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GASTROENTEROLOGY & HEPATOLOGY

Western University
London ON

Edited by

Keith McIntosh and Alan B.R. Thomson

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Thank you

Alan B. R. Thomson and Keith McIntosh

DEDICATIONS

To Jeannette…...With Love
Forever and Ever Alan

To my loving wife Kathy and our four wonderful children, Lewis, Seth, Sadie & Isaac. Thank you for all your love and support which has allowed me to pursue a career that I love. Without your patience and understanding, none of this would ever be possible.

Your loving husband & father, Keith

x

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Patience and patients go hand in hand. So does the interlocking of young and old, love and justice, equality and justice. No author can have thoughts transformed into words no teacher can make ideas become behaviour and wisdom and art, without those very special people who turn our creative minds to the practice- of getting the job done!

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TABLE OF CONTENTS

ESOPHAGUS

ESOPHAGEL MOTILITY TESTING

Rocio Sedano and Keith McIntosh

- High Resolution Esophageal Manometry (HREM)

➢ Indication

- Dysphagia with normal EGD
- Chest pain with normal EGD and rule out cardiac-based pain
- Refractory GERD when patient considering anti-reflux surgery.
- Confirm diagnosis of previously suspected primary/secondary esophageal motility disorder

Most important parameters to look for in a HREM

IRP: Mean of the 4 sec of maximal deglutitive relaxation in the 4-sec window, beginning at UES relaxation.

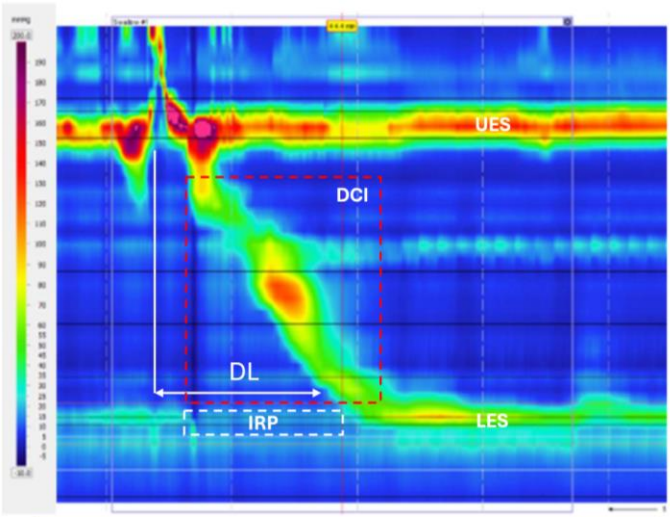
Normal< 15mmHg

DCI: Amplitude x duration x length (mmHg·s·cm) of the distal esophageal contraction exceeding 20 mmHg from the transition zone to the proximal margin of the LES.

Failed<100
Ineffective 100-450
Normal 450-8000
Hypercontractile >8000

DL: Interval between UES relaxation and CDP.

Normal > 4.5 sec



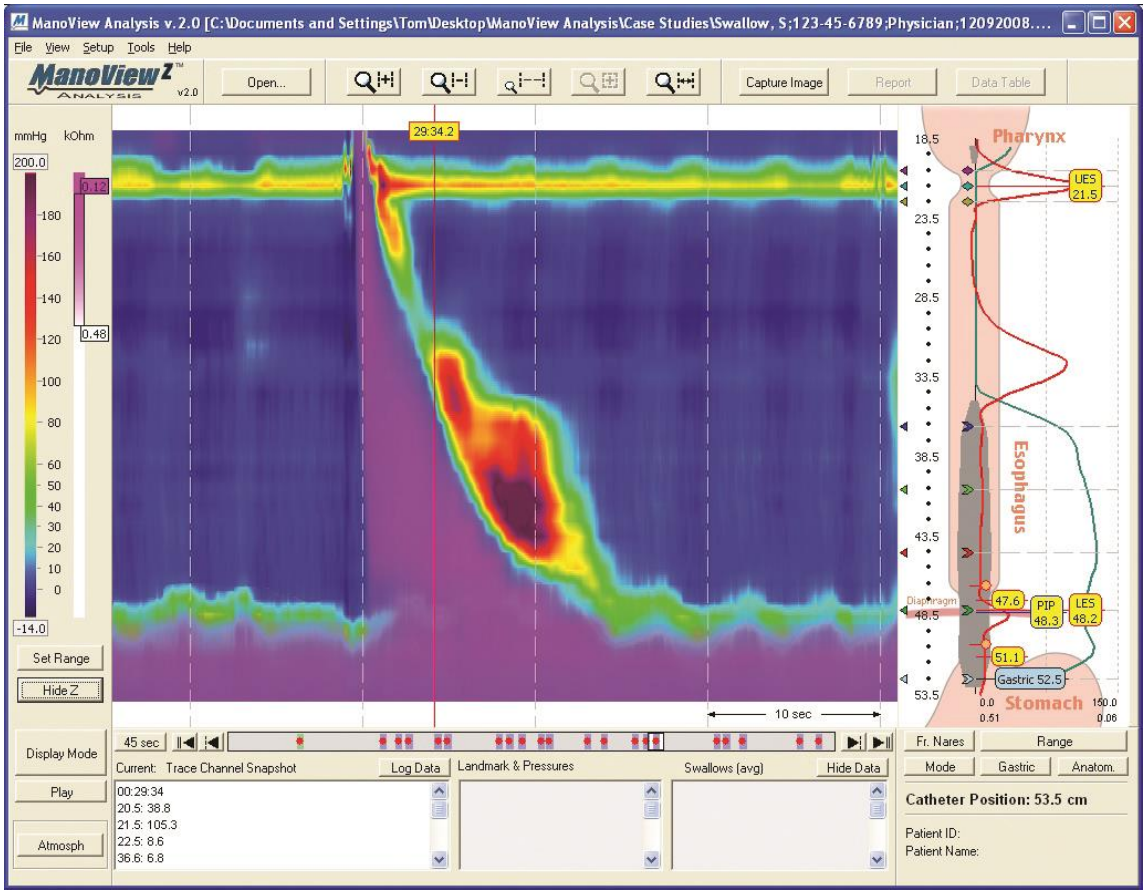
IRP: Integrated relaxation pressure; **DCI:** Distal contractile integral; **DL:** Distal latency; **CDP:** Contractile deceleration point

*Note

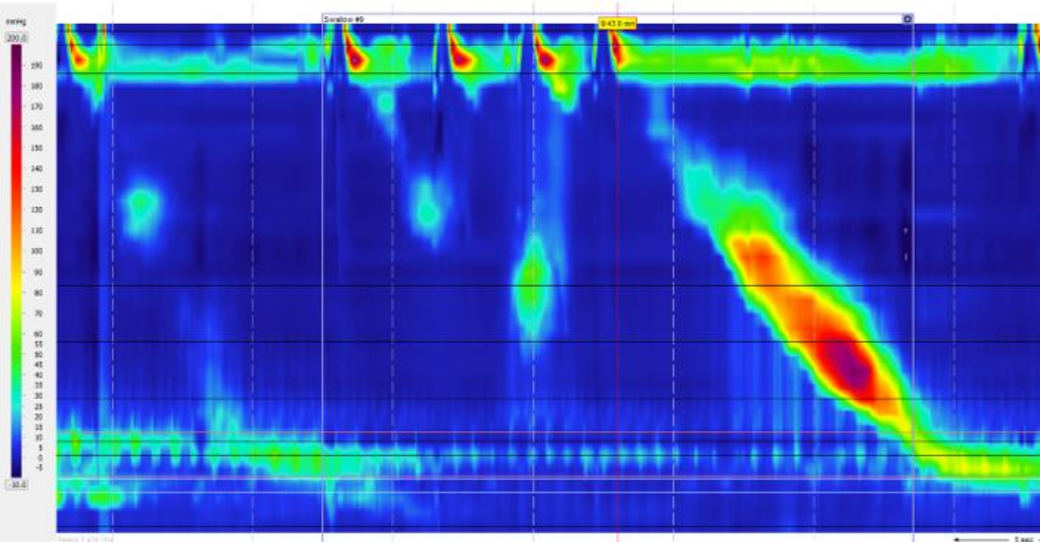
- Standard HREM does not determine whether a contraction results in the passage of a bolus

HREM plus Multichannel Intraluminal Impedance (MII)

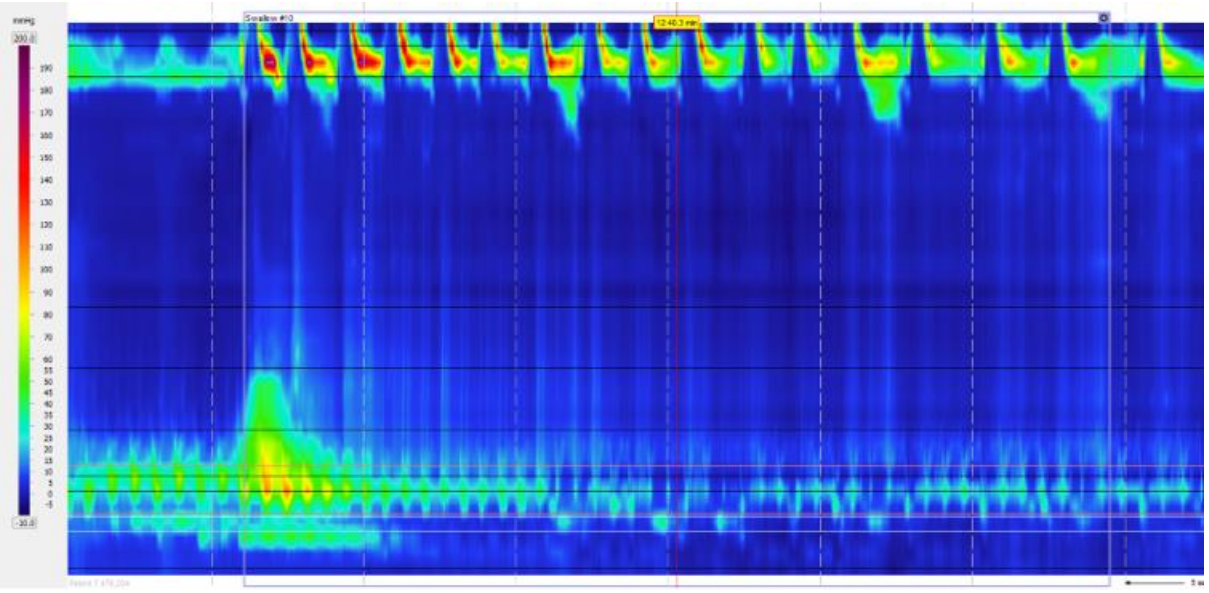
- Provides information about bolus transit



- HREM Provocative Testing
  - Multiple Rapid Swallows (MRS)
    - Five 2 mL swallows in 2-3 sec intervals.
    - Looks for significant augmentation of the peristaltic wave.
    - Most useful in patients with ineffective motility.
    - Abnormal may predict:
      - Post fundoplication dysphagia.
      - ↑ esophageal acid exposure time.



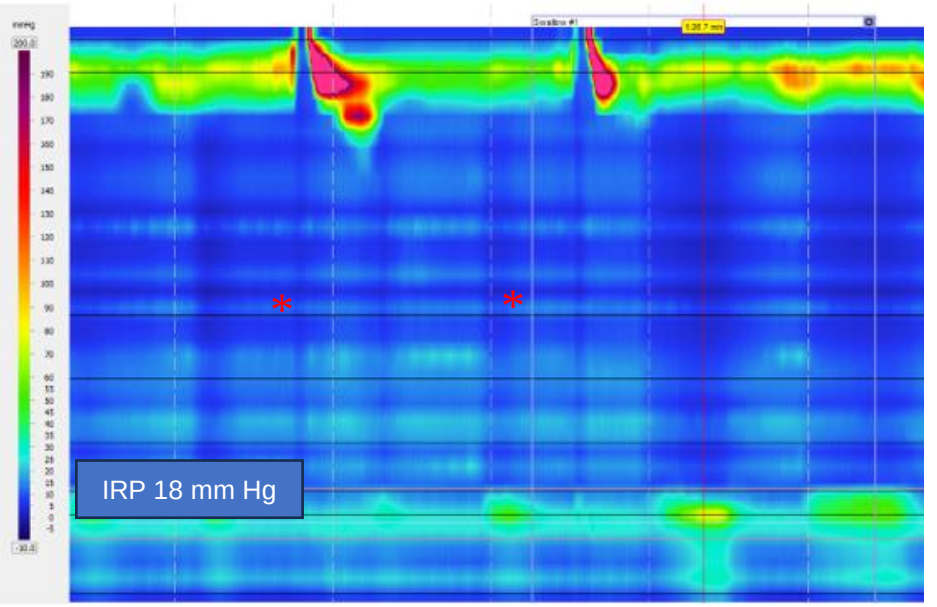
- Rapid Drink Challenge (RDC)
  - 200 mL water within 30 sec
  - Looks for significant complete relaxation of LES
  - Most useful in patients with
    - Borderline EGJ function or
    - Concern for achalasia
  - Achalasia:
    - ↑ IRP.
    - Panesophageal pressurization



- Chicago 4.0 Classification (Yadlapati R, et al. Neurogastroenterol Motil 2021; 33(1): e14058)
  - Disorders with EGJ outflow obstruction
    - Achalasia (Types 1, 2 & 3)
    - EGJ Outflow obstruction
  - Disorders of Peristalsis
    - Absent contractility
    - Distal esophageal spasm
    - Hypercontractile esophagus
    - Ineffective esophageal motility
  - Normal

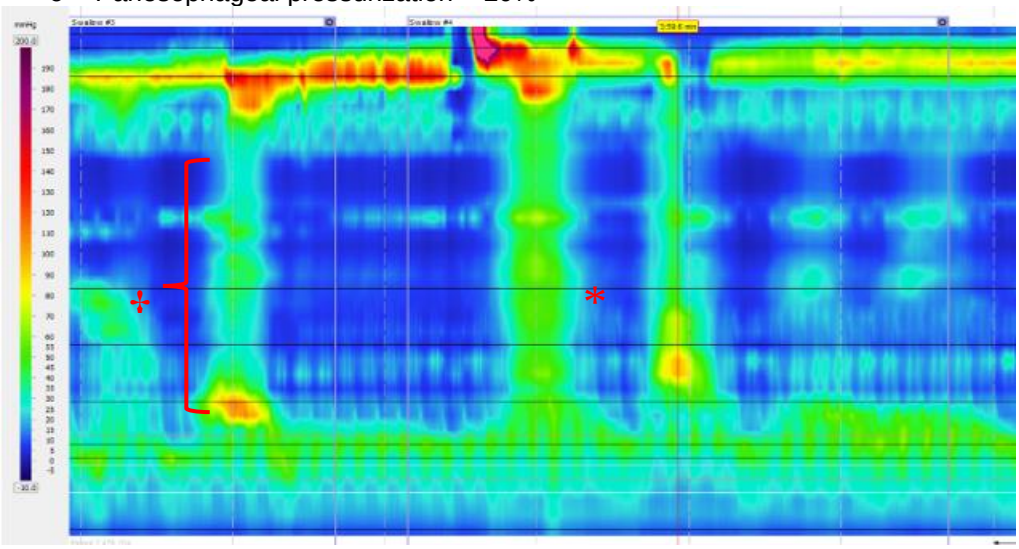
Type 1

- IRP > 15 mm Hg
- 100% failed peristalsis*



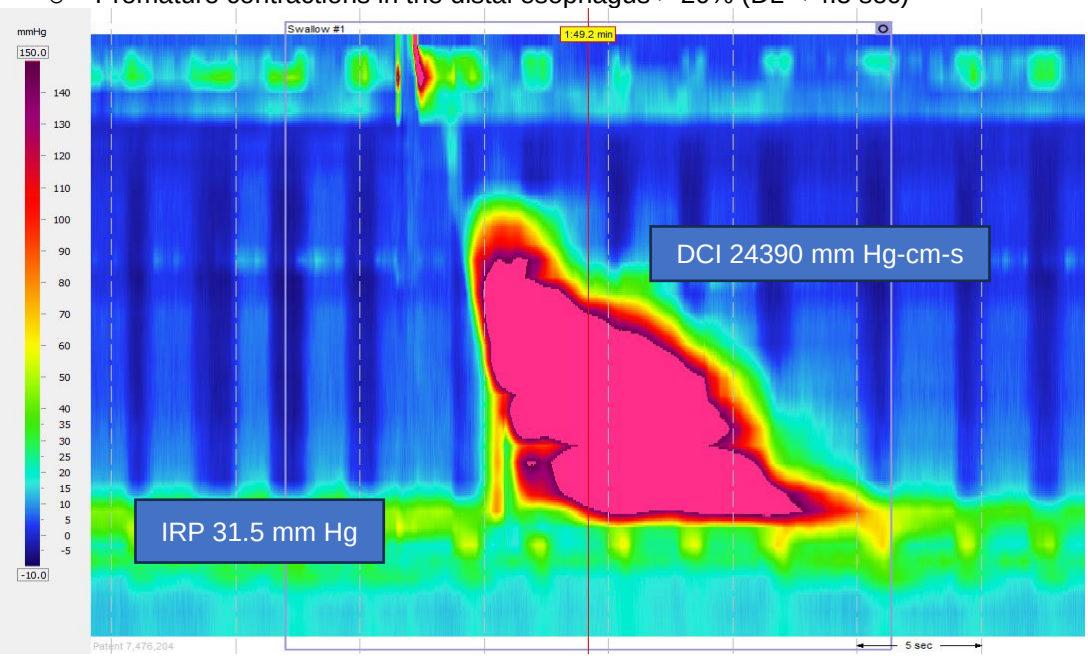
Type II

- IRP > 15 mm Hg
- Absence of normal peristalsis*
- Panesophageal pressurization > 20%†

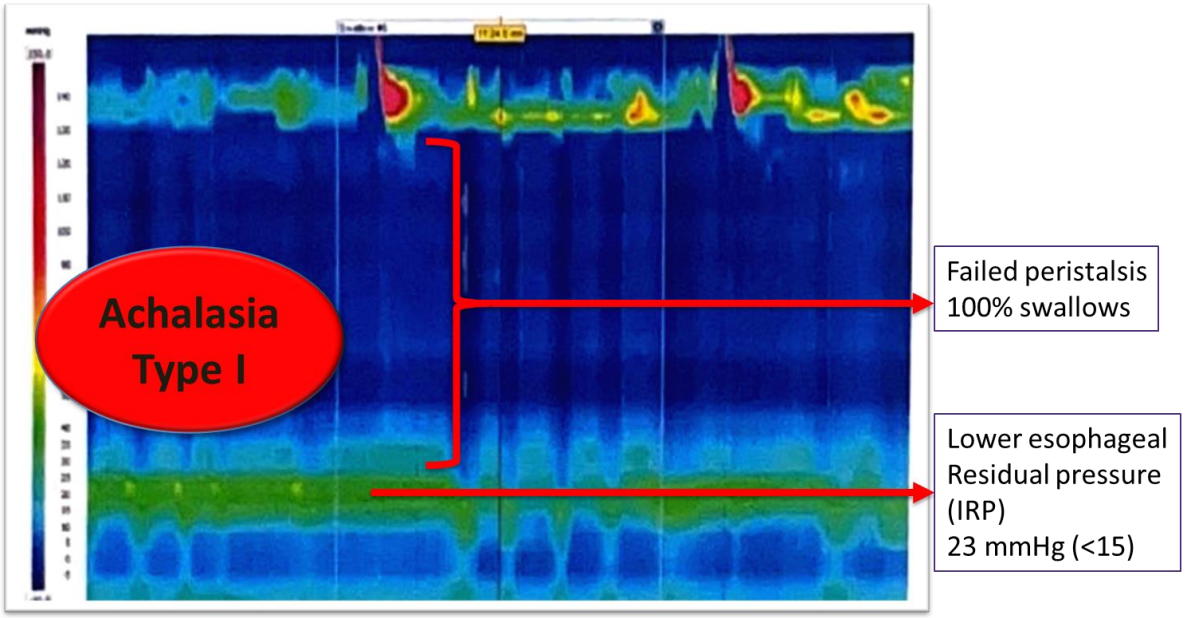


Type III

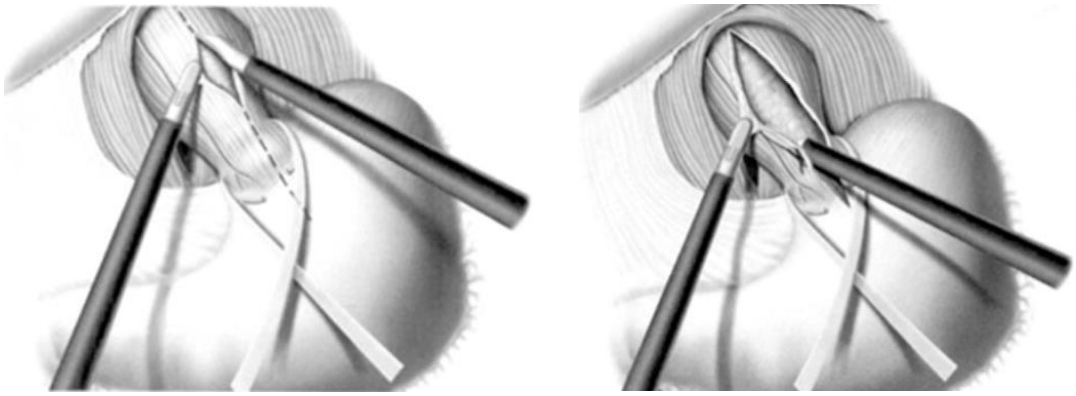
- IRP > 15 mm Hg
- Absence of normal peristalsis
- Premature contractions in the distal esophagus > 20% (DL < 4.5 sec)



Clinical Case: HREM – Swallows

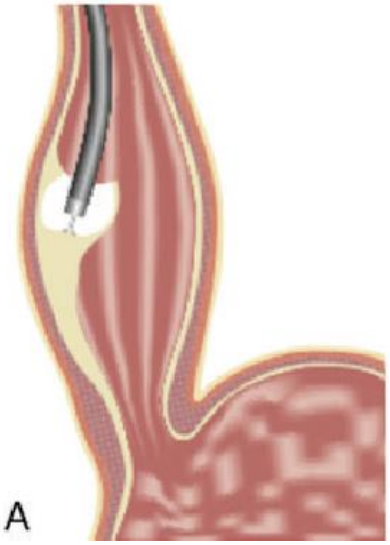


- Treatment
  - Pneumatic dilation
    - 3 to 4 cm balloon
    - ~80% success overall (better in type II) – Needs repeated sessions
    - Up to 5% perforation
  - Laparoscopic Heller Myotomy



Source: Bianchi ET, et al. Mini-invasive Surg 2017; 1:153-9.

- Per oral endoscopic Myotomy (POEM)



Printed with permission: Stavros N Stavropoulos SN, et al. BMJ 2016: 354: i2785.

➢ Comparisons

- POEM vs. PD
  - Among treatment-naive patients with achalasia on RCT of
    - Treatment with POEM compared with pneumatic dilation resulted in a significantly higher treatment success rate (Eckart score < 3, plus
      - No severe complications, or
      - Need for retreatment

      } At 2 yr
  - POEM, 92% (58/63)
    54% (34/63)

    } Absolute difference, 38% (95%CI, 22% - 52%, P < 0.001
  - Adverse effects
    - No difference in median barium column height
    - Median IRD
    - Reflux esophagitis
      - POEM, 41%, or
      - PD, 29%

      } Difference, 34% (95%CI, 12%-49%, P=0.01

- POEM vs. Surgery
  - POEM was non-inferior to Laparoscopic Heller Myotomy (LHM) plus Dor fundoplication in controlling symptoms of achalasia without use of additional treatments at 2 yrs
    - POEM, 83% (93/42)
    - LHM, 82% (89/109)
  - Adverse effects
    - Gastroesophageal reflux was more common among patients who underwent POEM than among those who underwent LHM.
    - No difference in IRP, QoL, pH monitoring
    - Reflux esophagitis
      - 3 mon 57% vs. 20% (OR 5.74; 95%CI 2.99-11.00)
      - 2 yr, 42% vs. 29% (OR 2.00; 95%CI: 1.03-3.85)
    - PPI use
      - 3 mon, 31% vs. 28%
      - 2 yr, 53% vs. 27%

The Efficacy of Peroral Endoscopic Myotomy vs Pneumatic Dilation as Treatment for Patients with Achalasia Suffering from Persistent or Recurrent Symptoms After Laparoscopic Heller Myotomy: A Randomized Clinical Trial

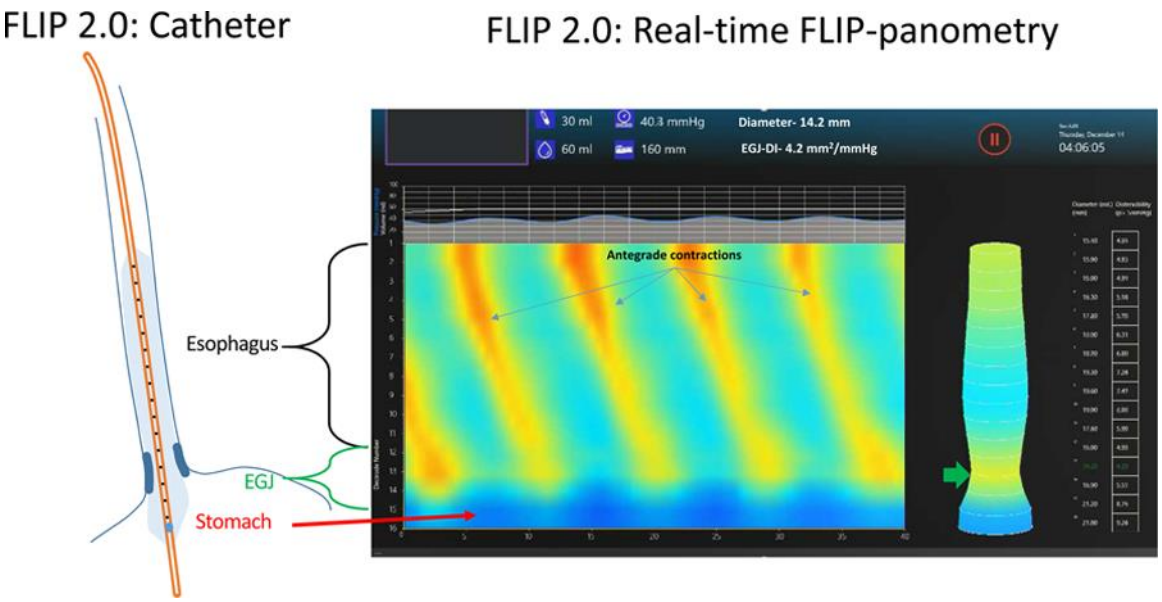
Saleh CMG, et al. Gastroenterology 2023;164(7):1108-1118

- Objective
  - Determine the efficacy of POEM vs PD for patients with persistent or recurrent symptoms after LHM
- Design
  - Multicenter RCT in patients after LHM with an Eckardt score >3 and substantial stasis (≥2 cm) on timed barium esophagogram. Follow-up duration was 1 yr after initial treatment
- Outcomes
  - Primary: Treatment success (Eckardt score of ≤3 and without unscheduled re-treatment)
  - Secondary: Presence of reflux esophagitis, HRM, and timed barium esophagogram findings.
  - POEM had a higher success rate (62.2%) than PD (26.7%); absolute difference, 35.6%; 95%CI, 16.4%-54.7%; P = .001; OR, 0.22; 95% CI, 0.09-0.54; RR for success, 2.33; 95%CI, 1.37-3.99)
  - Among patients with achalasia experiencing persistent or recurrent symptoms after LHM, POEM resulted in
    - A significantly higher success rate than PD, and
    - A numerically higher incidence of grade A–B reflux esophagitis

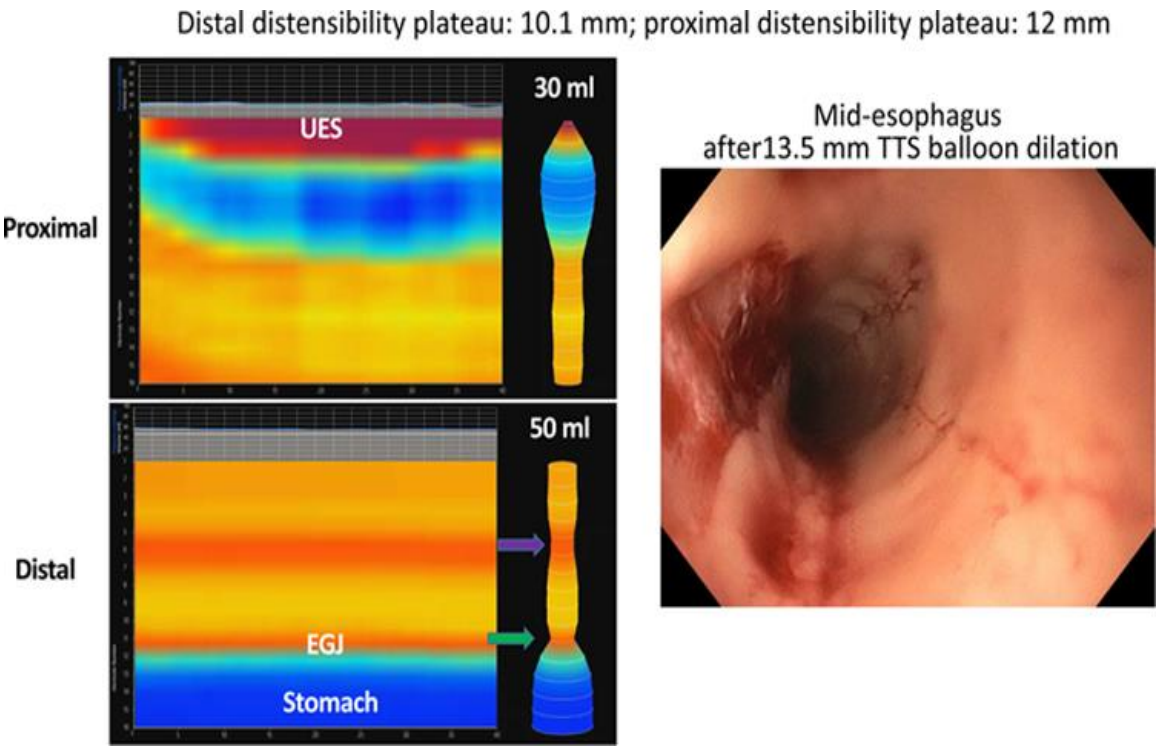
- Summary
  - POEM > PD in patients
    - Naïve to treatment
    - With previous failure to LHM
  - POEM is NOT inferior to LHM in patients naïve to treatment

Endoluminal Functional Lumen Imaging Probe (Endoflip)

- Use during EGD to measure
  - Esophageal dimensions
  - Movement, and
  - Pressure allowing calculation of distensibility (impedance planimetry)
  - 16 cm catheter with sensors located every 1 cm
    - A cylinder-shaped balloon filled to various volumes.
    - To measure 16 cross-sectional areas (CSA) along with the corresponding pressure measurements



Source: Donnan EN, et al. Gastroenterol Clin North Am. 2020; 49(3): 427–435.

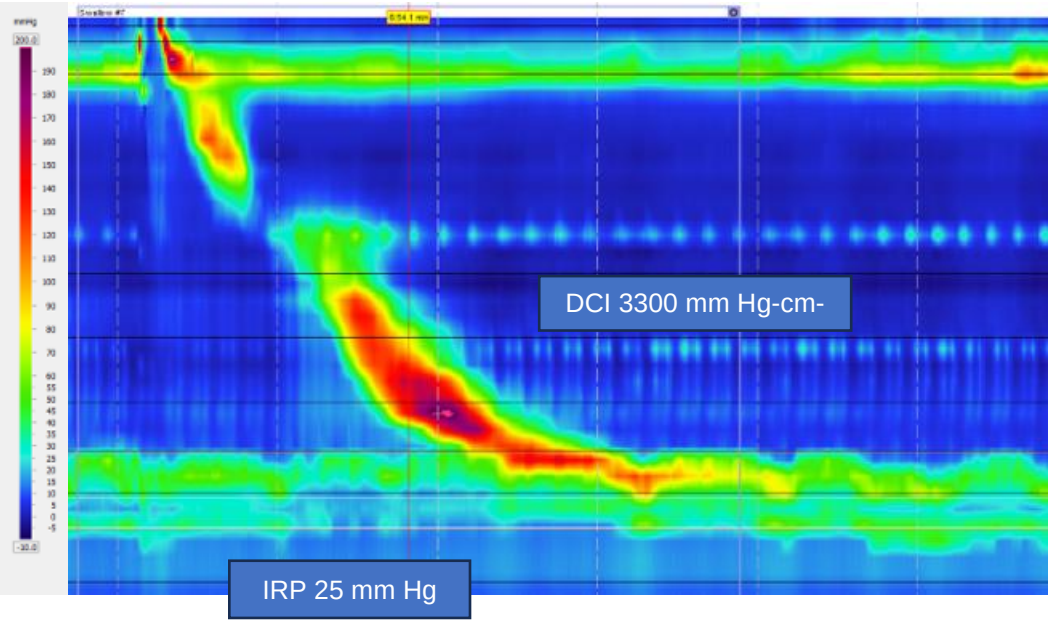


Source: Donnan EN, et al. Gastroenterol Clin North Am. 2020; 49(3): 427–435.

❖ Disorders with EGJ outflow obstruction

- Achalasia (Type 1, 2, and 3)
  - Autoimmune
  - Paraneoplastic achalasia
    - Extremely rare (~ 0.4% of cases of achalasia1.

- EGJ Outflow obstruction



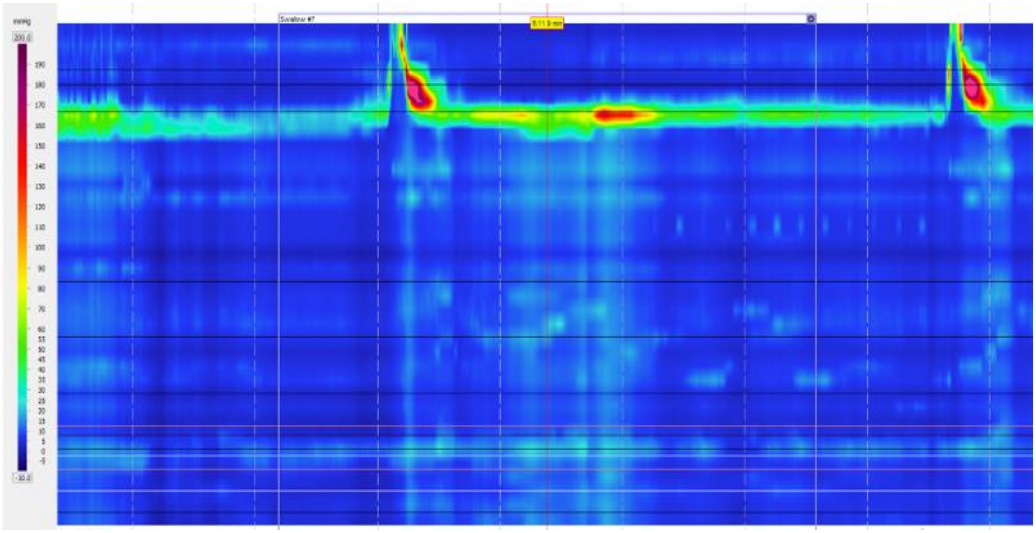
  - Symptoms
    - Dysphagia or
    - Chest pain (non-cardiac)
  - Diagnosis
    - ↑ IRP (integrated relaxation pressure – LES residual pressure) > 15 mm Hg
    - Normal/weak peristalsis (no achalasia features)
  - Causes
    - Mechanical
      - Benign GE junction stricture
      - Distal esophageal cancer
      - Extrinsic compression
      - Gastric band, EoE.
      - Infiltrative esophageal wall lesion (amyloid)
      - Post-fundoplication
      - Sliding/paraesophageal hiatal hernia
    - Functional
      - Narcotics
      - Early achalasia
      - Idiopathic
  - Investigation
    - EGD + esophageal biopsies
    - CT thorax/abdomen (consider EUS depending on findings)
    - Repeat EMS in 6-12 mon to ensure it doesn't evolve to achalasia.

Source: Katzka DA, et al. Dis Esophagus 2012:25(4):331-6; Yadlapati R, et al. Neurogastroenterol & Motil 2020;33:e14058; Pérez-Fernández MT, et al. Neurogastroenterol Motil 2016; (28) 116-126

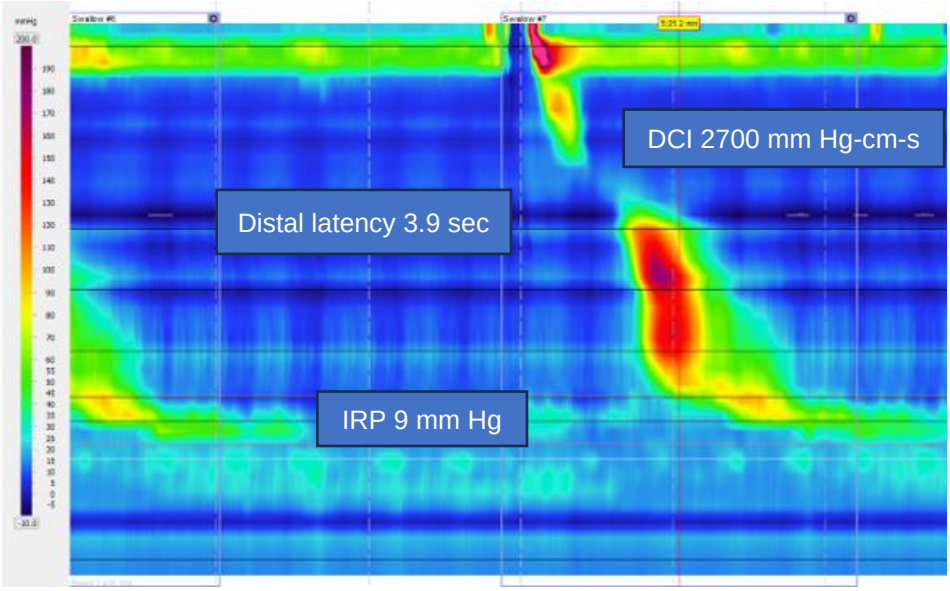
❖ Disorders of peristalsis (Normal IRP):

- Absent contractility
  - 100% swallows with failed peristalsis
  - Normal IRP

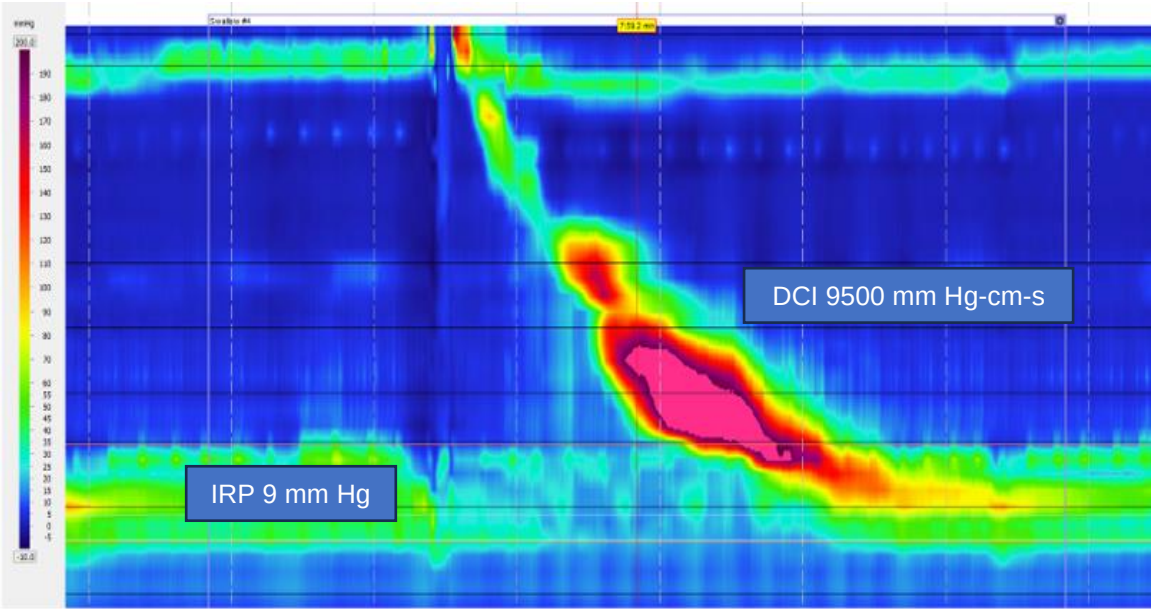
  (i.e., Scleroderma esophagus would be a secondary cause of this)



- Distal esophageal spasm
  - Distal latency (DL) <4.5 sec on >20% wet swallows



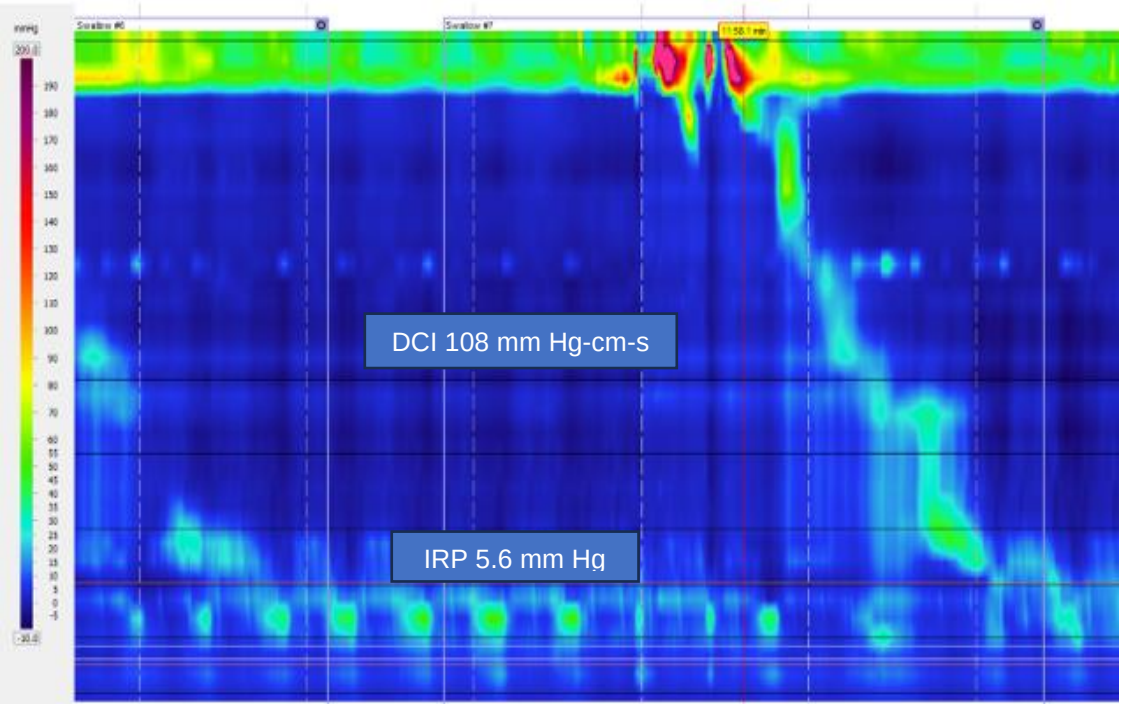
- Hypercontractile esophagus
  - DCI >8000 mm Hg-s-cm on >20% wet swallows



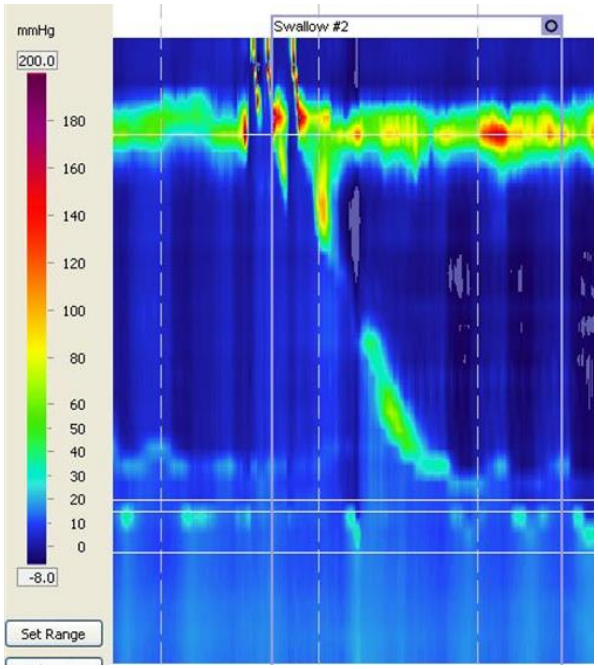
- Ineffective esophageal motility
  - >70% ineffective swallows:
    - Weak: DCI 100-450 mm Hg-s-cm
    - Fragmented: >5 cm break in peristalsis

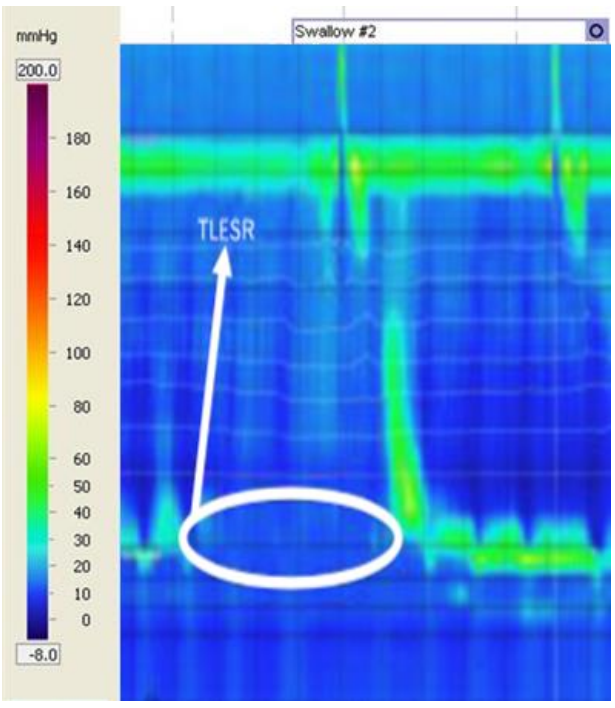
  or
  - >50% failed swallows
    - DCI<100 mm Hg-s-cm

* Support diagnosis: Incomplete bolus transit on impedance testing & abnormal MRS



- Disorders not addressed by Chicago Classification v4.0:
  - Hypotensive LES and Hiatus Hernia
  - Transient lower esophageal sphincter relaxation (TLESR)
    - Not triggered by swallowing
    - Longer than swallow-induced LES relaxation (10-45 sec vs 5-8 sec)
    - Unrelated to basal LES pressure
    - Not always related to acid reflux (40-60% vs 60-70% in patients with GERD)
    - Usually triggered by gastric distention (i.e., gas or meal)





Adapted from: Yadlapati R, et al. Neurogastroenterology & Motility 2020; 33: e14058.

- Measurements
  - EGJ distensibility index - CSA & Pressure relationship.
    - Normal: 3-9 mm^2/mm Hg
    - Achalasia/ EGJOO: Low distensibility, < 3 mm^2/mm Hg
    - Not well validated for high distensibility (> 9 mm^2/mm Hg)
  - Esophageal contractile response to distension
    - Normal
      - Repetitive anterograde contractions (RACS)
    - Abnormal
      - Repetitive retrograde contractions (RRCS) or
      - Absent contractility.

