemostasis is achieved (often on the same day of endoscopic hemostasis)
- In patients with warfarin related GI bleed
  - Resume anticoagulation within 4-7 days following the onset of GI bleeding

Recommendation 6

- GI bleeding leading to ACS should be scoped 48-72 hours post ACS[1]
  - Leads to faster cardiac catheterization in 43%
  - High likelihood of finding important lesions
    - HR 3.9 (1.8-8.5)
- Peri-procedure risks high (12%) in first 24 hours after ACS but decline to 1-2% by 30 days

ASGE Guidelines – Antiplatelet / Anticoagulation and Endoscopy
Gastrointestinal Endoscopy 2009; 70(6): 1060-1070.

- Procedure Risk and Risk of Bleeding
  - High Risk: Polypectomy, Biliary or Pancreatic sphincterotomy, Pneumatic or bougie dilation, PEG placement, Therapeutic balloon-assisted enteroscopy, EUS with FNA, endoscopic hemostasis, Tumor ablation by any technique, Treatment of Varices
  - Low Risk: Diagnostic (EGD/Colonoscopy) +/- Biopsy, ERCP without sphincterotomy, EUS without FNA, Enteroscopy and diagnostic balloon assisted enteroscopy, Capsule endoscopy, Enteral stent deployment (without dilation)
- Risk of thromboembolic complications (based on stopping antiplatelet/anticoagulant)
  - High risk: AF associated with valvular heart disease / prosthetic valves / CHF / LV EF < 35%, / History of thromboembolic event / HTN / Diabetes / Age > 75, Mechanical mitral valve, Mechanical valve in any position and previous thromboembolic event, Recent coronary stent (<1 year), ACS, Nonstented PCI after MI
  - Low risk: Uncomplicated or paroxysmal nonvalvular AF, Bioprosthetic valve, Mechanical valve in aortic position, DVT
- For Elective procedures
  - For patients on temporary anticoagulation therapy (eg: warfarin for DVT or antiplatelet for stents): defer elective endoscopic procedures be deferred until therapy completed (Low quality)

- ASA and/or NSAIDS may be continued for all endoscopic procedures (Low Quality)
- When high risk procedures are planned, to discontinue aspirin and/or NSAIDS for 5 to 7 days before the procedure (depending on underlying indication for antiplatelet therapy)
- Defer elective procedures if recently placed vascular stent or ACS until patient has received recommended duration (as per individual society guidelines).
    - Once this has passed
        - Stop clopidogrel or ticlopidine for 7-10 days before endoscopy (continue ASA) and
        - Restart as soon as safe based on therapy performed at time of endoscopy.
    - In those not taking aspirin, it may reduce the risk of thromboembolic events in the periendoscopic period.
    - Consult with cardiologist or other relevant provider (Moderate Quality)
- When taking clopidogrel and ticlopidine for other indications
    - Continue them for low risk procedures
    - Stop 7-10 days prior to high risk procedures. Restart when deemed safe
    - Consider addition of ASA in periendoscopic period if not already on it. (Low quality)
- Discontinue anticoagulation (i.e. warfarin) in patients with a low risk of thromboembolic events in whom it is safe to do so; Hold for 3-5 days
    - Continue anticoagulation in patients at higher risk of thromboembolic complications, switching to LMWH or UFH (bridging) in periendoscopic period when indicated for known or expected therapeutic indications (Low quality)

- Not enough data to recommend for or against prophylactic mechanical clips after polypectomy in patients on anticoagulation
- No consensus on optimal timing to reinitiate anticoagulant therapy: will depend on specific procedure circumstances.
  - If high risk for thromboembolic events
    - UFH or LMWH (bridging) when safe
    - Start warfarin on day of procedure
  - If low risk for thromboembolic events
    - Re-start warfarin on the evening after the endoscopy (Low quality) → ACC/AHA: within 24 hours

- Urgent and Emergent Procedures
  - Hold antiplatelet agents until hemostasis achieved (Low quality)
    - Administration of platelets may be appropriate for patients with life-threatening or serious bleeding.
    - In situations of significant bleeding within < 1 yr of placing a vascular stent and/or ACS
      - Cardiology consultation be obtained before stopping antiplatelet agents (Low Quality)
    - Holding ASA for 30 days vs. 3 to 5 days: After 2 months → more bleeding, but lower mortality in the group who held ASA for 3 to 5 days. Reasonable to restart and add PPI
  - Hold anticoagulants until hemostasis achieved (Low Quality)
    - Decision of Vitamin K, FFP, PCC: individualized
    - Protamine reserved for life threatening bleeds on heparin (risk of anaphylaxis, severe hypotension). (Low quality)

- In Warfarin with supratherapeutic INR
  - Correct anticoagulation (target INR has not been determined) (Moderate Quality)
- Note
  - Studies have shown: preprocedure INR was not a predictor for rebleeding
- Risk of rebleeding after hemostasis for those on anticoagulation is not known.
  - Decision on resumption should be individualized.
  - Small studies looking at a range of 4 to 15 days showed low rates of thromboembolism
  - In those with high risk stigmata for rebleeding (i.e. visible vessel). IV UFH can be used initially because of its relative short half life (Low Quality)

Elective Endoscopy Setting

- Low bleeding risk → continue
  - ASA / NSAID
  - Thienopyridines
  - Warfarin
- High bleeding risk
  - + High thromboembolic risk
    - Continue ASA
  - + Low / high thromboembolic risk
    - Discontinue thienpyridines for 7-10 d beforehand*
    - Start ASA
    - Discontinue warfarin

* If endoscopy is urgent, discontinue thienopyridines for as long as possible before the endoscopic procedure

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Note: Page number followed by f and t indicates figure and table respectively.