- Uses
  - Achalasia / EGJOO diagnosis with EMS
    - Equivocal Cases
      - Borderline IRP values (Both false positive & False Negative)
    - Normal FLIP predicts benign Manometry
  - Myotomy for Achalasia / Fundoplication for GERD
    - Intraoperatively / postoperatively to ensure adequate myotomy (↑ DI)
    - Intraoperatively / postoperatively to ensure adequate fundoplication (↓ DI)
  - Stricture Dilatation
    - Assessment of Esophageal Lumen diameter / Response to treatment

- Advantages
  - Good support data to EMS for borderline cases
  - Done during EGD
    - May obviate the need for EMS
  - Done with sedation
    - Useful when EMS is poorly tolerated
  - Might help in stricture dilatation

- Limitations
  - Currently, limited availability
  - Costly (~$350) and not reusable
  - Needs further validation

IN DEPTH: GERD PATHOPHYSIOLOGY AND TREATMENT (PART 1)

Aze Wilson

- Definition
  - Failure of normal anti-reflux barrier to protect esophageal mucosa against frequent or abnormal amounts of gastroesophageal reflux (GER)
  - GER is a normal physiological process
    - Occurs daily with no symptoms or mucosal damage
  - GERD is a spectrum of disease caused by GER
    - Heartburn and acid regurgitation
    - Often associated with normal endoscopy (NERD)
    - Complications: esophagitis; strictures; Barrett esophagus (BE); extraesophageal disease

- Demography
  - GERD is one of the most prevalent GI diseases in Western countries
    - Olmstead county (n=2200) = 40-45% (20% weekly symptoms)
    - Canada (n= 1000) = 17% (in last 3 mon – 13% weekly)
    - Complications like esophagitis are less frequent (2-10%)
    - GERD: M=F; esophagitis/BE: M>F
  - GERD prevalence is low in Africa and Asia (India = 7.5%; China = 0.8%; Malaysia = 3%)
    - Low dietary fat
    - Low body mass index (BMI)
    - Decreased gastric acid output secondary to HP infection

- Pathogenesis
  - Imbalance between
    - Defensive factors protecting the esophagus and aggressive factors from the stomach
    - Protective: anti-reflux barriers; esophageal acid clearance; tissue resistance
    - Aggressive: gastric acidity; bile acids & pepsin, gastric acid volume; duodenal contents

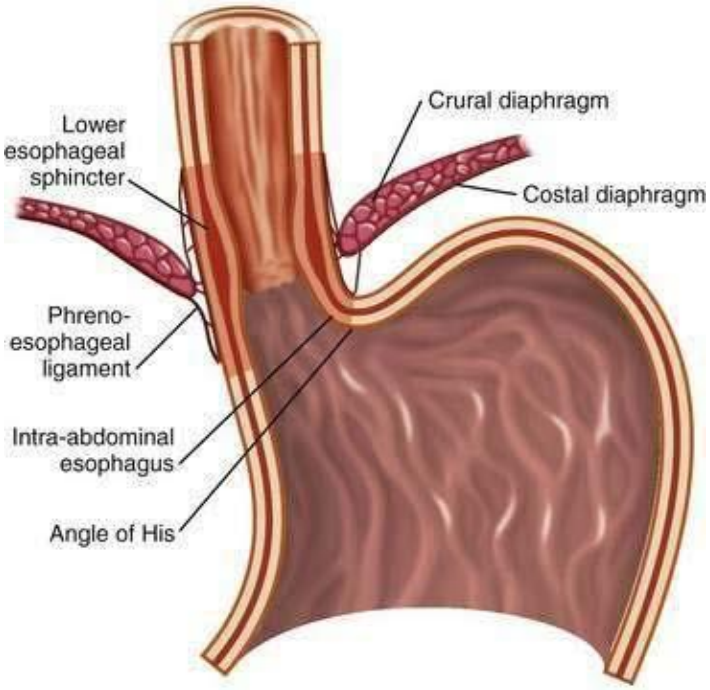
- Anti-Reflux Barriers
  - The LES: distal 3-4 cm of the esophagus
    - Contracted at rest
    - Proximal border is 1.5-2 cm above the squamo-columnar junction (SCJ)
    - Distal border is in the abdomen
    - Resting pressure: 13-42 mm Hg (only 5-10 mm Hg needed to prevent GER)
    - High pressure is maintained by:
      - Intrinsic muscle tone
      - Excitatory cholinergic neurons

- LES basal pressure varies based on the following:
  - Diurnal variation
    - Lowest after meals and at night
  - Circulating peptides; hormones
  - Foods
  - Drugs

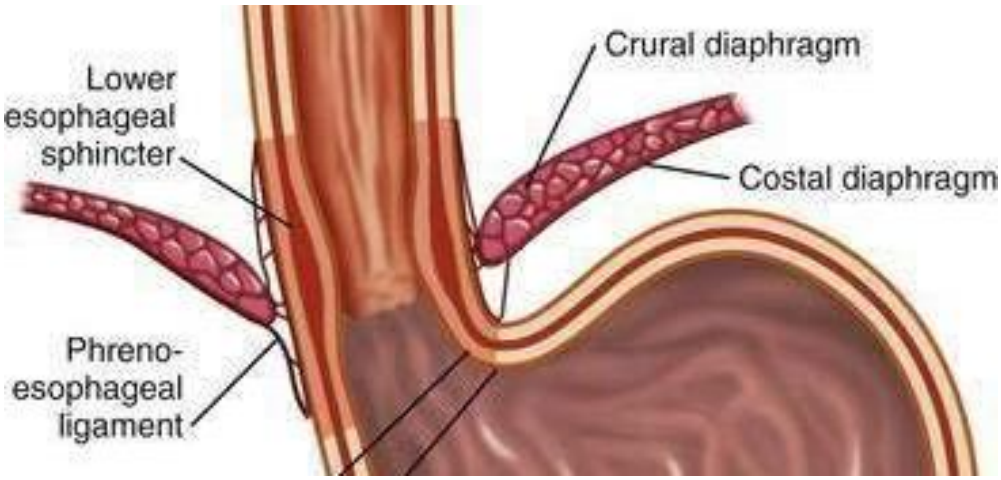
	↑ LES Pressure	↓ LES Pressure
Hormones/ peptides	− Gastrin − Motilin − Substance P	▪ Cholecystokinin (CCK) ▪ Secretin ▪ Somatostatin ▪ Vasoactive intestinal peptide (VIP)
Neural agents	− α-adrenergic agonists − β-adrenergic antagonists − Cholinergic agonists	▪ α-adrenergic antagonists − β-adrenergic agonists ▪ Cholinergic antagonist
Foods and nutrients	− Protein	▪ Chocolate ▪ Fat ▪ Peppermint
Other factors	− Antacids − Baclofen − Cisapride − Domperidone − Histamine − Metoclopramide − Prostaglandin F20	▪ Barbiturates ▪ Calcium channel blockers ▪ Diazepam ▪ Dopamine ▪ Meperidine ▪ Morphine ▪ Prostaglandins E2 and I2 ▪ Serotonin ▪ Theophylline

- The LES lies within the hiatus created by the right crus of the diaphragm and is anchored by the phrenoesophageal ligaments
- The crural diaphragm
  - Inhibited by esophageal distention, vomiting and transient LESRs
  - Provides extrinsic “squeeze” during inspiration and with periods of increased intra abdominal pressure (coughing, sneezing, bending)

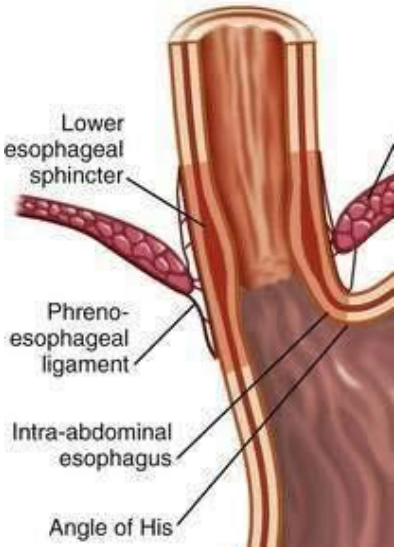
- Lower esophageal sphincter (LES) pressure
  - Diaphragmatic crura
  - Intraabdominal location of the LE
  - Phrenoesophageal ligaments
  - Acute angle of His



https://clinicalgate.com/gastroesophageal-reflux-disease-2/



- Oblique entrance of esophagus in the stomach creates a sharp angle (angle of His) at the greater curve
- Creates “flap-valve” against GERD



➢ Reflux Mechanisms

- Transient LES relaxations
  - Most frequent cause for GER in patients with normal LES pressures (60-70% GERD patients)
  - Occur independently of swallowing
  - Are not accompanied by peristalsis
  - >10 sec in duration vs swallow-induced relaxation (LESRs)
  - Accompanied by inhibition of the crural diaphragm
  - Most likely stimulus:
    - Distention of the proximal stomach by food or gas
      - Abdominal straining
      - Presence of a hiatus hernia
  - Mediated through vagal pathways
    - Gastric distention activates mechanoreceptors adjacent to the cardia

- Swallow-induced LESRs
  - 5-10% of reflux episodes occur during swallow-induced LESRs
    - Usually associated with defective or incomplete peristalsis
    - Usually associated with a hiatus hernia
  - Normally reflux is uncommon during swallow-induced LESRs
    - Crural diaphragm does **not** relax
    - LESR is short (5-10 s)
    - Oncoming peristalsis prevents retrograde reflux

- Hypotensive ↑, LESP
  - GER occurs due to hypotensive LES:
    - Strain-induced
    - Free reflux
  - Strain-induced: LES is “blown open” by an increase in intra-abdominal pressure (coughing, straining, bending) (unusual with LESP >10 mm Hg
  - Free: a fall in intraesophageal pH without change in intra-abdominal pressure (LESP <5 mm Hg)

- Role of the hiatus hernia (HH)
  - Controversial role in GERD
  - Data confirm its importance in
    - Esophagitis (54-94% of patients)
    - Barrett esophagus (BE)
    - Peptic stricture
  - Non-reducible HH worse than reducible
  - Impaired esophageal clearance

➢ Esophageal acid clearance

- Volume clearance
  - Removal of reflux materials from the esophagus
    - Performed by esophageal peristalsis when person upright and supine (but NOT during REM sleep)
  - Dysfunction of peristalsis (failed or weak - < 30 mm Hg) increases the severity of esophagitis
    - Unclear if esophagitis leads to peristaltic dysfunction, or if a motility disorder predisposes to reflux
  - Gravity contributes to bolus clearance
    - Elevation of head of the patient’s bed can be an important lifestyle modification

- Acid clearance: Salivary and Esophageal gland secretions
  - Acid clearance
    - Restoration of normal esophageal pH following acid exposure by titrating with base from salivary and esophageal gland secretions
  - Saliva: weak base (pH = 6.4-7.8)
    - Lozenges significantly decrease acid clearance time (accelerated acid clearance)
    - Decreased salivation in sleep may contribute to prolonged acid clearance time
    - Xerostomia and smoking associated with prolonged acid exposure and esophagitis
  - Esophageal gland secretions (bicarbonate-based)
    - Neutralizes acid; stimulated by acid refluxing into esophagus

➢ Tissue resistance

- Pre-epithelial
  - Poorly developed
    - No mucous layer and no surface cell buffering capacity
  - Lumen
    - Surface pH gradient = 1:10 (vs stomach and duodenum = 1: 1000 – 1: 10,000)
- Epithelial
  - Structural resistance
    - Tightly bound layer of squamous cells divided into 3 layers
      - Proliferating basal layer
      - Midzone layer of active squamous cells
      - Top layer of dead cells
    - Prevents penetration by H+
      - Can be overwhelmed by repeated or high volume luminal acidity
  - Functional resistance
    - Esophageal epithelium can actively extrude H^+ from cells using Na^+/H^+ pumps or Cl^-/HCO_3^- exchangers
- Post-epithelial
  - Provided by the blood supply to the esophagus
  - Provides HCO_3^- and removes H^+ and O_2
    - Maintains normal tissue acid-base balance

❖ Gastric Factors

- Gastric acid secretion
  - Volume and acidity of refluxate contribute to mucosal damage
  - Gastric refluxate: acid, pepsin
  - Animal studies suggest acid alone does not induce damage even at pH<3
  - Acid plus pepsin: disrupts the mucosal barrier → ↑ H^+ permeability
  - Of note
    - H. pylori infection → ↓ gastric acidity, protecting against esophagitis and BE
- Duodenogastric reflux (DGR)
  - Duodenal contents may also be injurious to the esophageal mucosa
    - Bile acids produced their greatest injury in the presence of acid and pepsin
    - Trypsin/deconjugated bile acids are more damaging at a neutral pH
  - More recent studies suggest 6-38% incidence rate of DGR in GERD patients
    - Should be considered in the patient with
      - Diabetes or
      - Autonomic neuropathy

➢ Treatment goals

- No esophagitis present
  - Relieve reflux symptoms
  - Prevent frequent relapse
- Esophagitis present (on EGD)
  - Relieve symptoms
  - Heal esophagitis
  - Prevent relapse and complications such as BE, stricture, bleeding

- Lifestyle changes
  - Most useful in uncomplicated disease / mild symptoms

Source: Pin on Esophagus from i.pinimg.com

➢ Over-the-counter (OTC) antacids

- Useful for mild, infrequent heartburn
- Antacids (Tums®, Rolaids®)
  - Buffer gastric acid (short periods only)
  - ↑ LESP
- Benefit
  - Rapid relief of heartburn

- Drawback
  - **Not** heal esophagitis
  - Relief in 20% over long term; 1-3 h benefit

- H2(R)-Antagonists
  - More effective for controlling nocturnal symptoms than meal-related reflux (due to post-prandial stimulation of parietal cells by gastrin and Ach)
    - Maintain intragastric pH > 4, 6-8 h
    - Esophagitis healing rates depends on severity of esophagitis
      - < 60% at 12 wk (MA)
  - Few drugs (4%) interactions or side effects

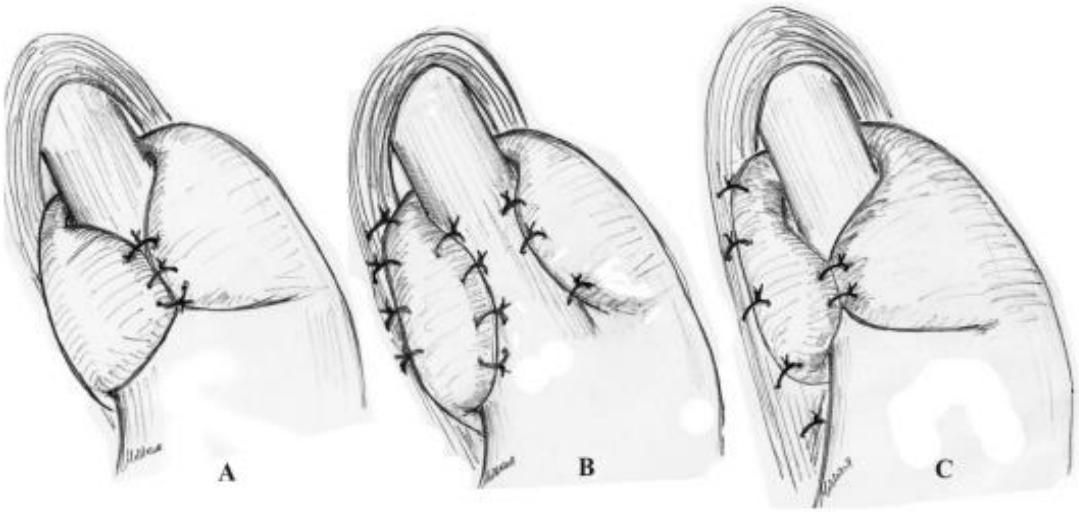
➢ Proton pump inhibitors (PPIs)
  - Inhibit meal-related and nocturnal acid secretion
    - PPI > HRA > placebo; more benefit in patients with esophagitis than NERD
  - After an oral ingestion, acid inhibition is delayed
    - PPIs need to accumulate in the parietal cell to irreversibly bind proton pumps (H^+/K^+ ATPase in canaliculi)
  - PPIs should be given 30-60 min before the first meal of the day when most PPs become active
    - Irreversible inhibitor of parietal cell acid secretion
    - Duration of H^+ inhibition ~ 14 h
    - H+ secretion returns when new parietal cells replace these which were present during exposure to PPI
    - Not all pumps are active at the same time; therefore, a second dose before an evening meal may be needed
  - PPIs are widely prescribed
  - Chronic use for prophylaxis against UGIB; GERD / peptic ulcer recurrence (persons who are negative for H. pylori infection and not taking NSAIDs)
  - FDA / Health Canada (HC): advisories over concerns of
    - C. difficile infection
    - Hypomagnesemia
    - Osteoporosis risk
  - Objective of PPI therapy in GERD
    - Maintain intragastric pH >4, 10-14 h
  - Healing of esophagitis 8 wk
    - PPI (80%); H2RA (51%); placebo (25%)
  - Relative benefit of different PPIs
    - Esomeprazole 40 mg > lansoprazole 30 mg, omeprazole 20 mg for healing esophagitis
    - Likely related to higher bioavailability, less interpatient variability
  - Among 16 head-to-head trials, no difference in PPI symptom-relief or healing of esophagitis
  - Similar time to relief of GERD (outcome measurement varied study to study)

- PPI: Maintenance therapy
  - Recurrence of esophagitis occurs in more than 80% of patients within 6 months after stopping PPI
    - Chronic PPI use in subjects with severe GERD is supported by data from Australia and the Netherlands
    - 230 patients with GERD receiving 11 yrs of PPI: asymptomatic; no stricture recurrence or BE progression
  - No difference in PPIs in terms of risk of relapse on therapy
  - Some clinicians step patients down from PPI to H2RA on demand

➢ Complications of PPIs

- Clopidogrel
  - Population study (n~ 13000 pts): ↑ risk of recurrent MI on omeprazole
    - Not seen with pantoprazole
  - Case-control study (n= 24471): no association seen with PPI and recurrent MI
    - FDA still recommends avoiding omeprazole and esomeprazole in patients on clopidogrel
- Omeprazole is an inhibitor of CYP2C19 and CYP3A4
  - Leads to interactions and reduced drug levels of other enzyme substrates (thyroid hormone, anti-fungals, chemotherapeutics, anti-retrovirals
- Malabsorption of B12, iron, magnesium
  - By altering intragastric pH, ↓ absorption of B12 and non-heme iron
  - Systematic Review of observational studies: PPI use > 2 yr associated with B12 deficiency
    - No screening recommendations; however consider judicious use in at risk populations
  - Reduced response to oral iron in PPI use > 2 mon
  - Hypomagnesemia reported in one study in patients on PPI > 5 yr
    - FDA: at risk cardiac patients should have periodic assessment of Mg^{2+}
- Osteoporosis
  - Metanalysis and systematic reviews suggest PPI use is associated with ↑ fracture risk (in men and women
    - Not seen with H2RA use)
  - Mechanism: ↓ calcium bioavailability and hypergastrinemia stimulate PTH for bone resorption or stimulation of osteoclasts
  - No specific recommendations
- Infections
  - ↑ C difficile infection
    - Stop PPI during C. difficile treatment
  - ↑ community acquired pneumonia
    - Minimize unnecessary use
    - PPI associated with increased risk of C diff recurrence

- Anti-reflux Surgery
  - Reduces GER
    - ↑ basal LESP
    - ↓ transient LESRs and
    - ↓ complete LESR
  - Reduce HH
    - Reconstruct the diaphragmatic hiatus
    - Reinforce the LES
  - Laparoscopic Nissen 360º fundoplication and the Toupet partial fundoplication are the most popular and successful procedures



A Nissen; B Toupet; C The combined technique

Source: Pavy G and Moldovanu R. Jurnalul de Chirurgie 2011; 7: 279–94.

  - Symptom resolution on PPI treatment predicts success of anti-reflux surgery
  - Surgery reduces symptoms and need for stricture dilation in 90% of patients
  - Long-term benefit not necessarily better than meds
    - 62% (OR) vs 92% (meds) need to return to PPI use 10 yrs post treatment
  - Consider referral for the following
    - Healthy patient with typical or atypical GERD responsive to meds wanting alternate treatment due to med cost, poor compliance, fear of long-term med use
    - Patients with volume regurgitation and aspiration not controlled by PPI

Abbreviations: BE, Barrett esophagus; BMI, body mass index; Cl-, chloride; F, female; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GI, gastrointestinal; H^+, hydrogen; HCO_3-, bicarbonate; Hg, mercury; HH, haitus hernia; LES, lower esophageal sphincter; LESP, lower esophageal pressure; LESR, lower esophageal relaxation; M, male; mon, month; Na^+, sodium; NERD, normal esophageal (endoscopy) reflux disease; OR, odds ratio; PPI, proton pump inhibitor; REM, rapid eye movement; sec, second

IN DEPTH: GERD PATHOPHYSIOLOGY AND TREATMENT (PART 2)

Maytham Hussain

- Global prevalence of GERD symptoms
  - Pooled Prevalence
    - Worldwide, ~13% persons report at least weekly GERD symptoms
    - In Canada, ~30% of persons report dyspepsia over 1 yr
  - Geographic Variation
    - Prevalence varies significantly across regions
      - Highest in South Asia and Southeast Europe (>25%) and lowest in Southeast Asia, Canada, and France (<10%)
    - Estimates range from 6% to 30%
    - Others may be due to the variability of the questionnaire

- Gender and GERD
  - In North America and Europe
    - Gender is not a significant factor in GERD.
  - In South America and the Middle East
    - Women have a 40% higher rate of GERD symptoms compared to men
  - Overall, men are at greater risk of developing esophagitis, Barrett esophagus, and adenocarcinoma

- Age and GERD
  - Advancing age is inconsistently linked to an ↑ in GERD symptoms, but
    - There is a strong association between ↑ age and complications of GERD, including esophagitis, esophageal stricture, and Barrett esophagus with cancer and adenocarcinoma.

- Race and GERD
  - In the US, there is a similar prevalence of GERD symptoms among different races
  - Complications by Race
    - However, whites are at ↑ risk for erosive esophagitis, Barrett esophagus, and adenocarcinoma of the esophagus

- Environmental Risk Factors for GERD
  - Obesity is the major risk factor for GERD
    - Central obesity (measured by the waist-to-hip ratio)
      - May be more important than BMI in association with complicated GERD
      - ↓ prevalence of H. pylori gastritis might explain the trends in GERD and its complications
  - Physical activity (e.g., stooped posture, bicycle riding, weight lifting, and swimming)
  - Use of
    - Tobacco
    - Alcohol

- Clinical features
  - Classic Symptoms
    - Heartburn (most common)
      - Burning sensation rising from the stomach/chest to the neck/throat
      - Triggers:
        - Alcohol
        - Chocolates
        - Citrus products
        - Fats
        - Large meals
        - Postprandial
        - Spicy foods
      - Exacerbating Factors:
        - Bending over
        - Sleep deprivation
        - Stress
        - Supine position
    - Regurgitation
      - Perception of flow or refluxed gastric contents into the mouth or pharynx
      - Associated with
        - Esophagitis
        - Gastroparesis
        - ↓ LES pressure
    - Dysphagia (less common)
      - Present in >30% of persons with GERD
      - Slowly progressive dysphagia for solids, typically in long-standing heartburn
      - Etiologies
        - Esophageal cancer
        - Esophageal inflammation
        - Peptic stricture
        - Peristaltic dysfunction
        - Schatzki ring
  - Less Common Symptoms
    - Water Brash
      - Sudden appearance in the mouth of slightly sour/salty fluid due to salivary gland response to acid reflux
    - Odynophagia
      - Painful swallowing
    - Burping/hiccups
    - Nausea/vomiting
    - Extraesophageal
      - Clearing of throat, voice change
      - Sinusitis, aspiration
      - Shortness of breath, cough
      - Dental erosions

- Asymptomatic GERD
  - Some GERD patients, especially older adults, may be asymptomatic
  - Suggested reasons
    - ↓ acidity of reflux material, ↓ pain perception
  - Complications
    - Older adults may present with GERD complications due to long-standing, minimally symptomatic disease, such as Barrett esophagus, adenocarcinoma

- GERD-Related Chest Pain
  - GERD-related chest pain is not fully understood but is likely
  - Secondary esophageal spasm and prolonged contractions of the longitudinal muscles of the esophagus leading possibly to an ischemia-based symptom
  - Esophageal can mimic angina pectoris
    - Squeezing/burning quality
    - Located substernally
    - Radiate to various areas, such as the back, neck, jaws, or arm, similar to angina
    - Often worse after meals
    - May worsen during emotional stress
    - May be eased with antacids
    - Can last for minutes to hours
    - It often resolves spontaneously
    - May be relieved by taking antacids

➢ Extraesophageal Manifestations of GERD

- Laryngitis
  - Symptoms
    - Hoarseness
    - Globus sensation
    - Throat clearing
    - Sore throat
    - Voice warm-up
    - Location
      - Typically in proximity to upper esophageal sphincter
  - GERD-related ENT signs
    - Posterior laryngitis
    - Vocal cord ulcers
    - Granulomas
    - Leukoplakia
    - Carcinoma

- Asthma
  - Estimated prevalence of GERD in asthmatics, 34% to 89%
  - Proposed mechanisms (causing bronchoconstriction)
    - Aspiration of gastric contents into the lungs and
    - Activation of a vagal reflex from the esophagus to the lungs
  - Data from randomized double-blind trials do **not** support the use of empirical treatment for acid reflux in even asymptomatic patients with poorly controlled asthma

➢ Pathogenesis

- Esophageal mechanisms
  - Transient lower esophageal sphincter (LES) relaxations
  - Swallow-induced lower esophageal sphincter relaxations
  - Hypotensive LES
- Gastric mechanisms
  - Acid secretion
  - Duodenogastric Reflux
  - Delayed Gastric Emptying
  - Hiatal Hernia

- Transient Lower Esophageal Sphincter Relaxations (tLESRs)
  - In GERD patients, tLESRs are responsible for 50% to 80% of episodes, depending on the presence of hiatal hernia and esophagitis severity
  - tLESRs are the most common mechanism for reflux in patients with the health sphincter pressures.
    - Occur independently of swallowing
    - Not accompanied by esophageal peristalsis
    - Persist longer (> 10 sec) than swallow-induced
      - Not always associated with GER
  - Possible factors influencing reflux during tLESRs:
    - Straining of abdominal muscles
    - Presence of hiatal hernia
    - Esophageal shortening
    - Duration of tLESRs
  - Dominant stimulus for tLESRs: Distention of the proximal stomach by food or gas
    - Stretch receptors play a significant role in triggering tLESRs
  - Other stimuli include dietary
    - Fat
    - Pharyngeal stimulation
    - Stress
  - Accompanied by inhibition of the crural diaphragm as the result of obstruction of the gastric fundus and release of nitric oxide (NO)

- Drugs which ↓ tLESRs
  - Baclofen
  - 5-hydroxytryptamine 3 antagonists
  - Anticholinergic drugs
  - CCK A (CCK-1) receptor antagonists
  - Morphine
  - Nitric oxide inhibitors
  - Somatostatin
  - γ-aminobutyric acid (GABA) agonists

- Swallow-Induced LES Relaxations
  - Reflux during swallow-induced LES relaxations is more common in individuals with hiatal hernias
  - Lower compliance of the esophagogastric junction (EGJ) in hernia patients
  - EGJ may open at pressures equal to or lower than intragastric pressure
  - This allows reflux of gastric juices from the hiatal hernia
  - During a normal swallow-induced LES relaxation (LESR)
    - The crural diaphragm remains contracted
  - The duration of LESR is short, 5 to 10 sec
  - Reflux is prevented by the oncoming peristaltic wave
  - Reflux during swallow-induced LES relaxations occurs in approximately 5% to 10% of the relaxations
  - Most episodes are associated with defective or incomplete peristalsis
  - These reflux mechanisms are frequently associated with the presence of a hiatal hernia
  - Diaphragmatic hiatus crucial in maintaining the functional integrity of the esophagogastric junction (EGJ)
  - When a hiatal hernia is present
    - Reflux can occur with only LES relaxation during periods of
      - ↓ LESP hypotension
      - Swallowing-induced relaxation, and
      - Straining
  - Free reflux is characterized by ↓ intraesophageal pH without an identifiable change in intragastric pressure, this often occurring when LES pressure < 5 mm Hg
  - Free reflux is uncommon
  - GER in this context occurs either via
    - Free reflux
    - Hypotensive LES
    - Strain-induced
  - Reflux occurs when a hypotensive LES is overcome by abrupt increases in intra-abdominal pressure (e.g., coughing, straining, bending over)
  - There is ↑ strain-induced reflux when LES pressure < 10 mm Hg, especially in the absence of a hiatal hernia

- Gastric Acid Secretion
  - Acid and pepsin are essential components of the gastric refluxate leading to esophagitis
  - Acid combined with even small amounts of pepsin/pepsinogen disrupts the esophageal mucosal barrier →
    - ↑ H+ permeability
    - Histologic changes, and
    - Hemorrhage
  - The degree of esophageal injury parallels the ↑ frequency and ↑ duration of acid reflux, pH < 4

Therapeutic Tip
- Physiological reflux (refluxate pH < 4) occurs about 6% of the time
  - Reflux > 6% of the time predisposes to GERD
  - The aim of therapy for GERD is to ↑ % of the time (24 h day) when pH > 4

- Helicobacter Pylori Infection
  - H. pylori infection, especially with the cagA+ virulent strain, has the potential to ↑ or ↓ gastric acidity, depending on the site of infection (gastric antrum or body)
  - Infection of the corpus
    - Can progress to multifocal atrophic gastritis (MAG) → ↓ parietal cells → ↓ gastric acid → ↓ chief cells
    - After eradication, the corpus regenerates parietal cells and acid secretion returns to normal
  - Infection of the antrum → ↑ gastrin H+ → ↑ GER symptoms
    - Heartburn and regurgitation often improve significantly after successful eradication therapy
  - GERD due to ↑ GER of H+ is more common in persons with acid hypersecretion, e.g., Zollinger-Ellison syndrome

- Duodenogastric Reflux (DGR)
  - Bile acids alter the integrity of the esophageal mucosal barrier
    - Disrupt cell function and
    - Damage membrane structure
  - Glycine conjugated bile acids produce their greatest injury in the presence of acid and pepsin
  - Esophageal exposure to bile is mixed with acid → ↑ severe grades of esophagitis

- Delayed Gastric Emptying
  - ↓ gastric emptying results in a greater volume of material in the stomach, including acidic material
    - ↑ volume in stomach → ↑ distention of the fundus → ↑ tLESR → ↑ acid reflux into the esophagus

- Hiatal Hernia (HH)
  - Many individuals with HH have GERD
    - HH serve as a persistent vestibule for gastric acid (acid pocket)
    - HH that are large (≥3 cm) and nonreducible are more prone to reflux
  - HH occurs in 54% to 94% of patients with reflux esophagitis, but
  - The presence of hiatal hernia → ↑ risk of erosive esophageal injury
  - Proximal displacement of the LES from the crural diaphragm into the chest → ↓ intra-abdominal LES segment → ↓ basal LES pressure and ↓ length of the high-pressure zone
  - Removes the ↑ LES pressure that occurs during straining and ↑ tLESR frequency during gastric distention

➢ Defense Against Esophageal Damage

❖ Anti-reflux Barriers

- The LES
  - Formed by distal 3-4 cm of the esophagus
  - Resting pressure, 10-30 mm Hg
  - Is the major component of the anti-reflux barrier
    - Can prevent reflux even when displaced by a hiatal hernia
- Diaphragmatic Crura
  - Provides extrinsic squeeze to the LES
    - Contributes to resting pressure during inspiration
    - ↑ LES pressure during periods of ↑ abdominal pressure
- Phrenoesophageal ligaments
  - Anchors the LES to the diaphragm
- Acute Angle of His
  - Creates a flap valve-effect
    - Contribution to gastroesophageal junction competency remains uncertain
- The intra-abdominal location of the LES
  - The proximal portion of the LES is normally 1.5 to 2 cm above the squamocolumnar junction
    - In contrast, the distal segment, about 2 cm in length, lies within the abdominal cavity.
  - This distal segment acts as an anti-reflux barrier
    - Due to a fold-like function related to the opposing sling and clasp fibres of the gastric cardia
  - This location maintains gastroesophageal competence during intra-abdominal pressure excursions

- Esophageal clearance mechanisms
  - Clears acid volume
    - When patient is in the upright or supine positions, but is **not** operative during deep rapid eye movement (REM) sleep
    - 1 or 2 primary peristaltic contractions completely clear a 15-mL fluid bolus from the esophagus
  - Primary peristalsis
    - Stimulated by swallowing
  - Secondary peristalsis
    - Initiated by esophageal distention from acid reflux
      - Less effective in clearing the refluxate (only an ancillary protective role)
  - Peristaltic dysfunction
    - Failed peristaltic contractions
    - Hypotensive / weak (<30 mm Hg) peristaltic contractions
      - Incompletely empty the esophagus)→ ↑ frequency with the severe esophagitis
  - ↑ GERD severity associated with
    - ↓ lower distal esophageal amplitude
    - ↑ prevalence of ineffective esophageal motility
    - Hiatus hernia ↓ fluid bolus transit
  - Concurrent pH recording and scintigraphy above the EGJ showed that
    - ↓ clearance caused by re-reflux of fluid from the hernia sac during swallowing
  - Gravity contributes to bolus clearance when reflux occurs in the upright position.
    - At night when supine, this mechanism is not operative unless the head of the bed is elevated

❖ Mucosal resistance Factors

  - Clearance mechanisms ↓ acid contact time with the epithelium, but even healthy persons have acid reflux during the day and sometimes at night, but
    - Only a few suffer from symptoms as a result
  - This is due to tissue resistance

- Pre-Epithelial
  - Swallowed saline, but no well-defined system for the surface cells to secrete bicarbonate ions into the unstirred water layer (UWL)
  - Esophageal secretion of glycoconjugate (predominantly mucin) and prostaglandin E2 may play a role in pre-epithelial defense

- Epithelial
  - Structural
    - The cell membranes and intercellular junctional complexes of the esophageal mucosa
    - The esophageal mucosa is a relatively “tight” epithelium
      - Resists ionic movement at the intercellular, as well as the cellular, level as the result of tight junctions and
      - The matrix of lipid-rich glycoconjugates in the intercellular space

- Luminal acid attacks the epithelial defenses by damaging the intercellular junctions, allowing H+ to enter and acidify the intercellular space
- Functional components of tissue resistance include
  - The ability of the esophageal epithelium to buffer and extrude hydrogen ions
  - Intracellular buffering is accomplished by
    - Negatively charged phosphates and proteins, and bicarbonate ions
- If the mucosal buffering capacity is exceeded and intracellular pH falls
  - The epithelium has the capacity to actively remove or neutralize H+
- When the epithelial cells are no longer able to maintain intracellular pH
  - ↓ ability to volume regulate
  - Cell swelling occurs
  - Balloon cells develop
  - Cell death follows

- Post-Epithelial
  - Esophageal blood supply
    - ↑ blood flow when ↑ in response to the stress of luminal acid
    - ↑ blood flow to the esophageal mucosa
      - Delivers oxygen, nutrients, and bicarbonate
      - Remove H+ and CO_2
  - Blood flow delivers oxygen, nutrients, and bicarbonate and removes H+ and CO2, thereby maintaining normal tissue acid-base balance

➢ Treatment of GERD

- Lifestyle modifications
  - Elevate the head of the bed
  - ↓ body weight (if overweight)
  - Restricting alcohol
  - Smoking cessation
  - Dietary changes: meal size, time (avoid bedtime snacks), content (fats, chocolate, citrus, spicy foods, tomato based, coffee, tea, cola)
  - ↓ lying down after meals

- Over-the-counter medications
  - Antacids → ↑ LES, ↑ buffering of gastric acid for short periods
  - Heartburn symptoms are rapidly relieved, but
    - Patients may need to take antacids frequently
  - Gaviscon, containing alginic acid and antacids
    - Mixes with saliva to form a viscous solution that floats on the gastric pool → acts as a mechanical barrier

  - Benefit
    - Do **not** heal esophagitis, and long-term trials suggest symptom relief in only 20% of patients

- Pro-kinetic drugs
  - Choices
    - Bethanechol - cholinergic agonist (flushing, blurred vision, headaches, abdominal cramps, and urinary frequency)
    - Cisapride - serotonin (5-hydroxytryptamine 4) receptor agonist (cardiac dysrhythmias (ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation)
    - Domperidone – peripheral dopamine agonist (hyperprolactinemia and nipple tenderness/discharge)
    - Metoclopramide – central dopamine antagonist (fatigue, lethargy, anxiety, restlessness, tremor, parkinsonism, dystonia, or tardive dyskinesia)
  - Mechanism of action
    - ↓ reflux symptoms
    - ↑ LES pressure
    - ↑ acid clearance
    - ↑ rate of gastric emptying
  - Do **not** alter tLESRs
  - Prokinetics provide a modest benefit in controlling heartburn, particularly in patients with delayed 4 gastric emptying
  - Their effectiveness decreases with disease severity
  - Unreliable efficacy in healing esophagitis unless combined with acid-inhibiting drugs
  - Greatly limited by their side-effect profile

- Inhibitors of tLESR
  - Baclofen, a GABAB agonist → ↓ tLESRs
    - Take 5 to 20 mg tid
    - Benefits ↓ acid and ↓ duodenal reflux, and ↓ symptoms in GERD patients treated for 4 wks to several months
  - Side effects
    - CNS
      - Dizziness
      - Drowsiness
    - GI
      - Nausea/ vomiting
      - Require discontinuation in ~20% of patients

- H2RAs
  - Names
    - Cimetidine
    - Famotidine
    - Nizatidine
    - Ranitidine
    - Have equal efficacy when used BID before meals
  - More effective in controlling nocturnal than meal-stimulated acid secretion
    - Useful to treat PPI resistant nocturnal breakthrough symptoms
  - ↓ GERD symptoms, but are rarely abolished
    - Overall esophagitis healing rates with 12 wk of H2RAs rarely > 60%
  - Use for > 2 wks often results in ↓ benefit due to development of tachyphylaxis
  - The main issue with these medications is tachyphylaxis
  - ↑ concentrations of phenytoin, procainamide, theophylline, and warfarin
  - Drug interaction with
    - Cimetidine > ranitidine (not with famotidine or nizatidine)
    - H2RAs do **not** inhibit the anti platelet effects of clopidogrel

- PPIs
  - Inhibits meal-stimulated and nocturnal acid and to a lesser extent nocturnal basal secretion, than the H2RAs
  - PPIs must be taken 30-60 min before the first meal of the day, when most proton pumps become active
  - PPIs need to accumulate in the parietal cell secretory canaliculus to bind irreversibly to actively secreting proton pumps
  - PPIs
    - ↓ concentration of H+ in the refluxate →
      - ↓ symptoms
      - ↑ healing of esophagitis
    - Do **not** ↓ volume of reflux has little benefit on regurgitation
  - Choices
    - Dexlansoprazole
    - Esomeprazole
    - Lansoprazole
    - Omeprazole
    - Pantoprazole
    - Rabeprazole
  - % pH > 4 is 10-14 h, rather than 6-8 h with H2RAs
  - Complete healing of even severe ulcerative esophagitis after 8 wks in more than 80% of patients taking PPIs, compared with 51% on H2RAs, and 28% receiving placebo

- Well tolerated
  - Most common side effects
    - Headaches
    - Diarrhea
- ↑ fasting serum gastrin levels with all the PPIs, but
  - The elevations generally do **not** exceed the upper limit of the normal range, and return to baseline values within 1 to 4 wks of PPI discontinuation
- Omeprazole → ↓ clearance of diazepam, warfarin, and clopidogrel owing to competition for the cytochrome P450 isoenzyme 2C19
- Safe drugs
  - Concerns about the development of gastric carcinoid tumours and colon cancer have **not** been confirmed
- Long-term PPI use was associated with up to a 4x ↑ risk of fundic gland polyps
  - These arise because of parietal cell hyperplasia and parietal cell protrusions resulting from acid suppression
- ↑ risk of infections
  - Pneumonia
  - Enteric infections (Salmonella, Campylobacter, and Clostridioides difficile)
  - Spontaneous bacterial peritonitis
- Chronic use of PPIs has mild affect to ↓ absorption of
  - Calcium
  - Iron
  - Magnesium
  - Vitamin B12
- Acute intestinal nephritis but appears to be a very rare idiosyncratic occurrence

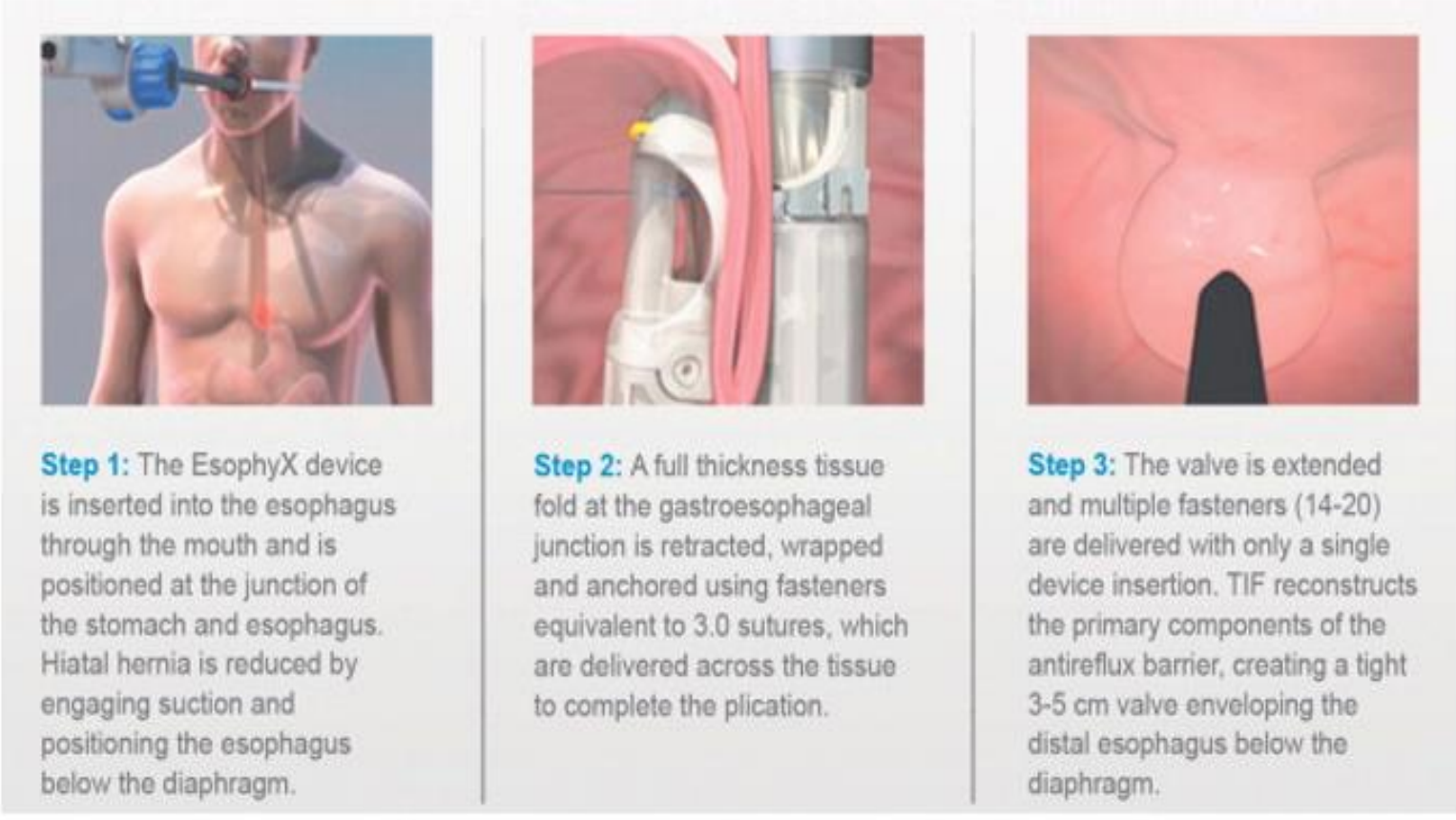
- Surgical therapy
  - Surgical fundoplication corrects the physiologic factors contributing to GERD → ↓ reduces acid / non-acid GER by
    - ↑ basal LES pressure
    - ↓ tLESRs
    - ↓ complete LES relaxation
  - This is achieved by
    - ↓ hiatal hernia into the abdomen
    - Reconstructing the diaphragmatic hiatus, and
    - Reinforcing the LES
  - Popular procedures, performed laparoscopically through the abdomen
    - Nissen 360-degree fundoplication and
    - Toupet partial fundoplication
    - Nissen fundoplication has better long-term durability, but it
      - More postoperative dysphagia and gas bloat symptoms
  - NB. Previous PPI RESPONDERS are most likely to benefit from anti-reflux surgery. Previous symptom resolution on PPIs helps to predict the success of anti-reflux surgery for classic and atypical symptoms

- Indications
  - Reasonable option in healthy patients
  - Typical or atypical GERD symptoms well controlled on PPIs
  - Desiring alternative therapy because of
    - Drug expense, poor medication compliance, or fear of possible long-term side effects of drugs
- Patients with volume regurgitation / aspiration symptoms not controlled on PPIs
- Recurrent peptic strictures in younger patients
- Note:
  - Patients who are unresponsive to PPIs may have another etiology for their complaints
    - Achalasia
    - Functional heartburn
    - Gastroparesis
    - Pill esophagitis
- Presurgical testing
  - Results in modification of the original operation or an alternative diagnosis in ~30% of patients
  - Endoscopy is necessary to exclude
    - Barrett esophagus
    - Dysplasia/carcinoma
    - Stricture
  - Barium esophagogram can show: (not a replacement for endoscopy however)
    - Non-reducible hiatal hernia
    - A shortened esophagus
    - Poor esophageal motility
  - Esophageal manometry combined with or without impedance
    - Identify a weak esophageal pump and previously misdiagnosed achalasia/scleroderma
  - Esophageal pH testing is necessary in patients with
    - Non-erosive GERD
    - Those with esophagitis not responding to PPI therapy
  - Gastric acid secretion measurements (if available), fasting serum gastrin assay, and gastric emptying tests may be indicated in selected patients

- Endoscopic therapies
  - Transoral incisionless fundoplication (TIF)
    - Recreates at 200- to 270-degree value using polypropylene fasteners placed endoscopically
  - Studies show symptom improvement, especially regurgitation and ↓ use of PPIs
    - Over time the fasteners tend to dislodge →
      - GERD symptom recurrence
      - Return to use of PPIs (often lower dose)

      } 60% of each

Schematic representation of the EsophyX® procedure



Printed with permission: Testoni PA and Vailati C. Digestive and Liver Disease 2012, 44(8), 631-635 (Figure 2).

- Management of peptic esophageal strictures
  - Dysphagia in patients with esophageal strictures and rings is related to
    - Stricture diameter
    - Severity of esophagitis
  - When the esophageal lumen diameter < 13 mm → dysphagia is common, and esophageal dilation is required
  - Short strictures can be dilated by blind peroral passage of dilation, e.g. Maloney
  - Complicated longer, tighter, or more irregular strictures
    - Require bougienage over a guidewire using hollow-centered, Savary, plastic-covered polyvinyl dilators or balloon dilators
  - Strictures not responding to PPIs and dilation therapy may
    - Intralesional injections of steroids or self-expanding plastic stents
  - Surgery is considered if the patient nonresponsive to the above measures

DIAPHRAGMATIC HERNIAS

Nisha Howarth

➢ Definition

- Protrusion of an organ or structure into an opening or into a pouch
- Subtypes
  - Reducible
  - Irreducible
  - Incarcerated (at danger of strangulation)
  - Strangulated (compromised vascular supply)

➢ Classification

- Hiatus
  - Type 1: sliding
    - Most common ~95%
    - GEJ and portion of stomach displaced above the diaphragm
    - Orientation of stomach axis **not** changed
  - Types 2,3,4: paraoesophageal
    - ~5%
    - Stomach protrudes through hiatus alongside esophagus
    - Type 2: fundus is lead point of herniation, GEJ normal
    - Type 3: elements of types 1+2 hernias; both GEJ and fundus herniate through hiatus
    - Type 4: large defect in phrenoesophageal membrane, other organs in hernia sac
- Diaphragmatic
  - Traumatic
  - Post-traumatic

➢ Clinical

- Type 1 (Sliding)
  - Small—mostly asymptomatic
  - Contributes to GERD
    - Sliding esophageal hiatus hernia →
      - ↓ LES pressure, ↑ distensibility at GEJ, malfunction of the GE barrier during periods of low LES pressure, swallow-associated LES relaxation or during sleep
    - Esophageal emptying → prolonged acid clearance and ”re-reflux” from hernia compartment due to loss of one-way valve from crural diaphragm
  - Dysphagia
  - Chest/abdominal discomfort

- Types 2-4 (Paraoesophageal)
  - Gastroesophageal reflux disease (GERD)
    - Esophagitis → bleeding
    - Iron deficiency anemia
  - Vague chest or abdominal pain
    - Post-prandial discomfort
  - Dyspnea (shortness of breath [SOB])
  - Gastric volvulus can be a complication

➢ Diagnosis

- Upper GI barium
  - Most sensitive study for paraesophageal hernias
  - Unreliable for small sliding hernias (must be 2 cm axial)
- Esophagogastroduodenoscopy (EGD)
  - Sliding
    - Gastroesophageal junction (GEJ) will be proximal to the impression of the diaphragm
  - Paraesophageal
    - May be missed if hernia is large mixed type
  - Cameron erosions may be associated
- CT scan
  - Stomach above the diaphragm in sliding/paraesophageal hernias

➢ Treatment

- Type 1 (sliding)
  - Symptomatic management → treat GERD (PPI, lifestyle changes)
  - Very large → refer for thoracic surgery and reduction of hiatus hernia
- Types 2-4 (paraesophageal)
  - Controversial
    - Perform pH monitoring and manometry before surgery to ensure no motility disorder
    - Previously thought that all paraesophageal / mixed hernias were a surgical emergency
    - Now it is clear that the risk of progression to gastric necrosis is lower than initially believed
    - Elective OR offered to patients with symptoms
  - Medical anti-reflux therapy

- Principles of Surgery
  - Reduce of the hernia
  - Reconstruction diaphragmatic hiatus
  - Fundoplication, plus provision of bulk at the hiatus to
    - Prevent prolapse into the chest
    - ↓ post-op reflux
  - Consider addition of gastropexy or gastrostomy tube to provide additional tacking mechanism for the stomach intraabdominally

❖ Congenital Diaphragmatic Hernias

➢ Etiology

- Failure of fusion of multiple developmental components of the diaphragm

➢ Demography

- 1/2000 to 1/10,000 births

➢ Subtypes

- Bochdalek hernias
  - Form posterolaterally at lumbocostal junction of diaphragm)
- Morgagni hernias form anteriorly at the sternocostal junctions of the diaphragm

➢ Clinical

• Bochdalek Hernia

- Great variation from death in neonatal period to asymptomatic finding in adults
- Associated chromosomal anomalies in 30%
- Respiratory distress
  - Major cause of death in neonates
  - When diagnosed in prenatal period → elective delivery with planned extracorporeal membrane oxygenation (ECMO)
- Abdomen scaphoid
- Chest mass
  - May be asymptomatic
  - Chest pain
  - Obstructive symptoms
  - Strangulation or gastric volvulus

- Morgagni Hernia
  - Usually presents in adult life
  - Asymptomatic or symptoms are
    - Non-specific (chest discomfort, cough, dyspnea)
    - Can present with acute symptoms if incarceration and ischemia develop
  - Contain omentum, stomach, colon or liver

➢ Complications
  - Can result in significant hypoplasia of the lung

➢ Prognosis
  - Pulmonary dysfunction (not the size of hernia)

➢ Treatment

- Bochdalek Hernia
  - Infants
    - Delivery of baby, intubation and ventilation if needed
    - ECMO if cardiopulmonary dysfunction
    - Surgical repair once pulmonary issues stabilized
  - Mortality rate still ~60% despite advances in crit care

- Morgagni Hernia
  - Surgically repair laparoscopically or open

DIAGNOSIS AND MANAGEMENT OF BARRETT ESOPHAGUS

Yousef Almahanna

❖ ACG 2022 Guideline Summary (2022)

➢ Background

- Definition
  - Metaplastic change from squamous epithelium to columnar epithelium in the distal esophagus
  - 5% to12% of patients with GERD have BE
  - BE is the only known precursor lesion to esophageal adenocarcinoma (EAC)
  - EAC diagnosed after symptom onset has poor survival (<20% at 5 yr)
  - Screening/surveillance for early and treat endoscopically is key
- Biopsy protocol
  - Take 4 quadrant biopsies from the high cardia just below the Z line from the top of the gastric folds (blue dots).
  - Each of the distal 2–3 cm of neosquamous epithelium
  - Biopsies taken of normal-appearing tissue above this range, even in previously long-segment disease, have not been demonstrated to have substantial additional yield for dysplasia or buried intestinal metaplasia.

➢ Suggested Approach to Barrett Esophagus

	Surveillance EGD	EET	Post-EET / CEIM EGD
○ No dysplasia	q3-5 yr	-	
○ Low-grade dysplasia	q6 mon x 2, then q1 yr	Remove BE tissue to CEIM	
○ HGD-Grade Dysplasia / Intramucosal Cancer (T1a)	-		EGD, control of GERD − Baseline − LGD q1, 3 then q1 yr − HGD/T1a 3, 6, 12 mon, then q1 yr
○ Submucosal Cancer (T1b)	− EET if SMI, well-differentiated, < 2 cm, no LVI, or − Esophagectomy		

Abbreviations: BE, Barrett esophagus; CEIM, complete eradication of intestinal metaplasia; EET, endoscopic eradication therapy; HGD, high-grade dysplasia; LGD, low-grade dysplasia; LVI, lymphovascular invasion

➢ Diagnosis

- The diagnosis of BE requires biopsy proven intestinal metaplasia (IM) in the tubular esophagus (conditional recommendation, very-low-quality evidence).

Recommendation(s)

- BE develops when metaplastic columnar mucosa replaces the normal esophageal squamous epithelium of the esophagus in response to damage caused by gastroesophageal reflux.
- The columnar-lined esophagus contains
  - Gastric fundic type epithelium
  - Junctional cardiac epithelium, and
  - Specialized columnar epithelium with intestinal type goblet cells
- There must be
  - ≥ 1 cm of length of columnar mucosa to make a diagnosis of BE, and that:
- Do **not** take routine endoscopic biopsies if there is normal-appearing Z line
- If there are no lesions, then patients with a Z line demonstrating <1 cm of proximal displacement from the top of the gastric folds should not undergo routine endoscopic biopsies (quality of evidence: low; strength of recommendation: conditional).
  - <1 cm
    - Low reliability of Prague criteria
    - Low risk of progression
  - A multicenter cohort study of 1,791 patients undergoing surveillance of BE (defined as a columnar-lined esophagus with IM on biopsies) found that:
    - None of the 167 patients with an irregular Z line (<1 cm) developed HGD or cancer.
    - IM was not found on follow-up biopsies in 53% of individuals with an irregular Z line

- Biopsies depending upon lengths of BE
  - The distribution of goblet cells within a segment of BE may be patchy, and sometimes, the mucosa is only sparsely populated with these cells.
    - Sampling error may lead to a false-negative examination for IM, especially in those with short segments of columnar-lined esophagus in whom few samples are taken.
  - ↑ yield of IM with
    - ↑ number of biopsies
    - ↑ length of the BE segment
    - Harrison et al. analyzed 1,646 biopsies taken from 296 endoscopies in 125 patients with endoscopic evidence of columnar-lined esophagus → any given biopsy in these patients demonstrated IM only 34% of the time but if 8 biopsies were analyzed from any given endoscopy the yield for IM in this group increased to 94%
  - In patients with short (1–2 cm) segments of suspected BE
    - ≥ 4 biopsies per cm of circumferential BE
    - Take 1 biopsy per centimeter length

Recommendation

- Take ≥ 8 endoscopic biopsies in screening examinations with endoscopic findings consistent with possible BE, using the Seattle protocol followed for segments of longer than 4 cm (quality of evidence: low; strength of recommendation: conditional).

- Confirmation of Biopsy Result
  - Interobserver agreement among pathologists across the spectrum of BE from no dysplasia to HGD/EAC is problematic, especially for the diagnoses of
    - Indefinite for dysplasia (IND), and
    - Low-grade dysplasia (LGD)
  - In an international study of 51 pathologists who reviewed 55 digitized biopsies, where
    - Excellent concordance among pathologists was seen for
      - Non-dysplastic BE (NDBE), 79%, and
      - HGD, 71%), but considerably less for LGD, 42% and IND, 23%
  - A standardized definition for an expert pathologist does not exist
    - Consider a pathologist with a “special interest in BE-related neoplasia who is recognized as an expert in this field by his/her peers”

Recommendation

- Confirm any grade of dysplasia detected on biopsies of BE by a second pathologist with expertise in gastrointestinal (GI) pathology (quality of evidence: low; strength of recommendation: strong).

➢ Screening:

- Do a screening EGD endoscopy for patients with chronic GERD symptoms (weekly for ≥ 5 yr), plus ≥ 3 additional risk factors for BE, including
  - Male sex
  - Age >50 yr
  - White race
  - Tobacco smoking
  - Obesity, and family history of BE/EAC in a first-degree relative (Strength of recommendation: Conditional; Quality of evidence: Very low).

Recommendation(s)

- Screening for Barrett esophagus (BE) and subsequent surveillance to detect dysplasia or EAC could potentially ↓ EAC incidence, but there is no randomized controlled trial evidence demonstrating reduced EAC mortality with BE screening.
- Most EAC cases are diagnosed outside of BE surveillance programs, indicating
  - A missed opportunity for cancer prevention through screening.
- BE is associated with various risk factors, including
  - Chronic reflux symptoms (weekly symptoms for ≥ 5 yr)
  - Male sex
  - Age over 50
  - Smoking
  - White race
  - Central obesity, and
  - Family history

- Swallowable Capsule Device plus TFF3 Biomarker
  - Endoscopy is the gold standard, but is invasive and expensive
  - Alternative: Swallowable Capsule Device plus TFF3 biomarker
  - Cytosponge is a polyester sponge compressed into a capsule and attached to a polyester string.
    - The patient swallows the capsule, which disintegrates in the stomach within 3 to 5 min.
    - The string stays outside the patient's mouth and is then pulled to retrieve the sponge.
    - The sponge collects cells from the gastroesophageal junction and the esophagus.
    - The collected cells are examined by immunohistochemistry testing for Trefoil factor 3 (TFF3). This protein is secreted from mucin-producing cells, and it is associated with the presence of BE.
  - Other developing screening modalities include
    - Unsedated transnasal endoscopy, and
    - Exhaled volatile organic compounds

Recommendation

- If available, consider using swallowable, non-endoscopic capsule sponge device combined with a biomarker is an acceptable alternative to endoscopy for screening for BE in those with chronic reflux symptoms and other risk factors (Strength of recommendation: Conditional; Quality of evidence: Very low).

- Follow-up after negative EGD screening
  - The yield of a repeat EGD for diagnosing BE following an initial negative BE screening endoscopy is low.
    - In over 24,000 patients undergoing repeat endoscopy, only 2.3% of patients had suspected BE on repeat endoscopy after an initial negative examination.
  - Caveat: Erosive esophagitis (LA Grade B or worse) may mask the presence of BE and these patients should undergo repeat endoscopy 8–12 wk after treatment with PPIs (to ensure healing of esophagitis and to determine the presence of BE).

Recommendation

- Do **not** repeat EGD screening in patients who have had an initial negative screening examination by endoscopy (Strength of recommendation: Conditional; Quality of evidence: Low).

- Surveillance:
  - With careful white light inspection, subtle lesions may be missed.
  - Routine use of chromoendoscopy may ↑ detection of dysplasia and carcinoma (with either acetic acid or by electronic chromoendoscopy with NBI)

Recommendation

- Use both white light endoscopy and chromoendoscopy in patients undergoing endoscopic surveillance of BE (quality of evidence: moderate; strength of recommendation: strong).

- Biopsy protocol
  - Use the Seattle protocol
    - Careful visual inspection of the Barrett segment
    - Biopsies of visible lesions, followed by
    - 4 quadrant biopsies at intervals ≤2 cm from the level of the lower esophageal sphincter (LES) to the squamocolumnar junction (SCJ)

- Detection of dysplasia
  - By using a structured biopsy protocol, there is a ↓ in sampling error (areas of dysplasia may not be visible, lesions are often focal, and the distribution is highly variable).
  - In a cohort study from the United Kingdom, the institution of a structured biopsy protocol led to ↑ detection of HGD and ↑ early EAC, as compared with the time period before the start of the protocol.

Recommendation

- Use structured biopsy protocol to minimize detection bias in patients undergoing endoscopic surveillance of BE (Quality of evidence: Low; Strength of recommendation: Strong).

- EGD surveillance interval
  - Do EGD surveillance in patients with BE at intervals dictated by the degree of dysplasia noted on previous biopsies (Quality of evidence: Very low; strength of recommendation: Conditional).

- Indefinite Dysplasia
  - Definition of Indefinite dysplasia (IND)
    - Occurs in 4-8% of BE biopsies when the pathologist is unable to determine whether the histology truly represents dysplasia or may be due to inflammatory changes
  - In confirmed cases of IND, ↑ anti-reflux therapy for 6 mon, then do a repeat endoscopy in 6 mon.

➢ Management of BE with LGD or HGD
  - Studies suggesting a mortality benefit for surveillance are all retrospective studies (Low quality of evidence at best)
    - The better designed case-control demonstrating no difference.
  - Previous American guidelines suggested that patients with NDBE undergo surveillance at intervals of 3 yr to 5 yr (based largely on expert opinion).

- International guidelines including those from Europe, the United Kingdom, and Australia now recommend stratifying surveillance intervals based on the length of the Barrett segment.

Recommendation(s)

- There is a large amount of evidence that BE length can risk stratify patients for development of HGD and EAC: A meta-analysis of 10 studies demonstrated that annual rate of progression was lower for short-segment than for long-segment BE: 0.06% vs 0.31% (OR 0.25; 95% CI 0.11–0.56; P < 0.001).
- Perform surveillance of NDBE depending upon the length of the BE
  - < 3 cm, q5 yr
  - > 5 cm, q3 yr

(Quality of evidence: Moderate; Strength of recommendation: Strong).

- Endoscopic Suspicion of BE (Salmon-Pink Esophageal Mucosal Proximal to GEJ)

					EGD Repeat
○ < 1 cm colour, or Z-line	− No biopsy needed				
○ > 1 cm colour	− ≥ 8 mucosal biopsies	○ Intestinal metaplasia	− No dysplasia	▪ < 3 cm BE	In 5 yr
				▪ > 3 cm BE	In 3 yr
			− Indefinite for dysplasia		▪ Confirm expert and pathologist ▪ PPI bid ▪ EGD in < 6 mon
			− LGD/HGD		▪ Confirm expert and pathologist, if confirmed ▪ See other algorithm
		○ No intestinal dysplasia			In 1 to 2 yr

- Approach to EGD +/- biopsy depends upon length of BE and dysplasia (please see above algorithm)

- WATS-3D
  - Wide area transepithelial sampling with computer assisted 3-D analysis (WATS-3D) is a novel technique of sample acquisition in BE.
    - It samples a larger surface area of the esophagus, and
    - Obtains cells from deeper tissue layers.
  - The sample is analyzed using a computer scan and suspicious areas are flagged for analysis by a pathologist.
  - In meta-analyses reviewed there was significant heterogeneity.
    - It is not clear if WATS-3D provides better detection of dysplasia by the analysis algorithm OR results in overdiagnosis of dysplasia and false-positive examinations.

Recommendation

- If available, use wide-area transepithelial sampling with computer-assisted 3-dimensional (WATS-3D) analysis in patients undergoing endoscopic surveillance of BE.

- Immunostaining for p53 protein/function and TissueCypher system
  - p53 is a tumour suppressor gene
    - In BE there is altered p53 function (↑/↓ p53 suppression
  - TissueCypher tissue systems pathology assay
    - Integrates the 15 best-performing quantitative image analysis features derived from fluorescence images of 9 protein-based biomarkers
    - Nuclear morphology, and
    - Tissue architecture to classify patients as low, intermediate, or high risk for progression to HGD/EAC within 5 yr

Recommendation(s)

- P53 protein/function, or
- The TissueCypher system

} ↓ sensitivity / ↓ specificity for screening BE

➢ Medical Treatment

- GERD, PPIs and BE-HGD/EAC
  - Observational studies have demonstrated that
    - GERD symptoms are a strong risk factor for EAC and
    - ↑ risk of EAC ↑ duration and severity of GERD symptoms
  - A systematic review and meta-analysis of observational studies showed that
    - PPI therapy was associated with a 71% reduction in the risk of HGD or EAC (adjusted OR 0.29; 95% CI 0.12–0.79)

Recommendation

- Use at least once-a-day PPI therapy in patients with BE without allergy or other contraindication to PPI use (Strength of recommendation: Conditional; quality of evidence: very low).

- Combining PPIs and ASA
  - ASA and NSAIDs ↓ pathways involved in oncogenesis, including the cyclooxygenase pathway, which is linked to inflammation and upregulation of oncogenic factors.
    - Patients taking ASA and NSAIDs may have ↓ risk of developing esophageal adenocarcinoma (EAC).
  - The AspECT chemoprevention study evaluated the efficacy of high-dose esomeprazole and ASA in patients with Barrett esophagus (BE).
    - High-dose PPI was superior to low-dose PPI in lengthening the time to combined endpoints of death from any cause, EAC, or high-grade dysplasia (HGD).
    - However, the use of ASA did not show a significant improvement in outcomes, except when NSAIDs were not used concurrently.
  - AspECT study's limitations and uncertainties prevent the panel from making a clear recommendation on the use of ASA along with PPI therapy for chemoprevention
  - While it's unclear if all patients with BE should be prescribed this combination, many patients with BE may receive ASA for cardioprotection alongside PPI due to their existing recommendations.

Recommendation

  - No recommendation on combination therapy with ASA and PPI in patients with BE to reduce the risk of progression to HGD/EAC.

- Anti-reflux Surgery
  - The risk of progression to cancer in the setting of NDBE is low that
    - Incurring the risks inherent in surgery may not be merited in patients who do **not** require fundoplication for symptoms not controllable by medical therapy.
    - Fundoplication has the potential for complications, which can be severe
    - Data do **not** demonstrate that patients with BE treated with surgical anti-reflux procedures have a lower risk of progression to neoplasia than those treated medically.

Recommendation

  - Do **not** use of anti-reflux surgery as an antineoplastic measure in patients with BE (Strength of recommendation: Conditional; Quality of evidence: Low).

- Endoscopic Treatment of BE
  - Endoscopic eradication therapy (EET) has revolutionized the management of patients with BE-related neoplasia and offers an effective, minimally invasive treatment approach, avoiding the morbidity and mortality associated with esophagectomy
  - The goal of EET
    - Complete eradication of IM (CEIM) (defined as 1-2 surveillance endoscopies w/o visible BE or IM on biopsies)
  - BE with HGD and intramucosal cancer (IMC) have a very low risk of lymph node metastasis (0% in HGD, up to 2% in IMC)

- Contemporary practice includes
  - Endoscopic resection (ER) of any visible lesion within the BE segment, followed by ablative techniques such as RFA and cryotherapy to achieve complete eradication of dysplasia (CED) and IM (CEIM).

Recommendation

- EET should be studied and compared with esophagectomy in patients with BE with HGD or IMC (Strength of recommendation: Strong; Quality of evidence: Moderate).

➢ Endoscopic Treatment

- Barrett esophagus (BE) with high-grade dysplasia (HGD) requires treatment action and surveillance is not recommended.
- A systematic review found no difference in overall 1-, 3-, and 5-yr survival and EAC-related mortality between endoscopic eradication therapy (EET) and esophagectomy.
  - Esophagectomy has
    - 2% mortality and ↑ morbidity compared to EET.
- Esophagectomy has traditionally been recommended in patients with EAC with submucosal invasion (T1b EAC) given the high risk of lymph node metastases
  - However, EET may be a viable alternative to esophagectomy in T1b EAC with superficial submucosal invasion and low-risk features.
  - High-risk histology patients are best treated with esophagectomy unless they are poor surgical candidates
  - In this case use options like adjuvant chemoradiation.
- Low-grade dysplasia (LGD) presents a management challenge due to variable progression risk and interobserver variability in diagnosis.
  - Expert GI pathologist review is crucial, as a substantial proportion of LGD diagnoses are not confirmed on review.
- For patients with confirmed LGD, options include endoscopic eradication therapy (EET)
  - May consider repeat endoscopy within 6 months, plus shared decision making with the patient.
- EET (specifically radiofrequency ablation [RFA]) has shown ↑ rates of complete eradication of LGD, and ↓ rates of progression to HGD/EAC compared to surveillance in randomized controlled trials (RCTs).
- Use shared decision making for LGD management, considering factors such as
  - Persistence of LGD
  - Potential regression, and
  - The risk of EET adverse events
- EGD surveillance intervals should be q6 mon for 1 yr then q1 yr unless there is reversion to non-dysplastic Barrette esophagus (NDBE)
  - Extend surveillance intervals to q3 yr

Recommendation

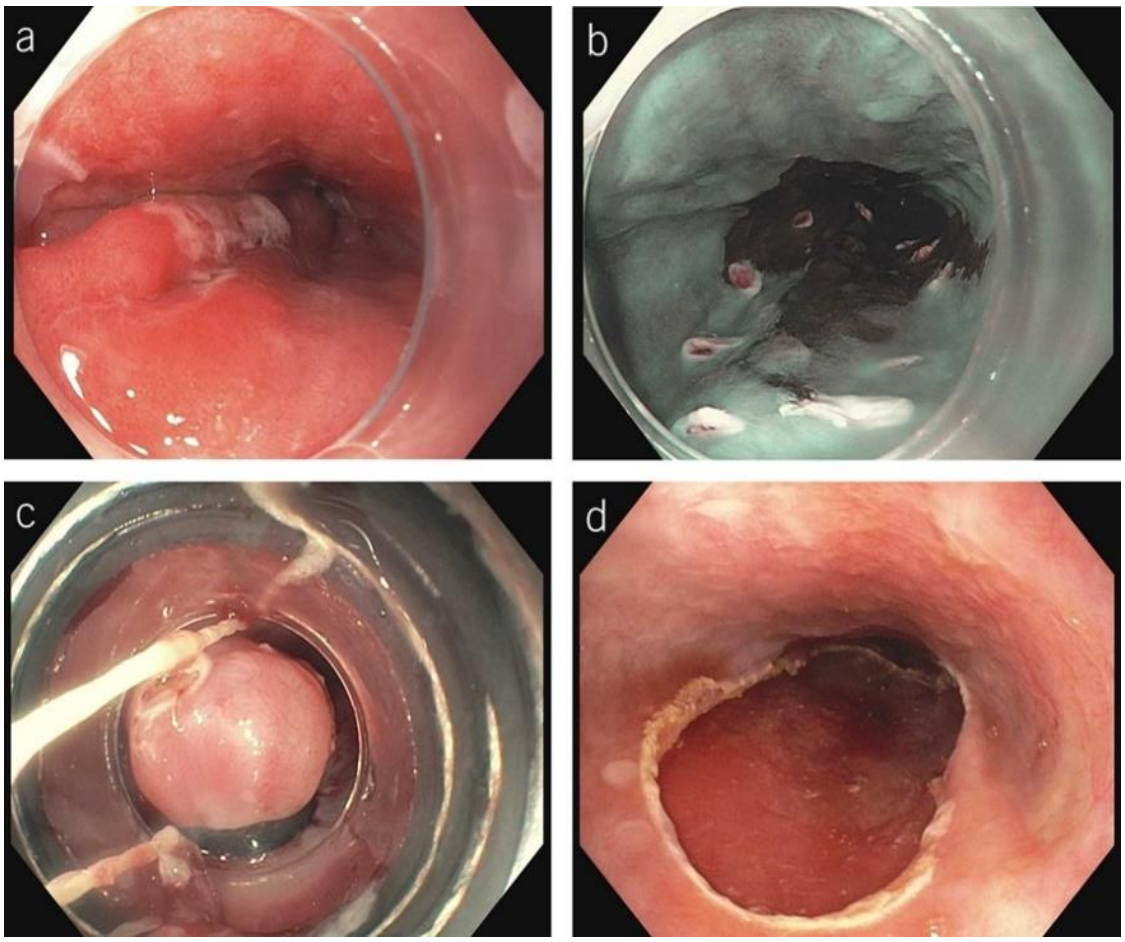
- Do endoscopic therapy in patients with BE with confirmed LGD to ↓ risk of progression to HGD/EAC
  - Endoscopic surveillance of confirmed LGD as an acceptable alternative (strength of recommendation: conditional; quality of evidence: moderate).

- Visible Lesions
  - Endoscopic resection (ER) of visible lesions in Barrett esophagus (BE) reduces interobserver variation associated with dysplasia assessment on biopsy.
    - Cap-assisted vs multiband endomucosal resection (EMR): Bigger sample for accurate tumour staging & prognostication
    - Endoscopic submucosal dissection (ESD)
      - Use en bloc resection of larger lesions
      - Submucosal invasion, or
      - Post- ablation lesions (with a steeper learning curve and higher complication rates)

Recommendation(s)

- Do initial ER of any visible lesions before the application of ablative therapy in patients with BE undergoing EET (strength of recommendation: conditional; quality of evidence: very low).
- Following successful ER, ablate of the residual BE segment (↓ risk of recurrent dysplasia/EAC)
  - Radiofrequency ablation (RFA; thermal ablation)
    - Most patients achieve CEIM in 3 sessions
    - Adverse events (AEs)
      - Esophageal stricture (4-7%)
      - Perforation (0.4-0.9%)
  - Endoscopic cryotherapy (spray vs balloon) works via rapid freezing, then slow thaw
    - Alternative modality in patients unresponsive to RFA Adverse events: esophageal stricture (9-12%)
    - Cryotherapy has been used for ablation, but lacks randomized trial data comparing efficacy to RFA.

Ligation-assisted endoscopic mucosal resection (EMR) technique in Barrett esophagus



(A) Irregular areas of Barrett mucosa with clear margins are marked circumferentially with electrocautery.

(B) Band ligation has been performed, creating a pseudopolyp, and now the snare has been placed above the band to perform electrocautery polypectomy.

(C) Post-snare polypectomy with visualization of the submucosa.

Source: Balmadrid B and Hwang JH. Gastroenterology Report 2015; 3(4): 330–338 (Figure 3)

- Necessary Skills for endoscopic eradication therapy (EET)
  - Adequate training and expertise in detecting mucosal lesions with neoplasia
  - Appropriate patient selection, and
  - Technical skills in performing EMR and RFA are crucial
  - There is a volume-outcome effect in EET for BE-related dysplasia and EAC
    - ↑ volume centers and endoscopists achieving better outcomes
    - Treatment sessions required to achieve complete eradication, to
      - ↓ risk of recurrence
      - ↓ adverse event
  - Centralization of care at high-volume facilities with
    - Trained endoscopists
    - Expert pathologists, and
    - A multidisciplinary team is recommended for patients with BE-related neoplasia

Recommendation(s)

- Treat patients with BE undergoing EET be treated at high-volume centers (Strength of recommendation: Conditional; Quality of evidence: Very low).
- Use endoscopic surveillance program in patients with BE who have completed successful EET (strength of recommendation: strong; quality of evidence: moderate).

- Complete Eradication of IM (CEIM)
  - Surveillance
    - CEIM is variably described as 1 or 2 surveillance endoscopies negative for visible BE and IM in biopsies taken from the GEJ and the tubular esophagus.
  - Definition
    - Recurrence is currently defined as the detection of IM after achieving CEIM
    - Continue EGD surveillance after EET to monitor for recurrences, and
    - Treatment of recurrent BE should follow similar principles as pre-ablation EET, including
      - Endoscopic resection for visible lesions and
      - Ablation for residual flat BE
  - Recurrence rates for IM range from ~9% to ~11% per yr
    - Rates for dysplastic IM is 2.0%
    - 75% of recurrences diagnosed at the GEJ, and most (60%) of these are not visible to the endoscopist.
    - Recurrences in the tubular esophagus are mostly visible (80%).
  - Most recurrences can be successfully treated endoscopically
    - The significance of nondysplastic IM recurrence at the GEJ/cardia is still unclear
  - Patients achieving CEIM
    - Placed into an EGD surveillance program, with tailored surveillance intervals based on preablation histology.

- Patients should have
  - Careful inspection of the GEJ and neosquamous epithelium for any visible lesions with
  - High-resolution white light endoscopy and virtual chromoendoscopy, followed by
  - Surveillance biopsies from the GEJ (in a separate bottle) and from the distal 2–5 cm of the esophagus (in a separate bottle)

Key Concepts:

- Stopping EGD Surveillance
  - Suggestion: Consider cessation of endoscopic surveillance when a patient is no longer a candidate for EET.
  - It is reasonable to cease endoscopic surveillance in patients with
    - With an estimated survival < 5 yr, and
    - Those who are no longer fit for repeated EGD, or
    - Those who cannot tolerate endoscopic, surgical, or oncological intervention for esophageal neoplasia.
  - A recent modeling study suggested that the optimal age of last surveillance of a patient with NDBE was
    - Between 69 and 81 yr, and
    - Dependent on the sex and comorbidities of the patient
  - Discuss cessation of further endoscopic surveillance when most patients reach 75 yrs of age, if it has not occurred prior.

- Quality Indicators
  - Quality indicators for screening and surveillance
    - Documentation of landmarks and extent of BE
    - Not obtaining biopsies in the setting of a normal-appearing squamocolumnar junction
    - Sampling using the Seattle biopsy protocol
    - Performing surveillance endoscopy in patients with NDBE no sooner than 3-5 yr
  - Suggestions
    - Published quality indicators to benchmark your unit's performance against published standards.
    - Use endoscopic cryotherapy may be considered as an alternative modality in patients unresponsive to RFA.
    - Provide patients before initiation of therapy with BE-related neoplasia embarking on EET with a clear understanding of the risks and benefits associated with these therapies.
    - Endoscopists and centers performing EET should monitor their rates of CEIM, CED, and adverse events.

❖ AGA Clinical Practice Guideline on Endoscopic Eradication Therapy of Barrett Esophagus and Related Neoplasia

Rubenstein JH, et al. Gastroenterology 2024; 166: 1020-1055

➢ Background:

- The incidence of esophageal adenocarcinoma (EAC) rose 5-fold from the 1970s to the
  - EAC now represents the most common form of esophageal cancer in the United States.
  - BE is the major associated precursor of EAC (except for heterotopic upper esophageal mucosa, and HIV-associated immunosuppression
  - Smoking and obesity are risk factors for GERD.
  - Smoking is a risk factor for stricture formation after endoscopic mucosal resection for BE-dysplasia / EAC
  - BE from metaplasia to low-grade dysplasia (LGD), then high-grade dysplasia (HGD), before developing into EAC.

➢ Referral

- Refer patients with dysplastic BE to
  - High-volume endoscopists with expertise in EET
  - Pathologists with expertise in BE neoplasia

  } Access to multidisciplinary care
- Substantial disagreement among pathologist for interpreting dysplastic BE (particularly LGD)
- The benefit of two experts interpreting biopsies of LGD
  - Upgrade to HGD/EAC, 10%
  - Downgrade to metaplasia / intermediate dysplasia

➢ GERD management

- Medical Therapy
  - Use PPI po bid, 30-45 min AC, because patients with BE have
    - Upgrade to HGD/EAC, 10%
    - Downgrade to metaplasia / intermediate dysplasia
- Surgery
  - Fundoplication for PPI-resistant continual gastroesophageal reflux disease (GERD)
- Endoscopy
  - The goal of endoscopic eradication therapy (EET) should be
    - Complete eradication of intestinal metaplasia (CEIM), and
    - Complete eradication of neoplasia (CEN)

- In patients with BE plus HGD or early EAC, who underwent only endoscopic resection of the visible lesion
  - There was recurrent HGD/EAC
    - Surveillance, 40%
    - Ablation of remaining BE, 3%
- If failure to achieve complete eradication of intestinal metaplasia is not achieved
  - Reassess and optimize control of reflux

- BE plus HGD
  - The critical outcome for this question was progression rate to cancer among patients with HGD who were treated with EET compared with endoscopic surveillance alone.
    - 2 RCTs compared participants in the EET group vs participants in the endoscopic surveillance group and ↓ progression to EAC, when EET was used compared with surveillance.
    - Harms/risks of EET
      - Stricture formation, 6%
      - Major bleeding, 0.6%
      - Perforations, 0.2%
    - Implementation Considerations:
      - After completion of EET
        - Perform surveillance at 3, 6, and 12 mon, then q1 yr.
        - At the surveillance endoscopies after EET should obtain targeted tissue sampling of visible lesions plus random biopsies of the cardia and distal 2 cm of the tubular esophagus.

Recommendation

- In individuals with BE with HGD
  - Perform EET rather than surveillance. (Strong recommendation, Moderate certainty of evidence)

- BE plus LGD
  - The incidence rate for progression to EAC was 0.3 per 100 patient-yrs
  - Pooled analysis of 3 RCTs with a total of 150 participants in the EET group vs 132 participants in the endoscopic surveillance group demonstrated no significant difference in progression to EAC.
  - Risks/harms
    - Strictures
    - Major bleeding (either requiring blood transfusion, intervention, or hospitalization)
    - Perforation, and
    - Serious adverse events.
  - Following completion of EET, EGD surveillance should be performed at years 1 and 3 after CEIM, then revert to surveillance intervals used in nondysplastic BE.
  - The tissue sampling protocol during surveillance should be performed the same as in surveillance after EET for HGD.

- LGD (even when confirmed by expert pathologists) will regress to nondysplastic BE (NDBE) during surveillance in 28%–66% of patients.
  - Reasons for this regression
    - Sampling errors
    - False-positive diagnoses, or
    - True regression

Recommendation

- In individuals with BE with LGD
  - Perform EET rather than surveillance (evidence derived from both RCTs and observation cohort studies) (Conditional recommendation, low certainty of evidence)
- Patient preference
  - Patients who place a higher value on the well-defined harms, and lower value on the uncertain benefits regarding reduction of esophageal cancer mortality would reasonably select surveillance.

- Patient with NDBE
  - No comparative evidence from RCT or cohort studies was found regarding EET of NDBE with outcomes of progression to EAC or esophageal cancer–related mortality.
  - In individuals with NDBE
    - The harms (bleeding, perforation, strictures, and chest pain) may outweigh any small benefit.
    - There is moderate cost associated with EET, particular as patients continue to undergo surveillance after EET.

Recommendation

- In patients with NDBE, do **not** routinely use of EET (based on systematic review and meta-analysis) (Conditional recommendation, very low certainty of evidence)

- Lesions Visible at EET

➢ First Choice

- One RCT had enrolled 47 patients and showed no difference in the CEN, but was significantly ↑ stenosis rate in stepwise or complete EMR (sEMR) (88%) vs focal EMR (fEMR) plus RFA (14%).
- The effect of sEMR on the critical benefits were trivial to small and the effect on harms were moderate, as compared with fEMR followed by ablation
- All nodularity (regardless of the extent) should be resected rather than ablated.
- In patients with only a small area of BE beyond the visible lesion, do complete endoscopic resection in the same setting
  - This may be preferred over repeated procedure to perform ablation.

- Multiple ablation techniques exist
  - RFA, cryoablation (including multiple different vendors, cryogenic gases, and tools), hybrid-argon plasma coagulation, and multi-polar electrocoagulation.
- RFA preferred ablative modality (has the highest-quality and most extensive evidence available from RCTs)

Abbreviations: CEN, complete eradication of neoplasia; EMR, endomucosal resection; fEMR, focal EMR; RFA, radiofrequency; sEMR, stepwise EMR

Recommendation

- In patients undergoing EET, resect visible lesions followed by ablation of the remaining BE segment rather than resection of the entire BE segment. (Conditional recommendation, very low certainty of evidence).

➢ Second Choice

- All nodularity should be resected rather than ablated.
- Patients with T1 EAC (particularly T1a)
  - Do endoscopic resection with EET completed to CEN/CEIM plus endoscopic surveillance continued.
- Because endoscopic ultrasound is not accurate for distinguishing T1a from T1b, and to a lesser degree from T2 cancers
  - Patients suspected endoscopically of T1 cancer should undergo endoscopic resection staging for tumour depth.
- Factors on endoscopic resection associated with favorable prognosis with EET alone include
  - Negative deep margin
  - T1a depth
  - Moderate or well differentiation, and
  - Lack of lymphovascular invasion
- Patients suspected of having T1 EAC should be referred for consideration of EET.
- Most neoplastic lesions may be managed with EMR rather than ESD.
- ESD may be preferred for
  - Patients with large bulky neoplastic lesions
  - Lesions highly suspicious of at least T1b invasion (for instance, those with depressed, Paris IIc or IIa + c lesions) and deemed candidates for endoscopic resection might benefit from ESD over EMR.
  - Patients with previously failed EMR might benefit from ESD.

ESOPHAGEAL TUMOURS

Tamoor Afzaal

- Classification
  - Benign
    - Epithelial
      - Adenoma
      - Inflammatory fibroid
      - Squamous papilloma
    - Non-epithelial
      - Fibrovascular Polyp
      - Granular Cell Tumour
      - Hamartoma
      - Hemangioma
      - Leiomyoma
      - Lipoma
  - Malignant
    - Epithelial
      - Carcinoma (EAC, ESCC)
      - Melanoma
      - Small Cell
    - Non-epithelial
      - GIST
      - Lymphoma
      - Metastasis
      - Sarcoma

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell cancers; GIST, gastrointestinal stromal tumour;

❖ Esophageal Carcinoma (ECA)

- Demography
  - Esophageal cancer is the 8th most common tumour worldwide
    - 456,000 incident cases representing 3.2% of all cases
    - 6th leading cause of cancer mortality
    - Accounts for 5% of all cancer deaths worldwide
  - The lifetime risk of esophageal cancer in the US is ~1 in 125 men and ~1 in 400 women
  - Predominant belts of high incidence of esophageal cancer
    - Central Asia (Caspian Sea to Northern China)
    - Eastern Coast of Africa (Ethiopia to South Africa)
- Clinical
  - The patient usually presents with dysphagia and weight loss

- Types

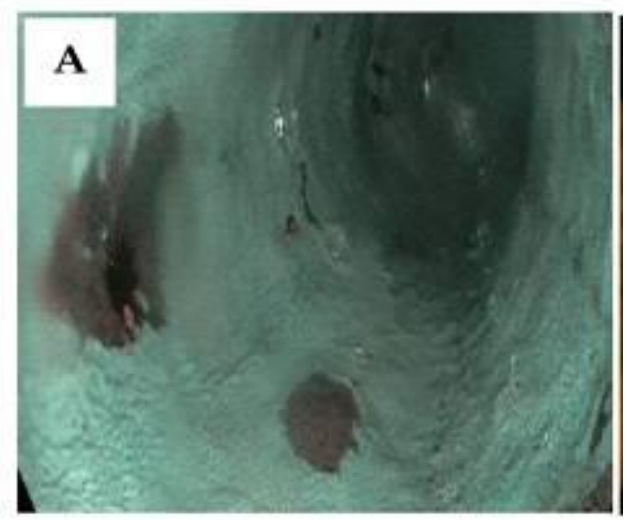
Squamous cell carcinoma (ESCC)	Adenocarcinoma (EAC)
○ Demography − Most common form of esophageal carcinoma worldwide ▪ The areas of highest risk for ESCC are in 2 geographic belts	− Second most common form of esophageal carcinoma ▪ Particularly common in Western countries ▪ ↑ incidence since 1990s in Western countries (GERD/Obesity)
○ Risk factors − Tobacco (3-9x ↑) − Alcohol use (3-5x ↑) − Diet ▪ ↓ consumption of fruits/vegetables ▪ ↓ socioeconomic status ▪ Micronutrient deficiencies (controversial) ▪ High-temperature foods − Nutritional deficiencies (developing countries) ▪ Vitamin A, C, and E ▪ Folic acid ▪ Zinc ▪ Selenium − Esophageal disease ▪ Achalasia ▪ Lye ingestion − Rare disorders ▪ Plummer-Vinson syndrome ▪ Fanconi anemia ▪ Tylosis	− Tobacco − GERD (4-8x ↑) − Obesity (2-5 ↑) − M>F (8:1) − Caucasian > African (5:1)
○ Site − Often occurs in mid-tract / esophagus	− Often occurs in the lower third of the esophagus
○ Protective factors	− Female sex hormone − H. Pylori infection − Iatrogenic (ASA, NSAIDs, PPIs, statins)

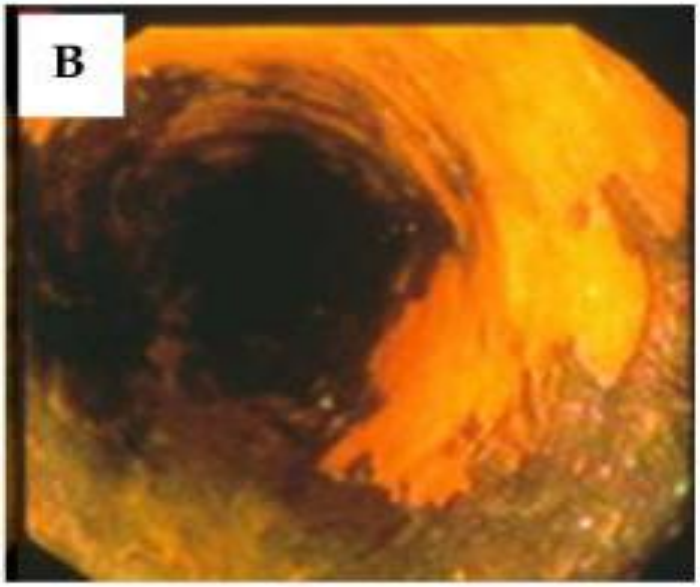
- Clinical Features
  - Similar clinical presentation for ESCC and EAC
    - Asymptomatic in early stages
  - Dysphagia (solids progressing to liquids) and weight loss
    - Solid food dysphagia typically occurs when luminal diameter ≤ 13 mm (39Fr)
    - Uncommon
      - Chest pain, cough, pneumonia, pleural effusion, UGIB
      - Metastasis usually to
        - Brain
        - Bone
        - Liver
        - Lung

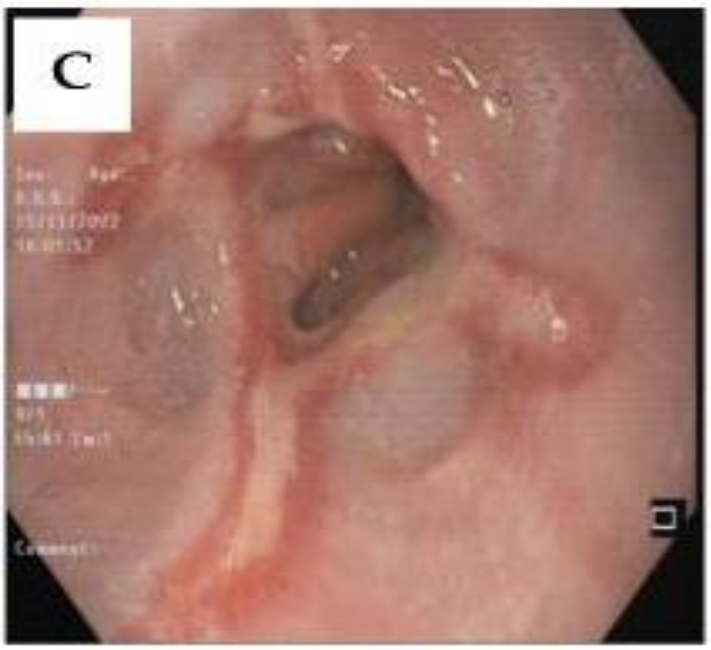
- Laboratory
  - Non-specific changes
    - ↓ albumin
    - ↑ Ca^{2+} (serum calcium concentration)

- Diagnostic imaging
  - Do pan-CT to assess extent of disease

- Endoscopic
  - Appearance of ESCC and EAC are similar
  - Location is different
    - 75% of EAC is distal esophagus
    - Majority of ESCC found in prox/mid esophagus
    - Can appear as a mass, raised nodule, ulceration, depression, stricture, or subtle irregularity in the mucosa



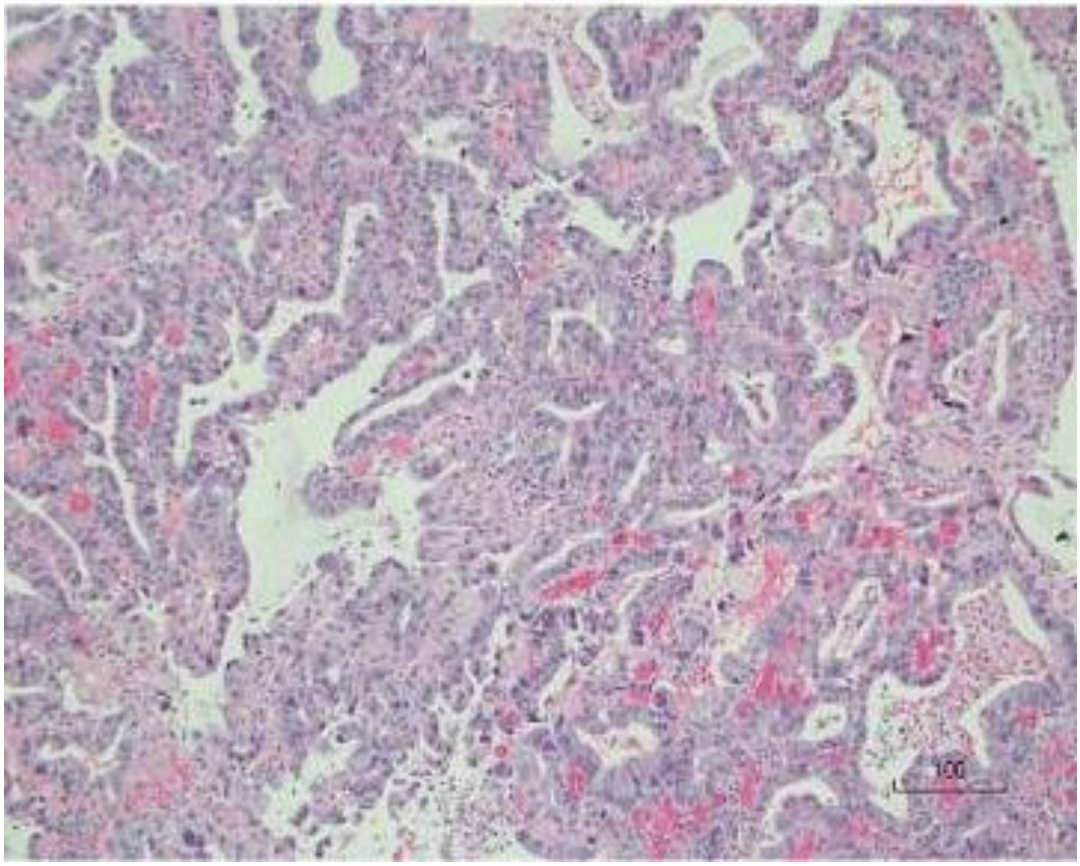




A,B) Chromoendoscopy with acetic acid using narrow-band imaging and Lugol iodine staining both increase identification of HGD and early ESCC, which makes targeted biopsy for diagnosis and ablation or resection of HGD the precursor of ESCC possible.
(C) Endoscopic image of Barrett esophagus visible as a salmon-colored metaplastic epithelium (columnar) replacing the normal bright-pink epithelium of the distal squamous esophagus.

Source: Sheikh M, et al. Cancers (Basel). 2023; 15(3):765.

- Pathology
  - Adenocarcinoma
    - Clusters of cells arranged in glands (variable nuclear size, nuclear staining, and nuclear shape

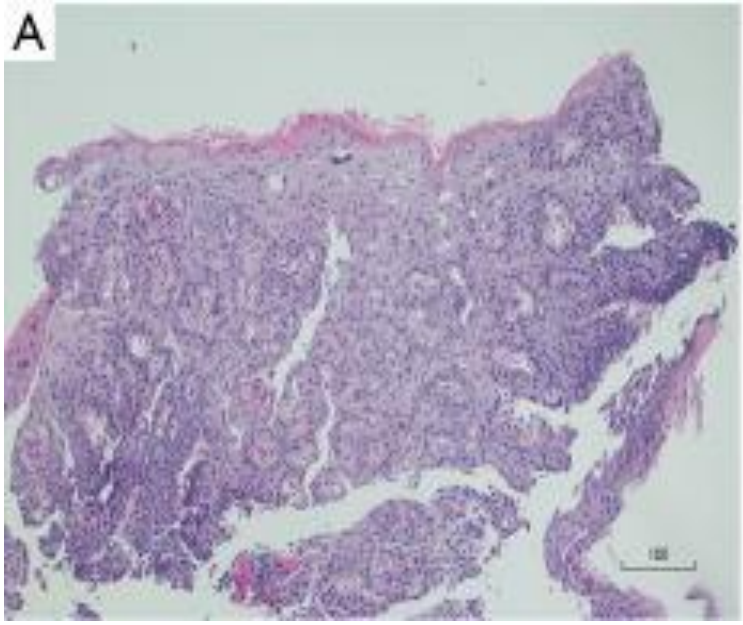


Barrett's esophagus with intramucosal adenocarcinoma. Hematoxylin and Eosin stain ×100

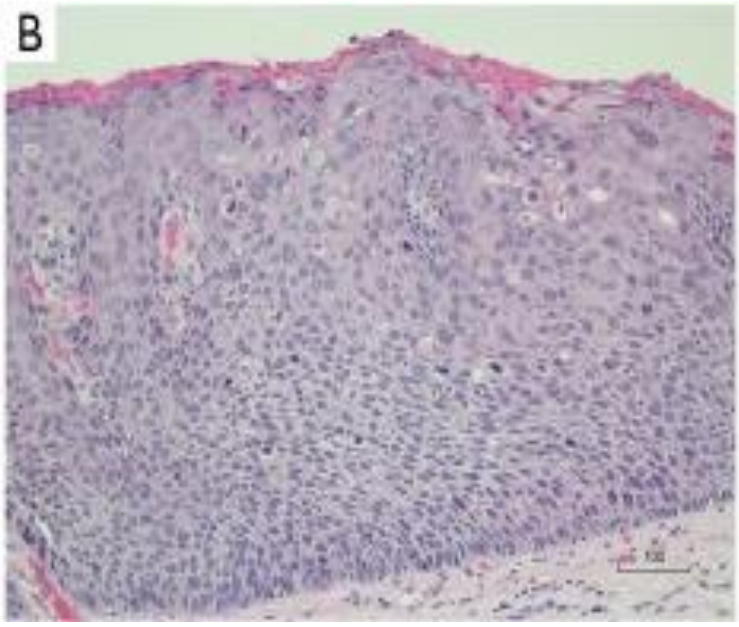
Source: Jain S and Dhingra S. Ann Cardiothorac Surg. 2017;6(2):99-109.

Squamous cell cancer

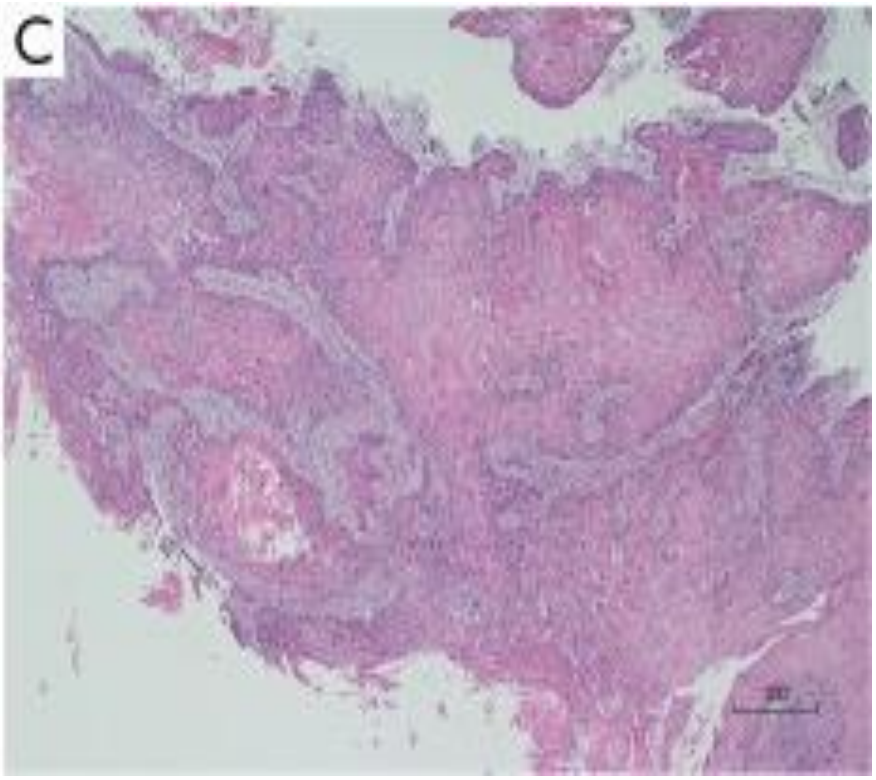
- Common malignant neoplasm of middle third of esophagus, strongly associated with the intake of alcohol /tobacco. and low socioeconomic status, with histologically demonstrated squamous differentiation, spindle cells, keratinization, and dysplasia /malignancy



(A) Squamous mucosa with low grade dysplasia. Hematoxylin and Eosin stain ×100



(B) squamous mucosa with high grade dysplasia/carcinoma-in-situ. Hematoxylin and Eosin stain ×200



C) invasive squamous cell carcinoma. Hematoxylin and Eosin stain ×40

Source: Jain S and Dhingra Ann Cardiothorac Surg 2017; 6(2):99-109.

- Screening
  - EAC
    - Screening for Barrett esophagus (BE)
    - BE is a precursor lesion
    - Early-stage carcinoma is associated with ↑↑ survival (up to 86% at 5 yrs) when treated surgically
  - ESCC
    - Not established

Recommendation(s) (Screening: ACG 2022)

- Do a single screening endoscopy in patients with chronic GERD symptoms
- ≥ 3 additional risk factors for BE include
  - Male sex
  - Age > 50 yr
  - White race
  - Tobacco smoking
  - Obesity
  - Family history of BE or EAC in a first-degree relative
- A swallowable, non-endoscopic capsule device combined with biomarkers is an acceptable alternative to endoscopy for screening for BE
- Do **not** repeat screening in patients who have undergone an initial negative screening examination by endoscopy

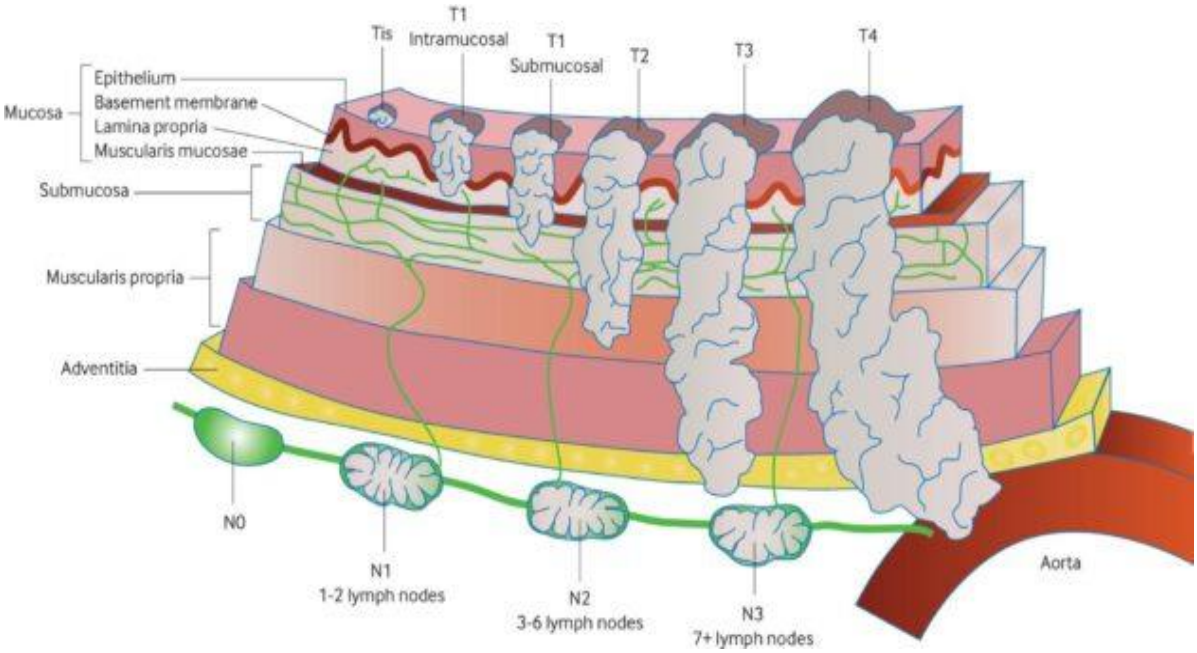
➢ Surveillance

- Basis for recommendations of timeframe for repeat EGD
- BE
  → LGD, 1% /yr
  → HGD, 0.7% /yr
  → EAC, 0.05% to 0.12%/yr
- Non-dysplastic Barrett esophagus, repeat EGD
  - If < 3 cm, 5 yr
  - If > 3 cm, 3 yr
- Dysplastic Barrett esophagus (DBE)
  - Confirm histopathological diagnosis with 2nd expert GI pathologist
  - Eradicate DBE with endoscopic therapies

Bennett C, et al. Gastroenterology 2012;143:336–346.
Halland, M, et al. World J Gastroenterol 2015; 21(21): 6479-6490
Peters Y, et al. Clin Gastroenterol Hepatol 2019;17(5):869-877.
Shaheen NL, et al. Am J Gastroenterol 2022;117(4):559-587.

➢ Staging

- The depth of tumour invasion (T stage) is an important factor in staging
- Need endoscopy with multiple mucosal biopsies, CT scan, FDG PET scans, EUS (assess depth of invasion)



Printed with permission: Thrumurthy SG, et al. BMJ 2019; 366: l4373 (Figure 1)

- Impact of tumour stage with patient survival

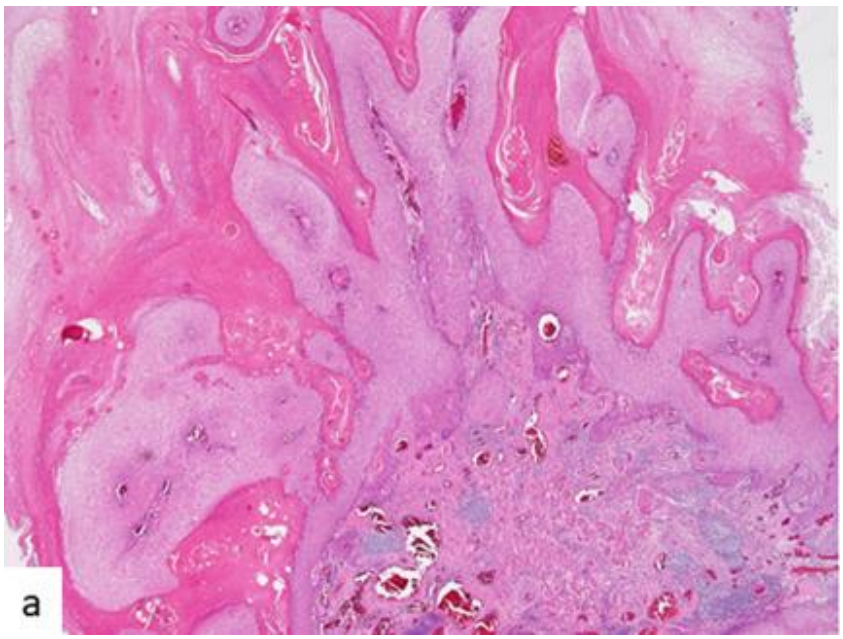
Stage	5-yr Survival Rate ESCC	EAC
pTis	80%	85%
pT1	65%	75%
pT2	40%	40%
pT3	30%	20%
pT4	15%	10%

Adapted from: Rice TW, et al. Dis Esophagus 2016; 29[7]:724-33.

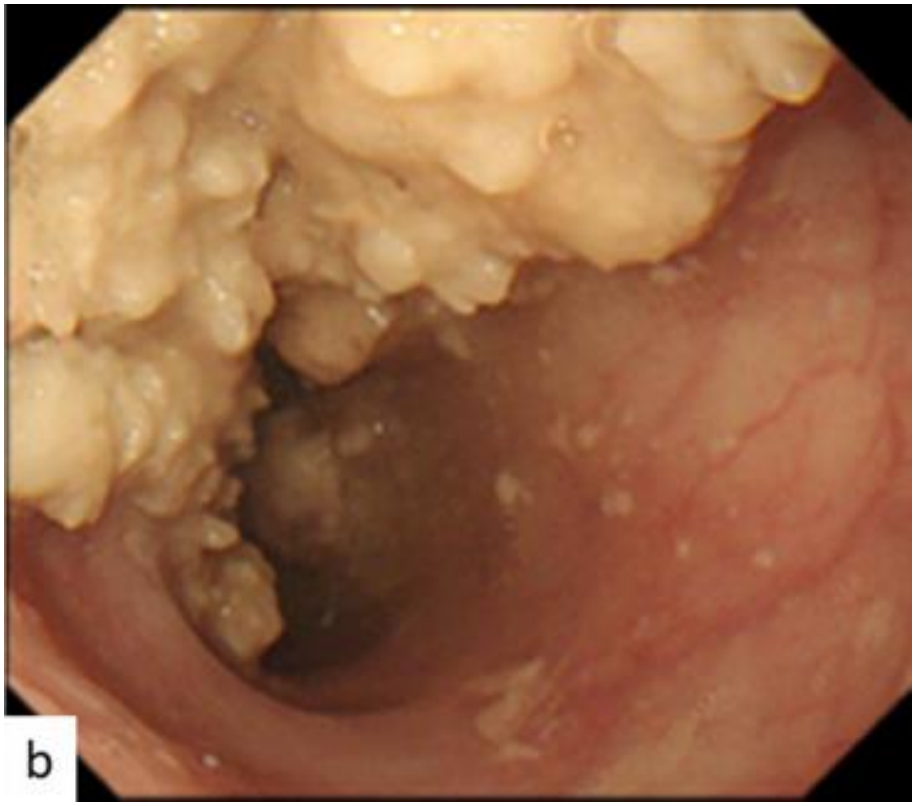
- Treatment (ESCC/ECA)
  - A multidisciplinary approach to the treatment of esophageal cancer is essential
    - Requires input from experts in surgical oncology, radiation oncology, medical oncology, gastroenterology, radiology, pathology, and often palliative care.
  - Treatment options depend on
    - Location
    - Staging
    - Histological type
    - Comorbidities
    - General principles are summarized below:
      - Surgery/Endoscopic curative therapy (EMR, ESD) is the standard treatment for a medically optimized patient with a localized, non-superficial tumour.
      - For a localized tumour in a patient who is not a surgical/endoscopic candidate do definitive chemoradiation with curative intent may be considered
      - For all others (metastatic disease) use palliation treatment
        - Radiation
        - Pain control
        - EMR/ESD

- Endoscopy

- ESCC variants: Verrucous Carcinoma



Verrucous Carcinoma



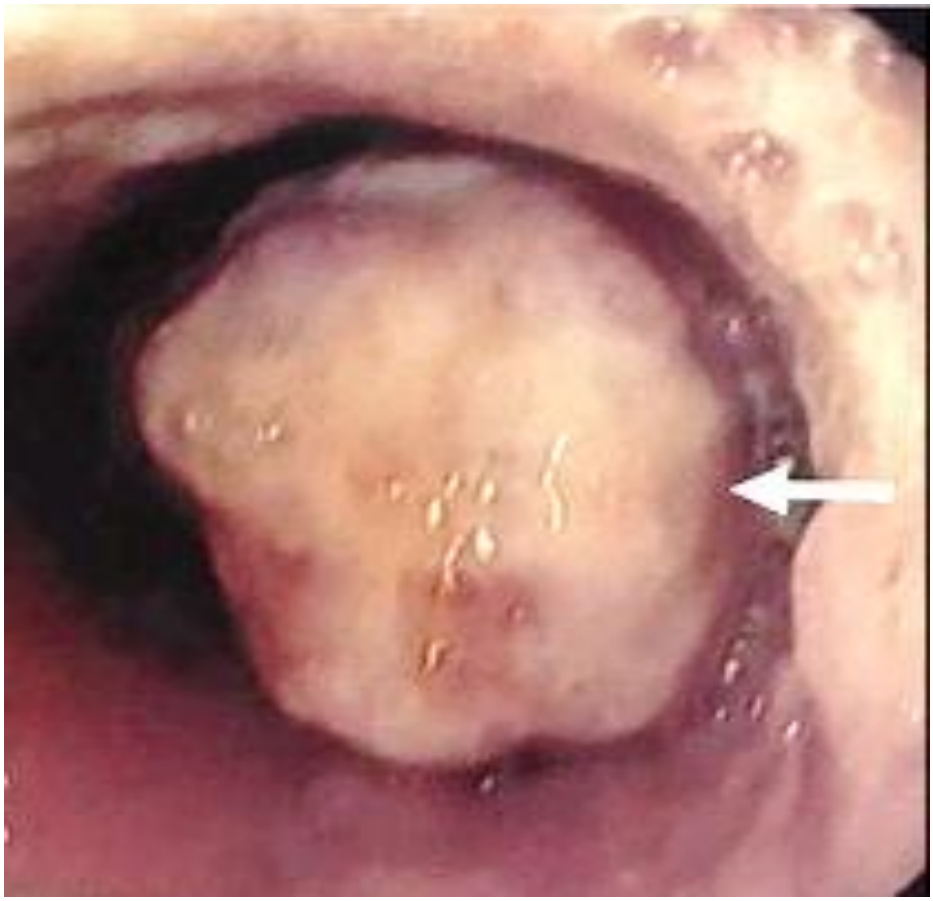
- Rare variant of ESCC (< 30 reported cases)
- Papillary or warty appearance

Source: Hashimoto M, et al. Surg Case Rep. 2022;8(1):128.

➢ Prognosis
- Poor, probably because of the usual delay in diagnosis

- ESCC variants – Carcinosarcoma
  - Also known as
    - Polypoid carcinoma
    - Pseudosarcoma
    - Spindle cell carcinoma

- Endoscopy
  - Solitary or multiple polypoid lesion



Ulceroproliferative polypoidal intraluminal growth

Source: Jain V, et al. Ochsner J. 2023;23(3):243-247.

- Prognosis
  - 2-yr survival rate, 25%

Esophageal Tumours

❖ Malignant

- Esophageal Squamous Cell Cancer (ESCC)

➢ Demography
  - Accounting for ~2% of all esophageal malignancies

➢ Clinical
  - Highly aggressive, with a very poor prognosis

➢ Risk factor
  - Strong association with history of
    - Tobacco use, 90%; and
    - Alcohol use, 70%

➢ Pathology
  - Location: middle third (52%) to lower third of the esophagus (35%)

❖ Benign

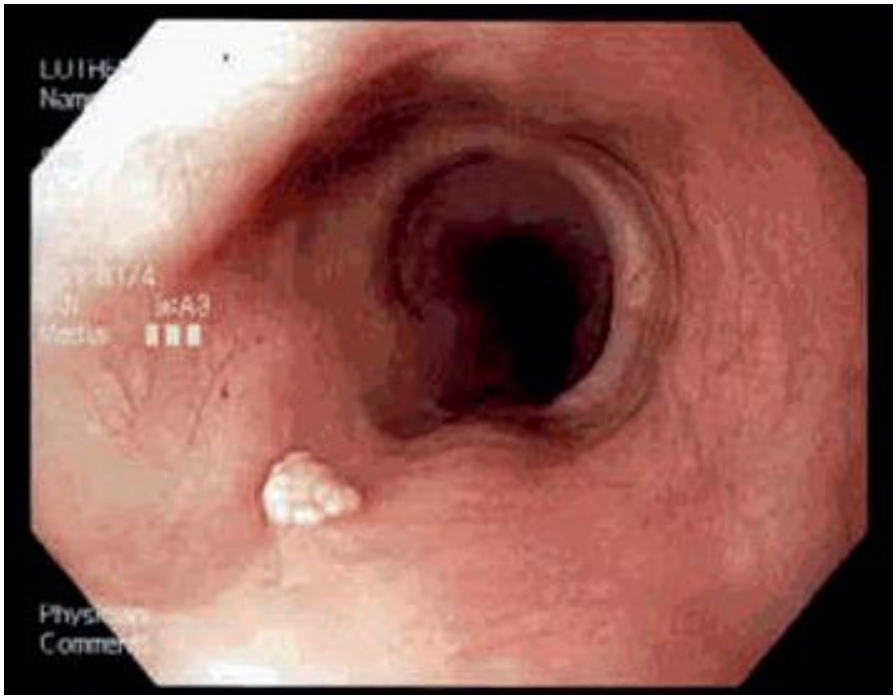
- Epithelial Tumours: Squamous Papilloma

➢ Demography
  - Rare, Prevalence 0.1%

➢ Risk
  - May be related to
    - Inflammation
    - GERD
    - HPV infection

➢ Clinical
  - Asymptomatic, benign epithelial tumours

➢ Pathology
  - Exophytic growth with wart-like projections on conventional endoscopy
  - Tend to have a white or pink color



Source: Uhlenhopp DJ, et al. Case Rep Gastrointest Med. 2020;2020:7645926.

- Treatment
  - Generally amenable to endoscopic resection (usually with forceps)

- Epithelial Tumours: Adenoma

- Demography
  - Rare
- Risk
  - Exclusively associated with Barrett esophagus (BE) metaplasia
- Pathology
  - Polypoid lesion with a segment of BE
- Treatment
  - Endoscopic resection
  - Dysplastic tubular glands covered by specialized intestinal epithelium

- Epithelial Tumours: Inflammatory Fibroid Polyp

➢ Demography
  - Presence of IFP usually in stomach and colon
  - Only 3% occur in esophagus

➢ Pathology
  - Characterized by a distinct histology
  - Submucosal polypoid lesion with
    - Perivascular/concentric fibroblastic proliferation
    - ↑ eosinophils
      - Express CD34 and are negative for CD117

- Non-epithelial Tumours: Leiomyoma

➢ Demography
  - Most common benign esophageal tumours
  - Men > Women 2:1

➢ Endoscopy
  - Submucosal solitary mass or
    - Masses in the middle to distal third of the esophagus
  - EUS is the diagnostic test of choice

➢ Pathology
  - Mucosal biopsy usually non diagnostic as overlying mucosa is normal

➢ Treatment
  - Only large symptomatic lesions require excision
    - Endoscopically (ESD) for smaller tumours (ESD)
    - Surgically for larger lesions

- Non-epithelial Tumours: Granular Cell Tumour

➢ Pathology
  - Usually located in oropharynx
    - When GI tract is involved
      - Most common site is the esophagus

- Endoscopy
  - Number of lesions is variable
    - Solitary, submucosal, yellowish appearance in the distal esophagus
- Histopathology
  - Granular cell tumours composed of round / polygonal cells with
    - Abundant eosinophilic cytoplasm
    - Acid-Schiff positive and diastase resistant
- Treatment
  - Endoscopic resection

- Non-epithelial Tumours: Fibrovascular Polyp

- Pathology
  - Almost exclusively seen in the cervical esophagus
  - Pedunculated polyps consisting of
    - Blood vessels
    - Adipose cells, and
    - Stroma covered by normal squamous epithelium
- Clinical
  - Most cases are identified incidentally
    - Can lead to dysphagia and globus sensation
  - Endoscopic or surgical removal is recommended
  - Hamartoma (rare) may be present
    - Look similar endoscopically as Fibrovascular polyps but different histopathology

- Epithelial Tumours: Malignant Melanoma

- Demography
  - Very rare (only ~300 cases described)
  - ~0.3% of all esophageal malignancies
- Clinical
  - Metastasizes early
    - Very poor prognosis
  - Due to the soft nature of the tumour, dysphagia may be delayed
    - >90% cases present with tumour > 2 cm

- Pathology
  - Nonulcerated, pigmented tumour
    - The colour may vary depending on the amount of melanin
      - Middle and distal thirds of the esophagus

- Non-epithelial Tumours: Lymphoma

- Demography
  - < 1% of esophageal malignancies

- Pathology
  - Primary or secondary (more common)
    - Primary esophageal lymphoma predominantly esophageal involvement with only regional lymph nodes affected

- Clinical
  - Dysphagia
  - Weight loss
  - GI bleeding
  - Non-specific B/systemic symptoms
    - Fevers
    - Night sweats
    - Fatigue

- Endoscopy
  - Submucosal nodules/masses
  - Ulcerations
  - Polypoid lesions

- Non-epithelial Tumours: Sarcoma

- Demography
  - Rare mesenchymal tumours
    - Leiomyosarcomas (most common subtype and difficult to distinguish from benign leiomyomas)
    - Gastrointestinal stromal tumours (GISTs)
    - Rhabdomyosarcoma
    - Fibrosarcoma
    - Liposarcoma
    - Fibrous histiocytoma
    - Kaposi sarcoma
    - Choriocarcinoma

- Endoscopy
  - Intraluminal
  - Polypoid
  - Infiltrative/invasive
  - Mucosal biopsy is **not** a useful diagnostic tool in most cases (because these lesions are submucosal)
    - EUS with FNA is be helpful for diagnosis
- Treatment
  - Esophagectomy with lymphadenectomy

- Non-epithelial Tumours: Gastrointestinal Stromal Tumour (GIST)

- Demography
  - Most common mesenchymal tumour
  - 1-3% of cases
  - Typically present after the age of 40
- Pathology
  - Arise from the muscularis propria and more specifically, the interstitial cells of Cajal
  - Risk of malignancy depends on size and mitotic rate
    - < 2 cm plus a mitotic rate < 5 per 50 high-power field (low malignant potential)
- Endoscopy
  - EUS most common accurate imaging modality
- Treatment
  - Endoscopic submucosal dissection (ESD)
  - Monitor with CT-PET

- Non-epithelial Tumours: Hemangioma

- Demography
  - Rare
- Pathology
  - Vascular malformation

- Clinical
  - Can present with GIB or dysphagia
- Types
  - Cavernous
  - Capillary (less common)
- Endoscopy
  - Blue- to red-coloured submucosal nodules, often will blanch with compression
- Treatment
  - Resection, surgically/endoscopically

- Non-epithelial Tumours: Lipoma

- Pathology
  - More commonly found in the colon, small intestine, and stomach than in the esophagus (proximal)
- Clinical
  - Almost all are asymptomatic and found incidentally on endoscopy
- Endoscopy
  - Slightly yellowish
    - Raised nodules in the proximal esophagus
  - Pillow sign
    - Indentation or cushioning with “palpation”
  - On EUS
    - Homogeneous
    - Hyperechoic submucosal lesion with smooth outer margins
  - Superficial mucosal biopsies will usually be nondiagnostic

➢ Screening

- ESCC
  - The primary screening strategy (in areas of high ESCC incidence)
    - Lugol chromoendoscopy, with
  - Obtain endoscopic biopsies obtained from the unstained areas and targeted biopsies can be obtained to confirm dysplasia/malignancy
  - Lugol chromoendoscopy
    - Sensitivity/specificity of >90%
    - Staining mucosa with iodine spray
    - Dysplastic, cancerous, and inflammatory cells are usually devoid of stain (because of less abundant glycogen) and targeted biopsies can be obtained to confirm dysplasia/malignancy

Risk Factor	Screening and Duration
○ Achalasia	− Yearly EGD q 1 yr for 10-15 yr after disease onset +/- Lugol solution
○ Asian/African high-risk population	− One time Lugol chromoendoscopy beginning at the age of 40 yr
○ History of caustic esophageal injury	− Endoscopy q2-3 yr for 10-20 yr following the injury
○ Head and neck cancer	− Endoscopy with Lugol or NBI q6 mon to 1 yr for 10 yr after completion of therapy for HNSCC
○ Tylosis	− 4 quadrant biopsies from proximal, middle, and distal esophagus, starting at age 30; then q1-3 yr

Note: There is some controversy surrounding the above suggestions

STOMACH

NAUSEA AND VOMITING

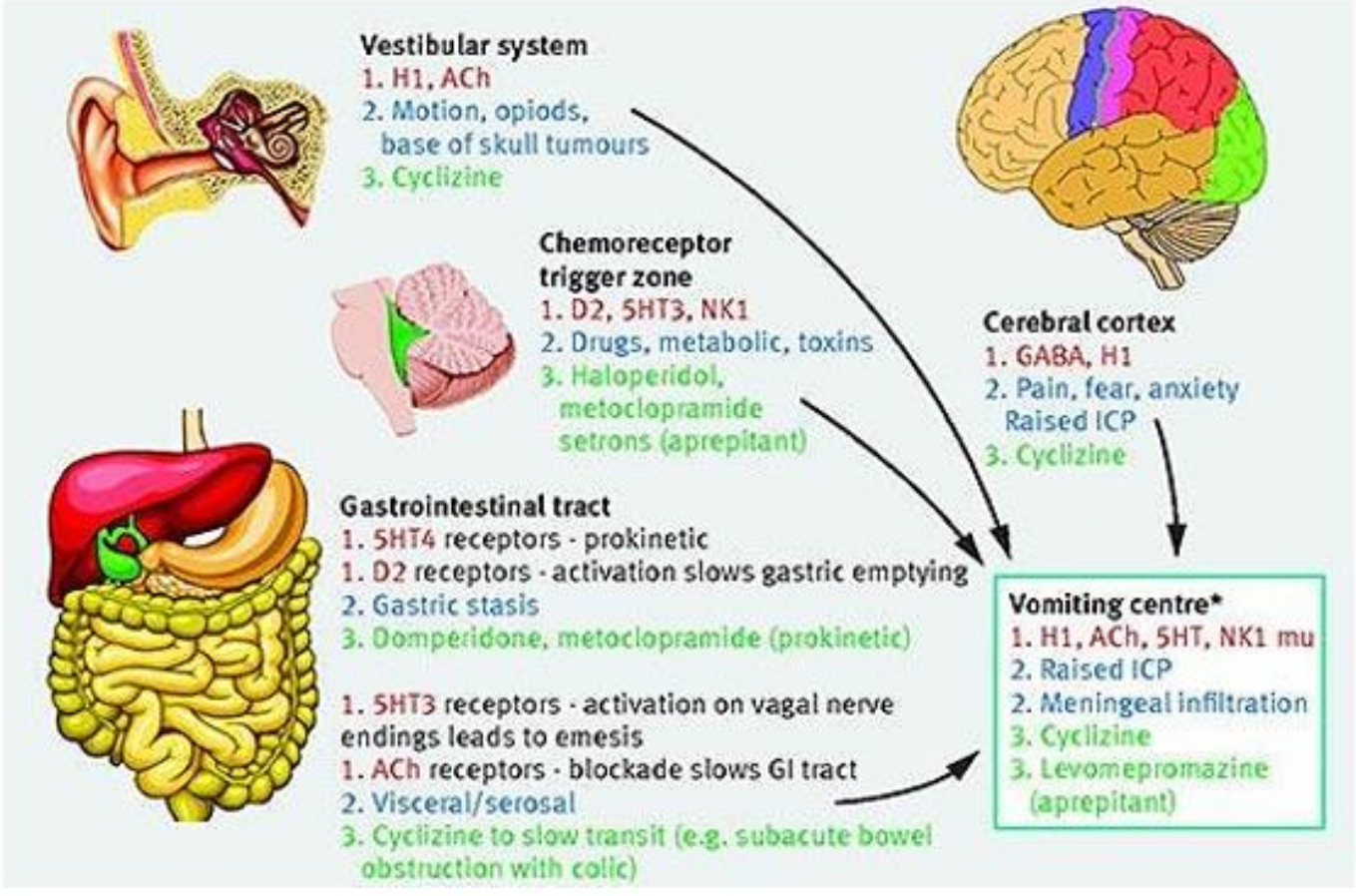
Nisha Howarth

- Pathophysiology
  - Interaction between gut and central nervous system (CNS)
    - Motor function of gut
      - Parasympathetic nervous system (PNS)
      - Sympathetic nervous system (SNS)
      - Enteric brain neurons
      - Smooth muscle cells

- Definition
  - Nausea
    - An unpleasant subjective sensation of impending vomiting
      - In many cases the sensation cannot be localized, but
      - Sometimes felt in epigastric region or throat
    - Correlates with either ↑ or ↓ gastric myoelectric activity
  - Vomiting
    - Reflex allowing the individual to rid oneself of toxins or poisons for forcing gastric contents up into the throat and out of the mouth
    - Can occur in isolation, but
    - Is more often part of the emetic sequence including nausea plus retching
    - Requires central neurogenic coordination

- Vomiting Pathway
  - Synchronized contraction and relaxation of several muscles
    - Diaphragm
    - Abdominal wall muscles
    - Pharyngeal muscles
    - Respiratory muscles
    - Afferent signals to initiate vomiting arise from
      - Heart
      - Pharynx
      - Small intestine
      - Stomach
      - Testicles
      - Chemoreceptor trigger zone of the area postrema (4th ventricle) also activates vomiting
      - Other CNS structures: brainstem, cortex, vestibular
  - Afferent signals carried via vagal fibres to the NTS in the medulla
    - Nausea not just vagally mediated

Receptor, Causes, and Suggested Treatment of Nausea/Vomiting



Abbreviations: 5HT4, serotonin type 4 receptor; Ach, acetylcholine receptor; H1, histamine type 1 receptor; ICP, intracranial pressure; NK1, neurokinin 1 receptor

Printed with permission: Collis E and Mather H. BMJ. 2015;351:h6249 (Figure 1)

- Receptors
  - 5HT3 serotonergic receptors → dopamine release → D2 receptors in brainstem
  - H1 histamine and M1 muscarinic receptors in the vestibular centre and solitary nucleus
    - Motion sickness, pregnancy-related sickness
  - CB1 cannabinoid receptor inhibits emetic reflex in the dorsal vagal complex
  - NK-1 receptors in area postrema and solitary nucleus → bind to substance P
    - Chemotherapy-induced emesis

- Sequence
  - Nausea
    - Activated cerebral cortex, stomach relaxes, inhibited intestinal and antral peristalsis
  - Retching
    - Activation of spasmodic contractions of diaphragm and intercostal muscles
    - Closure of glottis
  - Emesis
    - Somatic and visceral components activated simultaneously
      - Brisk contraction of diaphragm and abdomen muscles
      - Relaxation of lower esophageal sphincter (LES) and forceful retrograde contraction in jejunum
      - Soft palate raised glottis closed

➢ Causes/associations

Please see Rengarajan A and Gyawali CP. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 15.

- Clinical features which suggest etiology
  - CNS
    - CTZ or brainstem activation
      - Drugs
      - Functional
      - Metabolic
      - Pregnancy
      - Toxins
  - GI
    - Symptoms in morning on empty stomach or secretions in emesis
    - Retained or partially digested food in emesis
      - Gastric outlet obstruction (GOO)
      - Gastroparesis
    - After multiple episodes of vomiting, or gastroenteric anastomosis
      - Bilious emesis
    - Ileus, intestinal obstruction, longstanding GOO, gastrocolic fistula
      - Feculent or odorous emesis
    - CNS lesion or ↑ intracranial pressure (ICP)
      - Abrupt emesis without retching or nausea

- ❖ Vomiting Disorders

- Acute Vomiting

- ➢ Causes
  - GI
    - GOO
    - Intestinal
      - Obstruction
      - Infarction
    - Infectious and inflammatory causes,
    - Medications and toxins
    - Metabolic causes (electrolyte disturbances)
    - Neurologic causes
    - Post-operative nausea/vomiting

- ➢ Diagnosis
  - History and physical examination
  - Laboratory
    - CBC, electrolytes, Cr, TSH, LEs, glucose, lipase
    - Pregnancy test in women of childbearing age
  - Diagnostic imaging
    - Abdominal
      - X-ray
      - Ultrasound
      - CT/MRI
    - Endoscopy
      - EGD
  - Other investigations based upon above, e.g.
    - Blood alcohol
    - Blood culture
    - Blood trough measurement for drugs
    - Drug screen
    - Catecholamines
    - Lumbar puncture
  - For chronic vomiting also consider
    - Motility studies
      - GE study, manometry, autonomic function tests (tilt table)
    - Brain imaging

➢ Approach to Patient with Acute Vomiting

- Ensure **No:**
  - Need for acute medical support
  - Pregnancy
  - Bowel obstruction
  - Electrolyte imbalance / suspicion of adrenal insufficiency, or serious metabolic disorder
  - Suspected enteric/systemic infection
  - Drugs/toxins
- Iatrogenic
  - Drug, toxins, chemo-radiotherapy, recent surgery → continued nausea/vomiting after offending drug stopped
- Neurological / vestibular disorder suspected
  - CT/MRI head consider ENT referral → disease-oriented therapy

• Chronic Vomiting

- Please see following
  - History, physical exam
  - EGD or upper GI series
    - Test of choice for gastric outlet obstruction (GOO) or duodenal obstruction
  - Barium swallow
    - Achalasia, gastro paresis, neoplasm
  - CT
    - Malignancy/masses, more distal intestinal obstruction, retroperitoneal pathology
    - CT enterography

➢ Causes/associations

- GI
  - Motility
    - Gastroparesis
    - Partial intestinal obstruction
    - Functional dyspepsia
    - Chronic functional nausea / vomiting
- CNS
  - Migraine
    - Abdominal auras
    - Hydrocephalus

➢ Treatment

❖ Correct Metabolic Abnormalities

- Oral hydration
- IV hydration
  - NS (normal saline, 0.9% NaCl) or D5W (5% dextrose in water) with K supplementation
- Enteral or parenteral feeding if not adequately taking PO food by 5-8 days

- Medications
  - Dopamine-2 receptor (D2-R) Antagonists (metoclopramide, clebopride, domperidone)
    - Mechanism of action
      - ↑ peripheral 5HT4 (++prokinetic)
      - ↓ peripheral D2 receptors (poor BBB crossing from domperidone)
    - Optimal etiologies to treat
      - Motion sickness
      - Post-operative nausea
    - Adverse effects
      - Metoclopramide/clebopride: extrapyramidal effects (due to BB crossing), long QT
      - Domperidone
        - ↑ QT interval
  - Antihistamines and Antimuscarinics (cyclizine, diphenhydramine, hydroxyzine; scopolamine)
    - Mechanism of action
      - Central blocking of H1 or M1 in vestibular centre and solitary nucleus
    - Optimal etiologies to treat
      - Motion sickness
      - Other vestibular induced vomiting
      - Post-operative nausea/vomiting
    - Adverse effects
      - Scopolamine
        - Induce visual accommodation disturbances
      - H1 receptor blockers
        - Sedating effects
  - Serotonin (5-HT3 receptor) Antagonists (ondansetron, granisetron, tropisetron)
    - Mechanism of action
      - ↓ 5HT3 receptor in brainstem and gastric wall
        - Antiemetic
    - Optimal etiologies to treat
      - Chemoradiotherapy induced nausea/vomiting
      - Post-operative nausea/vomiting
      - Acute gastroenteritis
    - Adverse effects (ondansetron)
      - Safe in pregnancy
      - ↑ QT interval
  - Glucocorticoids
    - Mechanism of action
      - Not well understood for indication of nausea/vomiting
    - Speculations
      - ↓ central prostaglandin synthesis
      - Release of endorphins
      - Altered release/synthesis of 5-hydroxytryptamine (5HT)
    - Optimal etiologies to treat
      - Chemotherapy induced nausea/vomiting
      - Post-operative nausea/vomiting
      - Often used in combination with other antiemetic

- Adverse effects (ondansetron)
  - Carefully monitor blood glucose
  - Use concurrent PPI for gastroprotection if
    - History of peptic ulcer disease (PUD)
    - Gastroenteric anastomosis

- NK-1 Receptor Antagonists (aprepitant, fosaprepitant (IV), fosaprepitant)
  - Mechanism of action
    - ↓ substance P (SP) and ↓ NK-1-R (SP binds NK-1 R)
  - Optimal etiologies to treat
    - Post-operative nausea/vomiting
    - Chemoradiotherapy induced nausea/vomiting
    - Potent anti-emetics
    - Often combined with other drugs
- Gastric Prokinetic Agents (5HT4 agonist, motilin agonist, ghrelin agonist)
  - Mechanism of action
    - 5HT4 agonism (metoclopramide, prucalopride, cinitapride, cisapride) (caution re: cardiotoxicity—use low dose)
      - Optimal etiologies to treat
        - Gastroparesis
        - Intestinal pseudo-obstruction
        - Functional dyspepsia
    - Motilin agonism (erythromycin)
      - Optimal use
        - Acute nausea/vomiting due to gastroparesis
        - Poor symptom relief
      - Adverse effects
        - Do **not** use for long period
          - Tachyphylaxis
          - ↑ QT interval
    - Ghrelin agonism (ulimorelin, atilmolin)
      - Structurally similar to motilin and accelerates postprandial gastric emptying

❖ Gastric Electrical Stimulation

- Gastric pacing
  - Low frequency/high energy external stimulation → gastric pacing
  - External entrains the gastric slow waves → phasic contractions
  - Not typically done as, the amount of energy required to induce gastric slow waves is too high, such that a compact unit and battery is not possible.
- Gastric neurostimulation
  - Implantable neurostimulator → ↑ frequency/low energy impulses to stomach → ↓ proximal gastric tone → ↓ discomfort associated with distension
  - In case control studies, improvement in
    - ↓ nausea/vomiting
    - ↑ quality of life
    - ↑ nutritional status
    - Somewhat controversial, as in these case control studies, patients generally had improved symptoms whether the device was turned on versus turned off.
  - Complications
    - Electrode dislodgement → bowel obstruction (↑ cost)

- Cyclic Vomiting Syndrome (CVS)

➢ Definition

- Clustered, recurrent vomiting in absence of other etiology, but
  - Often associated with migraine, anxiety/depression (20%)
  - Similar to cannabinoid hyperemesis syndrome (CHS)
- Rome IV criteria
  - Stereotypical vomiting episodes (<1 wk duration)
  - ≥ 3 discrete episodes in prior yr
  - ≥ 2 episodes in last 6 months (each episode at least 1 wk apart)

➢ Risk factors

- Cannabis use (indistinguishable from CVS)
- History of migraines

➢ Clinical

- Acute nausea/vomiting lasting hours-days
- Symptom free intervals between typica vomiting episodes continue for prophylaxis

➢ Treatment

- Begin treatment at beginning if vomiting episode
  - Antimigraine medicines (5HT1 blocker)
  - Conventional antiemetics / benzodiazepines
  - Manage dehydration
- Prophylaxis
  - Beta blockers
  - Cyproheptadine
  - Erythromycin
  - Naloxone
  - Selective serotonin reuptake inhibitor (SSRIs)
  - Tricyclic antidepressants (TCAs)
  - Valproic acid
- Concurrent anxiety or depression
  - Manage as per best practice current guidelines

- Cannabinoid Hyperemesis Syndrome

➢ Definition

- Clustered, recurrent vomiting in absence of other etiology, but in a chronic user of cannabis
  - Similar to presentation of cyclic vomiting disorder, except
    - Chronic use of cannabis
    - Improves with cessation of cannabis
    - Often ↓ symptoms with hot showers or baths

- Pathology
  - CB1 receptors are in the gut and brain
    - CB2 receptors are in lymphoid tissue
    - Chronic stimulation of CB1 →
      - ↓ HPA axis
      - ↓ sympathetic response to stressful
      - Modulates gastric motility and sensation
  - Regular cannabis use → downregulates/desensitizes CB1 receptors
- Differential
  - Indistinguishable from cyclical vomiting syndrome (CVS)
  - Ritualistic hot baths (↓ symptoms of CVS)
  - Stop cannabinoids
    - Restores sensitivity of downregulated CB1 receptors
    - Need to stop Cannabis for at least 6 months before one can say that this isn't CHS
  - Hot bath
    - ↓ symptoms of CHS
  - Treat with prophylactic drugs
  - Poor cyclic vomiting syndrome (CVS; please see previous vomiting disorder)

- Functional Vomiting

- Definition: Rome IV criteria:
  - ≥ 1 episodes of vomiting per week for 3 mon
  - Onset ≥ 6 mon prior to diagnosis
  - Symptoms are not cyclical
  - Exclude other causes of vomiting
    - Chronic use of cannabis
    - Rumination
    - Eating disorders
    - Other structural/organic causes
- Pathophysiology
  - Speculations
    - CNS
      - Psychosocial stressors
      - Visceral hypersensitivity
    - GI
      - Altered gut microbiota
      - Altered gut-brain function
      - Motility disturbances,

- Diagnosis
  - Exclude other types/causes of vomiting
- Treatment
  - Avoid food triggers
  - Correct coexisting nutritional deficiencies,
  - Psychotherapy (no evidence for efficacy)
  - Supportive patient-physician relationship

- Hyperemesis Gravidarum

- Demography
  - Occurs in ~2% of pregnancies
  - May be associated with H. pylori infection during pregnancy
  - Usually occurs in
    - Young, primiparous mothers
    - More common ethnicities: Asian, Middle East
- Definition
  - Severe, persistent nausea/vomiting which occurs in pregnancy
- Causes/associations
  - Speculation
    - Changes in
      - Estrogen/progesterone
      - Ghrelin, leptin
      - Gestational thyrotoxicosis, mild)
      - ↑ thyroid activity
    - Hormone/gastric motility changes
    - May be genetic component
    - Role of psychosocial factors unknown
    - May occur in family clusters
      - Trisomy 21
      - Trophoblastic disease growth
  - Peaks at 6-12 wks and rarely occurs beyond 22 wks
- Complications
  - Mother
    - Electrolyte disturbances (especially hypokalemia)
    - Nutritional deficiency
    - Need for hospitalization
    - ↑ risk upper GI bleeding, including Mallory-lesions

- Rare complications
  - Psychological
    - Post-partum depression
    - Post-traumatic stress syndrome disorder
  - CNS
    - Central pontine myelinolysis
    - Korsakoff psychosis
  - Lung
    - Spontaneous pneumomediastinum
- Fetus
  - Low birth weight
  - Pre-term bleeding

➢ Treatment

- Lifestyle changes (frequent small meals, avoidance of triggers, OTC remedies such as ginger)
- 2nd line: dopamine antagonists and serotonergic antagonist
- Refractory: steroids, enteral feeding

➢ Differential diagnosis

- Uterus molar multiparous gestations

- Rumination Syndrome

➢ Definition

- Repetitive and effortless regurgitation of small amounts of recently ingested food into mouth → re-chewing / re-swallowing or expulsion of regurgitated food

➢ Clinical

- Classically, no nausea or autonomic manifestations (i.e. hypersalivation, sweating) that usually come with vomiting

➢ Diagnosis

- Clinical + manometry and pH impedance testing
  - Manometry doesn't diagnose rumination, but is helpful to exclude Achalasia & GERD as alternate etiologies

➢ Treatment

- Behaviour modification (most effective)
  - Diaphragmatic breathing techniques,
  - Biofeedback
- Reassurance and explanation of phenomenon
  - May allow patients to develop control over rumination
- Proton pump inhibitor (PPI if there is associated esophagitis
- Baclofen to ↑ LES pressure

- Superior Mesenteric Artery Syndrome (SMAS)

➢ Pathophysiology

- SMA branches off aorta at an acute angle → through mesentery → crosses over duodenum (R of midline)
  - When ↑ angle acuity → partial duodenal obstruction (D3, third part of duodenum)

➢ Clinical

- Epigastric fullness / pressure sensation after meals
- Nausea/vomiting (usually bilious)
- ↓ pain with knee-to-chest position

➢ Diagnosis

- CT scan / upper GI barium, showing contrast cut-off proximal to obstruction

➢ Treatment

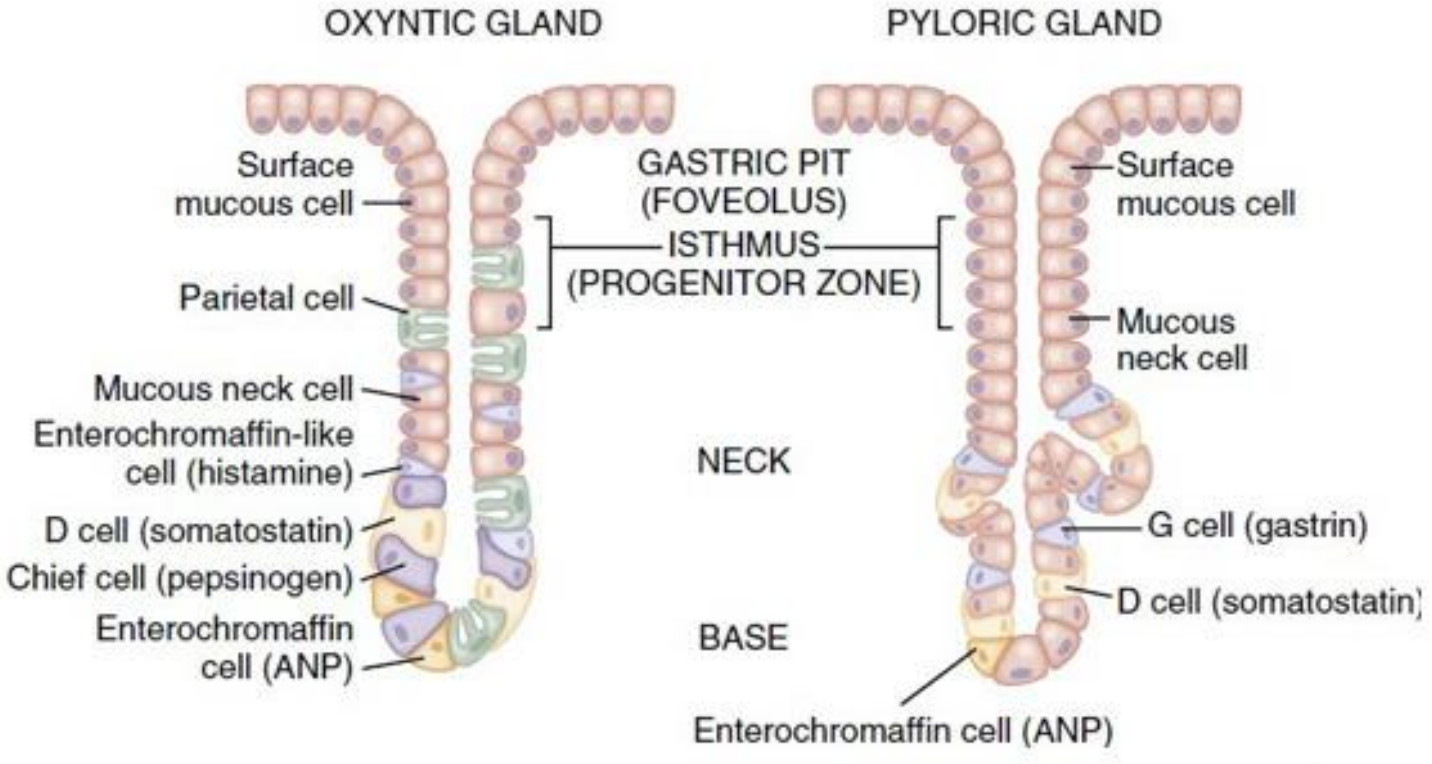
- Acute
  - NG tube decompress
- Chronic
  - Strong's procedure, gastrojejunostomy, and duodenojejunostomy

PEPTIC ULCER DISEASE AND DYSPEPSIA

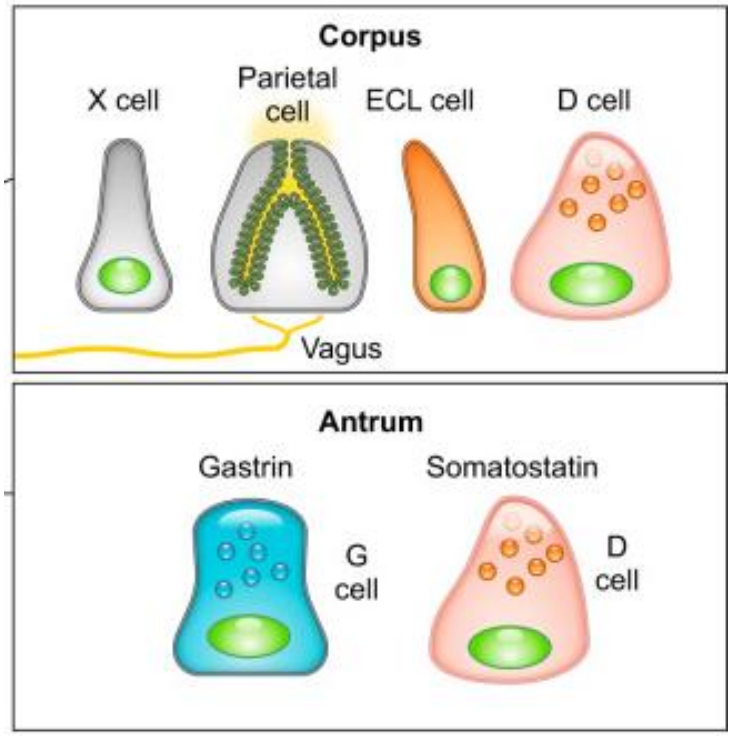
Khalid Alseiari

➢ Overview of Gastric Physiology

Oxyntic: Fundus and Body Pyloric: Antrum



Printed with permission: Schubert ML and Kaunitz JD. Sleisenger and Fordtran's gastrointestinal and liver disease: 11th edition. Chapter 51, page 766 (Figure 51.4).



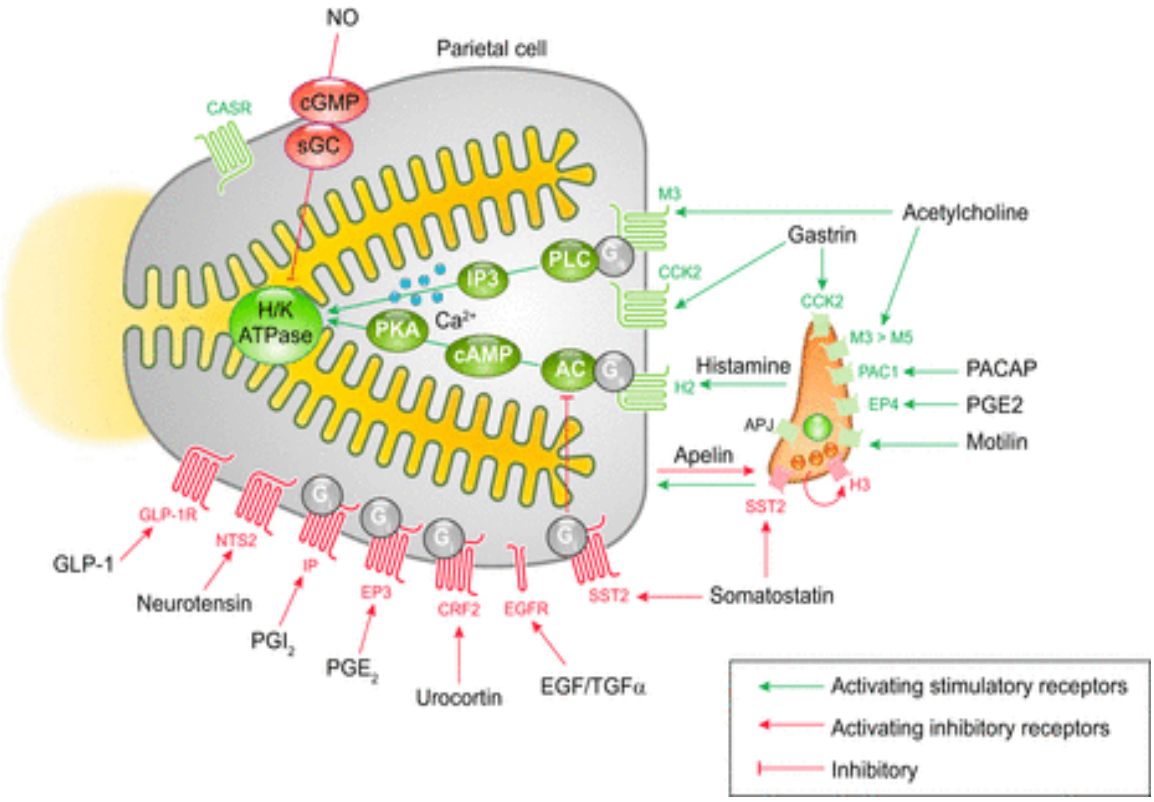
- **Secreting area:**
  - Key cell: Parietal Cell
    - Releases HCl and Intrinsic Factor into the lumen

- **Sensing area:**
  - Key cell: G-cell- releases gastrin
  - Senses food and acid content leading to hormonal release

Source: Engevik AC, et al. Physiol Rev. 2020;100(2):573-602 (Figure 3)

- Controlling acid production
  - Proton pumps are the end pathway causing acid secretion in parietal cells ‘
  - Activators of proton pumps:
    - Acetylcholine
    - Gastrin
    - Ghrelin
    - Histamine
  - Inhibitors of proton pumps:
    - Prostaglandins
    - Somatostatin

Membrane receptors on parietal and enterochromaffin-like (ECL) cells and intracellular signaling pathways that regulate gastric acid secretion.



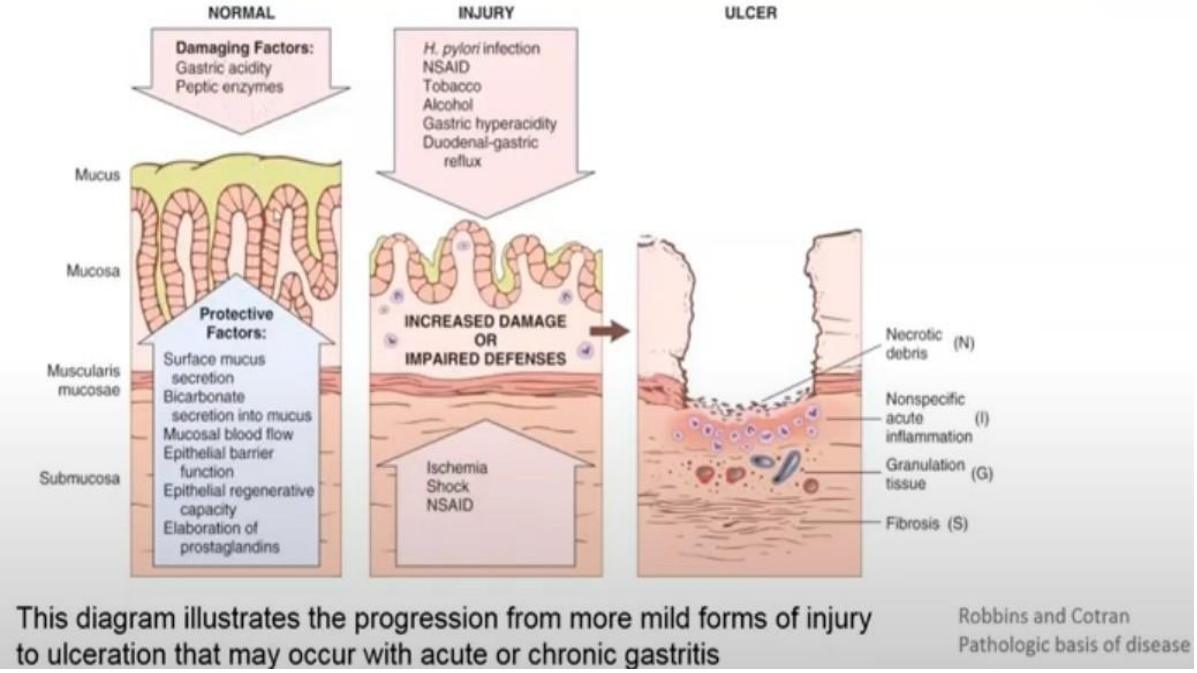
Source: Engevik EC, et al. Physiological Reviews 2020 100:2, 573-602 (Figure 4)

- The parietal cell expresses G protein-coupled receptors (GPCRs) for acid secretagogues, including
  - The muscarinic receptor (M3) for acetylcholine, the gastrin receptor (CCK2), and the histamine receptor (H2).
- M3 and CCK2 receptors are coupled to G protein Gq that
  - Activates phospholipase C (PLC), which
  - Leads to intracellular Ca2+ release to potentiate acid secretion.
- Binding of histamine to the H2 receptor
  - Activates adenylate cyclase (AC) to
  - generate cAMP through Gs signal, which p
  - potently ↑ H^+-K^+-ATPase (H/K) activity via cAMP-dependent protein kinase (PKA).
- Histamine release from ECL cells is stimulated by a variety of receptors, including
  - CCK2, PAC1, EP4, and
  - the motilin receptors

- Several receptors for inhibitors of gastric acid secretion are present on parietal cells including
  - GLP-1R
  - NTS2, IP
  - EP3
  - CRF2
  - EGFR, and
  - SST2 receptors
- The inhibitory G protein (Gi)
  - ↓ AC activities to
  - ↓ cAMP-mediated secretory pathways
- Nitric oxide (NO)
  - Inhibits acid secretion through the cGMP pathway
- Angiotensin-like peptide receptor (APJ), activated by parietal cell-derived apelin
  - Exerts both inhibitory and stimulatory effects.
- The H3 histamine receptor, expressed on ECL cells, contributes to
  - negative feedback for histamine release

- Prostaglandin Pathway
  - Prostaglandins
    - Maintain gastric blood flow to gastric mucosa
      - Have a tropic effect
    - ↑ bicarbonate (HCO_3^-) and mucus secretion from mucosa
    - ↓ acid secretion from parietal cells
      - Misoprostol has gastric protective effect
  - NSAIDs
    - Block the prostaglandin pathway by inhibiting COX enzymes
    - COX-1 is constitutively active in the GI tract, and
      - ↑ blockage can cause gastric wall damage and ulceration
      - COX-1 dependent synthesis of prostaglandins E_2 and I_2
      - ↑ defense”
      - ↑ mucus
      - ↑ bicarbonate
      - ↑ phospholipid secretion
      - ↑ mucosal blood flow epithelial restitution
      - ↓ mucosal acid production
    - COX-2 has minimal GI expression
      - Selective inhibition can ↓ GI side effects
      - May have adverse cardiac risk

- Mechanisms of Gastric Injury and Protection



Source: [The Gastrointestinal Tract - Clinical Tree (clinicalpub.com)]

➢ Terminology

- Gastritis
  - Inflammation of gastric mucosa
- Acute gastritis = Active gastritis
  - ↑ neutrophils and acute inflammation
- Chronic gastritis
  - Chronic inflammation
    - Lymphocytes and plasma cells
- Helicobacter pylori gastritis
  - A chronic but “active” gastritis
    - Neutrophils plus lymphocytes
- Gastropathy
  - Reactive mucosal changes are present
  - Inflammatory cells are rare

- Dyspepsia
  - Word is derived from the Greek word ‘duspepsia’, from duspeptos ‘difficult to digest’
    - Often referred to as indigestion
      - A term used to describe group of symptoms affecting the upper digestive tract
  - Several definitions were developed in
    - Rome I and II are broad, then
    - Rome III to be more restricted then
    - Followed by Rome IV

➢ Classification

- Uninvestigated dyspepsia
  - EGD history
    - Abnormal
      - Dyspepsia likely due to EGD-detected disease
    - Normal
      - Functional dyspepsia
        - Meal-related epigastric
          - Burning
          - Pain
        - Post-prandial (possible motility disorder)
          - Early satiety
          - Fullness, post-prandial

➢ Causes of dyspepsia

- Infectious
  - H. pylori
  - TB
  - Other infections (i.e., phlegmonous/suppurative)
- Iatrogenic (medications)
  - NSAIDs
  - Other Meds/Toxins
  - Radiation
- Inflammatory/Immune
  - Granulomatous
    - Crohn disease
    - Sarcoid
  - Lymphocytic/collagenous
  - Systemic Mastocytosis
  - Eosinophilic gastritis
  - Graft vs host disease

- Ischemic
- Injury
  - Surgical/anastomotic
    - ↓ blood flow
- Gastritis
- Hiatal Hernia associated – prolapse related
- Stress/Critical illness
  - 48 h of ventilation
  - Coagulopathy
- Infiltration
  - Malignancy

- Etiology-based classification of gastropathy and gastritis
  - Gastropathy
    - Reactive (chemical) gastropathy
      - Alcohol
      - Bile reflux
      - Iron salt
      - Non-steroidal anti-inflammatory drugs (NSAIDs
      - Other agents (e.g., alendronate, sodium phosphate)
    - Vascular gastropathy
      - Portal hypertensive (congestive) gastropathy
      - Gastric antral vascular ectasia
    - Ischemic gastropathy
      - Burns
      - Cocaine
      - Hypovolemia
      - Sepsis
      - Trauma, mucosal prolapse
  - Gastritis
    - Infectious gastritis
      - Bacterial
        - Helicobacter pylori (phlegmonous gastritis)
        - Mycobacterial
        - Syphilitic
      - Fungal
      - Parasitic
      - Viral
    - Autoimmune gastritis
    - Granulomatous disease
      - Crohn disease
      - Sarcoidosis
    - Uncertain etiology
      - Collagenous gastritis
      - Eosinophilic gastritis
      - Lymphocytic gastritis

- Acute Gastritis: - Neutrophil predominant infiltrate
  - NSAIDs – COX inhibition
  - Uremic – Inhibition of gastric bicarbonate transporters
  - High altitude – decreased O_2 delivery
  - Chemical, alcohol, NSAIDs, chemorads – direct injury to mucosal cells
  - Bile acids – inhibits mucosa defense mechanism (mucus-bicarbonate barrier)
- Chronic Gastritis: - lymphoplasmacytic infiltrate
  - H. pylori
  - Autoimmune
  - Radiation
  - Chronic bile reflux
  - Mechanical injury – surgery, NG trauma
  - Systemic disease – Crohn disease, amyloid, graft versus hose disease

Note: There is a variable relationship between symptoms of dyspepsia and associated gastritis/gastropathy

- Peptic Ulcer Disease (gastric ulcer [GU] and duodenal ulcer [DU]

➢ Demography

- Hp infection, ~75%
- NSAIDs, ~25%
- ZES
- Other
- Unknown

} < 1%

➢ Symptoms of gastritis/PUD

- Dyspepsia
  - Abdominal Pain
  - Bloating
  - Early Satiety
  - Nausea

Alarm Features in Patients with UGI Symptoms*

- Patient
  - Age > 60 yr with new onset dyspepsia
  - Family history of UGI cancer
- Symptoms
  - GI bleeding
    - Acute or chronic, including unexplained iron deficiency
  - Jaundice
  - Persistent vomiting
  - Progressive dysphagia
  - Unintended weight loss
- Signs
  - Left supraclavicular lymphadenopathy (Virchow node)
  - Palpable abdominal mass

*These features should prompt EGD and often other testing to establish a definitive diagnosis

Adapted from: Chan FKL and Lau JYW. Sleisenger and Fordtran's gastrointestinal and liver disease: 11th edition. Chapter 53, page 809 (Box 53.1)

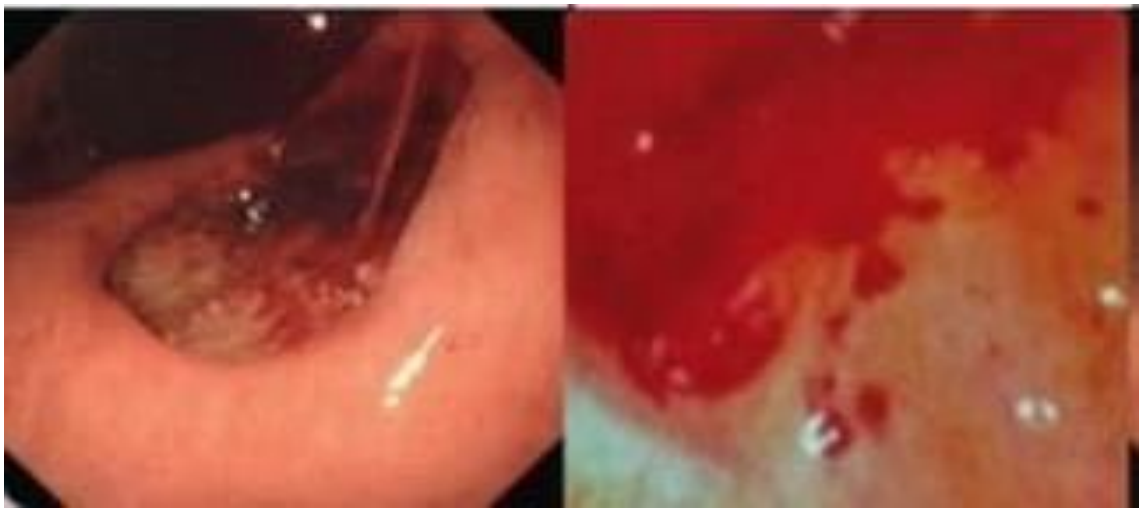
- Complications
  - Easy mnemonic to remember the complications of PUD is HOPP (Hemorrhage, Obstruction, Penetration, Perforation)
  - Bleeding (15-20% of ulcers)
  - Perforation
  - Gastric outlet or duodenal obstruction
  - Penetration into
    - Pancreas (most common)
    - Colon
    - Liver/biliary tree
    - Adjacent vessels
    - Peritoneum/retroperitoneum

- Bleeding Peptic Ulcers (GU, DU)

Forrest Classification		
Stage	**Characteristics**	**Re-bleeding**
Ia	Spurting Bleed	60 - 100 %
Ib	Oozing Bleed	50%
IIa	Non-Bleeding Visible Vessel	40 - 50 %
IIb	Adherent Clot	20 - 30 %
IIc	Flat Spot in ulcer crater	7 - 10 %
III	Clean Base Ulcer	3 -5 %

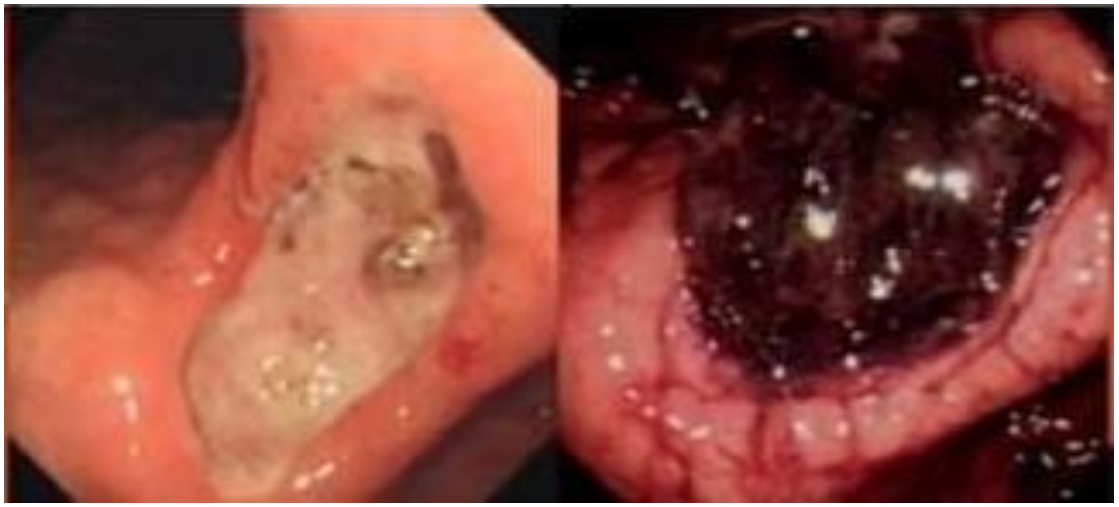
Ia
Spurting Bleed

Ib
Oozing Bleed



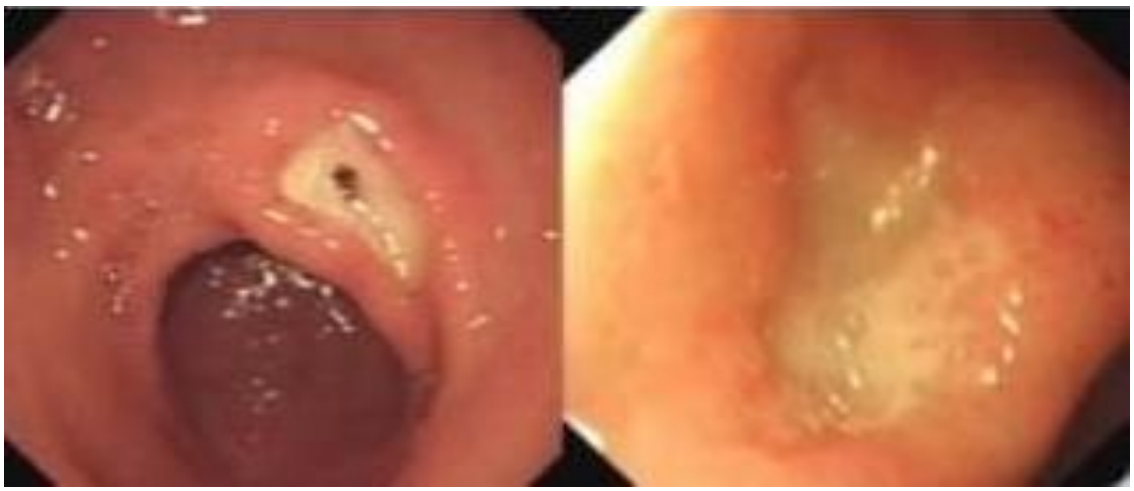
IIa
Non-bleeding visible vessel

IIb
Adherent Clot



IIc
Flat Spot in Ulcer Crater

III
Clean Base Ulcer



Printed with permission: Alzoubaidi D, et al. Frontline Gastroenterology 2019; 10(1):35-42 (Figure 1)

➢ Treatment

- If active bleeding, hospitalize and resuscitate (ABC's IV hydration; proton pump inhibitor (PPI) infusion
  - Pantoloc® 80 mg bolus, then 8 mg/h for 72 hours
- Respect ACG guidelines for upper GI bleeding (2021)

- Endoscopy for UGIB
  - Timing of endoscopy
    - Admit patients to or under observation in hospital for UGIB
    - Do upper EGD within 24 h of presentation (conditional recommendation, very low quality evidence)
  - Endoscopic hemostatic therapy for ulcers with active bleeding or non-bleeding visible vessels
    - Do endoscopic therapy in patients with UGIB due to ulcers with active spurting, active oozing, and non-bleeding visible vessels (strong recommendation, moderate quality evidence
  - Endoscopic hemostatic therapy for ulcers with adherent clot
    - No recommendation for or against endoscopic therapy in patients with UGIB due to ulcers with adherent clot resistant to vigorous irrigation
  - Choice of endoscopic hemostatic
    - Do endoscopic hemostatic therapy with hemostatic clips bipolar electrocoagulation, heater probe, or injection with epinephrine for patients with UGIB due to ulcers (strong recommendation, moderate quality evidence)
    - Do **not** use epinephrine injection alone for patients with UGIB due to ulcers but rather in combination with another hemostatic modality (strong recommendation, very low to moderate quality evidence)
    - Use hemostatic therapy with hemostatic powder spray TC-325 for patients with active bleeding ulcer (conditional recommendation, very low quality of evidence)
    - Use over-the-scope clips as a hemostatic therapy for patients who develop recurrent bleeding due to ulcers after previous successful endoscopic hemostasis (conditional recommendation, low quality evidence)

- Anti-secretory therapy after endoscopic hemostatic therapy for bleeding ulcers
  - Give high-dose PPI therapy given continuously or intermittently for 72 hours after successful endoscopic hemostatic therapy of a bleeding ulcer (strong recommendation, moderate to high quality evidence)
    - In high-risk patients with UGIB due to ulcers who received endoscopic hemostatic therapy followed by short-term high-dose PPI therapy in hospital continue on twice-daily PPI therapy until 2 wk after index endoscopy (conditional recommendation, low quality evidence)

Source: Laine L, et al. ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding. Am J Gastroenterol 2012; 116(5): 899-917.

- During initial EGD
  - Biopsy of solitary GU (but not DU) to rule out malignancy
    - Only if bleeding risk is low
- If biopsy shows any atypical changes, then consider a review of the biopsies by a second examination of the material by an expert GI pathologist, and a second EGD with further biopsies.
  - If bleeding risk is low, then also take multiple biopsies by the Sydney protocol to diagnose H. pylori infection.
  - Beware if biopsies repeated to be negative when taken in a patient with bleed in the stomach at the time of the UGIB the biopsy results may be falsely negative.
  - If biopsies not taken at time of UGIB, then once bleeding has stopped, do a test for active H, pylori infection.
- In patient with gastric ulcer seen on upper endoscopy, repeat EGD after two months treatment with daily PPI (to establish complete healing).

Source: Laine L, et al. Am J Gastroenterol 2012; 116(5): 899-917; ASGE Standards of Practice Committee; Banerjee S, et al. Gastrointest Endosc 2010;71(4):663-8.

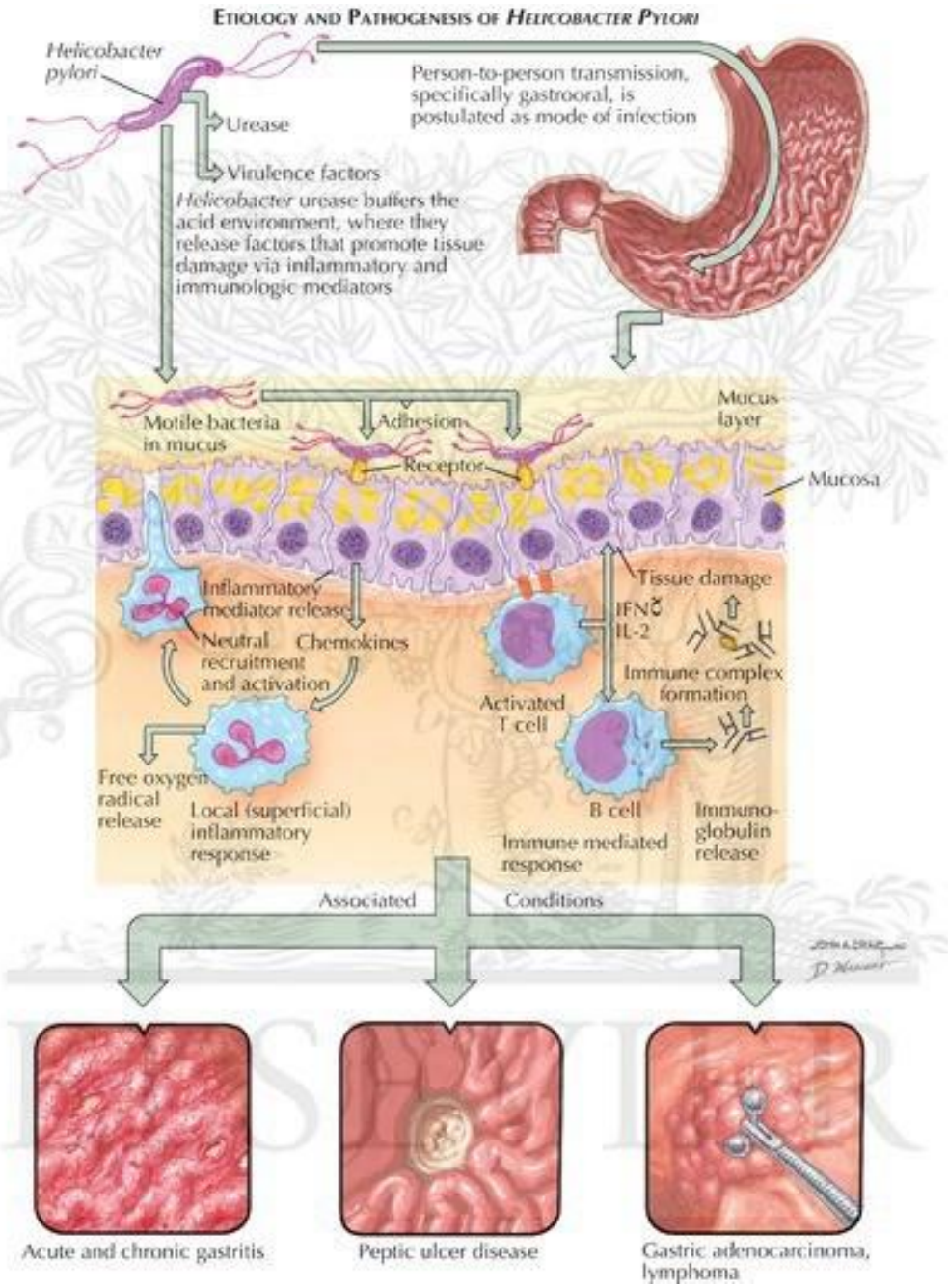
- H. pylori

➢ Demography

- H. pylori is
  - One of the most common chronic bacterial infections of humans worldwide
  - Leading cause of infection-associated cancer globally
  - Chronic and usually acquired in childhood
- About 50% of people worldwide are likely infected
  - Decreasing roles in North America, but still around 30-40%

➢ Pathophysiology

- Colonizes the stomach
  - Flagella to move through the stomach lumen and penetrate mucoid lining
  - Adhesion molecules allow to bind to epithelial cells
- Mixed effects on acid secretion
  - Antral gastritis
  - Pangastritis → ↓ HCl (↓ parietal cells) (↑ gastrin, ↓ somatostatin)
- Produces urease – breaks down urea into CO_2 and ammonia (NH_3; neutralizes the acid)
  - NH_3 secreted proteases, vacA protein and phospholipases



Source: https://jpabs.org/misc/peptic-ulcer-antibiotic.html

- H. pylori associated disease
  - Peptic ulcer disease
  - Gastric adenocarcinoma and MALT lymphoma
  - Iron deficiency anemia
  - Dyspepsia
  - Idiopathic thrombocytopenia (ITP)

- Indication for H. pylori testing and treatment
  - Test and treat H. pylori infection[a] in
    - Peptic ulcer disease prior history or active disease
    - Marginal zone B-cell lymphoma, MALT type
    - Uninvestigated dyspepsia in patients who are under the age of 60 yr
      - In high-risk populations for gastric cancer, test and treat at age 45-50 yr
    - Functional dyspepsia
  - Adult household members of individuals who have a positive non-serological test for H. pylori
    - Patients taking long term NSAIDs or starting long term treatment with low-dose aspirin
    - Patients with unexplained iron deficiency anemia
    - Patients with idiopathic (autoimmune) thrombocytopenic purpura
  - Primary and secondary prevention of gastric adenocarcinoma
    - Current or history of gastric premalignant conditions (GPMC)[b]
    - Early gastric cancer resection
    - Current prior history of gastric adenocarcinoma
    - Patients with gastric adenomas or hyperplasia polyps[c]
    - Persons with a first degree relative with gastric cancer[d]
    - Individuals at ↑ risk of gastric cancer including
      - Certain non-White racial/ethnic group
      - Immigrants from high gastric cancer incidence regions/countries
      - Hereditary cancer syndromes associated with an increased risk for gastric cancer
    - Patients with autoimmune gastritis

[a] In the absence of contraindications, H. pylori treatment should be offered to all patients with active H. pylori infection, as indicated by a positive non-serological test. Serological testing is not recommended in low-prevalence populations in the absence of a high pre-test probability (e.g., peptic ulcer)
[b] GPMC includes strophic gastritis, intestinal metaplasia, and dysplasia
c Patients with adenomas and hyperplastic polyps often have associated GPMC
d A decision to test and treat should follow shared decision-making between the patient and provide

Adapted from: Chey WD, et al. Am J Gastroenterol 2024; 119(9): 1730-1753 (Table 4)

H. pylori testing

- Performance characteristics for current infection with H. pylori have a sensitivity (Sn) of between 90 % to 98 %, and specificity (Sp) of 90% to 95%
  - Serological test for current or past H. pylori infection, Sn, 85%, and Sp, 80%

- Reduced sensitivity
  - PPI use (last 2 wk)
  - Antibiotics (last month)
  - Active GI bleeding
  - False positive stool antigen with active GI bleeding

➢ Treatment

- Recent changes since 2017
  - ↑ resistance to antibiotics in previous regimen (especially clarithromycin and levofloxacin)
  - New treatment regimens featuring new antibiotic options (i.e., rifabutin)
    - Potassium-competitive acid blockers; PCABs) in treatment-naive individuals

➢ Terminology

- Optimized bismuth quadrupole
  - PPI (any PPI, usual dose), bid
  - Bismuth subcitrate, 120-300 mg qid
  - Tetracycline, 500 mg qid
  - Metronidazole 250 mg qid

- Rifabutin triple
  - Omeprazole, 10 mg
  - Amoxicillin, 250 mg
  - Rifabutin, 12.5 mg
  - Metronidazole, 500 mg tid/qid

  } 4 capsules tid

- PCAB dual
  - Vonoprazan, 20 mg, bid
  - Amoxicillin, 1000 mg bid

- PCAB triple
  - Vonoprazan, 10 mg bid
  - Clarithromycin, 500 mg bid
  - Amoxicillin, 1000 mg bid

Adapted from: Chey WD, et al. Am J Gastroenterol 2024; 119(9): 1730-1753 (Table 5)

➢ Treatment for H. pylori Infection

- Naïve (sensitivity unknown)
  - No penicillin allergy
    - Bismuth quadrupole therapy (BQT)
    - PCAS dual
    - POAB triple (potassium-competitive acid blocker, bismuth, nitroimidazole and tetracycline)
    - Rifabutin triple
  - Penicillin Allergy
    - BQT

H. pylori Antibiotic Resistance Rates in US (2021)

Antibiotics	% resistance
○ Clarithromycin	22% - 32%
○ Levofloxacin	38% - 69%
○ Metronidazole	42% - 69%
○ Tetracycline	0.9%
○ Amoxicillin	1% - 3%
○ Rifabutin	0.2%
○ Dual Metronidazole / Clarithromycin	12%

Antibiotics susceptibility testing performed on 2669 strains from US between 2011-2021

Adapted from: Ho J, et al Am J Gastroenterol 2022; 117: 1221

- H. pylori Treatment
  - Treatment-naïve
    - Use BQT (strong recommendation, moderate quality evidence)
    - Use rifabutin triple therapy (conditional recommendation, low quality evidence)
    - Dual therapy with PCAB and amoxicillin (conditional recommendation, moderate quality evidence)
    - Unknown clarithromycin susceptibility, PCAB-clarithromycin triple therapy is suggested over PPI. Clarithromycin triple therapy (conditional recommendation, moderate quality of evidence)
    - Concomitant therapy is not suggested over bismuth quadruple therapy (conditional recommendation, low quality evidence)
  - Treatment-experienced patients
    - Previously received bismuth quadruple therapy
      - Use optimized bismuth quadruple therapy (conditional recommendation, low quality evidence)
    - Previously received PPI-clarithromycin triple therapy
      - Use rifabutin triple therapy (conditional recommendation, low quality evidence)
    - Previously received bismuth quadruple therapy
      - Use rifabutin triple therapy (conditional recommendation, low quality evidence)
    - Previously received optimized bismuth quadruple therapy
      - Use optimized bismuth quadruple therapy (over quinolone-based therapy) (conditional recommendation, low quality evidence)
    - Levofloxacin triple therapy is suggested in patients with known levofloxacin-sensitive H. pylori strains, and when optimized bismuth quadruple or rifabutin triple therapies have previously been used or are unavailable (conditional recommendation, low quality of evidence)
    - Probiotic therapy ↑ efficacy or ↑ tolerability of H. pylori eradication therapy (conditional recommendation, low quality evidence)

Abbreviations: BQT, bismuth quadruple therapy; PCAB, potassium-competitive acid blocker; PICO, Population, Intervention, Comparison, and Outcome; PPI, proton pump inhibitor

Adapted from: Chey WD, et al. Am J Gastroenterol 2024; 119(9): 1730-1753 (Table 2)

- "TTRT": test, treat, retest
- Retest 1 mon after treatment, and
  - Off PPI ≥ 2 wk
  - Off bismuth/antibiotics ≥ 4 wk

For Recurrent/persistent H. pylori

- Previous failed treatment (sensitivity unknown)
  - Failed PPI-clarithromycin triple, or failed non-optimized BQT
  - No penicillin allergy
    - ↑ PPI / PCAB dual
    - Rifabutin triple
  - Penicillin allergy
    - BQT

Treatment of Persistent H. pylori based on sensitivity

- If sensitivity known (proven failed previous therapy)
  - Levofloxacin, sensitive
  - Clarithromycin, sensitive
    - BQT
    - Rifabutin triple
    - Levofloxacin triple
    - Clarithromycin triple
  - Clarithromycin, sensitive
  - Levofloxacin, resistant
    - BQT
    - Rifabutin triple
    - Clarithromycin triple
  - Levofloxacin, sensitive
  - Clarithromycin, resistant
    - BQT
    - Rifabutin triple
    - Levofloxacin triple
  - Clarithromycin, resistant
  - Levofloxacin, resistant
    - BQT
    - Rifabutin triple
    - ↑ PPI / PCAR dual

Regimens for *H. pylori* Treatment		Rx Naïve	Rx Experienced (Salvage)	
		Empiric	Empiric	Proven Rx Sensitivity
Optimized bismuth quadruple	• PPI b.i.d. • Bismuth subcitrate (120-300 mg) or subsalicylate (300 -524 mg) q.i.d. • Tetracycline 500 mg q.i.d. • Metronidazole 500 mg t.i.d. or q.i.d. *Doxycycline is not a recommended substitute for tetracycline*	✔	✓	✓
Rifabutin Triple	• Rifabutin 50 mg t.i.d. (if dose unavailable, substitute rifabutin 150 mg b.i.d.) • Amoxicillin 1000 mg t.i.d. • Omeprazole 40 mg t.i.d.	✓	✓	✓
PCAB Dual	• Vonoprazan 20 mg b.i.d. • Amoxicillin 1000 mg t.i.d.	✓	!	!
PCAB Triple	• Vonoprazan 20 mg b.i.d. • Clarithromycin 500 mg b.i.d. • Amoxicillin 1000 mg b.i.d.			✓
Levofloxacin Triple	• PPI b.i.d. • Amoxicillin 1000 mg b.i.d. • Levofloxacin 500 mg b.i.d.			✓

✔ Recommended ✓ Suggested ! May be considered when no other options

Source: https://gi.org/wp-content/uploads/2025/01/ACG-Hpylori-Guidelines-Highlights-2024-FINAL.pdf.pdf

- NSAIDs Ulcer

➢ Pathophysiology

- Due to an imbalance of both mucosal protective factors and risk factors
- Most damage is secondary to ↓ prostaglandin synthesis
  - COX1 normally expressed in gastric epithelium
  - Maintains barrier integrity and
  - ↑ secretions to form a defensive mucous barrier
  - Neutrophil (PMNs) adherence to the gastric mucosa is the initiating event in NSAIDs injury
    - Adherence in the microcirculation release
      - Obstructs capillary blood flow
      - Oxygen-free radicals
      - Proteases
- NSAIDs can also disrupt
  - Cell membranes
  - Mucus phospholipids
  - Uncouple mitochondrial oxidative phosphorylation
- Gastric acid plays a secondary role by
  - Turning a superficial mucosal lesion into a deeper injury
  - ↓ platelet aggregation, and
  - ↓ ulcer healing

➢ Risk Factors

Risk Factors for NSAIDs Ulcer	Risk Ratio
History	
− Complicated ulcer	13.5
− Uncomplicated ulcer	6.1
Use of	
− Multiple NSAIDs (including aspirin, COX-2 inhibitors)	9
− High doses of NSAIDs	7
− Anticoagulant	6.4
− Glucocorticoid	2.2
Age > 70 yr	5.6
Hp infection	3.5

Adapted from: Chan FKL and Lau JYW. Sleisenger and Fordtran's gastrointestinal and liver disease: 11th edition. Chapter 53, page 813 (Table 53.1)

- Recommendatons
  - Test for H. pylori before initiating chronic NSAIDs therapy (strong recommendation, moderate evidence)
  - Consider also testing before initiation of chronic ASA therapy (conditional recommendation, moderate evidence)

- Prevent bleeding from NSAIDs ulcer
  - Avoid use of 2 NSAIDs (or 1 NSAIDs plus ASA), if possible
    - Use lowest risk type of NSAIDs (e.g., ibuprofen)
    - Use lowest effective dose of NSAIDs
  - Test for H. pylori and treat if positive, retest to prove eradication
  - Depending upon risk of bleeding: NSAIDs plus PPI, COX-2 inhibitor, COX-2 plus PPI
  - Use COX-2 inhibitor if ↑ bleeding risk and ↓ cardiovascular (CV) risk (do **not** give COX-2 inhibitor to patient with ↑ CV risk)
  - Use PPI or misoprostol prophylaxis if risk factors for NSAID-induced PUD, if patient is on anti-coagulants

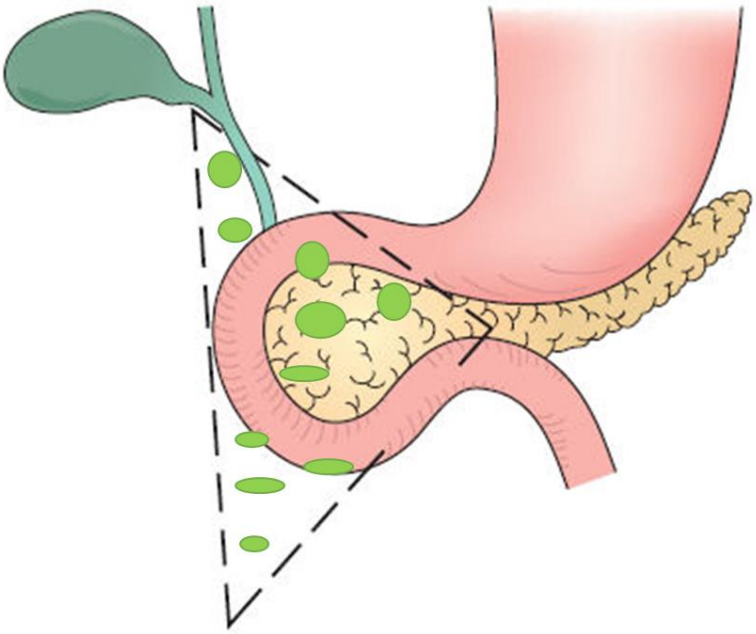
- Secondary Prevention
  - Treat NSAIDs-associated ulcer with daily PPI for 2 months
  - If possible
    - Stop NSAIDs or ASA
    - Limit dosage, or
    - Use COX- 2 inhibitor if low CV risk
  - If not possible to stop NSAIDs or ASA
    - Stay on PPI prophylaxis long-term
  - PPI superior to other drugs (H2RA, Antacids)
  - Treat H. pylori if present, and confirm eradication

- Zollinger Ellison Syndrome (ZES)
  - Associated with MEN1 in 20-25% of cases
  - Clinical
    - Multiple ulcers
    - Severe gastritis
    - Dyspepsia, and
    - Diarrhea
  - Cause
    - Gastrinoma (40-90% duodenal, rest are usually pancreatic)
      - Usually within “gastrin triangle”
  - Laboratory
    - Ideally
      - Off PPI for 3-7 days and fasting)
      - ↑ gastrin (≥ 10-fold) and gastric pH <2
      - ↑ gastrin (< 10-fold), gastric pH > 2, and a positive secretin test
    - Suspected from ↑ fasting gastrin in patient
      - Not on PPI
      - Not having H. pylori-associated pangastritis
      - Not having atrophic gastritis

- Secretin test: gastrin measured pre and post secretin injection
  - In normal secretin → ↓ acid production
  - In ZES, secretin → ↑ gastrin
- Ca2+ infusion, pentagastrin infusion
- ↑ basal gastric acid output (BAO), ↑ food stimulated maximal gastric acid output (MAO)
- BAO >> MAO (BAO/MAO > 60%)

NCCN Guidelines, May 2020

- Diagnostic imaging
  - Start with multiphasic CT or MRI to localize tumour
    - May need
      - PET/CT
      - Somatostatin scintigraphy, or
      - EUS



Gastrinoma Triangle

Modified from: https://www.surgicalcore.org/popup/427774

➢ Management for Dyspepsia

	BQT	PCAB Dual	PCAB Triple	Rifabutin triple	PPI / PCAB Dual
• Sensitivity Unknown					
○ Naïve					
− No penicillin allergy	+	+	+	+	
− Penicillin allergy	+				
○ Failed therapy (PPI-Clarithromycin BQT)					
− No penicillin allergy	+			+	+
− Penicillin allergy	+				
• Sensitivity known					
○ Levofloxacin sensitive ○ Clarithromycin sensitive	+			+	Levo triple Clari triple
○ Levofloxacin sensitive ○ Clarithromycin resistant	+			+	Levo triple
○ Levofloxacin resistant ○ Clarithromycin sensitive	+			+	Clarithromycin triple
○ Levofloxacin resistant ○ Clarithromycin resistant	+			+	

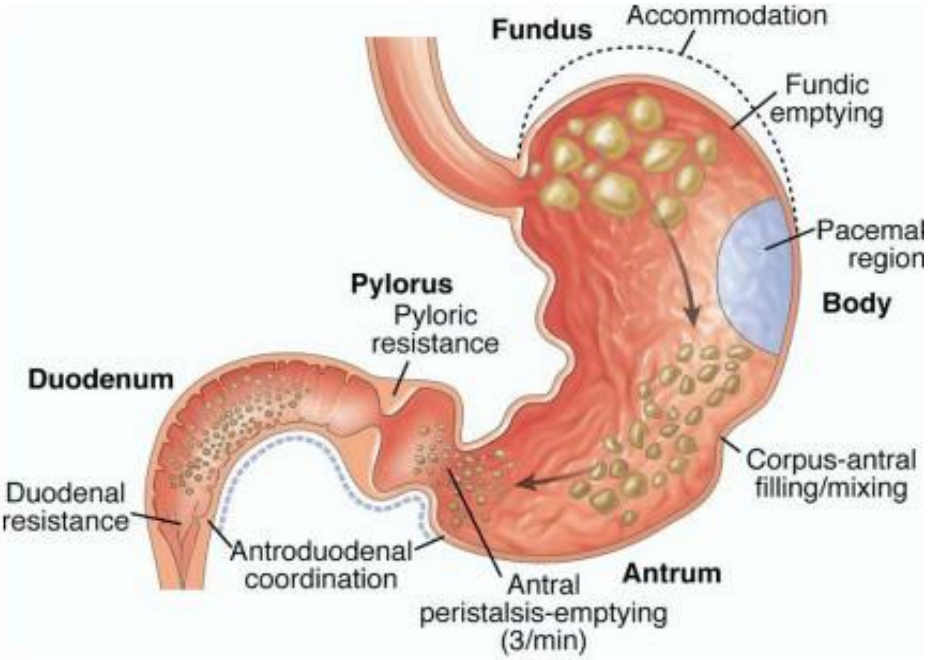
➢ Treatment

- ○ High dose PPI (e.g., Omeprazole 40 mg bid, Pantoprazole 80 mg bid)
  - – Consider
    - ▪ Lanreotide
    - ▪ Octreotide
- ○ Surgery
  - − Sporadic (no (no MEN1)
    - ▪ Malignant in 60% - 90% → resect tumour
    - ▪ If cannot find tumour still advise explorative laparotomy
  - − With MEN1
    - ▪ Surgical resection of tumour > 2 cm (controversial)
- ○ Chemotherapy
  - − Metastatic disease
  - − Local tumour spread

- Normal Gastric Emptying

➢ Anatomical approach

- Fundus
  - Liquid emptying
  - Accommodation/storage
- Body (Pacemaker)
  - Interstitial cells of Cajal (ICCs)
- Antrum
  - Mixed and grinding food < 2 mm (chyme)
- Pylorus
  - Contractions from postprandial grinding
- Antroduodenal
  - Coordination of relaxation of pylorus with contract of antrum (gastric emptying rate)



Source: Brandstaeter S, et al. GAMM - Mitteilungen 2019; 42:e201900001 (Figure 3)

- Gastroparesis

➢ Definition

- Gastroparesis
  - Abnormal gastric emptying in the absence of a mechanical obstruction
- Symptoms
  - Nausea
  - Vomiting
  - Bloating
  - Early satiety
  - Abdominal pain
  - Weight loss

- Functional Dyspepsia* (Rome IV Criteria)

➢ Definition

- Bothersome epigastric pain / burning postprandial fullness, early satiety (including normal upper endoscopy)

➢ Symptoms

- Postprandial distress syndrome (PDS)
  - Meal related symptoms
- Epigastric Pain (EPS)
  - Pain/burning that may or may not be related to meals
- Nausea/vomiting be present

➢ Diagnostic criteria**

- ≥ 1 of the following bothersome
  - Postprandial fullness
  - Early satiation
  - Epigastric pain
  - Epigastric burning

  plus
- No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

*Must fulfil criteria for B1a. PDS and/or B1b. EPS
**Criteria fulfilled for the last 3 mon, with symptom onset at least 6 mon prior to diagnosis

Rome IV Criteria – Postprandial Distress Syndrome

B1a. Postprandial distress syndrome (PDS)

- Diagnostic criteria
  - Must include one or both of the following at least three days per wk
    - Bothersome postprandial fullness (i.e., severe enough to impact on usual activities)
    - Bothersome early satiation (i.e., severe enough to prevent finishing a regular-size meal)
  - No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)
  - Supportive remark
    - Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
    - Vomiting warrants consideration of another disorder
    - Heartburn is not a dyspeptic symptom, but may often coexist
    - Symptoms that are relieved by evaluation of feces or gas should generally not be considered as part of dyspepsia
    - Other individual digestive symptoms or groups of symptoms e.g., from gastroesophageal reflux disease and the irritable bowel syndrome may coexist with PDS.

B1b. Epigastric pain syndrome (EPS)

- Diagnostic criteria
  - Must include at least one of the following symptoms at least one day a week:
    - Bothersome epigastric pain (i.e., severe enough to impact on usual activities) and/or
    - Bothersome epigastric burning (i.e., severe enough to impact on usual activities)
  - No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)
  - Supportive remarks
    - Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting
    - Postprandial epigastric bloating, belching, and nausea can also be present
    - Persistent vomiting likely suggests another disorder
    - Heartburn is not a dyspeptic symptom but often coexist
    - The pain does not fulfil biliary criteria
    - Symptoms that are relieved by evacuation of fees or gas generally should not be considered as part of dyspepsia
    - Other digestive symptoms (such as from gastroesophageal reflux disease and the irritable syndrome) may coexist with EPS

- Pathophysiology
  - Inherited
    - Genetic Predisposition:
      - Some association in studies -> GNB3
  - Infection/microbiome
    - H. pylori infection
      - Eradication leads to relief of dyspepsia in a minority of patients (unclear mechanism)
    - Altered gut microbiome
      - Disruption by medications or recent infection (after gastroenteritis) (Low grade Duodenal inflammation)
  - Inflammation/immune
    - ↑ duodenal eosinophils and mast cell
    - Likely multi-factorial, possible changes in
      - Mucosal immunity
      - ↓ mucosal integrity
      - Microbiome
      - Diet related – unclear
  - Psychosocial comorbidity
    - Depression, generalized anxiety, somatization
    - History of abuse
  - Altered functional
    - Gastric emptying
    - Gastric accommodation
    - Visceral hypersensitivity
    - Dysfunction
      - Mechanoreceptor
      - Chemoreceptor
    - Abnormal processing of afferent input in spinal cord or brain
    - ↑ perception of visceral stimulus

- Gastroparesis

- Causes/Associations
  - Commonly idiopathic
    - Diabetic or post-surgical
      - Risk of gastroparesis
      - Idiopathic gastroparesis
        - 90% females (depression and anxiety are common)
      - Post-infection
        - Ask about viral prodrome (suggests viral – 80% will resolve after 1 yr)
      - Post-surgical
        - Fundoplication)
        - Gastro-jejunostomy
        - Vagotomy
        - Whipple
        - Post-fundoplication gastroparesis resolves in 90% of patients within 1 yr

- Iatrogenic (drugs)
  - GLP-1 agonist (i.e., glutide)
  - Amylin agonist (pramlintide)
  - Opioids, tramadol, marijuana, anticholinergic, TCA, dopamine agonists
  - Other
- Endocrine
  - T1DM, 5%, over 10 yr
  - T2DM, 1%, over 10 yr
  - Hypothyroid
  - Hyperparathyroid
  - Addison disease
- Musculoskeletal
  - Scleroderma
- Neurological
  - Parkinson disease

- Clinical
  - Nausea/vomiting
  - Abdominal pain
  - Early satiety / bloating

- Diagnosis:
  - EGD +/- imaging to rule out gastric outlet obstruction (GOO)
  - Laboratory work to evaluate for underlying treatable etiology
  - Scintigraphic gastric emptying
    - Retained meal at 4 h
      - Mild, 11-20%
      - Moderate, 21-35%
      - Severe, 35-50%
      - Very severe, >50%
  - Wireless Motility Capsule (no longer available)
  - Spirulina C-13 Breath test

- Treatment
  - Treat associated condition
    - Co-existing constipation (can exacerbate)
    - Fluid and electrolytes imbalance
    - Stop offending medications
  - Nutrition
    - Small, low fat, low residue diet
      - Small particle diet (“easy to mask with a fork”)
      - Nasoduodenal preferred; venting gastrostomy, jejunostomy or PEG-J

- Medications (prokinetics)
  - Metoclopramide
  - Domperidone
  - Erythromycin
  - Avoid (do **not** work for gastroparesis)
    - Tricyclic antidepressant (TCAs)
    - Intrapyloric injection of botulinum toxin
  - Surgery (if refractory)
    - Gastric electrical stimulation
    - Gastric per-oral endoscopic myotomy (G-POEM)
      - Larger studies needed

- Overlap
  - Functional Dyspepsia and Gastroparesis likely represent a spectrum and distinct disorders
    - Mild-moderate delayed gastric emptying
      - More like functional dyspepsia
      - Severe delay in gastric emptying
      - More specific for gastroparesis

- Treatment
  - Make a positive Diagnosis
    - Give patient explanation and reassurance
  - Diet
    - Eat multiple small meals
    - Avoid
      - High fatty meals
      - Carbonated beverages
      - Spices
  - Lifestyle
    - Avoid
      - Smoking
      - Alcohol
      - Coffee
  - Avoid NSAIDs, where possible
  - Test and treat for H. pylori infection
    - H. pylori eradication showed significant improvement in symptoms compared to the control group
      - RR 1.18; 95% CI: 1.07 – 1.30, P< 0.01 (Kang SJ, et al. J Clin Med 2019;8(9): 1324)

- PPIs
  - PPI ↓ in global symptoms of dyspepsia superior to placebo (RR 0.89; 95% CI: 0.84-0.94)
    - Most trials dosed the PPI at a dose of once daily

    (Pinto-Sanchez MI, et al. The Cochrane database of systematic reviews 2017, 3(3), CD011194)
  - PPIs superior to prokinetics (PKs) RR 0.90 (95%CI: 0.81-1.00
  - Pro-motility agents may be beneficial as additive therapy
  - However, in patients with functional dyspepsia PPI therapy is favored and preferential to the use of prokinetic agents
  - Note: The main agent studied is cisapride which has been withdrawn from the Canadian market

  (Moayyedi P, et al. Am J Gastroenterol. 2017l;112(7):988-1013)

- Tricyclic antidepressants (TCA)
  - Amitriptyline and imipramine are the main TCA – studied: Amitriptyline 10 mg daily and increase at 2-wk intervals Until a dose of 20-30 mg reached
  - TCAs ↓ pain-predominant symptoms
  - Not helpful in idiopathic gastroparesis (this result has been demonstrated in multiple additional randomized clinical trials (RCTs)
    (Talley NJ, et al. Gastroenterology 2015, 149(2), 340–9)
  - 40-80% of patients with functional disorders of the gut-brain axis have reported visceral hypersensitivity (assessed via gastric balloon distension)
    - “decreased sensory thresholds to pain/discomfort”

- Prokinetic
  - Pro-motility agents
    - Improve clinical outcomes and ↓ symptom burden
  - There is no consistent relationship between symptomatic improvement and gastric emptying utilizing different drugs.
    - This finding questions the utility of following or even using gastric emptying to quantify disease

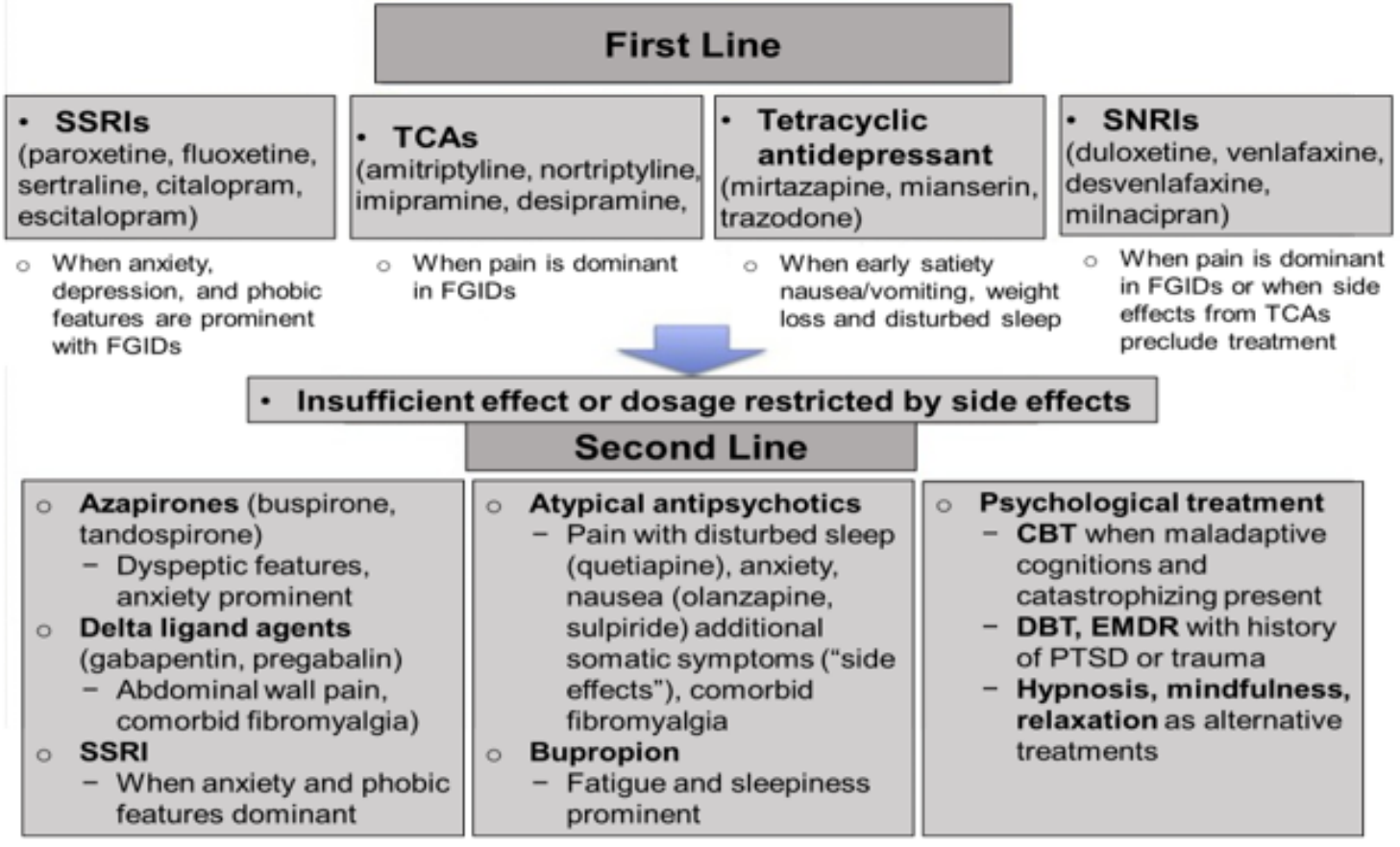
    (Janssen P, et al. Am J Gastroenterol. 2013 Sep;108(9):1382-91)

  - Pro-motility agents may be beneficial as additive therapy
  - However, in patients with functional dyspepsia PPI therapy is favored and preferential to the use of prokinetic agents
  - Note: The main agent studied is cisapride which has been withdrawn from the Canadian market

- Psychotherapy
  - Most commonly studied and recommended psychotherapy – Cognitive Behavioural Therapy (CBT)

  (Moayyedi P, et al. Am J Gastroenterol. 2017;112(9):1484)

Summary of the clinical characteristics that can be considered when selecting gut-brain neuromodulating pharmacotherapy to treat FGIDs.



Those drugs in the upper part of the figure can be considered as first-line options. In the lower part of the figure, the pharmacologic options most often used to augment treatment effects are depicted, as well as some non-pharmacologic treatment alternatives

Adapted from: Drossman DA., et al. Gastroenterology 2018; 154(4): 1140–1171 (Figure 5)

GASTRITIS AND GASTROPATHY

Alan BR Thomson

Atrophic Gastritis (AG)

- Definition
  - "… a preneoplastic condition defined by replacement of appropriate gastric glandular structures with
    - Non-metaplastic atrophy
      - Connective tissue
    - Metaplastic atrophy
      - Chronic inflammation
  - The first of a multi-step precancerous of
    - Intestinal metaplasia (IM)
    - Dysplasia
    - Gastric adenocarcinoma (GAC)

- Cause
  - H. pylori (HP) infection (HpAG)
    - Atrophy +/- IM
  - Autoimmune disease (AIG)
    - Antral sparing
    - Molecular mimic of Hp and gastric ATPase
    - Autoantibodies to parietal cells and intrinsic factors → T-cell-mediated destruction of oxyntic
      - Possible trigger for immune response

- Demography (US)
  - AG ~15% of population
    - Varies with
      - Prevalence of Hp in which risk factors include
        - Family history
        - Non-white racial / ethnic minority groups
        - Early-generation immigrants from high-risk countries (i.e., SE Asia, S. America)
        - Low socioeconomic status
      - Diet
        - ↑ salt
      - Smoking
      - Bile acid reflux, chronic
  - Prevalence
    - Hp-AG, 0.5% to 2%
    - AIG, 0.15% to 1% (Hp-AG > AIG)
  - AIG associated with other autoimmune disease e.g.,
    - Addison disease
    - Diabetes mellitus (DM)
    - Thyroid disease
    - Autoimmune

- Natural History
  - Progression from AIG to GAC 0.1% to 0.3% per yr
  - ↑ risk (2 to 4x) of GAC if associated pernicious anemia (PA)
    - ↑ risk of neuroendocrine tumours of GI tract (incidence, 0.4 to 0.7% per yr)
  - Atrophy
    - Closed (C)
    - Open (O)

    } Grade based on border of atrophy

    - Mild
      - C1 type
      - C2 type
    - Severe
      - O2 type
      - O3 type

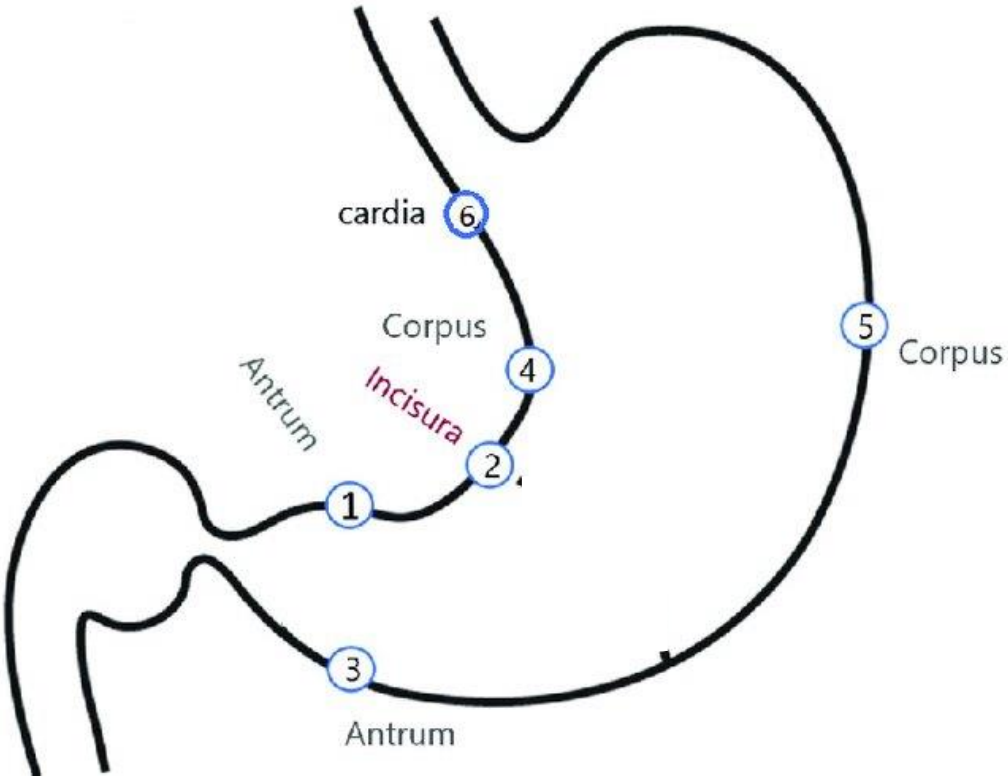
- Laboratory: Serology
  - Parietal cell antibodies (PCAs)
    - ↑ sensitivity
    - ↓ specificity (↑ FPV (false positive predictive value)
      - FPV: PCA+ in
        - H. pylori infection
        - Autoimmune conditions (other than AIG)
  - Intrinsic factors antibodies (IFA)
    - ↓ sensitivity (30%)
    - ↑ specificity; ↑ specificity with ↑ duration of disease
  - Pepsinogens (PGs)
    - Body, fundus
    - Pylorus, Brunner glands
    - Severe atrophy of body
      - PG I < 70 µg/L
      - PG I/II ratio < 20

      } Suggests high sensitivity/specificity

- Endoscopy

- Evaluation
  - Slow/careful
  - Insufflation of air
  - Cleaning
    - Defoaming
      - Simethicone

- Colour/texture
- Gastric rugae
- Blood vessels / more prominent due to thin (atrophic) mucosa
- Border of atrophy
- Focal abnormalities
  - High-definition white-light endoscopy (HD-WLE)
  - Narrow band imaging (NBI)
- Photograph all portions of stomach

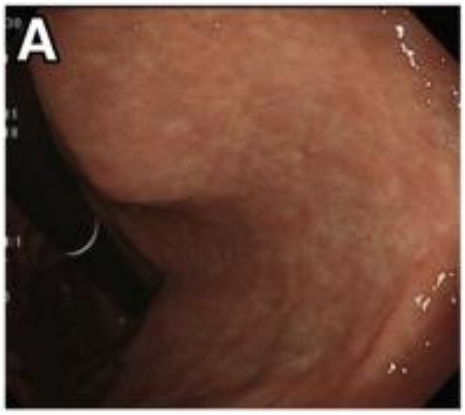


Sites: 1: Antrim: Prepyloric, Pylorus, 2: Distal antrum, Lesser Curvature, 3: Mid antrum, Greater Curvature, 4: Mid Body(corpus), Lesser Curvature, 5: Mid corpus, Greater Curvature, 6: Cardia

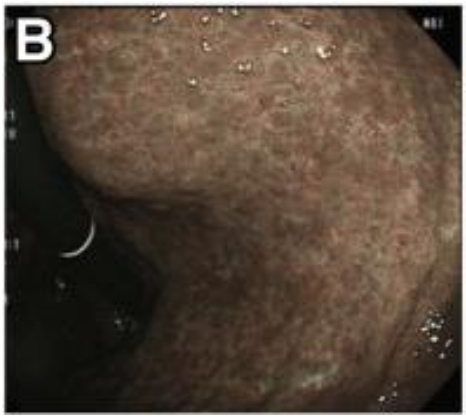
Source: Soltani G, et al. Arch Iran Med 2022;25(6): 394-398 (Figure 1)

- Endoscopic Scoring System

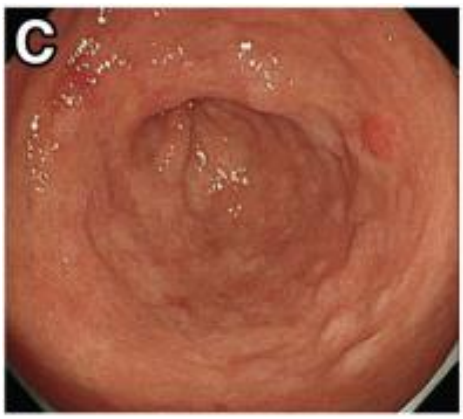
Chronic AG



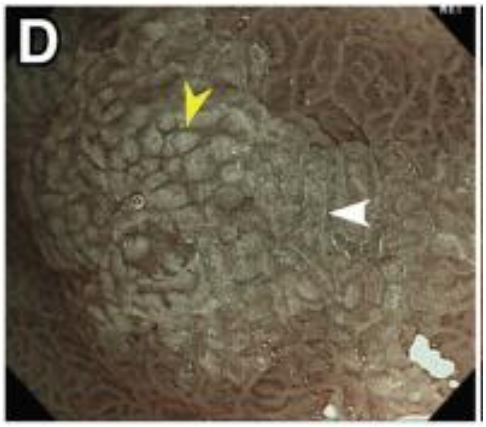
HD-WLE ↓↓ rugal folds



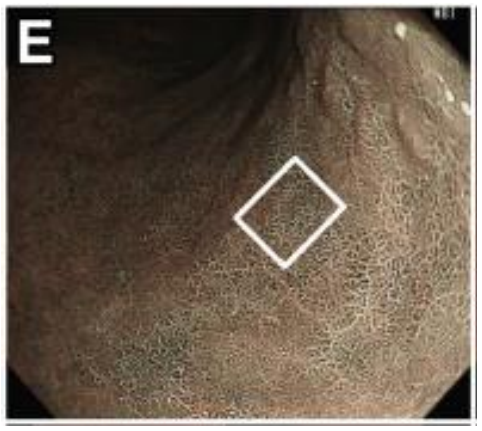
NBI Mucosa Atrophied epithelium
↑ prominence of blood vessels



Nodular on UD-WLE (C)



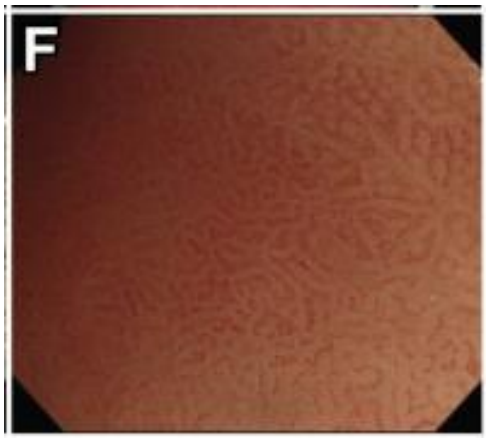
IM (D) Light blue crest (white arrow head) crests on epithelial surface



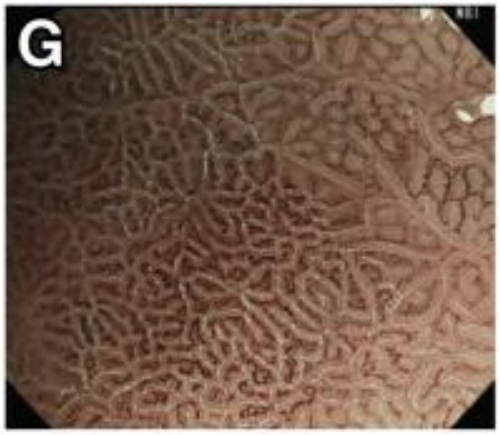
(E) White opaque field (WOF; yellow arrow head; aka white opaque substance [WOS], light scattering on microscopic lipid droplets in the mucosa

Use NBI to see LBC and WOF/WOS

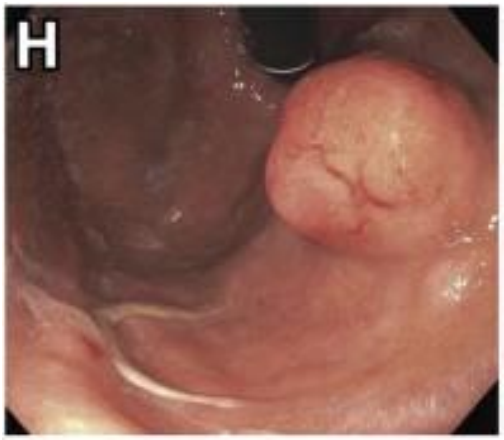
IM No NBI ↓ visibility of IM



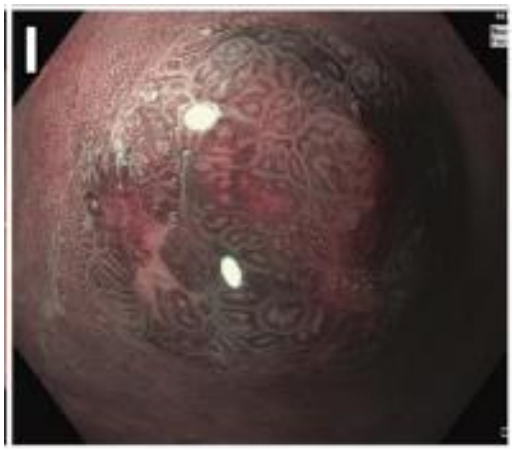
With NBI



LBCs in IM, plus non-IM (top R)



NETs on HD-WLE



NETs in near-focus NBI

Printed with permission: Shah SC, et al. Gastroenterology 2021; 161(4): 1325-1332.e7 (Figure 2).

➢ Performance Characteristics

Diagnostic	Endoscopy	Findings	Performance Characteristics Sn	Sp
○ AG in body	− Chromoendoscopy − Image-enhanced − Magnification	▪ Loss of Rugal folds − Moderate − Severe		67% 85%
○ IM dysplasia	− AD-WLS / WBI	▪ Nodular	87%	97%
		▪ Ridge	92%	99%
		▪ Tubulovillous ▪ Light-blue crest (LBC) (fine, blue-white lines on crests of epithelial surface)		90% PPV, 8.98 NPV, 0.12
		▪ White opaque substance (opaque fields of microscopic droplets of lipids)	50%	100%

Abbreviations: LBC, light-blue crest; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

➢ Histopathology

- Hp AG
  - Incisura
  - Antrum transitional mucosa small foci
    − ↓ gland atrophy
    − IM
    → Large patches
    − Lesser curve
    − Antrum
    ▪ Atrophy
    ▪ IM
  - Body
    − Spread from antrum → body

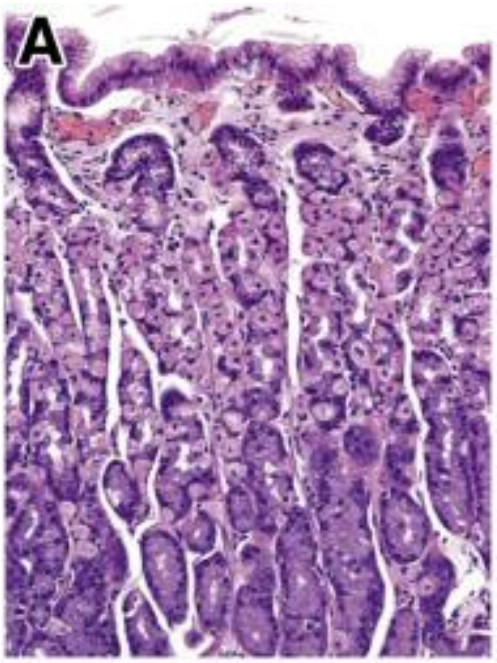
- AIG
  - Body
    − ↓ individual oxyntic glands
    − Lymphocytes
    → ▪ Pseudopyloric metaplasia mucosa
    ▪ IM

○ Gastric IM can be identified in superficial/deep biopsies

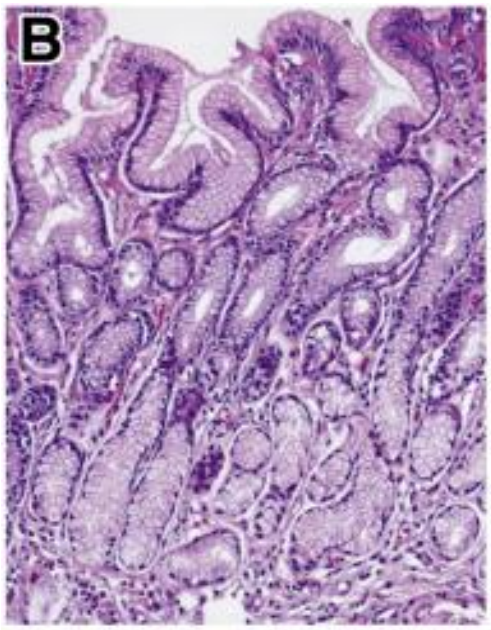
  - Antrum
    − Involvement in AIG suggests associated Hp infection
    − Spread from body/fundus
      ▪ No spread to antrum

- Stains: gastrin (antrum) / pepsinogen I body
    - Distinguish antral mucosa from pseudo pyloric metaplasia

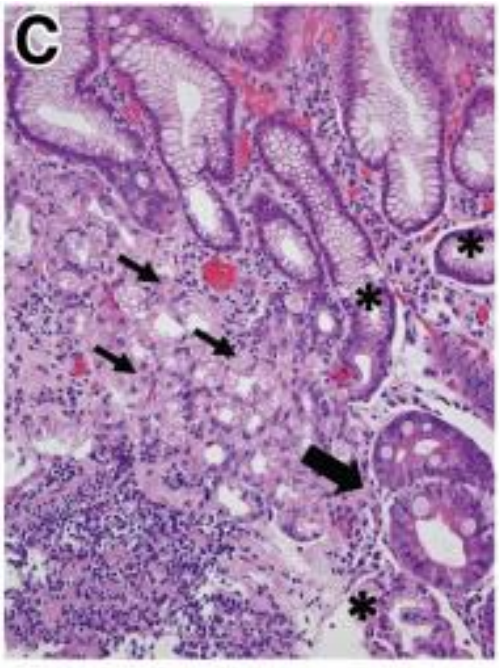
Histopathologic features of normal gastric mucosa, chronic AG, and gastric NET. (A) Normal gastric oxyntic mucosa, characterized by short foveolae (pits) and tightly packed, straight glands.



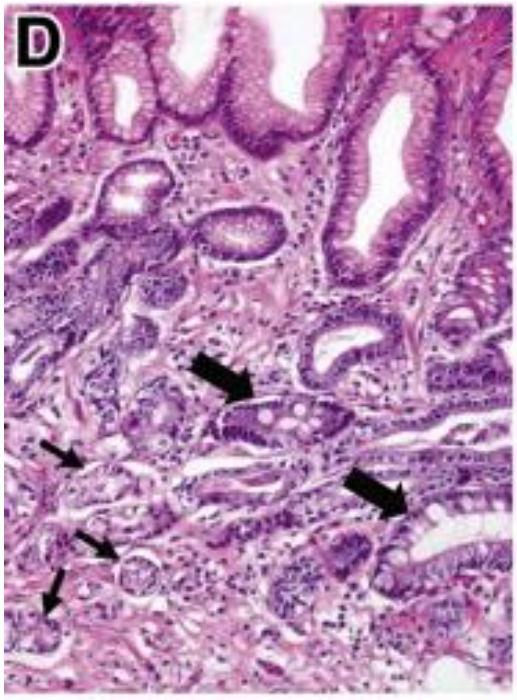
- Normal mucosa
    - Oxyntic area
        - Pits/foveolar
            - Short
            - Packed
        - Glands
            - Straight
            - Upper 2/3 pink parietal cells
            - Lower 1/3 purple chief cells



- Normal antrum
    - Foveolar
        - Wide
    - Packed
        - Loosely
    - Cells
        - Mucus-secreting
        - G-cells

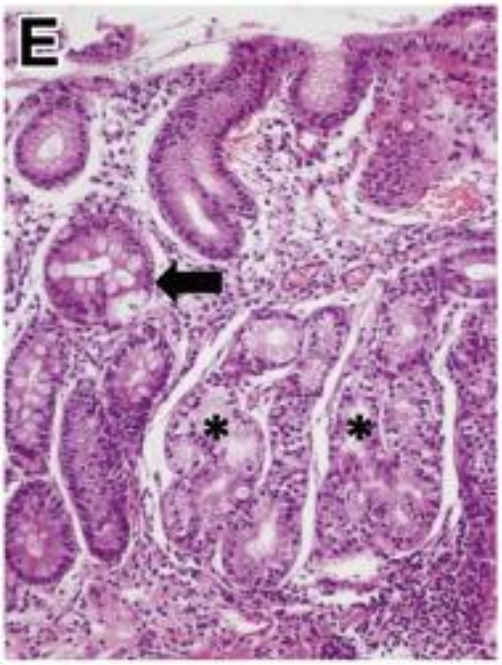


- Chronic gastritis
  - Inflammatory cell, chronic
  - Glands
    - Wide
    - ↓ oxyntic cell
      - Short (thin arrows)
      - Disorganized: in severe chronic gastritis, oxyntic atrophy
    - Metaplasia
      - Pseudopyloric (asterisks)
      - Intestinal metaplasia (IM; thick arrow)

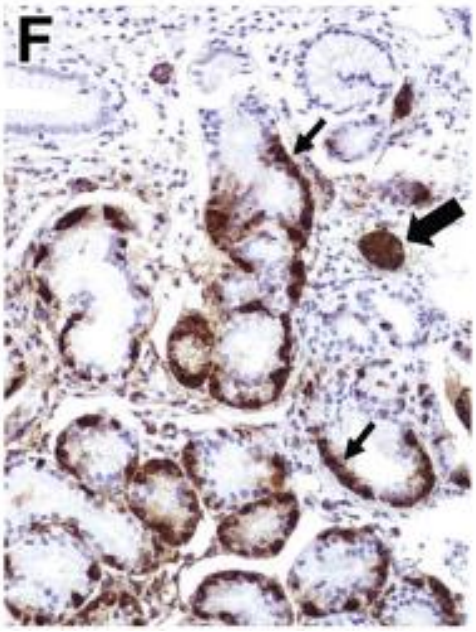


- Autoimmune gastritis
  - Antrum
    - Glands small (thin arrows)
    - IM, focal (thick arrows)
    - Fibromuscular tissue, lumen propria

- Body
  - ↓ oxyntic cells / ↑ lymphocytes



- Metaplasia
  - Pseudopyloric (asterisks)
  - Intestinal (arrow)



- ECL hypermetaplasia
  - Linear (thin)
  - Micronodular
  - Pseudopyloric
  - Chromogranin positive

Printed with permission: Shah SC, et al. Gastroenterology 2021; 161(4): 1325-1332.e7 (Figure 1).

- Classification
  - Predictions of progression of IM to GCA
    - Operative Link for Gastritis Assessment (OLGA)
  - Kimura / Takemoto
    - Operative Link for Gastritis Metaplasia Assessment (OLGIM)
  - Predictors of diagnosis
    - Gastric biopsy showing IM
      - Suggests AG
    - Extensive atrophy plus IM
      - Suggests ↑ risk of GCA
  - Sydney protocol for topographic biopsies
    - Sensitivity to diagnose H. pylori infection, 100%
    - Site (separate, if possible)
      - Antrum, 2 (1 from lesser and one from greater curve), within 2 to 3 cm of pylorus
      - Gastric body, 2 within
        - 1 from lesser curve, 4 cm proximal to incisura angularis
        - 1 from greater curve, 8 cm from cardia
      - Incisura angularis biopsies from endoscopically abdominal areas

      *also take targeted

- Treatment

- Overall
  - Test for H. pylori infection (acute) with breath or stool biopsy studies
    - If positive
      - Treat and repeat study for Hp to confirm eradication
      - Only some patients with cleared Hp infection will return to normal ("point-of-no-return"), and continue to have risk for progression of AG to dysplasia → GCA
    - For these patients with gastritis associated with Hp infection, treated but not eradicated
      - Continue surveillance with EGD plus biopsies (because of their risk of developing GCA)
  - Treat any associated iron/B12 deficiencies
  - Treat any associated autoimmune conditions
  - Implement an appropriate surveillance program (EGD plus 5 gastric mucosal biopsies.

Recommendation(s): Non-EGD

- Test for Hp, treat If positive and confirm eradication
- Evaluate for anemia
- Evaluate for micronutrient deficiency, such as iron and vitamin B12 (irrespective of anemia)

- In patients with AIG
  - Screen for autoimmune thyroid disease
  - Low threshold to evaluate other autoimmune diseases based on clinical presentation (type I diabetes)
- Check PCA and IFA in patients with endoscopic/histological findings consistent with AIG, corpus-predominant pattern with astral sparing.

Clinical Cautions

- The rate of progression of AG → metaplasia → dysplasia → GCA if AG is associated with Hp infection.

- Surveillance: EGD plus 5 gastric biopsies
  - Suggestions, but no evidence base
    - Advance AG – q3 yr
    - ↑ frequency / ↓ interval if patient has multiple high risk factors
      - Family history of GCA
      - Migration from geographical area with ↑ risk of GCA
      - Persistent Hp infection despite multiple trials of guideline-based eradication therapy
      - Smoking
      - Dietary risks
  - Known pernicious anemia
    - EGD plus 5 biopsies within 6 mon of diagnosis of PA (highest rate of GCA in PA is first yr after diagnosis of PA)
    - Development of upper gastrointestinal symptoms (e.g., dyspepsia)

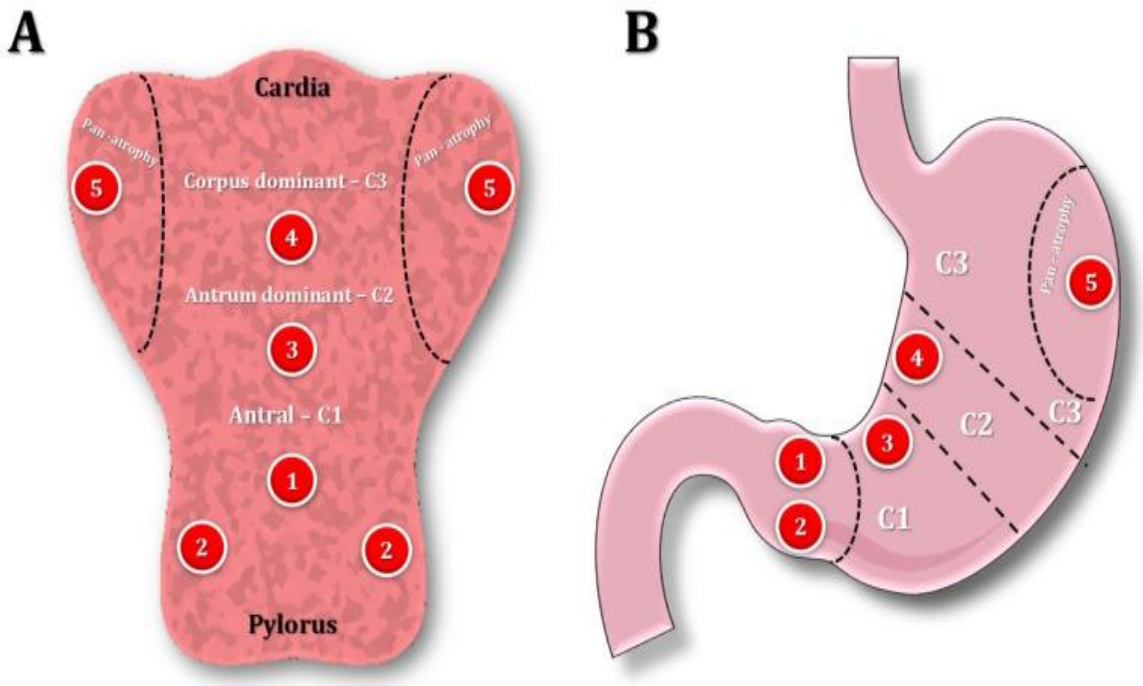
Recommendation(s): Endoscopic

- Obtain topographic biopsies to determine anatomic extent and histologic severity for risk stratification.
- Surveillance endoscopy should be considered in patients with
  - Advanced AG: q3 yr
  - AIG: interval based on individualized assessment
- In patients with newly diagnosed PA, upper endoscopy should be considered for risk stratification and to evaluate for prevalent gastric neoplasia and NETs

- Neuroendocrine Tumours (NETs)
  - 80% to 90% associated with AG
    - Most gastric NETs are associated with Hp
  - Small NETs (< 10 mm)
    - Gastric body/fundus
    - Well-differentiated
    - Polypoid
    - Yellow/red on HD/WLE
    - Slow growing
    - EGD
      - Resection, followed by repeat EGD plus biopsies q1-2 yr
      - Interval depends upon
        - Size/number (tumour burden)
        - Depth
        - Mitotic activity of tumour
  - Large NETs
    - > 1 cm to 2 cm
      - Perform endoscopic ultrasound (EUS) to establish tumour
        - Depth
        - Metastases, local
    - > 2 cm
      - Surgical resection plus invasion into
        - Submucosa
        - Lymph nodes
  - Rate of metastases
    - ≤ 2 cm, 10%
    - > 2 cm, 20%

- Classification System
  - Kimura–Takemoto classification systems and
  - Updated Sydney

  } For the endoscopic and histopathologic staging of CAG



  - Images depict the stomach
    - opened along the greater curvature (A) and
    - in a traditional coronal view (B)
  - Endoscopic atrophy grading according to the Kimura–Takemoto classification system 60:
    - antral (C1)
    - antral-predominant (C2)
    - corpus-predominant (C3), and
    - pan-atrophy
  - The circled numbers refer to the location of gastric biopsies, taken according to the updated Sydney system.

Source: Tziatzios G, et al. Curr Oncol 2024; 31(7):3923-3938 (Figure 4)

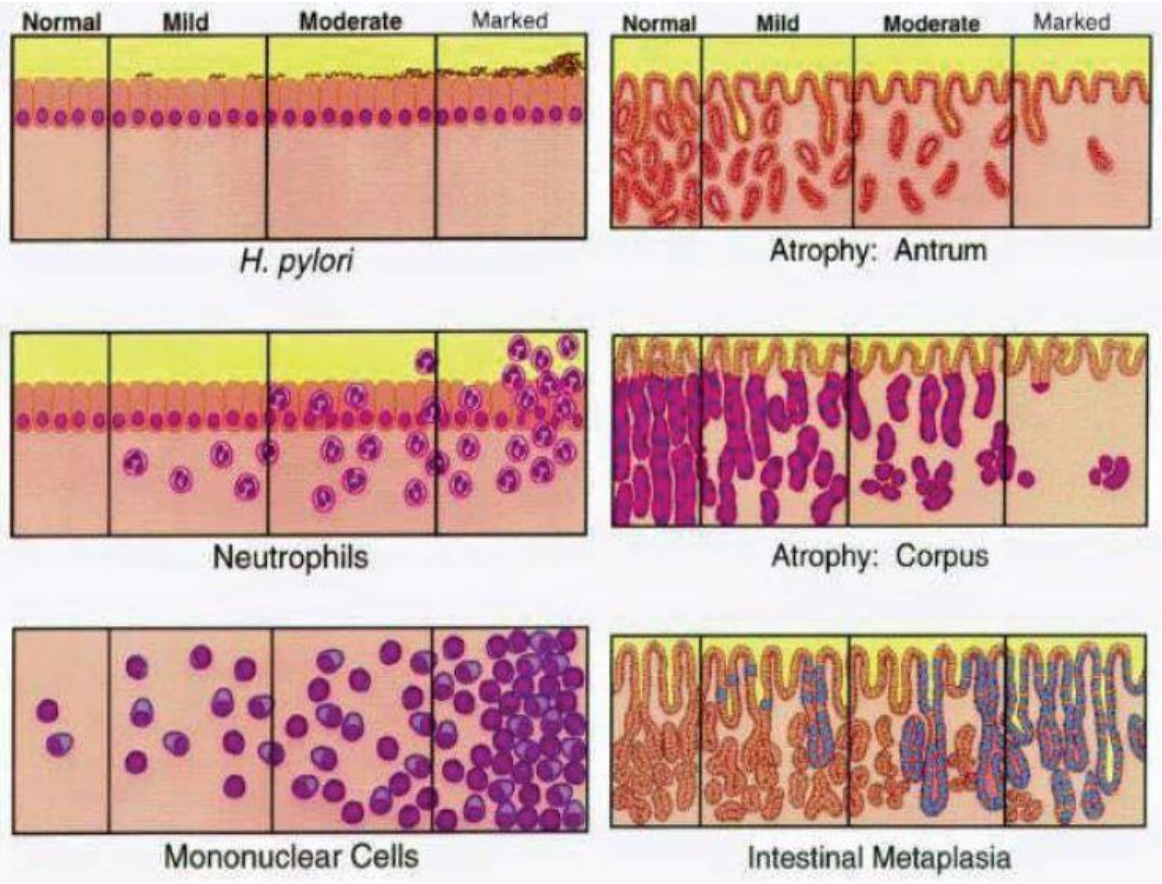
- Updated Syndney Classification for Histopathological Staging of chronic AG
- The Kimura-Takemoto classification "…categorizes AG…based on the extent of the atrophic border, e.g.
  - Closed type
    - C1, atrophy limited to the antrum
    - C2, limited to the antrum and the lesser curve of the distal gastric body
    - C3, limited to the antrum and the lesser curve of the proximal gastric body
  - Open type
    - C1 to C3 plus atrophic border extending from the anterior wall (0-1) to the greater curve
    - The risk of GCA is greater for extreme AG (open-type) versus closed type (particularly C1-C2)

➢ OLGA Classification System for Risk Assessment in AG

Atrophy score Antrum	Corpus			
	No atrophy (score 0)	Mild atrophy (score 1)	Mod atrophy (score 2)	Severe atrophy (score 3)
No atrophy (score 0) (incl incisura angularis)	STAGE 0	STAGE I	STAGE II	STAGE III
Mild atrophy (score 1) (incl incisura angularis)	STAGE I	STAGE I	STAGE II	STAGE III
Mod atrophy (score 2) (incl incisura angularis)	STAGE II	STAGE II	STAGE III	STAGE IV
Severe atrophy (score 3) (incl incisura angularis)	STAGE III	STAGE III	STAGE IV	STAGE IV

Source: Sipponen P and Maaroos HI. Scandinavian J Gastroenterology 2015, 50(6), 657–667 (Figure 8)

- Sydney classification for gastric biopsy



Source: Bontha VK. J. Gastroenterology Pancreatology and Hepatobilary Disorders. 1(1). doi. 10.31579/2641-5194/003 (Figure 1)

- OLGA classification for risk assessment in AG
  - For assessment of AG risk for GCA
  - Kimura-Takemoto and OLGA systems correlate

GASTROPARESIS

Yousef Almahanna

- Definition
  - It is the objective evidence of delayed gastric emptying in the absence of mechanical obstruction
  - Derived from the ancient Greek:
    - Gaster = stomach
    - Paresis = partial paralysis
- Demography
  - Prevalence: ~14 to 268 per 10^5 adults
  - Females > males
- Anatomy and physiology
  - The gastric motor function depends on 3 levels of control
    - Autonomic nervous system:
      - Parasympathetic through the vagal nerve and sympathetic nervous systems
    - Enteric neurons and interstitial cells of Cajal (ICC)
    - Smooth muscle cells control
  - Peristaltic reflex – responsible for propulsion of food from stomach to intestine
    - This has two components:
      - Ascending contraction secondary to distention from food bolus (depends on acetylcholine [ACh])
      - Descending inhibition below the level of distention to allow the bolus to travel down (depends on nitric oxide [NO] and VIP)
- Pathogenesis of gastroparesis
  - Each region of the stomach can be affected by a pathologic process that can lead to ↓ gastric emptying.
    - Fundus:
      - Vagal nerve injury
      - Diabetes mellitus (DM)
    - Antrum
      - Antral motor function is critical for the grinding, mixing, and emptying of solids from the stomach.
      - ↓ antral contractions/function secondary to neuropathic disease or infiltrative disease i.e., systemic sclerosis, or
      - Autonomic neuropathy and
      - Hyperglycemia (by DM)
    - Pylorus
      - Idiopathic hypertrophic pyloric stenosis: (secondary to loss of inhibitory NO)
      - Diabetic gastroparesis
        - ↑↑ tonic and phasic pressure activity at the level of the pylorus

- Idiopathic

➢ Causes/associations

- Most common cause of GP (40% of patients per yr; incidence %)
- Associated with gastric dysrhythmia secondary to severe loss of intestinal cells of Cajal (ICC)
- Sometimes be attributed to triggers such as:
  - Post-viral
    - Norwalk or rotavirus usually improves within 1 yr
    - CMV/EBV, VZV may lead to persistent symptoms due to dysautonomia
  - Drug-induced
    - Cannabinoids (CCB)
    - Dopamine agonists
    - GLP-1 agonists
    - Immune checkpoints inhibitors (ICIs)
    - Narcotics
    - Octreotide
    - Tricyclic antidepressants (TCAs)

- Diabetic gastroparesis

➢ Pathophysiology:

- ↓ ICC and abnormal enteric nerve endings →
  - Abnormal postprandial proximal gastric accommodation/contraction
  - ↓ frequency of antral contractions.
  - Possible component of pylorospasm

➢ Cumulative incidence over 10 yr

- DM1, 5%; DM2, 1%

- Functional pyloric obstruction
  - Secondary to pylorospasm:
    - Prevents normal gastric peristaltic waves emptying chyme into duodenum
      - May be associated with tachygastria, leading to coordination of antral contraction and pyloric relaxation
- Post-surgical (20%)
  - Intended / accidental injury to vagal nerve
    - Vagotomy
    - Fundoplication
    - Billroth 1, Billroth 2, Roux-en-Y
    - Post radiofrequency ablation (RFA) for atrial fibrillation
    - Post botulinum toxins for achalasia treatment

- Ischemic gastroparesis:
  - Secondary to chronic mesenteric ischemic from underlying ie atherosclerosis.

- Systemic diseases
  - Neurological
    - Amyloid neuropathy
    - Multiple sclerosis (MS)
    - Parkinsonism
  - Autoimmune GI dysmotility

➢ Clinical

- History
  - Abdominal pain
  - Bloating
  - Early satiety / post prandial fullness
  - Nausea / vomiting
  - Weight loss
- Physical
  - Abdominal tenderness / distension
  - Volume depletion / poor nutrition
  - Features of associated systemic disease

➢ Laboratory

- Hemoglobin, fasting plasma glucose, serum total protein, albumin, TSH, ANA.
- HbA1c (to assess their glycemic control)
- ANNA-1 or anti-Hu antibody (in search for possible paraneoplastic gastroparesis)

➢ Diagnostic Imaging

- CT/MR enterography (rule out mechanical obstruction)
- Upper GI series (if CT not available)
- Scintigraphic gastric emptying
  - Avoid/stop drugs that can cause delayed gastric emptying at least for 48 hours.
  - Control blood glucose < 10 mmol/L
  - Give low fat radiolabeled egg-white meal
    - Image immediately afterwards (time 0), then at 1, 2, 4 h following ingestion
  - Interpretation
    - Positive study if
  - There is ↑ gastric retention, which signifies ↓ gastric emptying (rate)
    - 2 h, > 60%
    - 4 h
      - 10-15%, mild
      - 15-35%, moderate
      - > 35%, severe

➢ Management

- **Mild** (gastric retention on scintigraphy at 4 h: 10 to 15%)

↓

Dietary modification, blenderize food when symptomatic, restore fluids and electrolytes, glucose control in diabetics

↓

Nutritional support (rarely needed)

↓

Metoclopramide liquid 10 mg po tid, when necessary

↓

Diphenhydramine 12.5 mg orally q6-8 h, when necessary

- **Moderate** (gastric retention on scintigraphy at 4 h: 15 to 35%)

↓

Dietary modification, blenderize food when symptomatic, restore fluids and electrolytes, glucose control in diabetics

↓

Calories, liquids orally, rarely by jejunostomy tube

↓

Metoclopramide liquid 10 mg orally 3-4 times daily, or 5-10 mg SC tid before meals

↓ continued symptoms

Domperidone 10 mg po tid before meals

↓ continued symptoms

Erythromycin base 40 to 250 mg orally tid before meals

↓

Diphenhydramine 12.5 mg orally q6-8 h, when necessary

↓ continued symptoms

Ondansetron 4-8 mg po tid

↓ continued symptoms

Prochlorperazine 5-10 mg po tid or 5-25 mg bid per rectum, when necessary

- **Severe** (gastric retention on scintigraphy at 4 h: 15 to 35%)

↓

Dietary modification, blenderize food when symptomatic, liquid nutrient supplements as routine, restore fluids and electrolytes, glucose control in diabetics

↓

Caloric liquids orally by jejunostomy tubes

↓

Metoclopramide liquid 10 mg orally 3-4 times daily, or 5-10 mg SC tid before meals

↓ continued symptoms

Domperidone 10 mg po tid daily before meals

↓ continued symptoms

Erythromycin base 40 to 250 mg po tid before meals

↓

Diphenhydramine 12.5 mg po q6-8 h, when necessary

↓ continued symptoms

Ondansetron 4-8 mg po tid

↓ continued symptoms

Prochlorperazine 5-10 mg po tid or 5-25 mg bid per rectum, when necessary

↓

Gastrostomy tube for decompression and jejunostomy for feeding
Compassionate use gastric electrical stimulation or surgical therapy

Adapted from: https://www.uptodate.com/contents/treatment-of-gastroparesis?search=Gastroparesis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

- Diet and life-style modifications:
  - Dietician consultation
  - Avoid
    - Alcohol
    - Carbonated beverages
    - Fatty/spicy food
    - Fibre, non-digestible
    - Smoking
  - Optimize glycemic control

- Prokinetics
  - 1st line: metoclopramide
    - D2 receptor antagonist
    - 5-HT4 agonist
    - Weak 5-HT3 receptor antagonist
    - ↑ gastric antral contractions

- ↓ postprandial fundus relaxation.
- Start with (5 mg) 10-15 min before meals and at bedtime, up to 40 mg daily (divided doses)
- FDA approved to be used for <12 wk.
- Consider brief drug holidays
- Side effects
  - Side effects
    - CNS
      - Extrapyramidal signs (i.e., tardive dyskinesia and dystonia)
    - CVS
      - QTc prolongation
    - Endocrine
      - Hyperprolactin

- 2nd line: Domperidone
  - D2 receptor antagonist
    - 10 mg tid
  - Side effects
    - CVS
      - QTc prolongation (higher risk)
    - Endocrine
      - Hyper-prolactin

- 3rd line: Macrolides (i.e., erythromycin or azithromycin for longer half life)
  - Motilin agonist
    - ↑ fundic contractility
    - ↓ accommodation response of the proximal stomach after food ingestion
    - Limit use to < 4 wk
  - Side effects
    - CNS
      - Ototoxicity
    - CVS
      - QT prolongation
      - ↑ resistance
    - GI
      - GI toxicity
    - Pharmacology
      - Tachyphylaxis

- Anti-emetics (for add-on therapy for symptoms of nausea / vomiting)
  - Dimenhydrinate:
    - H1 plus muscarinic receptor inhibitor, 12.5 mg q6-8 h prn
  - Ondansetron
    - 5HT3 antagonists, 4-8 mg tid, prn

❖ Refractory cases

- Endoscopic approaches
  - Gastric endoscopic pyloromyotomy [G-POEM]
  - Botox injections of LES
  - G-tube
    - Venting and decompression with J-tube for enteral feeding +/- small volume liquid meals via mouth
    - First confirm that patient can tolerate feeding at ~80 cc/hr; nasogastric tube administration of enteral feed
    - Some patients with G-tube feeding welcome use of a tricyclic-antidepressant (TCA)
  - Ballon dilatation of pylorus.
  - Parenteral nutrition

- Surgery
  - Laparoscopic (pyloroplasty)

Resources

https://www.uptodate.com/contents/gastroparesis-etiology-clinical-manifestations-and-diagnosis?search=gastroparesis&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2

GASTRIC ADENOCARCINOMA

Raaed AlRamdan

- Epidemiology
  - Gastric cancer (GC) was the leading cause of cancer deaths in the world until the 1980s
  - This overall decrease incidence occurred despite older population

Year	Incidence	
	US	Japan
1950	36	10
2015	2	5

- Pathogenesis
  - Suggestions for ↓ incidence of GCA
    - ↑ H. pylori eradication
    - Better socioeconomic status
    - Better diet, fresh food
    - Possibly refrigeration

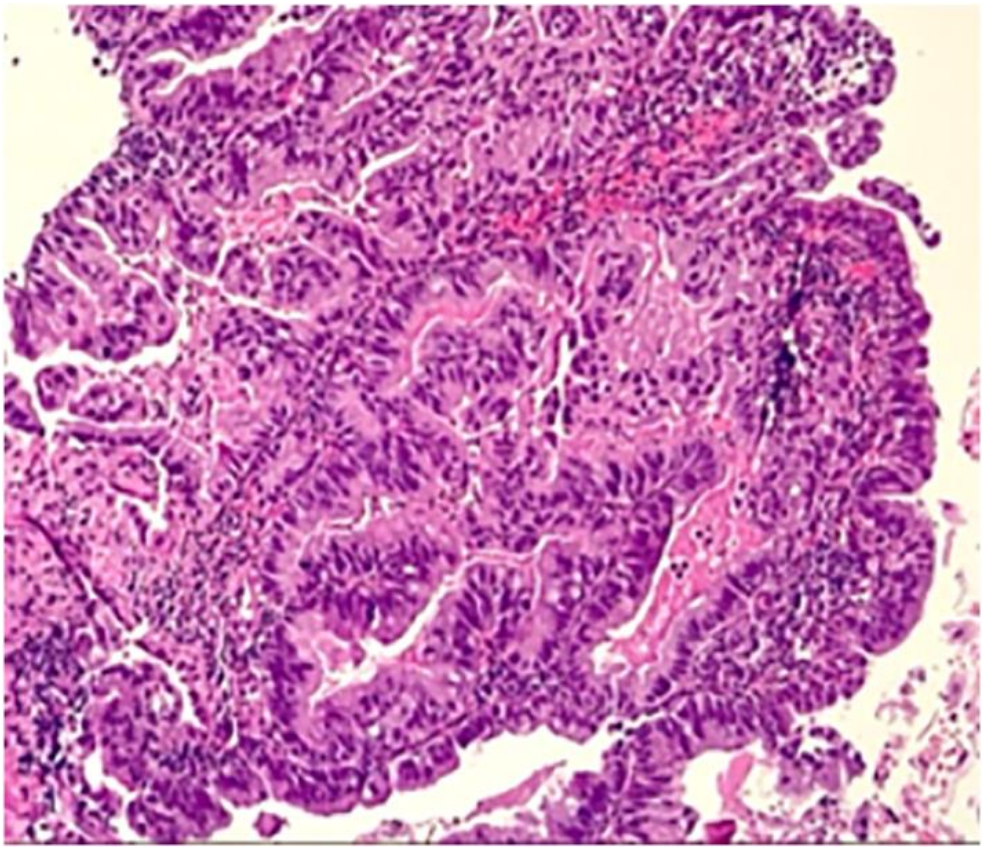
Progression of Gastritis Associated with H. pylori Infection

Normal → Inflammation (Acute → Chronic) → Metaplasia → Low/high grade → Adenocarcinoma of stomach

↑

DIET, e.g., SALT, N-nitrosocarcinogens
pH↑, acid ↓, reactive oxygen species

- Classifications
  - Histology
    - WHO and Laurén
  - Adenocarcinoma
    - Intestinal type (53%)
      - Older patient
      - Lower socioeconomic (SE) status
      - Distal stomach
      - Decreasing incidence
      - Higher differentiated gland-like structure

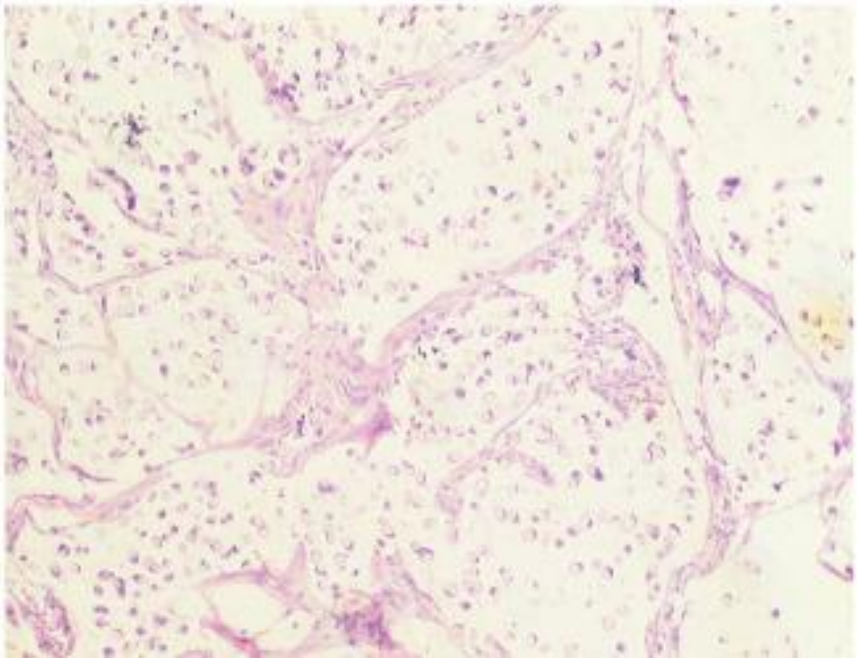


Source: Trujillo-Guerrero L, e Int J Surg Case Rep. 2023;102:107849.

- Diffuse type (15%)
  - Younger patient
  - Higher SE status
  - Proximal stomach
  - Increasing Incidence
  - Poor differentiated signet rings (invasive tumour cells with mucin and no glands)

Signet ring cell type mucinous carcinoma.

A



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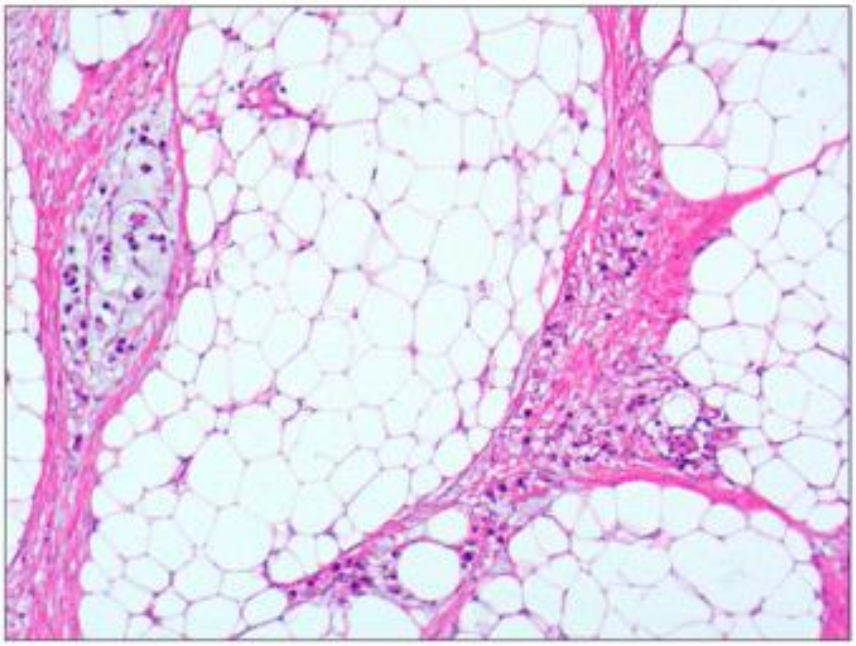

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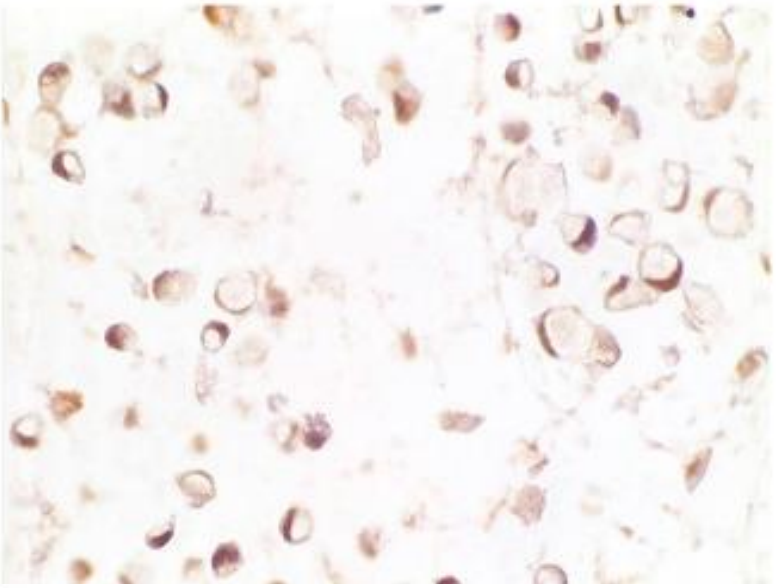

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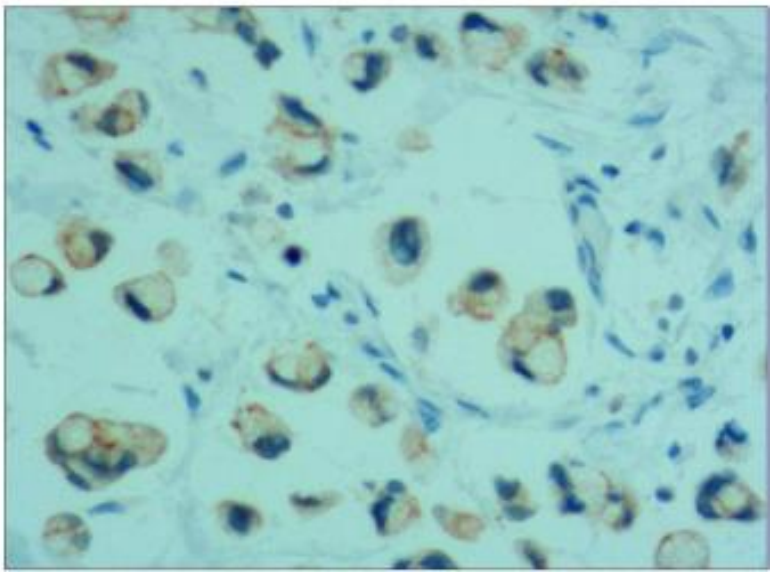
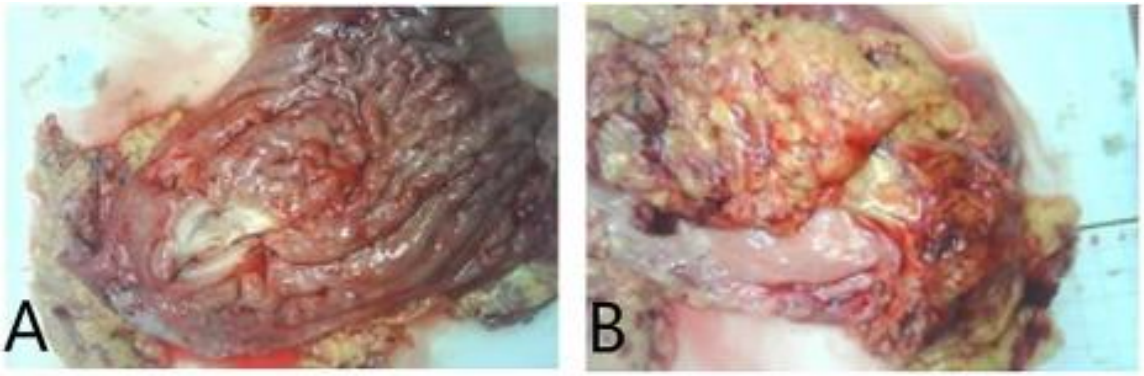


- It was composed of signet ring cell carcinoma cells and mucinous tissues.
  - The cells accounted for 20-80% of the tumour; H&E, × 100.
- (B) The tumour's primary invasion feature was to grow diffusely, jumpily, and invasively and then invade the spaces among the surrounding tissues, lymphatic vessels, and blood vessels to destroy the tissues; H&E, × 100.
- (C) CKpan was positively expressed in the cancer cells; EnVision method™, × 400. (D) DX2 was positively expressed; EnVision method™, × 400.

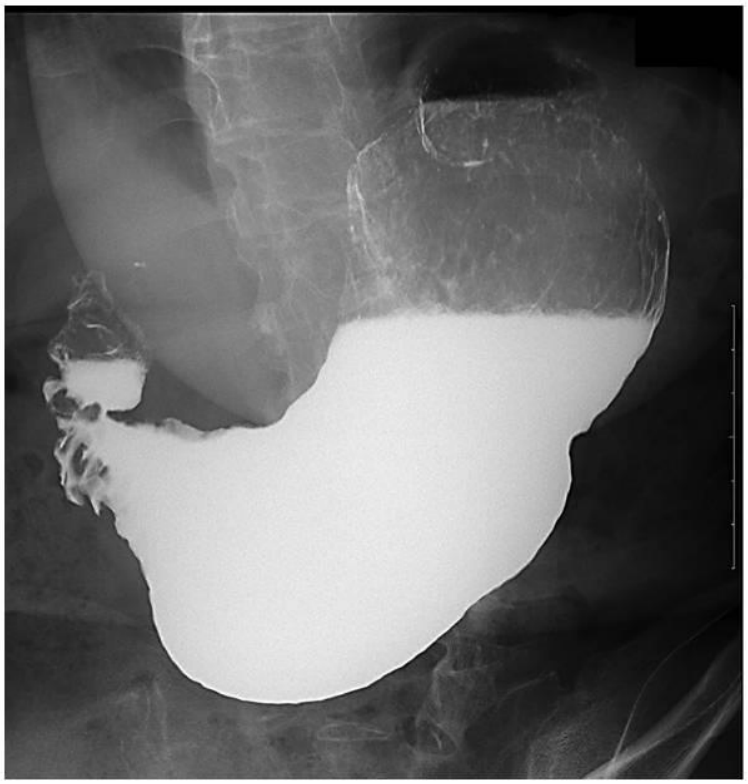
Source: Meng NL, et al. Front Med (Lausanne). 2022; 9:829702.



(A) In the excised specimen of gastric tumour, a hard region of 5x7 cm was observed 6 cm from the distal margin. (B) The retinal tissue excised during the operation was 25x13x1.5 cm in size.

Source: Lin J, et al. A Case Report. Front Oncol. 2021;11:775147.

Gastric Linitis Plastica

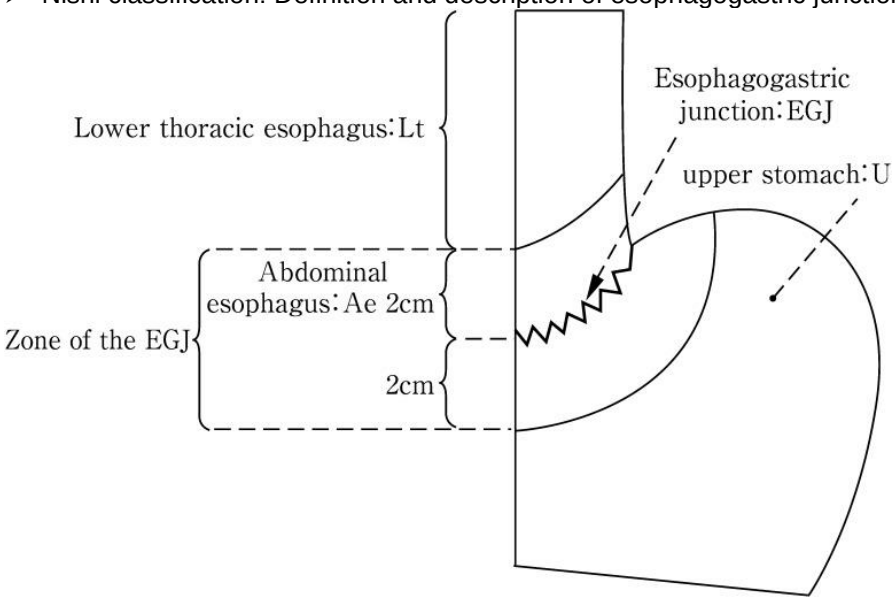


Stomach X-ray of the patient, indicating poor distension of the gastric body.

Source Maeda E, et al. A case report. Oncol Lett. 2015;9(1):262-264. doi: 10.3892/ol.2014.2688.

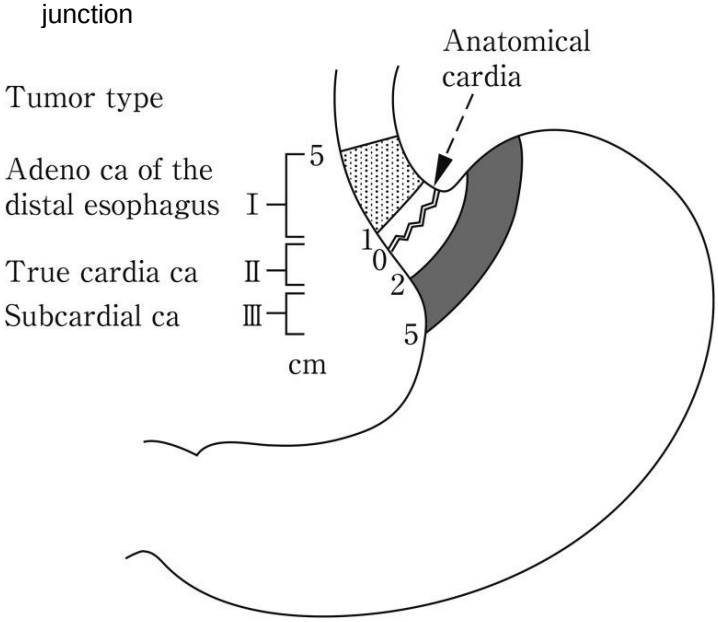
- Lymphoma
- Gastroesophageal junction (18%)
- Location
  - Cardia, 10%
  - Fundus/body, 10%
  - Lesser curve, 25%
  - Greater curve, ~5%
  - Pyloric area, 50%
  - Proximal (junctional)
    - EGJ and cardia
    - Increasing
  - Distal (non-junctional)
    - Fundus, body and antrum
    - Decreasing

➢ Nishi classification: Definition and description of esophagogastric junction



Source: Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. Esophagus. 2017;14(1):37-65.

- Siewert classification: Definition and description of adenocarcinoma at the esophagogastric junction



Source: Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. Esophagus. 2017;14(1):37-65.

  - Depth of invasion
    - TNM
    - Early and advanced

- Risk Factors
  - History of gastric surgery (esp. Billroth II)
  - Patient
    - ↑ age
    - Family history (first-degree relative)
      - Familial adenomatous polyposis (FAP with fundic gland polyps)
      - Hereditary nonpolyposis colorectal cancer (HNPCC)
      - Peutz-Jeghers syndrome
    - Cigarette smoking
  - Genetics
    - The precise genes involved in each step of this progression are not defined
      - The premalignant stages of gastric cancer are not readily identifiable during endoscopy as those of colon cancer

- Stomach
  - Chronic atrophic gastritis
  - H. pylori infection
    - H. pylori classified as a class I definite carcinogen by IARC, WHO
    - Can develop intestinal and diffuse type and mucosa associated lymphoma
    - Phenotype of Hp infection
  - Simple gastritis asymptomatic
  - Duodenal ulcer (10-15%): ↑ gastric acidity → ↓ risk of GCA
  - Gastric ulcer: Atrophic gastritis → ↓ gastric acid →↑ risk of GCA
    - H. pylori is capable of directly modifying DDR (DNA Damage)-related genes
  - Intestinal metaplasia /dysplasia
  - Adenomatous gastric polyps
  - EBV

*The above provides a test of definite risk factors; for probable, possible and questionable risk factors,

- It is considered to be probable/possible that
  - Diet high in salt, pickled food, processed meat (2x ↑ risk of GCA)
  - Preserved food are risk factors for GCA
- Protective factors include ASA, NSAIDs, statins, fresh fruits/vegetables, vitamin C

- Gastric polyps
  - Types
    - Fundic
    - Hyperplasic
    - Adenomatous
  - Caution
    - Endoscopic biopsy of gastric polyps can be associated with significant sampling error.
  - The British Society of Gastroenterology (BSG) guidelines in 2010
    - Biopsy all gastric polyps
    - Remove all gastric adenomas, symptomatic polyps, and polyps with dysplasia
    - Eradicate all H. pylori infections, including in patients with hyperplastic or adenomatous polyps

➢ Clinical

- Early
  - Asymptomatic
- Advanced
  - ↓ weight / pain (the most common)
  - GI
    - Obstruction
    - Dysphagia
    - Early satiety

- Paraneoplastic
  - DIC
  - Nephropathy
  - Neuropathy
  - Trousseau sign
- Skin
  - Acanthosis nigricans
  - Leser-Trelat
- Metastasis
- Laboratory
  - Anemia
  - Albumin
  - Liver enzymes

SO YOU WANT TO BE A GASTROENTEROLOGIST!

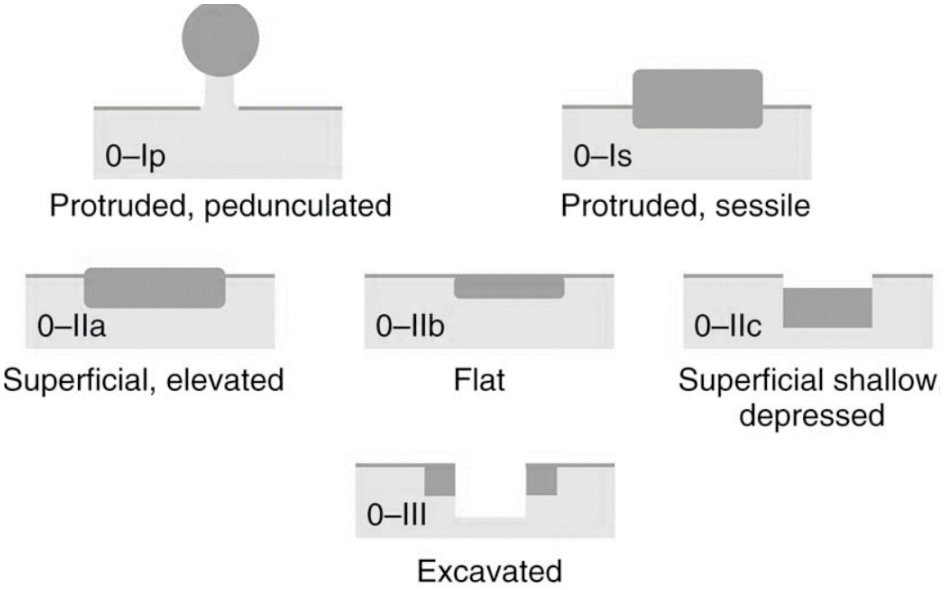
- Give the physical findings which suggest GCA.

Finding	Location
Blumer shelf tumour	Pouch of Douglas
Irish node	Left anterior axillary lymph node
Krukenberg tumour	Ovaries
Sister Mary Joseph node	Umbilicus
Virchow node	Left supraclavicular lymph node

- Premalignant conditions
  - Chronic atrophic gastritis
    - Environmental
      - Multifocal: H. pylori → metaplasia (10x ↑ risk of GCA)
    - Autoimmune
      - Anti-parietal anti-intrinsic factor
  - Intestinal metaplasia
  - Gastric polyps
  - Previous Gastrectomy (Billroth II > I)
  - Gastric ulcer (↓ HCl → ↑ GCA)
  - Ménétrier disease (protein losing gastropathy)

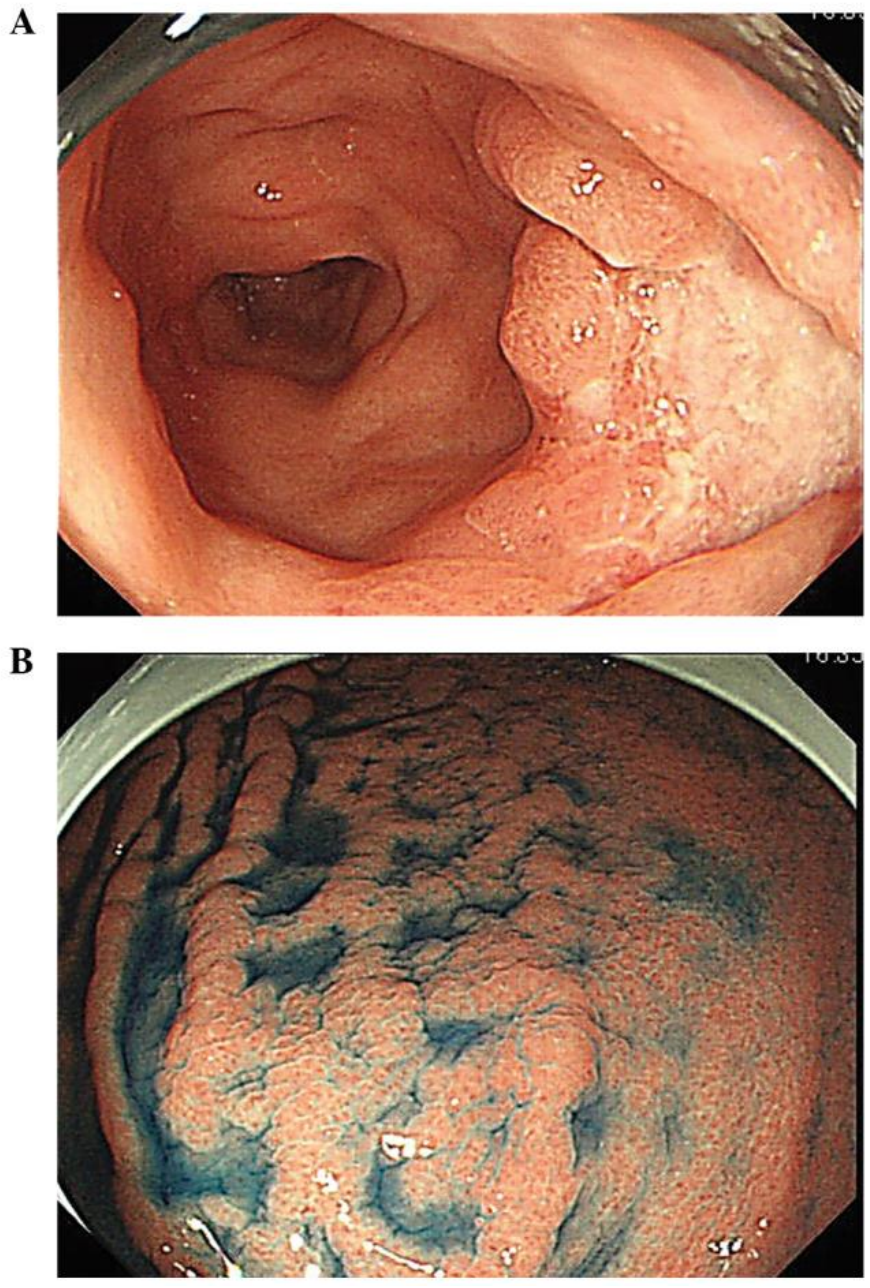
- Diagnosis
  - Serum Marker
    - No reliable serum marker has been identified with high sensitivity and specificity for the diagnosis of gastric cancer.
    - ↑ CEA / ↑ CA 19-9 suggests:
      - Recurrence
      - Poor prognostic
  - Endoscopy
    - Non-healing (8-12 wk) gastric ulcer (take 6-8 biopsies from edge and base of ulcer)
    - EGD for persons > 55 yr with new onset dyspepsia, alarm symptoms or non responders to treatment of gastric ulcer (AGA guidelines)
    - EGD has replaced upper GI series as the initial step according to guidelines

Paris Classification



Printed with permission: Neilson LJ, et al. Frontline Gastroenterol 2015;6(2):117-126.

- Endoscopy

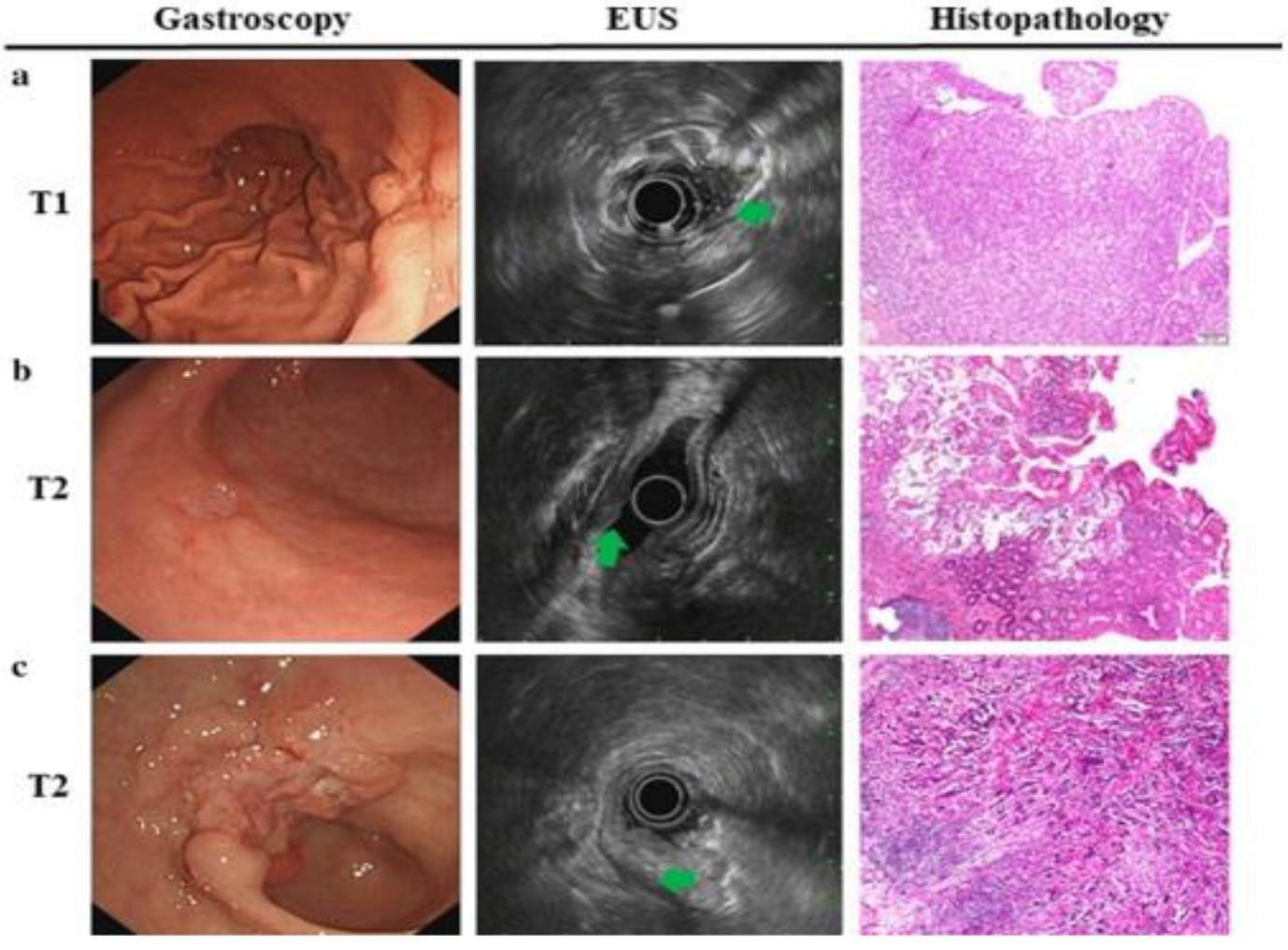


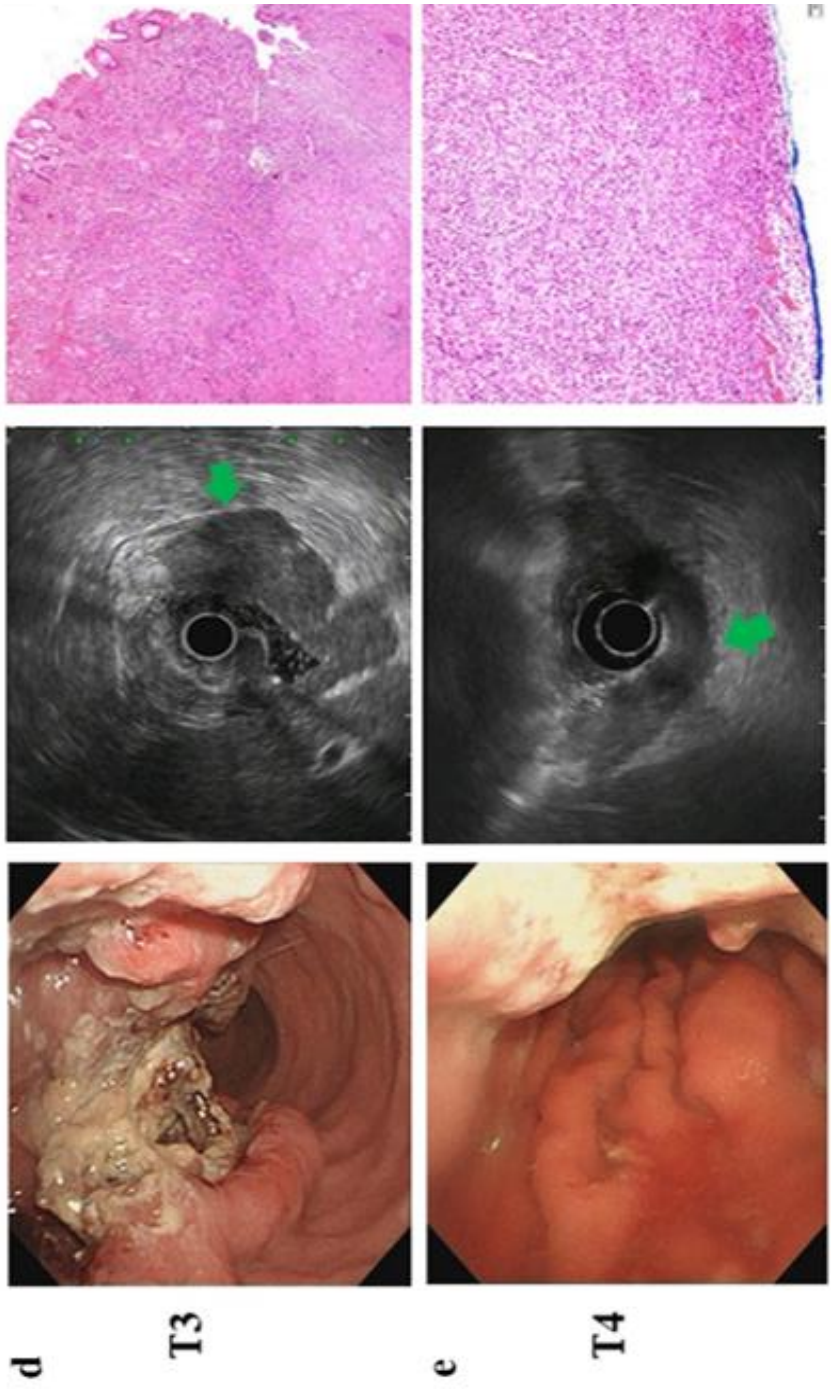
(A) the primary depressed lesion at the posterior wall of the gastric antrum and (B) the crossed folds with a waffle-like appearance on the greater curvature of the upper gastric body.

Source Maeda E, et al. A case report. Oncol Lett. 2015;9(1):262-264. doi: 10.3892/ol.2014.2688

➢ Pathology

- Tumour T stage depend on AJCC 7th/8th edition system and EUS image features for each tumour T stage.




d
T3
e
T4

- a) Endoscopic image of the lesion showed an ulcer located in the posterior wall of the body with peripheral mucosal consolidation.
  - EUS image showed disappearance of first hyperechoic layer, mild thickness and hypoechoic change of the second hypoechoic layer, and normal third hyperechoic layer (arrows).
  - Surgical resection confirmed poorly-differentiated and partial signet-ring cell gastric cancer confined to submucosal layer;
- b) Gastroscopy showed an ulcer located in the anterior wall of gastric angulus.
  - EUS image of the lesion showed disappearance of the first three layers and companied by muscularis propria visible indistinctly (arrows).
  - The surgical specimen confirmed poorly-differentiated gastric cancer confined to the submucosal layer;
- c) Endoscopic image showed a neoplasm located in the anterior wall of the antrum. EUS image of the lesion showed disappearance of the first three layers and companied by muscularis propria obvious thickening (arrows). The surgical specimen confirmed tumour infiltrated to the muscularis propria layer;
- d) Endoscopic image of the lesion showed a neoplasm located in the lesser curvature side of the antrum with dirty surface.
  - EUS image showed a thick hypoechoic lesion spreading from the mucosal to muscularis propria layer with an intact serosa layer (arrows).
  - The surgical specimen confirmed tumour infiltrated to the subserosa;
- e) Endoscopic image showed a large ulcer located in the upper posterior wall of the gastric body.
  - EUS image showed an obviously thick hypoechoic lesion that spread throughout the entire wall and invaded the serosa infiltration (arrows).
  - The serosal layer was irregularities in the outer edge of the gastric wall. The surgical specimen confirmed lesion confined to the serosal layer

Source: Han C, et al. BMC Gastroenterol. 2021;21(1):255.

Classification and Staging

TNM Staging

T
Tumor size and penetration

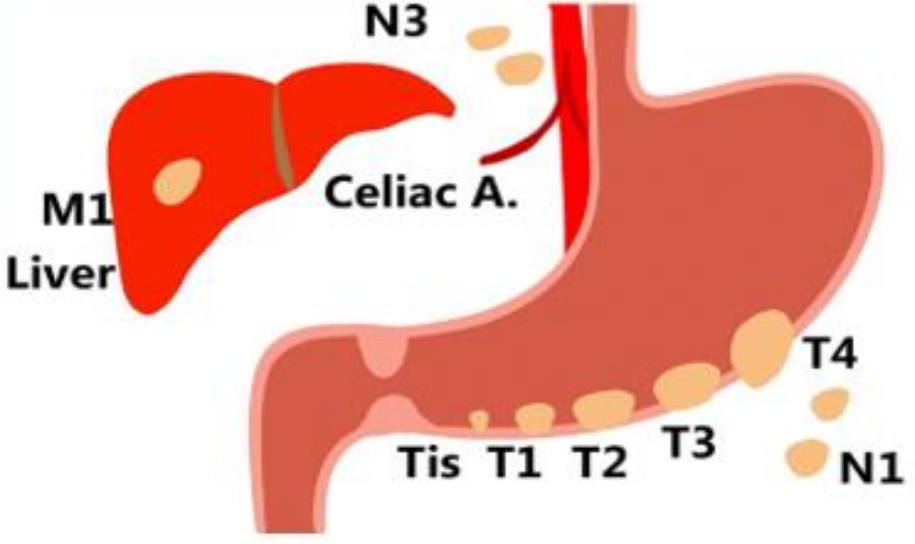
Tis: Tumor "in situ:"caught very early and has not grown beyond stomach lining.
T1: Tumor has grown through lining and into connective tissue.
T2: Tumor has grown into thick inner muscle.
T3: Tumor has spread through outer lining but not to any nearby organs or tissues.
T4: Tumor has spread into nearby tissues or organs.

N
Spead to lymph nodes

NO: Cancer has not spread to nodes.
NI: Cancer in 1 to 6 nodes.
N2: Cancer in 7 to 15 nodes.
N3: Cancer in >15 nodes.

M
Spead to other organs

MO: No metastasis
MI: Metastasis



NCCN Guidelines Gastric cancer v.1.2009
Infographics Raaed AlRamdan.

Source: NCCN Guidelines Gastric cancer v1.2009. Infographics from Raaed AlRamdan

➢ Prevention

- Screening program
  - High incidence region
    - Since 1960, the Japanese have been performing mass screening using upper GI barium studies followed by endoscopy if any suspicious lesions are found.
      - This continues to represent the recommended approach based on current Japanese cancer screening guidelines.
    - Screening starts at age 40 to 50 yrs with upper gastrointestinal series or endoscopy q2-3 yr
    - Under these protocols, two-thirds of gastric cancers cases detected are in an early stage, leading to ↑ 5-yr survival rate
    - Long-term follow-up data from the Japanese Public Health Center cohort showed that subjects who underwent screening had a nearly 50% ↓ risk of death from gastric cancer
  - Low incidence region
    - European consensus guidelines recommend EGD surveillance q3 yr in patients with extensive atrophy of the gastric mucosa

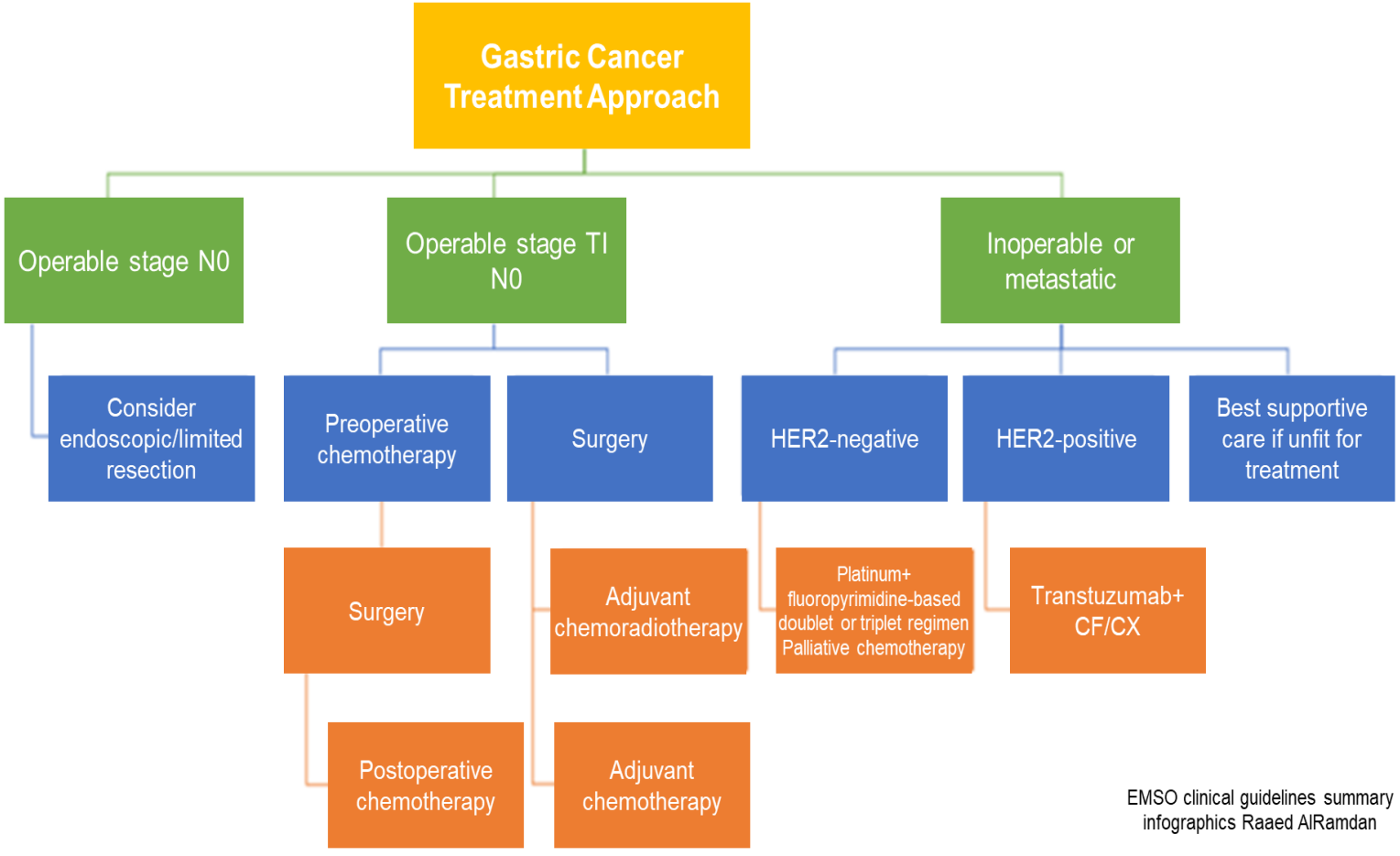
- Eradication of H. pylori Infection
  - Associated with a significant 35% ↓ risk of GCA, ↓ progression of premalignant conditions
- NSAIDs/ASAs
  - ↓ risk of gastric cancer (RR: 0.78 ASA and non-ASA NSAIDs)
- Statin
  - Observational level of evidence to ↓ risk of GCA
- Others
  - Antioxidants, green tea and garlic

➢ Prognosis and treatment

- 5 yr survival (US)
  - 10% to 27%
- Survival related to
  - TMN
  - Tumour > 5 cm (may be independently associated with worse survival, independent of nodal status or overall tumour stage)

➢ Treatment

- Summary of EMSO clinical practice guidelines for diagnosis, treatment, and follow-up.



EMSO clinical guidelines summary infographics Raaed AlRamdan

Infographics Raaed AlRamdan

- Surgery
  - Curative treatment, although
    - 5-yr survival only 20-50%
    - Improved outcomes with chemotherapy as adjuvant or neo adjuvant treatment
  - Palliative
    - Obstructive symptoms
  - Surgical planning
    - Gastrectomy
      - Partial
    - Distal tumours
      - Total
    - Proximal tumours and diffuse cancer
    - Extensive Lymphadenectomy
    - Do **not** perform splenectomy increase morbidity and worsen survival

- EMR and ESD
  - Curative treatment for early GCA
    - Lesions < 4.5 cm
      - More likely to be endoscopically resectable because of the likelihood of no lymph node involvement.
  - Criteria for EMR
    - Intestinal type cancer at the mucosal level
    - No lymph node involvement by EUS
    - Solitary lesion
      - <2 cm if elevated
      - <1 cm if flat
  - Criteria for ESD en bloc resection
    - Intestinal type
    - Size
      - Ulceration, < 3 cm
      - Submucosal invasion, < 0.5mm
      - Otherwise, any size

Abbreviations: EMR, endoscopic mucosal resection; ESR, endoscopic submucosal resection; EUS, endoscopic ultrasound

- Chemoradiotherapy
  - At the time of diagnosis
    - Perigastric lymph node or distant metastasis in 75%
  - Adjuvant chemotherapy → ↓ mortality by 15% to 20%
  - MAGIC trial showed benefit for neoadjuvant chemotherapy
  - FLOT Trial showed (Fluorouracil/Leucovorin) better survival than cisplatin

GASTRIC LYMPHOMA

- Represent 7% of gastric cancers
- GI and stomach are the most common sites
- Endoscopic pattern
  - Exophytic polypoid
  - Ulcerative
  - Hypertrophic folds
- Biopsy large
  - Jumbo forceps
  - Snare
  - Bite on bite
- Lugano staging (location)
  - Stage 1: GI wall
  - Stage 2: into the abdomen lymph node / serosa
  - Stage 4: Disseminated bone, liver, etc.

- Other Gastric Cancers
  - Gastrointestinal Stromal Tumours (GIST)
    - Interstitial Cajal cells (pacemaker cells)
  - Neuroendocrine
    - Enterochromaffin-like cells (ECLs) of the gastric mucosa
  - Metastatic disease
    - Breast
    - Melanoma
    - Lung, liver
    - Colon

References

1. Kim GH, et al. Screening and surveillance for gastric cancer in the United States: is it needed? Gastrointest Endosc 2016; 84: 18-28.
2. Choi KS, et al. Screening for gastric cancer in Korea: population-based preferences for endoscopy versus upper gastrointestinal series. Cancer Epidemiol Biomarkers Prev 2009; 18: 1390-8.
3. Ford A.C, et al. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ England 2014; 348: g3174.

SMALL BOWEL

THE INTESTINAL MICROBIOME

Yousef Almahanna

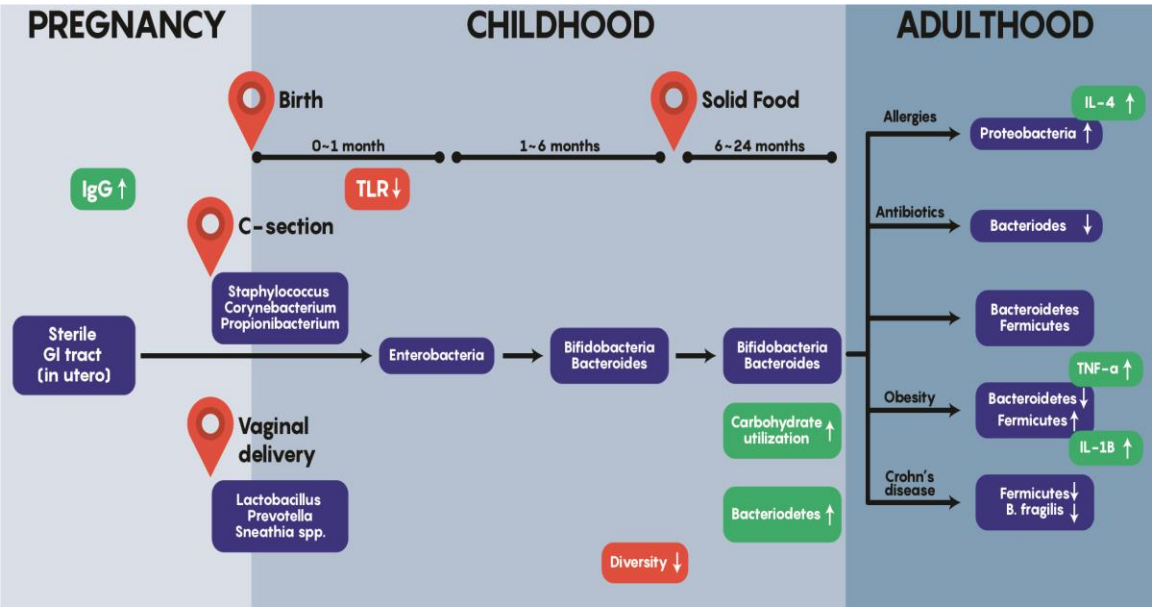
- The Human Microbiome

➢ Definition

- The collection of microbes, their genes and their products that colonize our body since birth and are transferred vertically.

➢ Background

- Microbial colonization of the human gut begins at birth.
  - The initial gut colonization is instrumental in shaping the composition of the adult's gut microbiota.
  - The stability within the gut is reached around 1-2 yrs of age and is maintained into adulthood
  - Different organisms appear



Source: https://ecampusontario.pressbooks.pub/neurosciencecdn3/chapter/chapter-1-the-gut-microbiome-and-its-impact-on-the-brain/

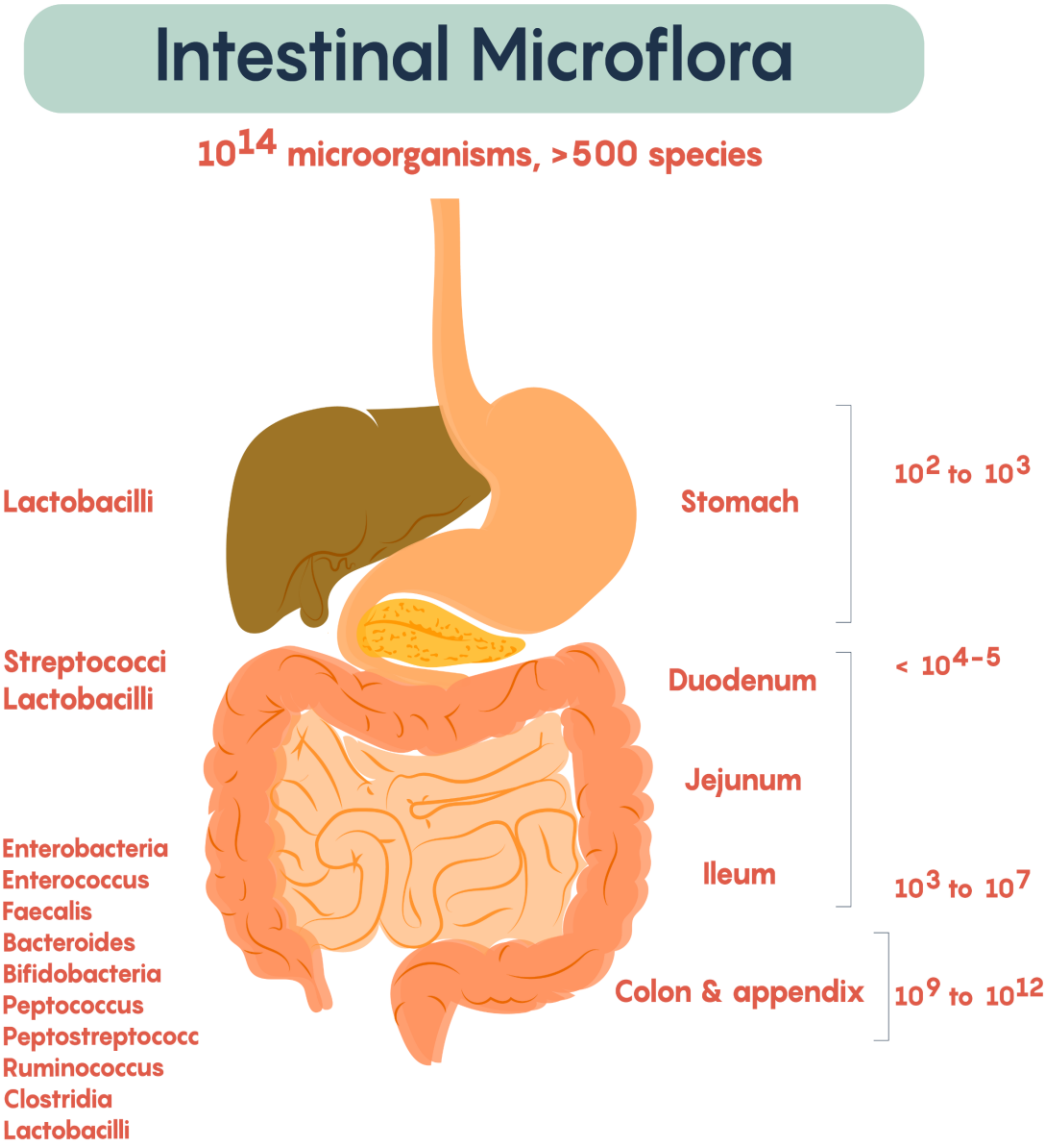
- The gut microbiome refers to the collective genomes of all the microbial organisms living in that space.
- There are trillions of microorganisms living in the gut, comprised of dozens of different species performing important metabolic functions:
  - Archaebacteria: ancient bacteria-like single-celled organisms
  - Bacteria: simple single-celled organisms that are studied most often in the microbiome
  - Bacteriophage: viruses that hunt and destroy specific types of bacteria
  - Fungi: only a few species of fungi are usually found living within the human gut; we don't know exactly what they do
  - Protozoans: single-celled organisms that are more complex than bacteria

- The bacterial load varies along the GI tract

	Bacterial Load	pH	pO_2 (mm Hg)
– Skin	10^{11}	5.0-5.5	145
– Oral cavity	10^{11} - 10^{12}	6.2-7.5	83-113
– Stomach	10^{7}	5.7-7.5	10-34
– Duodenum	10^{7}	5.6-8.0	30
– Jejunum	10^{7}	5.7-7.5	10-34
– Ileum	10^{11}	5.7-7.5	10-34
– Colon	10^{14}	6.7-8.5	0.5-11

- Gut Microbiome/Intestinal Microflora
  - The alimentary tract represents an interface between the external environment and the body.
    - The microbiome
      - Exists as a complex polymicrobial ecology that interacts with the internal and external environment
      - Has an important influence on health and disease
      - Has been implicated both directly and indirectly on human health
  - The type and number of bacterial vary along the length of the luminal GI tract
  - The intestine is an anaerobic environment, the majority of the gut bacteria species are anaerobic.
  - Microbial density in the gut. Overall, there are 10^{14} microorganisms residing in the human gut, with over 500 unique species.
  - In the stomach, the majority are the Lactobacilli, making up about 10^{2} to 10^{3}. In the Duodenum, there are Streptococci and Lactobacilli, with a concentration of 10^{4} or 10^{5}.
  - As we descend past the jejunum and into the ileum, the concentration of bacteria increases dramatically – up to ten million bacteria reside here.
  - Bacteria such as
    - Bacteroides
    - Bifidobacteria
    - Clostridia
    - Enterobacteria
    - Enterococcus
    - Faecalis
    - Lactobacilli
    - Peptococcus
    - Peptosteptococcus
    - Ruminococcus

- These bacteria are also common in the colon and appendix, but the microorganism concentrations increase yet again, to 10^9 to 10^{12}.
- There is a general trend that complexity and concentration of bacteria increase as we descend the GI tract.



Source: https://ecampusontario.pressbooks.pub/neurosciencecdn3/chapter/chapter-1-the-gut-microbiome-and-its-impact-on-the-brain/

- 50 bacterial phyla are in the human gut
  - In most healthy adult individuals, the most abundant phyla include:

Phyla	Species
− Firmicutes (60-80%) (Gram+)	▪ Clostridium ▪ Enterococcus ▪ Lactobacillus ▪ Ruminococcus
− Bacteroidetes (15-25%) (Gram-)	▪ Bacteroides ▪ Prevotella ▪ Xylanibacter
− Actinobacteria (3-5%)	▪ Bifidobacterium
− Proteobacteria (1-10%)	▪ Enterobacteriaceae ▪ Escherichia
− Verrucomicrobia (0.1-2.2%)	▪ Akkermansia muciniphila

➢ Normal Function of Intestinal Microbiome

- Metabolism
  - Produce a variety of vitamins
    - Synthesize all essential and nonessential amino acids, and
    - Carry out biotransformation of bile
  - Provides the vital biochemical pathways for the metabolism of nondigestible carbohydrates
    - Large polysaccharides, such as
      - Cellulose
      - Gums
      - Hemicellulose
      - Pectins
      - Resistant starches
    - Some oligosaccharides (escape digestion)
      - Unabsorbed sugars
      - Alcohols from the diet
      - Host-derived mucins

    → This results in
      - The recovery of energy and absorbable substrates for the host, and
      - A supply of energy and nutrients for bacterial growth and proliferation.

- Immune system development
  - Helps the body tell the difference between
    - Dangerous disease-causing microbes, and
    - Helps the immune system learn not to attack itself

- The Gut–Brain Axis
  - A bidirectional communication system, which enables the brain to influence
    - Peristalsis
    - Mucin production
    - Immune functions
  - Physical/psychological stress alters
    - The integrity of the gut epithelium
    - Peristalsis, secretions, and mucin production → alters the habitat of the intestinal microbiota → promotes changes in microbial composition and/or metabolism.

➢ Factors Altering the Gut Microbiome

- Epidemiological Factors
  - Age
  - Sex
  - Ethnicity (significant variation in regional prevalence of irritable bowel syndrome [IBS])
- Others
  - Antibiotics and some other medications
  - Diet
    - Plant-based proteins
      - ↑ commensal organisms (Bifidobacterium and Lactobacillus)
      - ↓ pathogenic organisms (Bacteroides fragilis and Clostridium perfringens)
    - Animal-based protein has been associated with ↑ Bacteroides, Alistipes and Bilophila
    - High-fat diets associated with ↑ anaerobes and Bacteroides in the gut.
    - High fibre associated with ↑ Bifidobacterium and Lactobacillus
  - Hygiene
  - Immune system
  - Lifestyle

Source: https://ecampusontario.pressbooks.pub/neurosciencecdn3/chapter/chapter-1-the-gut-microbiome-and-its-impact-on-the-brain/

➢ Pathophysiology of gut microbiome changes (multiple mechanisms)

- ↓ growth
  - Salivary lysozyme
  - Gastric acid
  - Secretion of defensins
- More barrier
  - Separate organisms from the host by creating a physical barrier (e.g., the mucus barrier).
- In disease states (i.e., intestinal inflammation, NSAIDs) → disruption of the mucus barrier.
  - Once this occurs
    - Bacteria migrate toward the mucosa → build dense layers adherent to epithelial cells → cytopathologic effects leading eventually to dysbiosis.

- Dysbiosis

➢ Definition

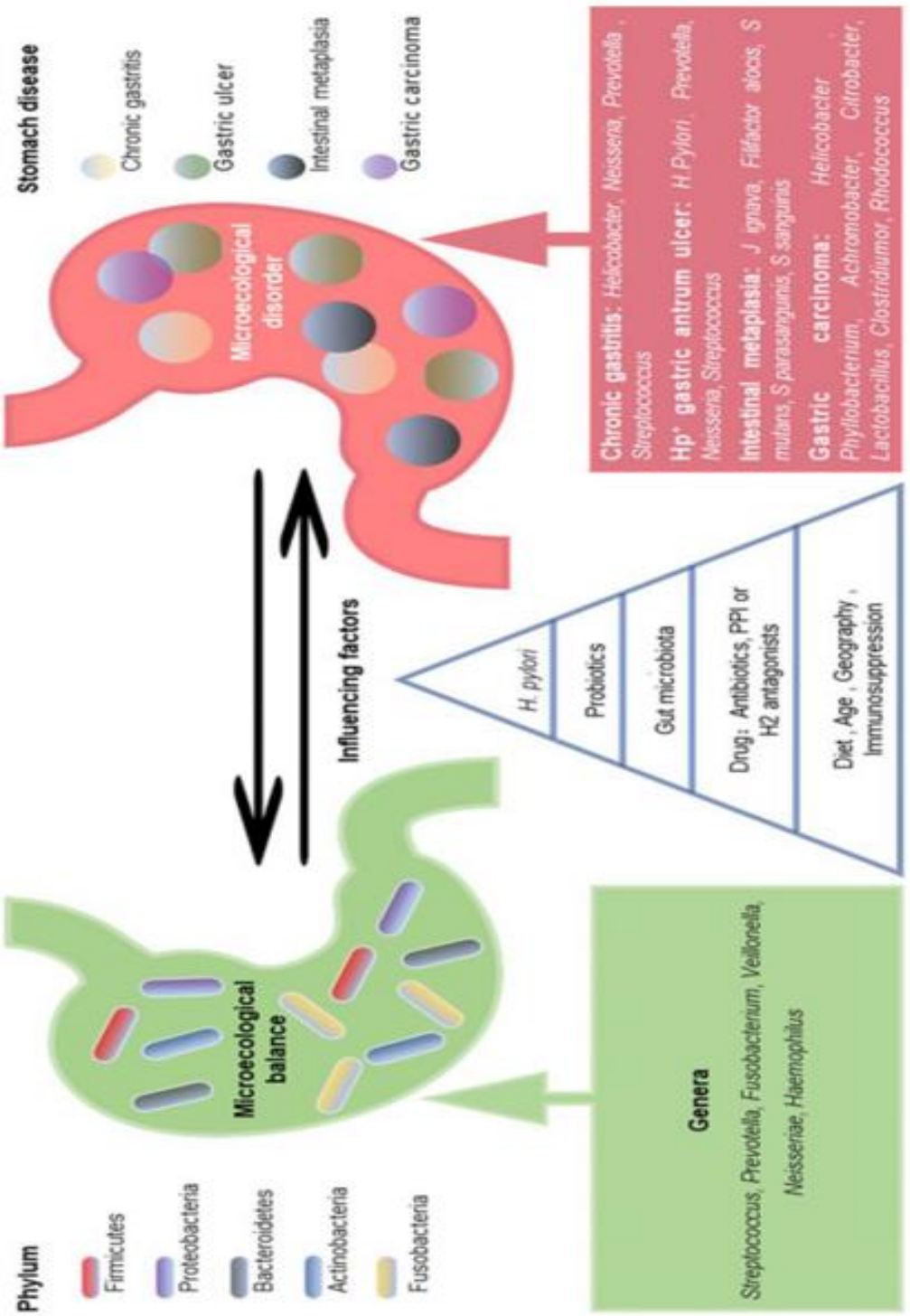
  - Changes of the colonic microbial biostructure due to alteration/imbalance in the composition of the normal microbiota
    - Leads to a shift towards an unfavorable population of microbiota with disturbed colonic fermentation.
  - Certain commensal bacteria produce favorable compounds for the host such as
    - Short-chain fatty acids (SCFA) or
    - Anti-inflammatory substances
    - Bacteria producing pro-inflammatory metabolites and endotoxins are regarded as harmful

- Gut microbiome and diseases

➢ Background

  - The gut microbiome influences
    - Remote organs
      - Cardiovascular
      - Neurological
      - Respiratory
    - GI conditions
      - Gastric adenocarcinoma
      - H. pylori infection
      - Inflammatory bowel disease (IBD)
      - Irritable bowel syndrome (IBS)
      - Peptic ulcer disease

- H. pylori Infection, Peptic Ulcer Disease, Gastric Adenocarcinoma
  - The oral–gut axis microbiota has a major effect in H. pylori's
    - Colonization
    - Infection
    - Pathogenicity
  - Several factors can affect the gastric microbiome such as
    - Aging
    - Diet
    - Geographic area of residence
    - Medications (PPI and antibiotics)
  - As compared with healthy individuals, there is ↓ number of Bacteroidetes and ↑ numbers of Firmicutes and Proteobacteria in patients with gastritis
    - H. pylori infection disturbs commensal bacterium equilibrium
    - In the gastric mucosa in addition to the disturbance of microbial changes in the human gut
    - Probiotic supplementation and antibiotic treatment → beneficial gut microbiota profile after eradication therapy achieved with antibiotic/PPI treatment of H. pylori infection



Source: Elghannam MT, et al. Infection; 2024; 52: 289–300 (Figure 1)

- Irritable bowel syndrome (IBS)

➢ Cause

  - The cause of IBS is multifactorial, and include
    - Genetic factors
    - Motor dysfunction of the GIT
    - Visceral hypersensitivity
    - Infection
    - Inflammation
    - Immunity
    - Psychopathological factors
    - Changes in microbiome

- Microbiome
  - In a healthy person, gut microbiome helps to metabolize poorly absorbed carbohydrates.
  - Dysbiosis/variations in the normal gut microbiota
    - Have a role to play in low-grade intestinal inflammation associated with IBS.
  - Key differences have been found in the gut microbiome composition in IBS:
    - ↑ Firmicutes
    - ↓ Bifidobacterium and ↓ Faecalibacterium spp.
      → associated with maintaining gut mucosal health: considered as the main butyrate producing and anti-inflammatory organism.
  - However, characterization of the IBS intestinal microbiome remains inconsistent, and no distinct signature has been accepted.

➢ Treatment (the microbiome as a Target in IBS)

  - Low FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols).
    - FODMAPs are poorly absorbed in the small intestine, and thereby
      - ↓ intestinal osmolality
      - ↑ water absorption
      - ↑ gas production via fermentation in the large colon.
    - Restriction these FODMAPs modulate
      - Microbial composition
      - Microbial metabolite production
    - There are potential baseline differences in microbiome activity and composition in IBS patient, which can distinguish between low FODMAP diet responders and non-responders.

- Inflammatory Bowel Disease (IBD)

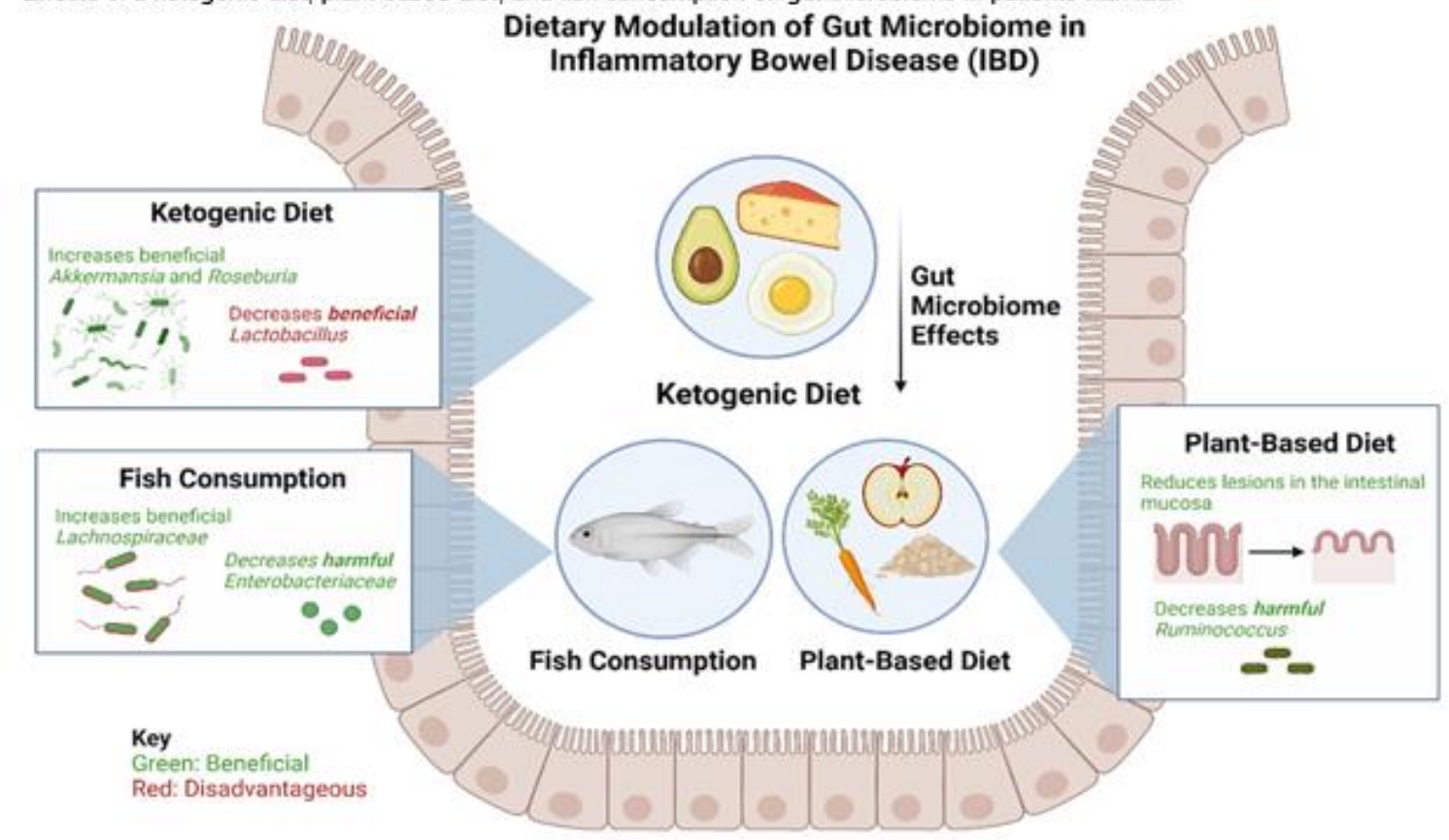
➢ Overview

- Ulcerative colitis and Crohn disease, are characterized by chronic and relapsing inflammation of the GI tract.
- Gut microbes are essential components in the development of mucosal lesions.
- Microbial dysbiosis in IBD is characterized by ↓ diversity and stability of the microbiota.
  - ↓ Firmicutes & Bacteroidetes and ↑ Proteobacteria taxa
  - This dysbiosis leads to ↓SCFA production (acetate & butyrate) which have potent anti-inflammatory properties.

➢ Potential dietary therapies

- Crohn Disease Exclusion Diet (CDED):
  - High protein, low-fat diet that includes foods such as
    - Chicken,
    - Eggs
    - Fish
    - Potatoes
    - Rice
    - Various fruits and vegetables
  - This intervention has been effective for mild to moderate CD in children, as well as for patients whose response to anti-TNF biologic treatments plateaued.
- Fibre in fruits and vegetables
  - Prolonging remission and ↓ lesions in the intestinal mucosa.
- SCFAs (butyrate, acetate, and propionate)
  - Main energy source for colonocytes, enhances
    - ↑ epithelial barrier integrity, and
    - Anti-inflammatory effects in IBD.
- Fish
  - ω3FAs (found in fish) support anti-inflammatory processes when interacting with microbes and
    - Alter microbiota diversity
    - ↑ beneficial bacteria, and
    - ↓ harmful bacteria

Effects of a ketogenic diet, plant-based diet, and fish consumption on gut microbiome in patients with IBD



- The ketogenic diet has been shown to ↑ beneficial bacteria Akkermansia and Roseburia and consequently decrease beneficial Lactobacillus.
- The plant-based diet has been found to be beneficial in ↓ lesions of the intestinal mucosa and reducing harmful Ruminococcus.
- Fish consumption leads to an ↑ in beneficial Lachnospiraceae and a decrease in harmful Enterobacteriaceae.

Source: Gubatan J, et al. Microorganisms 2022;10: 1371 (Figure 2)

- Small Intestine Bacterial Overgrowth (SIBO)

➢ Definition

- SIBO is an overgrowth of bacteria in the small intestine, typically containing microbes that are normally found in the colon.
  - This leads to a range of gastrointestinal symptoms like bloating, abdominal pain, constipation/diarrhea, as well as clinical/biochemical signs of malabsorption/nutrition.

➢ Protective Mechanisms

- The body has several mechanisms to prevent excessive bacterial growth in the small intestine, such as gastric acid, bile, proteolytic enzymes, and intestinal motility, and secreted factors such as
  - Defensins
  - Gut associated lymphoid tissue
  - Mucus
  - Secreting IgA
  - Trefoil factors

➢ Associations

- Anatomical abnormalities, motility disorders, metabolic conditions like diabetes, and immune disorders like HIV, and various gastrointestinal and systemic disease

➢ Pathophysiology

- When bacterial counts in the proximal small intestine are > 10^3 colony forming units/mL), there is inflammation leading to nutrients malabsorption
- SIBO causes maldigestion and malabsorption of nutrients, particularly carbohydrates, fats, proteins, and vitamin B12.
  - This results from bacterial degradation of these nutrients and their impact on the intestinal mucosa, leading to symptoms such as diarrhea and deficiencies in essential nutrients.
- Fat malabsorption arises from dehydroxylation and deconjugation of bile acids, leading to maldigestion/malabsorption of lipids and fat soluble

➢ Treatment

- Treat the underlying cause of SIBO
  - E.g., IBD, slow transit
- Rifaximin
  - Recommended as first-line antibiotic therapy for SIBO
  - Neomycin can be added in cases of intestinal methanogen overgrowth. Deficiencies of certain vitamins and minerals (e.g., vitamin B12, fat-soluble vitamins, iron) associated with severe SIBO should be supplemented.
  - Mechanism of action
    - ↓ one of the steps in the transcription of bacterial DNA to RNA
    - ↓ bacterial protein synthesis
    - ↓ bacterial/endotoxin translocation
    - ↓ bacterial growth

- Persistent or Recurrent Symptoms
  - ~40% of SIBO patients experience persistent symptoms post-treatment, and 40% experience recurrence within 9 mon.
- A second course of antibiotics is considered for partial responders or early recurrences (<3 mon).
  - For patients with later recurrences, repeat testing (e.g., carbohydrate breath test, small bowel aspirate culture) may be performed to confirm SIBO.

➢ Etiology Evaluation and Recurrence Prevention

- Use antibiotic prophylaxis for selected patients at high risk of recurrence (e.g., short bowel syndrome, jejunal diverticulosis).
  - Other therapeutic options like an elemental diet are reserved for patients who are unable to tolerate or are unresponsive to antibiotics.

- Liver and gut axis
  - The gut and the liver interact through multiple avenues:
    - Blood drains from the gut back to the liver through the portal circulation.
    - The gut interacts with the liver through the enterohepatic circulation whereby bile acids synthesized in the liver are secreted in the small intestine and reabsorbed in the ileum back to the liver.
    - An intact gut barrier is critical in controlling bacteria, bacterial antigens and toxins; (such as Lipopolysaccharide [LPS], also known as endotoxin, a component of the outer cell wall of Gram-negative bacteria) from reaching to the liver.

https://www.nature.com/articles/s41579-023-00904-3

- Fatty Liver Disease

Metabolic Associated Liver Disease (MASLD), and Alcoholic-associated Liver Disease (ALD)

- MASLD/ALD are associated with
  - Dysbiosis and ↑ intestinal permeability:
  - These lead to the translocation of many gut microbiota-derived components to the liver through the portal vein.
  - These components cause
    - Hepatic metabolic alterations, and
    - Series of inflammatory reactions
- Common pathophysiologic processes in MASLD/ALD
  - SIBO / altered composition of microbiome
  - ↓ gut barrier function / ↑ intestinal permeability
  - Interaction of bile acids (BAs) with the host and microbiome, modulating
    - Microbiota
    - Microbial metabolites and
    - Shifts in primary and secondary BAs profile

- Diagnosis
  - Suspect from
    - ↓ hemoglobin, albumin, electrolytes; depending upon underlying conditions, ↑ CRP, ↑ NBC/ESR
  - Interrupted extrahepatic circulation
    - ↑ stool FA/lipids
    - ↑ duodenal aspect 2^{o} BA / deconjugated BA
    - Abnormal BA breath test with labelled glycocholate acid
  - Inhibition of
    - Trimethylamine
    - Tryptophan

- Alcoholic Liver Disease and the “leaky gut”
  - Chronic alcohol users have
    - ↓ TJ function / ↑ gut permeability
    - SIBO
    - ↑ aerobic / anaerobic bacteria on jejunal aspirate
    - Altered colonic bacteria
      - Associated cirrhosis vs. alcoholic non-cirrhotic patients
  - ↓ proportion of Bacteriodetes and ↑ proportions of Proteobacteria

- Cirrhosis
  - Cirrhosis patients have altered gut-liver axis, associated with
    - Changes in liver disease according to severity.
    - ↑ portal hypertension →
      - ↑ endotoxin levels
      - ↑ gastrointestinal permeability
      - ↑ translocation of bacteria damage → inflammation
  - Changes in the composition and function of gut microbiota
  - Complications
    - SIBO (35–61%) in patients with cirrhosis.
    - Suggested the pathogenesis
      - ↓ intestinal motility
      - ↓ gastric acid secretion
      - Luminal IgA deficiency and malnutrition

- Hepatic encephalopathy (HE)

- Pathophysiology
  - Alterations in gut microbiota and their by-products such as
    - Amino acid metabolites (indoles, oxindoles)
    - Endotoxins, etc. → ↑ urease-active bacteria in the gut than controls → ↑ intestinal hydrolysis of urea and absorption of nitrogenous products → ↑ blood NH_3

- Treatment
  - Lactulose
    - Works as a “prebiotic” → ↑ growth of endogenous bacteria that are potentially beneficial to the host like Lactobacilli → indirectly ↓ potentially more harmful urease producing bacteria.
  - Rifaximin
    - A gastrointestinal selective antibiotic with a wide range of antimicrobial activity
    - Minimal drug interactions, and
    - Negligible effect on the overall gut microbiome
    - Mechanism of action
      - ↓ endotoxemia, and
      - ↑ serum long-chain fatty acids (LCFAs)

- Spontaneous Bacterial Peritonitis (SBP)

- Pathophysiology
  - Overgrowth of Gram-negative and oral bacteria / Dysbiosis → low-grade chronic inflammatory state → ↓ intestinal barrier function, which is already affected by portal hypertension, leading to a condition known as “leaky gut” → bacterial translocation → inflammatory cascade

- Treatment
  - Antibiotics or beneficial bacterial strains could be considered as a potential treatment for cirrhotic patients with SBP.

- Definitions
  - Probiotics
    - Live microorganisms such as bacteria or yeasts of human origin that
      - Provide health benefits when consumed
    - Probiotics regulates the gut microbiota by
      - ↑ growth of beneficial bacteria and
      - ↓ reducing harmful bacteria in the gut
    - Mechanism of action
      - ↑ intestinal barrier integrity
        - ↓ epithelial cell death
        - ↑ mucin production
      - ↑ immune system activity
        - ↓ inflammation
        - ↑ host production of anti-inflammatory cytokines
        - ↓ production of proinflammatory cytokines
        - ↑ immune response
      - ↓ invading pathogens from adhering to the gut wall

- Prebiotics
  - Food ingredients that induce the growth or activity of beneficial microorganisms in the gut
  - The food ingredients feed the gut microflora, → products of their breakdown such as short chain fatty acids (SCFAs) are released into the blood circulation → affect not only the gastrointestinal tract, but also other distant organs
  - Sources of prebiotics include
    - Barley, unrefined
    - Breast milk
    - Carbohydrates, undigestible
    - Inulin
    - Oligosaccharides, undigestible
    - Raw oats
    - Soybeans
    - Wheat, unrefined
  - Mechanism of action
    - Compete with pathogens for adherence site
    - Blocking of pathogen-pathogen communication molecules
    - Secretion of bacteriocin (antimicrobial effect)
- Synbiotics
  - Formulations that consist of a probiotic and a prebiotic packaged into one capsule.

Recommendation(s)

Role of Probiotics in the Management of Gastrointestinal Disorders: AGA Clinical Practice Guidelines 2020

- In patients with *C difficile* infection
  - Use of probiotics only in the context of a clinical trial.
- In adults and children on antibiotic treatment,
  - S boulardii
  - The 2-strain combination of L acidophilus CL1285 and L casei LBC80R;
  - The 3-strain combination of L acidophilus, L delbrueckii subsp bulgaricus, and B bifidum; or the 4-strain combination of L acidophilus, L delbrueckii subsp bulgaricus, B bifidum, and S salivarius subsp thermophilus (over no or other probiotics for prevention of C difficile infection) (Strength of recommendation, conditional; quality of evidence, low)
  - Comment
    - Patients who place a high value on the potential harms (particularly those with severe illnesses) or a high value on avoiding the associated cost and a low value on the small risk of *C difficile* development (particularly in the outpatient setting), would reasonably select no probiotics.
- In adults and children with Crohn disease
  - Use of probiotics only in the context of a clinical trial (No recommendation; quality of evidence, very low)
- In adults and children with ulcerative colitis, we recommend the use of probiotics only in the context of a clinical trial. (No recommendation; knowledge gap)

- In adults and children with pouchitis
  - *Use the 8-strain combination of* L paracasei subsp paracasei**,** L plantarum**,** Lacidophilus**,** L delbrueckii *subsp* bulgaricus**,** B longum subsp longum**,** B breve**,** B longum subsp infantis**,** and S salivarius subsp thermophilus over no or other probiotics. (Strength of recommendation, conditional; quality of evidence, very low)
  - Comment: Patients for whom the feasibility and cost of using this combination of bacterial strain is problematic may reasonably select no probiotics.
- In symptomatic children and adults with irritable bowel syndrome
  - Use the use of probiotics only in the context of a clinical trial (No recommendation; knowledge gap)
  - In children with acute infectious gastroenteritis, do **not** use of probiotics (Strength of recommendation, conditional; quality of evidence, moderate)
- In preterm (less than 37 wks gestational age), low-birth-weight infants
  - Use a combination of Lactobacillus spp *and* Bifidobacterium *spp (*L rhamnosus *ATCC 53103 and* B longum subsp infantis*;* or L casei and B breve*;* or L rhamnosus**,** L acidophilus**,** L casei**,** B longum subsp infantis**,** B bifidum**,** and B longum subsp longum*;* or L acidophilus and B longum subsp infantis*;* or L acidophilus and B bifidum*;* or L rhamnosus ATCC 53103 and B longum Reuter ATCC BAA-999*;* or L acidophilus**,** B bifidum**,** B animalis subsp lactis*,* and B longum subsp longum*),* or B animalis subsp lactis (including DSM 15954), or L reuteri (DSM 17938 or ATCC 55730), or L rhamnosus (ATCC 53103 or ATC A07FA or LCR 35) for prevention of NEC over no and other probiotics (Strength of recommendation, conditional; quality of evidence, moderate/high)

Adapted from: Grace SL. et al. Gastroenterology 2020; 159; 697-705

DIAGNOSIS AND MANAGEMENT OF CELIAC DISEASE

Zaki Alhashimalsayed

Rubio-Tapia A, et al. Am J Gastroenterol 2023;118: 59–76.

- Objective
  - Diagnosis
    - Should non-invasive serology tests vs. duodenal biopsy be used for diagnosing CD in children and adults?
  - Diet and long-term outcomes
    - Should mucosal healing vs. clinical and serological remission be the goal of GFD therapy to improve long-term outcomes in adults with CD?
  - Medical device use
    - Should gluten detection devices vs. standard care be used to monitor GFD adherence and influence dietary decisions?
  - Probiotics
    - What is the effect of adding probiotics to GFD on clinical remission and mucosal healing in CD patients compared to GFD alone?
  - Nutrition
    - What is the impact of GFD without oats vs. with oats on clinical remission and mucosal healing in newly diagnosed CD patients?
  - Pneumococcal vaccine
    - Does the pneumococcal vaccine reduce the risk of serious infection in CD patients compared to no vaccine?
  - Screening
    - Should case finding vs. mass screening be used to improve CD detection in the general population?
  - Testing in children
    - Are tTGA and DGP antibodies together more accurate than tTG alone in diagnosing CD in children under 2 yrs?
- Demography
  - ~1% in all populations
- Background
  - Initial screening
    - Detection of CD-specific antibodies like tTG
  - Confirmation
    - Intestinal biopsy required for most patients
  - Treatment
    - Strict adherence to gluten-free diet (GFD)
  - Follow-up
    - Lifelong medical monitoring for complications

- Challenges in Celiac Disease Management
  - Non-responsive CD
    - Persistent symptoms despite GFD adherence
    - Systematic workup to rule out gluten contamination
  - Refractory CD
    - Rare cause of nonresponsive CD
    - Often associated with poor prognosis
  - Treatment burden
    - High costs of outpatient care
    - Expensive gluten-free foods

- Diagnosis
  - Should a combination of non-invasive serology tests vs duodenal biopsy be used to confirm the diagnosis of CD in children and adults?

- Serological testing, is it enough?
  - CD-Specific Serological Tests
    - Facilitate recognition of CD and its diverse clinical manifestations
    - Positive serological test supports diagnosis but no single test is 100% specific
    - Diagnostic accuracy varies between laboratories.
  - Laboratory study findings
    - Sensitivity: 63% to 93%
    - Specificity: 96% to 100%
    - Variability found in tTG assays among various research and clinical labs
  - Histological confirmation
    - Diagnosis confirmed by histological changes according to Marsh or Corazza classifications
    - Small bowel biopsy useful for differential diagnosis of other enteropathies or malabsorptive disorders.
  - Diagnostic approach for adults
    - Incorporates both serologic and histologic data
    - No changes since the last ACG Guidelines publication.
    - Testing should be considered for patients with:
      - Signs or symptoms suggestive of CD (e.g., diarrhea, weight loss, abdominal pain, bloating).
      - Laboratory abnormalities (e.g., unexplained elevated serum aminotransferase levels).
      - Asymptomatic individuals in high-risk populations.

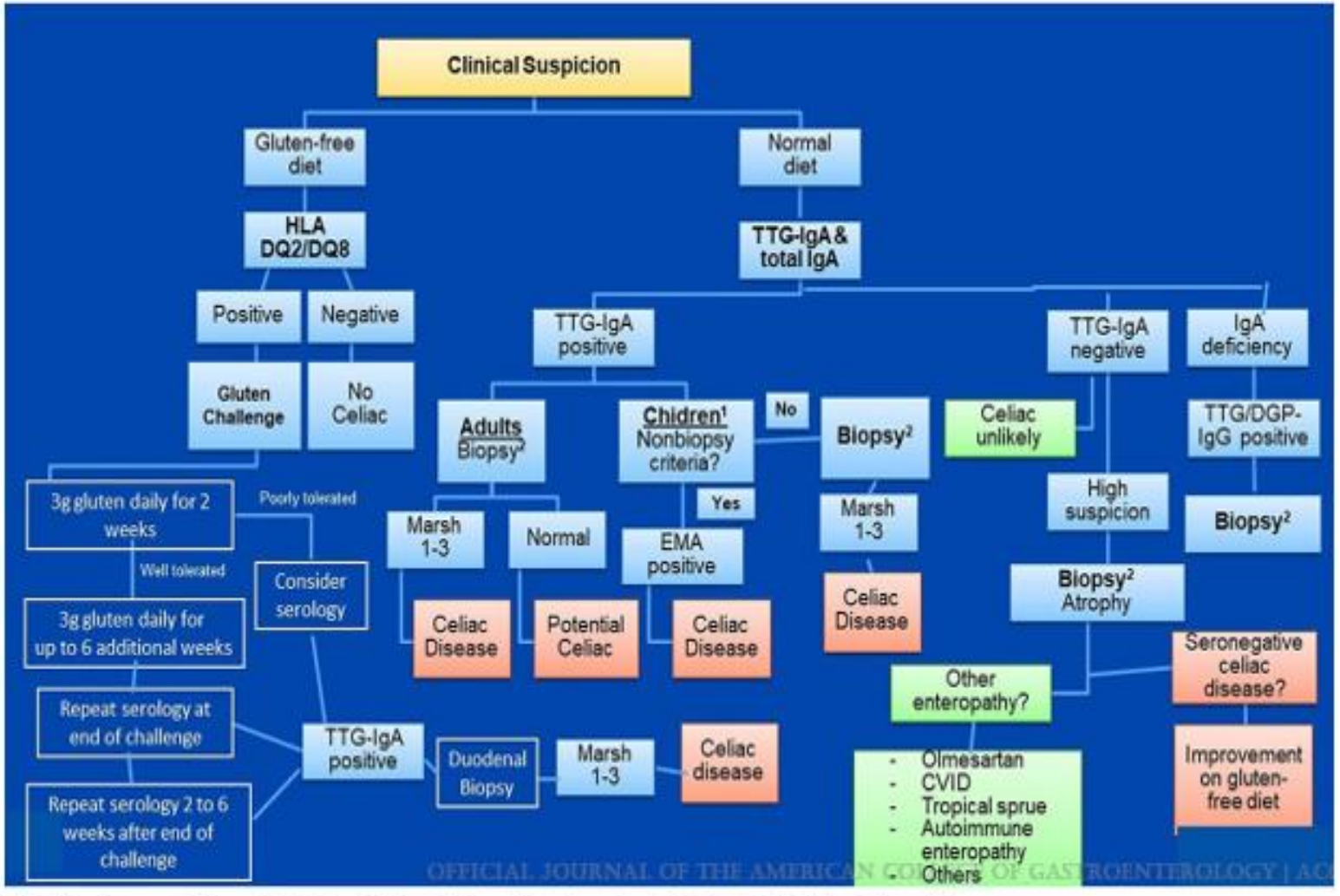
- Histological Evaluation and Classification

Classification	Marsh	Corazza
Normal	Type 0	Grade A
Increased intraepithelial lymphocytes	Type 1	Grade A-
Crypt hyperplasia	Type 2	Grade A
Partial villous atrophy	Type 3a	Grade B1
Subtotal villous atrophy	Type 3b	Grade B2
Total villous atrophy	Type 3c	Grade B2

- Serological Testing: The First Line of Diagnosis
  - Initial screening
    - Begin with tissue transglutaminase (tTG) IgA testing while the patient is on a gluten-containing diet. Concurrent measurement of total IgA is recommended to rule out IgA deficiency.
  - Interpreting results
    - ↑ tTG IgA levels indicate the need for further investigation
    - In cases of IgA deficiency, IgG-based tests (DGP or tTG IgG) should be performed.
  - Additional testing
    - Endoscopy with biopsy.
  - Special Circumstances
    - Negative tTG IgA (without IgA deficiency) has a high negative predictive value if the pretest probability is low-moderate
    - Endoscopy done first, no serology?

- Endoscopic Evaluation and Biopsy Techniques
  - Multiple biopsy sites
    - Perform multiple biopsies, including 1-2 from the duodenal bulb and at least 4 from the distal duodenum, to account for patchy distribution of lesions. (1.8% vs 0.7%, $P < 0.0001$)
  - Targeted Sampling
    - Consider targeted biopsies from the 9 o'clock or 12 o'clock position in the duodenal bulb to improve diagnostic yield. (sensitivity, 96%)
  - Specimen handling
    - Obtain only one biopsy specimen per pass of the forceps to potentially improve tissue orientation and quality. (Expert opinion)

➢ Diagnostic Algorithm



Printed with permission: Rubio-Tapia A, et al. Am J Gastroenterol 2023;118: 59–76. (Figure 1)

- Special Considerations for Adult Diagnosis
  - Biopsy recommendations
    - Adults should generally undergo endoscopy with biopsy for CD diagnosis, especially those with high pretest probability (>5%), regardless of serology results.
  - Non-biopsy approach
    - In select cases where biopsy is not feasible or advisable, a diagnosis of "likely CD" can be made in symptomatic adults with tTG IgA >10x upper limit of normal and positive EMA.
  - Genetic testing
    - HLA testing for CD-compatible haplotypes can be helpful in cases of serology-histology discrepancy or when evaluating patients already on a gluten-free diet.
  - Differential Diagnosis
    - Consider other causes of enteropathy, particularly in cases of lymphocytic duodenosis without villous atrophy, as CD is not the only cause of this finding.

- Challenges in Celiac Disease Diagnosis
  - Serology variability
    - Diagnostic accuracy of serological tests varies between laboratories, with sensitivity ranging from 63% to 93% and specificity from 96% to 100%.
  - Patchy distribution
    - Histological abnormalities in CD can be patchy, necessitating multiple biopsies to avoid false negatives.
  - Lymphocytic duodenosis
    - This finding is not specific to CD and can be caused by various other conditions, complicating diagnosis.
  - Gluten-free diet initiation
    - Patients who start a gluten-free diet before proper evaluation can complicate the diagnostic process, potentially requiring gluten challenge.

Non-Biopsy Approach in Pediatric Patients

Criteria for Non-Biopsy Diagnosis	Benefits	Limitations
− Characteristic CD symptoms − tTG IgA >10x upper limit of normal − Positive EMA on second blood sample − Family agreement with approach	− Avoids invasive procedures − Reduces healthcare costs − Faster diagnosis and treatment initiation − Widely adopted in Europe since 2012. updated ESPGHAN guidelines	− Lack of standardization across tTG assays − Risk of misdiagnosis if criteria not strictly followed − Limited data on long-term outcomes − May miss other enteropathies

- Future Directions in Celiac Disease Diagnosis
  - Serological cutoffs
    - Research is needed to determine optimal serologic value cutoffs for non-biopsy diagnosis across different commercial laboratories and patient populations.
  - Genetic markers
    - Further investigation into genetic markers beyond HLA typing may improve diagnostic accuracy and risk stratification.
  - Novel therapies
    - Development of non-dietary therapies may necessitate new diagnostic criteria for clinical trials and treatment eligibility.

Recommendation(s) (for intestinal healing as a goal)

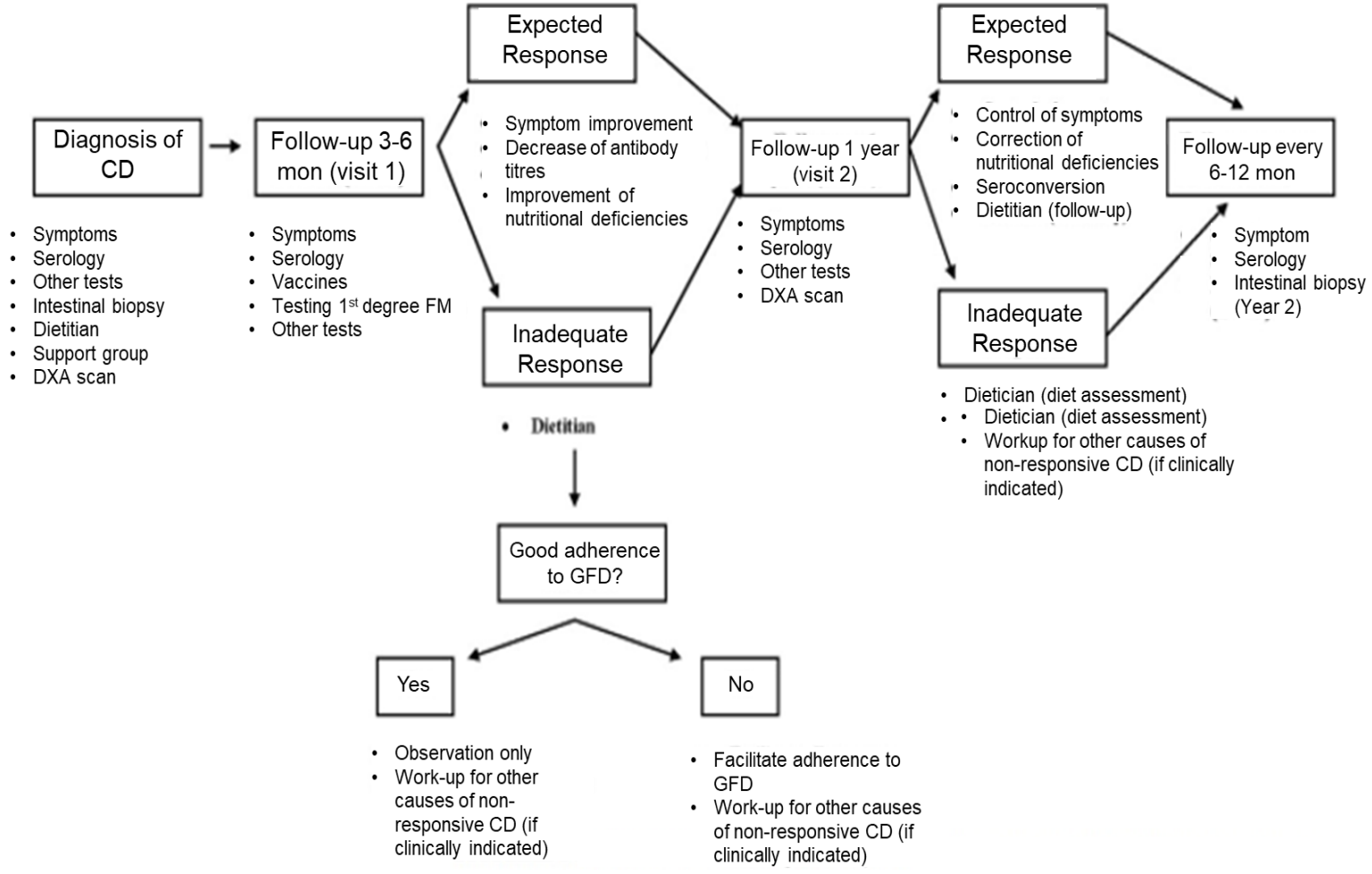
- Suggested goal
  - Setting intestinal healing as an end point of GFD therapy
- Recommendation type
  - Conditional recommendation
- Evidence quality
  - Low quality of evidence
- Consensus
  - No dissent (0) among experts

- Key Concepts in Monitoring CD
  - Upper endoscopy with biopsies
    - Helpful for monitoring in cases with lack of clinical response or relapse of symptoms despite a GFD
  - Follow-up biopsy consideration
    - Could be considered for assessment of mucosal healing in adults after 2 yrs of starting a GFD
  - Shared decision-making
    - Important for determining the need for follow-up biopsy in the absence of symptoms

- Benefits of Strict GFD Adherence
  - Symptom improvement
    - Diarrhea improved in 80% of patients within 60 days of strict GFD adherence
  - Healthcare utilization
    - Adherence to GFD is effective in reducing healthcare utilization
  - Quality of life
    - Strict adherence to GFD improves quality of life for CD patients
  - Risk reduction
    - ↓ risk of complications associated with CD

Haines ML, et al. Alimentary pharmacology & therapeutics. 2008; 28(9): 1042-66.

- Monitor



Printed with permission: Rubio-Tapia A, et al. Am J Gastroenterol 2023;118: 59–76. (Figure 2).

- Challenges in Assessing Mucosal Healing
  - Serology correlation
    - Poor correlation between serology and mucosal healing
  - Seroconversion limitations
    - Negative celiac serology ↑ probability of mucosal healing, but correlation is not reliable
  - Reliable method
    - Repeat intestinal biopsy is currently the only reliable method to assess mucosal healing

- Mucosal Healing and Long-Term Outcomes

Outcome	Mucosal Healing
Lymphoproliferative Disorder	↑ risk (HR = 2.81; 95%; 95% CI = 2.10-3.67)
Bone disease / hip fracture risk	↑ risk (HR = 1.67; 95%; 95% CI = 1.05-2.66)
Mortality	Borderline lower risk (HR = 0.13; 95%; 95% CI = 0.02-1.06, P = 0.006)
Serious Infection	No significant impact (HR = 0.00, 95%; 96% CI: 0.88-1.11)
Cardiovascular Disease	No significant impact on ischemic heart disease or atrial fibrillation
Pregnancy related outcome	No impact on intrauterine growth retardation, low birth weight, preterm birth, or cesarean section

Adapted from: Rubio-Tapia A, et al. Am J Gastroenterol. 2010; 105(6): 1412–1420.

- Directions
  - Follow-up biopsy strategy
    - Investigate the effect of follow-up biopsy strategy on GFD adherence and quality of life in asymptomatic individuals with CD
  - Biomarker development
    - Identify biomarkers that can predict the presence of mucosal healing vs persistent villous atrophy in treated CD
  - Long-term outcomes
    - Further study the impact of mucosal healing on long-term outcomes such as mortality and cancer risk
  - Medical Device Use
    - Should gluten detection devices vs current standard of care be used to monitor adherence to GFD and/or patients' dietary decision-making?

- Key Concepts
  - Standard of care
    - Interview with a dietitian with expertise in gluten-free diet (GFD) is the standard for assessing diet adherence
  - Detection limitations
    - Technologies may not distinguish between clinically significant and trivial gluten exposure
  - Limited evidence
    - Paucity of evidence suggesting gluten detection technology enhances diet adherence or quality of life
  - Research needed
    - Studies required to evaluate utility of gluten detection technologies in improving GFD adherence and clinical outcomes in CD

- Gluten Detection Technologies
  - 1991
    - Concept of patient-directed testing for gluten introduced
  - Early 2000s
    - Commercially available kits for home use developed (Glutentox and EZ gluten)
  - Recent Years
    - Nima sensor introduced - a portable lateral flow gluten sensor device

Portable gluten sensor developed by MIT researchers.

Source: MIT News, "Portable sensor can test for gluten in food," July 6, 2016

Nima Sensor Performance (Nima, the portable gluten tester, is now available for purchase," January 26, 2017)

Sensitivity for gluten >40 ppm	>98%
Correct negative results for gluten-free foods	> 94%
“Gluten found” for 10-19 ppm (false-positive)	> 50%
Limitation	Unable to detect gluten in fermented forms

- Biospecimen Gluten Detection

Stool Detection	Urine Detection	Clinical Significance
○ Gluten fragments detectable up to 4 days after ingestion. − Present in nearly 30% of CD patients attempting GFD adherence.	○ Gluten fragments detectable for up to 2 days. − Stronger predictor of persistent villous atrophy than elevated serology.	○ Uncertain clinical significance of highly sensitive tests. − Can detect as little as 25 mg of ingested gluten, possibly below toxicity limit for many CD patients.

- Challenges in Gluten Detection Technology
  - ○ Sampling limitations
    - − Point-of-care sampling without homogenization may miss gluten in unsampled food fragments
  - ○ Clinical significance uncertainty
    - − Highly sensitive tests may detect gluten below toxicity thresholds for many patients
  - ○ Lack of outcome studies
    - − Limited evidence on impact of gluten detection technology on adherence, quality of life, or clinical outcomes

➢ Evaluation of Persistent Symptoms

Confirm CD Diagnosis	Assess Gluten Exposure	Coexisting Conditions	Selective Testing
○ Review and confirm the initial diagnosis of celiac disease	○ Evaluation by expert dietitian and serology testing	○ Assess for functional disorders, food intolerances, and other potential causes	○ Based on clinical suspicion, test for conditions like microscopic colitis or small intestinal bacterial overgrowth

➢ Future Research Directions

- ○ Impact assessment
  - − Evaluate the impact of gluten detection technology prescription on GFD adherence, symptom control, and mucosal healing

- Optimal counseling
  - Determine the best dietary counseling approach for patients adopting gluten detection technology
- Clinical relevance
  - Investigate whether the presence of gluten in food or biospecimens below traditionally regarded toxic doses results in clinically relevant outcomes

- Understanding Celiac Disease and Dysbiosis

Celiac Disease	Dysbiosis	Gluten-Free Diet (GFD)
○ An autoimmune disorder triggered by gluten ingestion. It causes intestinal damage and various symptoms.	– An imbalance in gut microbiota. It's a feature of CD, but its exact role remains uncertain.	▪ The primary treatment for CD. It helps heal the intestine and alleviate symptoms.

- Rationale for Probiotic Use in CD
  - Dysbiosis in CD
    - Altered gut microbiome in CD patients before and after diagnosis
  - Microbiome restoration
    - Probiotics might help restore balance to the disrupted gut microbiome in CD
  - Symptom Management
    - Probiotics could potentially alleviate ongoing symptoms, especially in functional disorders associated with CD.

➢ Current Evidence: Pilot Studies

- Microbiome alteration
  - Bifidobacterium strains admiration (3 mon) showed potential in normalizing gut microbiota ratios in CD compared with control. (pediatric).
- Growth improvement
  - Marginal ↑ height percentile in children taking Bifidobacterium probiotics. No change in symptoms.
- Symptom reduction
  - Adults (22) with ↑ CD serologies showed improved gastrointestinal symptoms and lower IgA levels with Bifidobacterium natren (life start).

- Probiotics for Ongoing Symptoms
  - IBS-like symptoms
    - Many CD patients experience ongoing symptoms similar to irritable bowel syndrome.
  - Probiotic trial
    - A study used a combination of Lactobacilli and Bifidobacteria for 6 wks.
    - Results
      - The probiotic group showed improvement in IBS severity scores compared to placebo.
    - Limitations
      - Quality of life scores did not improve, and long-term effects remain unknown.

- Uncertainties and Concerns
  - Long-term effects
    - The durability of symptom responses in short-term trials is uncertain.
  - Safety concerns
    - Long-term probiotic use raises safety questions, especially with lax regulatory standards.
  - Gluten contamination
    - Some probiotics labeled gluten-free may contain detectable gluten levels.
  - Efficacy doubts
    - A study suggested probiotics might delay recovery from antibiotic-induced dysbiosis.

Recommendation

- Insufficient evidence to recommend for or against probiotic use in CD
  - Quality of evidence
    - Very low
  - Dissent
    - 0
  - Key concept 1
    - Dysbiosis is a feature of CD, but its role is uncertain
  - Key concept 2
    - Benefit of probiotics in CD management is **not** established

➢ Future Research Directions

- Causal role
  - Investigate if microbiome changes play a causal role in CD development.
- Microbiome Modification
  - Explore if altering the microbiome with probiotics improves CD outcomes.

➢ Nutrition (Gluten-Free Oats)

- In patients with newly diagnosed CD, give the effect of GFD without oats on rates of clinical remission and mucosal healing compared with a gluten-free diet with oats.

- Key Concepts
  - Safety
    - Oats safe for most, but immunogenic for some
  - Tolerance Factors
    - Origin, harvesting, and quantity affect tolerance
  - Monitoring
    - Optimal intervals for symptom and serology monitoring after gluten free oat is unknown
  - Benefits of oats
    - Fibre
      - Adds soluble fibre to diet.

  - Nutrients
    - Provides B vitamins, iron, and thiamine
  - Digestion
    - Offers laxation benefits
- Conflicting evidence
  - Tolerance
    - Some studies show good tolerance to oats.
  - Intolerance
    - Others report ↑ symptoms and villous atrophy
  - Uncertainty
    - Cause of intolerance remains unknown.

- Recent Studies
  - Systematic review
    - 28 studies show no negative effects after 12 mon
  - Finnish Study
    - Long-term oat consumption safe, improves quality of life
  - Children's study
    - Pure oat products safe for children with CD.

- Oat Varieties
  - Finnish pure oats
    - Considered safe for celiac patients
  - Avena Sativa
    - Specific varieties lack in vitro immune reaction
  - Others
    - Variable toxicity. Different oat varieties may have varying effects

Recommendation(s)

- Consume gluten-free oats in the diet of those with CD.
  - Gluten contamination of oats, variable toxicity in different varieties of oats, and the small risk for an immune reaction to the oat protein avenin require monitoring for oat tolerance (Strength, Strong recommendation; Evidence Quality, moderate quality of evidence)
- Future research
  - Initial strategy
    - Effects of oats-avoidant strategy after CD diagnosis
  - Immune Response
    - Proportion of patients reacting to pure oats
  - Benefits
    - Advantages of pure oats vs. any oats

- Pneumococcal Vaccination
  - For patients with CD, the use of pneumococcal vaccine ↓ future risk of serious pneumococcal infection compared with no pneumococcal vaccine.

➢ Background

- ↑ risk in CD patients
  - Pneumococcal infection
    - 2x ↑ risk in CD patients
  - Hyposplenism
    - One-third of CD patients have reduced spleen function
  - Pre-diagnosis vulnerability
    - Higher pneumonia risk, especially before CD diagnosis

- CDC Vaccination Recommendations (In General)
  - Children
    - Vaccinate all children < 2 yr.
  - Adults 65+
    - Vaccinate all adults over 65 yr.
  - At-risk adults 19-64 yr
    - Vaccinate adults 19-64 with certain high-risk conditions.

- Indications for pneumococcal vaccination in adults
  - All adults ≥ 65 yr of age
  - Adults 19-64 yr of age with any of the following
    - Predisposing medical conditions
      - Alcohol use disorder
      - Chronic heart disease
      - Chronic lung disease
      - Chronic liver disease
      - Diabetes mellitus
    - ↑ risk of meningitis
      - Cerebral fluid leak
      - Cochlear implant
    - Immunocompromising conditions and other conditions associated with altered immunocompetencies
      - Congenital or acquired immunodeficiency
      - Generalized active malignancy
      - Human immunodeficiency virus infection
      - Iatrogenic immunosuppression
      - Hodgkin disease

        - Leukemia
        - Lymphoma
        - Multiple myeloma
        - Solid organ transplant
        - Chronic kidney disease and nephrotic syndrome
    - History of invasive pneumococcal disease

Source: Kobayashi M, et al. MMWR Recomm Rep 2023;72(3):1-39.

Recommendation

- Vaccination to prevent pneumococcal disease in patients with CD (Strength, Conditional recommendation; Evidence Quality, Low quality of evidence; Consensus, Dissent zero)

➢ Future Research Directions

- Effectiveness comparison
    - Compare vaccine efficacy in CD vs general population.
- Early vaccination impact
    - Assess benefits of vaccination before age 65.
- Optimal regimen
    - Determine best vaccination schedule for CD patients.

• Screening (Case Finding vs Mass Testing)

➢ Key Concepts in CD Detection

- Symptomatic patients
    - Test for CD if signs of malabsorption present.
- Family history
    - Test first-degree relatives of confirmed CD patients.
- Associated conditions
    - Consider CD testing in related disorders.
- Asymptomatic screening
    - **Not** recommended for general population.

➢ Case Finding Strategy

- Identify high-risk groups
    - Target patients with symptoms or family history.
- Serologic testing
    - Perform blood tests to detect CD antibodies.
- Intestinal biopsy
    - Confirm diagnosis with endoscopy and biopsy.
- Treatment
    - Implement gluten-free diet for confirmed cases.

- Conditions to be Consider for Testing Celiac Disease

CD Common	CD Less Common but Treatable
○ GI	
− Symptomatic malabsorption	▪ Pulmonary hemosiderosis
− Diarrhea with weigh loss	▪ Male or female infertility
− Chronic diarrhea with or without abdominal pain	▪ Dyspepsia
− Postprandial bloating and gaseousness	▪ Apparent malabsorption of thyroid replacement medication
− Unexplained weight loss	▪ Epilepsy or ataxia
− Abnormal elevated liver enzymes	▪ Constipation
− Incidental discovery of villous atrophy endoscopically or histological	▪ Recurrent abdominal pain
− Oral aphthous ulcers	▪ Recurrent headache or migraine
− Growth failure	
− Discoloured teeth or developmentally synchronous enamel loss	
− Irritable bowel syndrome	
− Unexplained recurrent pancreatitis	
○ Metabolic	
− Metabolic bone disease and premature osteoporosis	▪ Chronic fatigue
− Thyroid disease	
○ Hematological	
− Chronic iron deficiency and unexplained anemia	▪ Amenorrhea
○ Skin	
− Dermatitis herpetiformis	▪ Chronic arthralgia
○ CNS	
− Peripheral neuropathy	▪ “Brain fog”
− Depression	
− Anxiety	
○ Genetic	
− Down and Turner syndrome	
○ GU	
− Infertility	

Abbreviations: CD, celiac disease; GFD, gluten-free diet

Conditions in which CD occurs more frequently than in the general population and for whom a GFD may be beneficial are listed on the left column. On the right column are conditions in which CD is less common, but reversible, treatable cause.

Adapted from: Rubio-Tapia A, et al. Am J Gastroenterol 2023;118: 59–76 (Table 4)

- Pros and Cons of Case Finding
  - Advantages
    - Cost-effective
    - Targets high-risk groups
    - Improves detection rates
  - Limitations
    - May miss asymptomatic cases
    - Relies on clinical suspicion
    - Inconsistent implementation

- Challenges of Mass Screening
  - High cost
    - Significant resources required for widespread testing.
  - Uncertain natural history
    - Lack of understanding about asymptomatic CD progression.
  - No consensus
    - Lack of agreement on treatment for asymptomatic cases.
  - Psychological impact
    - Potential anxiety from diagnosis in asymptomatic individuals.

Recommendation(s)

- Case finding
  - Recommended to ↑ CD detection in clinical practice.
- Mass screening
  - **Not** recommended for general population.
- High-risk groups
  - Consider testing first-degree relatives and associated conditions.
- Symptomatic patients
  - Test for CD if malabsorption or suggestive symptoms present.

➢ Future Research Directions

- Quality of life impact
  - Assess effects of screening on asymptomatic individuals
- Seroconversion rates
  - Study CD development in high-risk populations over time
- Screening intervals
  - Determine optimal frequency for serologic testing
- Long-term outcomes
  - Evaluate benefits of early detection and treatment

- Testing in Children
  - tTGA and DGP antibodies in combination more accurate in diagnosing CD in children >2 yr compared with tTG alone

Recommendation(s)

- tTG-IgA test
  - Preferred single test for non-IgA-deficient children < 2 yr
- IgG-based antibodies
  - Recommended for IgA-deficient children.
- DGP-IgG and tTG-IgA combination
  - Not recommended when testing for CD in children < 2 yr who are not IgA-deficient.

Recommendation(s) (for celiac disease testing in children)

- The immunoglobulin IgA anti-tTG antibody (tTG-IgA) is recommended as the preferred single test for detecting CD in children < 2 yr who are not IgA-deficient (Strength, Strong recommendation; Evidence Quality, Moderate quality of evidence; Consensus, Dissent [0])
- Testing for CD in children with IgA deficiency should be performed using IgG-based antibodies (DGP-IgG or tTG-IgG) (Strength, Strong recommendation; Evidence Quality, Moderate quality of evidence; Consensus, Dissent [0])

- Future Research Directions
  - DGP antibodies
    - Investigate positive predictive value of isolated elevations.
  - Age-specific markers
    - Explore potential new biomarkers for young children.
  - Long-term outcomes
    - Study impact of early diagnosis on child development.

MANAGEMENT OF REFRACTORY CELIAC DISEASE (RCD)

Nisha Howarth

- Introduction
  - Celiac disease
    - Present in 1% of US population
    - RCD occurs in ~1% of patients with CD
  - Causes myriad of symptoms and manifestations from most body systems
  - Diagnosis
    - Positive antibody testing for anti-tissue transglutaminase, anti-endomysial antibody, and/or anti-deamidated gliadin peptide
    - Characteristic findings on duodenal biopsies
  - Treatment
    - Strict adherence to gluten-free diet (GFD): Results
      - ↓ symptoms (usually)
      - Normalization of associated antibody titres
      - Reversal of small bowel (SB) villous atrophy
  - Caution
    - There may be post-withdrawal of dietary gluten
    - Persistent/recurrent symptoms or ↑ celiac antibodies (alone or in combination)
    - Raises possibility of non-responsive celiac, including refractory celiac disease (RCD)

- Definition
  - CD with persistent symptoms of malabsorption and villous atrophy despite ≥ 12 mon of strict adherence to GFD

- Symptoms
  - Persistent or recurrent symptoms/signs
    - Continued diarrhea
    - Weight loss
    - Bleeding/Anemia
    - Malabsorption with nutritional deficiencies
    - Fever / Night sweats
    - Bowel obstruction
    - Patients with no initial response to GFD or
    - Patients who get remission with GFD and subsequently develop symptoms
  - Exclude ongoing gluten ingestion (accounts for 40-50% of poorly or nonresponsive CD)
    - Dietitian
    - ↑ celiac antibodies (note, negative serologies don't completely exclude intermittent or low-level gluten ingestion)
    - Gluten immunodominant peptides are stool and urine biomarkers of gluten ingestion (commercially available in US, not validated in Canada or Europe)

- Celiac disease can be associated with and overlap with other GI conditions
  - Functional bowel conditions
  - IBD
  - Lactose or fructose intolerance
  - Microscopic colitis
  - Non-celiac gluten sensitivity
  - Pancreatic insufficiency

- Laboratory
  - ↑ antibodies
    - Suggests patient not on GFD
    - The above symptoms suggestive of RCD may occur in patient on GFD
  - Caution
    - Exclude false positive antibody tests
      - Associated immune disorders
      - Discordance with time if appearance of tTG and enteropathy
      - Mistaken/missed diagnosis of early histological changes

- Histopathology
  - Ensure biopsy samples show “specific celiac changes”
    - There is a differential for ↑ IELs, and villous atrophy
    - Crypt hyperplasia and IELs with villous atrophy are not specific
    - If non-specific changes, ensure that tTG-IgA, DGP-IgA and IgG, +/- anti-endomysial antibodies repeated
  - HLA-DQ2/8 haplotypes if prior workup is equivocal or discrepant for CD
  - EGD and small bowel (SB) biopsies essential
    - Diagnosis of CD
      - 1 to 2 biopsies from D1, and
      - ≥ 4 biopsies from D2
    - Biopsy protocol for follow up or RCD not well-defined
    - Target biopsies of any endoscopically abnormal areas
  - If high suspicion for RCD and severely ill patient → consider obtaining additional 6 biopsies from distal duodenum for
    - Flow cytometry
    - Immunohistochemistry (IHC)
    - T cell receptor rearrangement studies (help distinguish type 1 vs 2)

Abbreviations: D1,2, first and second portion of duodenum

- Diagnosis
  - Clinical
    - RCD diagnosis requires symptoms of malabsorption and villous atrophy in duodenal biopsies

- Diagnostic imaging (RCD1, for EATL / ulcerative jejunoileitis)
  - Video capsule endoscopy (VCE)
  - After RCD2 is diagnosed, complications such as EATL or ulcerative jejunoileitis should be excluded (impacts management) video capsule endoscopy
    - Better show the extent and severity of villous atrophy and can look for the complications
  - CT enteroscopy / MR enteroscopy
    - Complimentary to VCE and
    - Show
      - Mesenteric adenopathy
      - Small bowel (SB) masses
      - SB thickening
      - Ulcerative jejunoileitis
  - Not needed in RCD1 as the risk of lymphoma is very low, only indicated if not doing well on therapy
- Histopathology
  - Biopsies for flow cytometry must be fresh and in RPM1 medium or normal saline (NS) (not in the orange-topped containers for normal biopsies!)

➢ Subtypes

	RCD1	RCD2
Clinical	Mild	Moderate/severe
IELs, abnormal phenotype		+
– Abnormal flow cytometer, rearrangement studies (aberrant clonal T-cell expansion)	-	+
– Surface markers		
▪ CD3+, CD8+ TCR β/ɣ +	+	
▪ CD8-		+
Villous atrophy		
– Ileojejunitis		+
– Progression to EATL (no progression of RCD1 to RCD2)		+
– Poor prognosis		+

Best Practice Advice 1:

- In patients believed to have celiac disease who have persistent or recurrent symptoms or signs, confirm the initial diagnosis of celiac disease, review prior diagnostic testing, (including serologies, endoscopies, and histologic findings)

Persistent/ Recurrent Celiac Signs/Symptoms

- Review all aspects of diagnosis serology, biopsies, adherence to gluten-free diet
  - Negative
    - Exclude other GI causes/associations → treat
      - Bile acid wastage (BAW)
      - Collagenous colitis
      - Disaccharide deficiency
      - IBS-D
      - Pancreatis insufficiency
      - SIBO
    - Exclude unrelated diseases, e.g., colorectal cancer
    - Exclude RCD ½, EATL IHC of biopsies, flow cytometry → consulting hematology
- Refractory CD (RCD), types
  - Nutritional support, as appropriate, including parenteral nutrition
  - Expert follow-up
- Refractory CD, type 2
  - As above, plus
  - Investigations
    - CTE/MRE, VCE
  - Treatment
    - Prednisone/budesonide (open capsule)
    - Azathioprine/6-MP
    - Infliximab
    - Cladribine

Best Practice Advice 2:

- In patients with confirmed celiac disease with persistent or recurrent symptoms or signs (non-responsive celiac disease)
  - Exclude ongoing gluten ingestion
  - Serological testing
  - Dietitian review
  - Detection of immunogenic peptides in stool or urine
  - Esophagogastroduodenoscopy bowel biopsies look for villous atrophy
- If villous atrophy persists / initial diagnosis of CD was not confirmed
  - Consider other cause of villous atrophy, such as
    - Autoimmune enteropathy
    - Common variable immunodeficiency
    - Medication-induced enteropathy
    - Tropical sprue

- Differential diagnosis of villous atrophy
  - Infection
    - CVID
    - Giardiasis
    - HIV enteropathy
    - MAC
      - Requires travel (of course), often have B12 and folate deficiency
    - Tuberculosis (TB)
    - Tropical sprue
  - Immune
    - AI enteropathy (anti-goblet cell, anti-enterocyte)
    - EATL
    - Low-grade CD4+ lymphoma
    - Whipple's disease
  - Iatrogenic/drugs
    - Azathioprine
    - Methotrexate
    - Mycophenolate
    - Olmesartan >>other angiotensin receptor blockers (ARBs)

Best Practice Advice 3:

- For patients with non-responsive CD, after exclusion of gluten ingestion
  - Perform a systemic evaluation for other potential causes of symptoms, including
    - Functional bowel disorders
    - Inflammatory bowel disease (IBD)
    - Lactose or fructose intolerance
    - Microscopic colitis
    - Pancreatic insufficiency
    - Small intestinal bacterial overgrowth
- Exclude other potential causes of symptoms
  - Intake/diet
    - Fructose/lactose breath tests
    - FODMAP diet
  - Infection
    - Hydrogen breath test for SIBO
  - Immune
    - Colonoscopy to r/o microscopic colitis
  - Iatrogenic
    - Ensure that if pancreatic enzymes used, they are gluten-free
- Celiac Disease (CD) coexists in ~6% of patients with microscopic colitis (MC; lymphocytic and microscopic)
- MC coexists in ~6% of patients with CD

Nimri FM, et al. Ann Gastroenterol 2022;35(3):281-289.

Best Practice Advice 4:

- To distinguish between subtypes of RCD, and to exclude enteropathy-associated T-cell lymphoma
- Use
  - Flow cytometry
  - Immunohistochemistry
  - T-cell receptor rearrangement studies
- Type 1 RCD is characterized by a normal intraepithelial lymphocyte population
- Type 2 RCD is defined by the presence of an aberrant, clonal intraepithelial lymphocyte population
- Consultation with an expert hematopathologist is necessary to interpret these studies.

Best Practice Advice 5:

- At initial diagnosis of type 2 RCD
- Perform small bowel imaging with capsule endoscopy
- Computed tomography / magnetic resonance enteropathy (to exclude enteropathy-associated T-cell lymphoma and ulcerative jejunoileitis

Best Practice Advice 6:

- Complete a detailed nutritional assessment, including investigation for possible micronutrient and macronutrient deficiencies.
- In patients diagnosed with RCD
- Albumin concentration (an independent prognostic factor)

Best Practice Advice 7:

- Correct deficiencies in macro- and micronutrients using oral supplements and/or enteral support
  - Consider parenteral nutrition (PN) for patients with severe malnutrition due to malabsorption
- Patients with CD may have both micro- and macronutrient deficiencies
  - Test for
    - ADEK fat soluble vitamins (thiamine)
    - INR (for vitamin K)
    - Folate / B12 / iron / copper / zinc / magnesium / selenium
- Diet optimization may be achieved with
  - Consultation of an expert registered dietitian and
  - Oral supplements can be used to correct nutrient deficiencies
- Enteral support and parenteral support may need to be considered

➢ Treatment

- Pharmacotherapy (po)
  - Minimal prospective data on management of RCD
    - No US FDA approved therapies
  - Goals of therapy:
    - ↓ symptoms and duodenal mucosal abnormalities
    - Improve malnutrition
    - Prevent development of lymphoma
  - Glucocorticoids = 1st line
    - Budesonide generally best option
      - Open label study (92%) clinical improvement in 92% and histological (89%) improvement
      - Give as 3 mg tid (1st pill opened in applesauce, 2nd pill opened with water, 3rd capsule intact)
    - IV methylprednisolone can be used for severe disease followed by
      - po prednisone or budesonide
      - Taper regimens and duration not examined rigorously
      - Resolution of molecular and genetic abnormalities in RCD2 after steroid therapy
      - ↓ risk of lymphoma remains uncertain
  - Second line therapies – immunosuppressants
    - Optimal choice unknown
    - RCD1/RCD2
      - Azathioprine (AZA) / mercaptopurine
      - Tioguanine plus corticosteroids are effective, but
      - AZA linked to villous atrophy

MCQ Alert

- Immunosuppressants recommended for treatment of RCD1, RCD2 (concern for accelerated lymphoma development)

    - Alternatives for RCD2
      - Autologous SCT
      - Biologics in life threatening cases
      - Cladribine (purine antimetabolite that targets lymphocyte subtypes)
      - Elemental diet
      - Small bowel (SB) release mesalamine (e.g., Pentasa)

Best Practice Advice 8:

- First-line therapy in either type 1 or type 2 RCD
- Corticosteroids or more commonly
  - Open-capsule budesonide
  - If unavailable prednisone, are the medications

➢ Follow-up

- Medical follow-up for patients with RCD is based only on expert opinion
  - Advised to have MDT approach (including GI and RD)
    - Clinic visits q3 mon until medically well
    - Assess clinical and laboratory parameters at each visit
- Dietitian to follow malnutrition management, adherence assessment
- Frequency of intestinal biopsy not well defined
  - 3-6 mon after starting therapy is advised to assess response
  - Mucosal recovery seen in RCD1 but less likely in RCD2
- If lacking response to initial therapy
  - Repeat intestinal biopsy after 3-6 mon with alternative medication/intervention
- Perform imaging surveillance with VCE/MRE/CTE/PET FDG on case-by-case basis

Best Practice Advice 9:

- Patient with refractory celiac disease require regular follow-up by multidisciplinary team (to assess clinical and histologic response to therapy), including
  - Gastroenterologists
  - Dietitians
- Also, identify local experts with expertise in celiac disease to assist with management
- Patients with RCD without response to corticosteroids may benefit from referral to a center with expertise for management or evaluation in clinical trials.

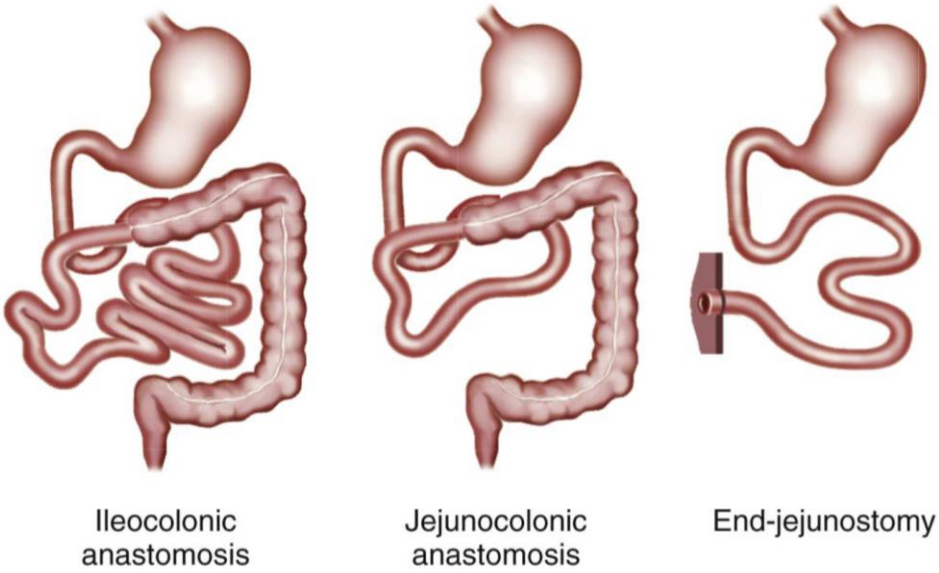
SHORT BOWEL SYNDROME

Hisham Akhtar

- Definition
  - Malabsorption due to congenital absence or resection of large portions of the small intestine, typically leaving the adult with 150-200 cm's of functional small intestine
  - Insufficient intestinal surface area such that they are unable to absorb sufficient fluid, macronutrients, micronutrients and micronutrients, and thereby lose nutritional autonomy → Intestinal failure
  - Not all individuals with SBS have intestinal failure and that intestinal failure may be caused by conditions other than SBS (that lead to functional SBS)
  - Spectrum of SBS ranges from limited ileocolonic resections with moderate nutritional compromise to extensive small intestinal and colonic resections with duodenostomy, proximal jejunostomy, or jejunocolonic anastomosis and severe nutritional consequences

- Demography
  - SBS requiring total parenteral nutrition (TPN) ~ 2-4 cases per 10^5 per yr (Europe)
    - Becoming less due to biologic
    - 10,000 – 20,000 home TPN patients for SBS in US
  - ~ 50-70% patients with SBS requiring TPN can be weaned off therapy

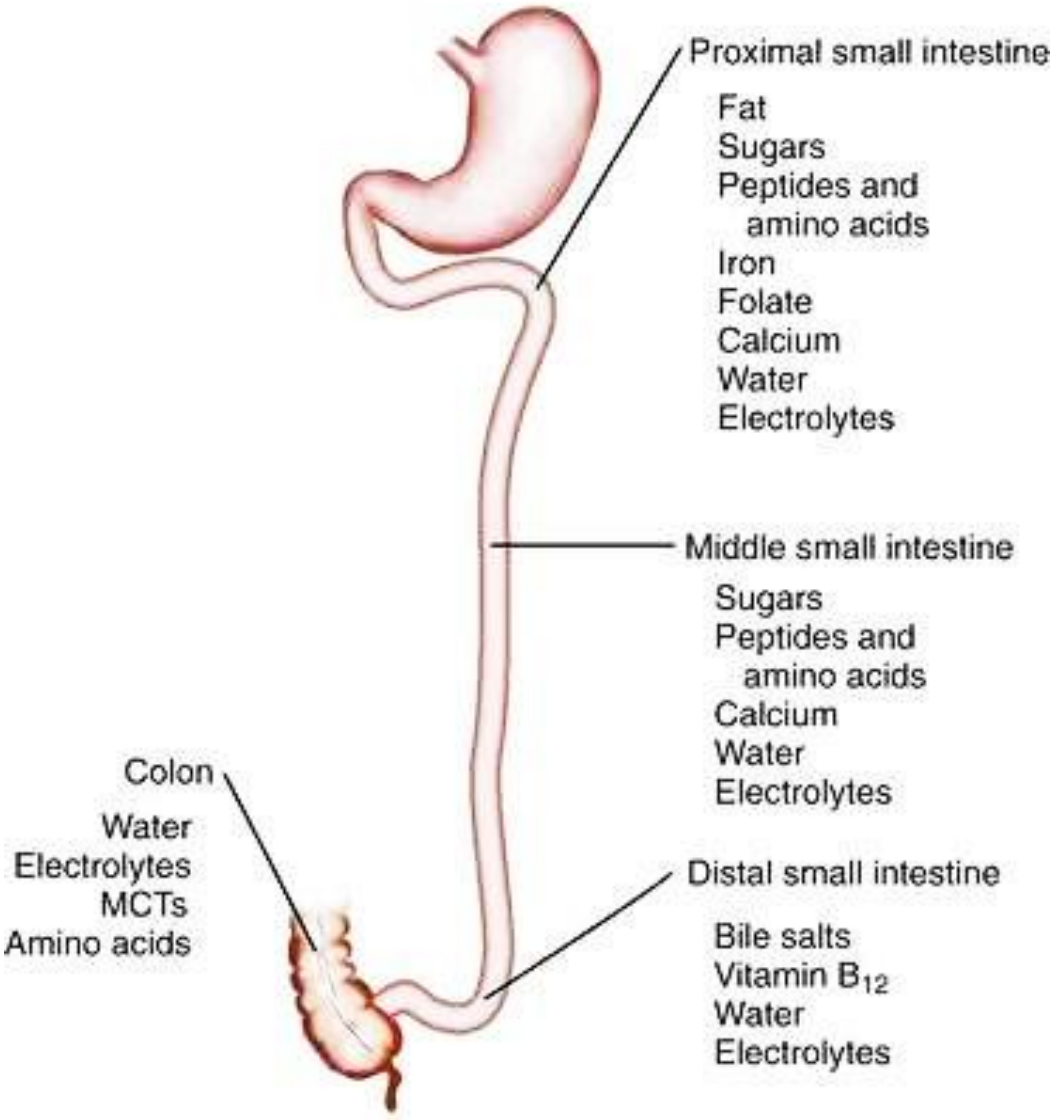
- Pathophysiology
  - Three common types of intestinal resection:
    - Limited ileal resection for Crohn +/- cecectomy + jejunocolonic anastomosis
    - Extensive ileal resection +/- colectomy + jejunocolonic anastomosis
    - Extensive small intestinal resection + total colectomy → proximal jejunostomy



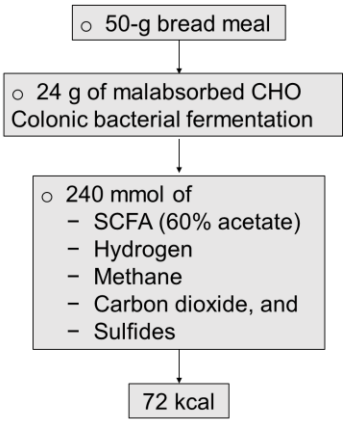
Printed with permission: https://abdominalkey.com/short-bowel-syndrome/ (Figure 103-1)

- Degree of malabsorption determined by:
  - Length of Absorptive Surface Area
    - Nutrient Malabsorption
    - Water and electrolyte malabsorption
  - Loss of Site-Specific
    - Transport Processes
    - Endocrine cells + GI hormones
  - Loss of ileocecal valve (“ileal brake”)

- Nutrient Malabsorption (Loss of Absorptive Surface Area)
  - Small bowel ~ 3-8 meters; nutrient absorption preserved until > half of small intestine resected
  - Normal digestion and absorption depend on gradual gastric emptying of partially digested nutrients
  - Nutrients mixed with bile + pancreatic enzymes in duodenum + rapid digestion and absorption of the digestive products in proximal small intestine.
  - Most macronutrients (carb, fat, protein) absorbed in proximal 100-150 cm intestine
  - Distinct proximal-to-distal absorption gradient exists in both morphology + function (villi taller + crypts deeper in jejunum than ileum)
  - Activity of microvillus enzymes + nutrient absorptive capacity per unit length of intestine several-fold higher in proximal compared to distal small bowel
  - Ileum eventually able to compensate for loss of jejunum (but jejunum unable to compensate for ileal absorption of bile salts and B12)
  - Proximal jejunostomy:
    - ↑ rate of gastric emptying of liquids + ↑ intestinal transit rate because of ↓ release of GLP-1, GLP-2 and PYY → compromises gastric phase of digestion → inadequate mixing with biliary + pancreatic secretions, insufficient enzymatic digestion, and nutrient maldigestion
    - ↑ intestinal transit rate → ↓ nutrient-enterocyte contact time → ↓segmental absorption.
    - Net secretors of salt and fluid (jejunal fluid secretion stimulated by oral intake and gastric emptying of nutrients) → fluid management may be challenging
  - Jejunum < 100 cm + no colon require long-term TPN
    - Colon preservation highly beneficial for nutrient absorption (small bowel should be anastomosed to colon as soon as patient stable)
    - IC valve acts as brake to slow transit
    - Malabsorbed carbohydrates fermented by bacteria in colon to SCFA’s → absorbed by colonocytes (~ 1000 kcal per day absorption)



Printed with permission: https://abdominalkey.com/short-bowel-syndrome/ (Figure 103-2)



- Colonic absorption of malabsorbed carbohydrate (CHO) in a hypothetical patient with short bowel syndrome following ingestion of a 50-g bread meal.
- Unabsorbed carbohydrates (~24 g), non-starch polysaccharides, and soluble fibre are fermented by colonic bacterial flora to
  - Hydrogen
  - Methane
  - Carbon dioxide
  - Sulfides, and
  - ~240 mmol short-chain fatty acids (SCFAs, including acetate, butyrate, and propionate) to generate 72 kcal.
- By comparison, normal persons absorb 220-720 mmol SCFA from fermentation of 30-60 g non-starch polysaccharides.

Printed with permission: https://abdominalkey.com/short-bowel-syndrome/ (Figure 103-3)

- Water + Electrolyte Malabsorption
  - ↓ absorptive surface = ↑ stomal/fecal loss of electrolytes, water, mineral + trace elements
  - Proximal small bowel receives 7-9 L of fluid → 6-8 L reabsorbed
  - Proximal jejunostomy (+ unrestricted diet) → ↓ reabsorption difficult → diarrhea + hypovolemia, hyponatremia + hypokalemia
  - Jejunum tight junctions leaky, require high NaCl concentration (>90 mmol/L) to achieve Na^+ / water absorption (possible by sipping oral rehydration solution (ORS) throughout the day)
  - Na^+ absorbed by active electrogenic coupling with Cl^- and exchange with H^+; water transport proportional to Na^+ transport

- Give the Daily Stomal or Fecal Losses of Electrolytes, Minerals, and Trace Elements in Severe Short Bowel Syndrome.

Component	Amount Lost
Sodium*	90-100 mEq/L
Potassium*	10-20 mEq/L
Calcium	772 (591-950) mg/day
Magnesium	328 (263-419) mg/day
Iron	11 (7-15) mg/day
Zinc	12 (10-14) mg/day
Copper	1.5 (0.5-2.3) mg/day

*For sodium and potassium, the average concentration per litre of stomal effluent is given

  - The values for minerals and trace elements are mean 24-hour losses, with the range in parenthesis.

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- Loss of Site-Specific Transport Processes
  - Most patients with SBS have intact duodenum + variable jejunum length
  - Development of iron, phosphorus, or water-soluble vitamin deficiency relatively uncommon (even in patients with a proximal jejunostomy)
  - Malabsorption of calcium + magnesium consequence of fat malabsorption; precipitated intra-luminally by unabsorbed long chain fatty acids (LCFAs)
  - Active absorption of vitamin B12 and bile acids is restricted to the ileum (by specific transport protein in ileal enterocytes)
    - B12 malabsorption usually when > 60 cm ileum resected
    - Bile acid malabsorption if > 100 cm ileal resection
      - ↓ bile acid pool size if acid loss > hepatic synthesis
      - ↓ micellar solubilization of lipolytic products → steatorrhea (+ fat soluble vitamin deficiency)
      - Essential fatty acid deficiency rare
      - Loss of unabsorbed LCFA can exacerbate diarrhea if hydroxylated by colonic bacteria (stimulate electrolyte colonic electrolyte + water secretion)
    - < 100 cm resection = moderate cholerheic enteropathy

- Loss of Site-Specific Enteroendocrine Cells and GI Hormones
  - GI hormone synthesis = site specific
  - Proximal GI tract hormones (regulate secretion and motility)
    - Cholecystokinin (CCK)
    - Gastrin
    - Gastrin inhibitory polypeptide (GIP)
    - Motilin
    - Secretin
    - Usually intact for SBS patients; 50% of extensive intestinal resections = hypergastrinemia (+ increased gastric acid secretion) in early post-op phase
  - Ileum/proximal colon (delay gastric emptying + slow intestinal transit); “ileal brake”
    - GLP-1/GLP-2
    - Neurotensin
    - Peptide YY
    - Preserved colon = increased GLP-1/GLP-2 with normal gastric emptying

❖ Intestinal Adaption to Resection

- Ileum attains jejunal characteristics (taller villi, deeper crypts) and increase in diameter/length → increased absorption, improved mineral absorption
- Adaptive changes take 1-2 yrs + dependent on presence of food, biliary and pancreatic secretion (changes more profound in younger patients)
- ↑ lactobacillus species + decreased clostridium (leptum, coccoides) and bacteroides species
- Vascular endothelial growth factor (VEGF), CCK, gastrin, insulin, neurotensin, GLP-2, PDGF-α + L-glutamine → ↑ intestinal growth in animals
- Elucidation of mediators that regulate enterocyte proliferation eventually can lead to development of pharmacologic interventions to accelerate intestinal adaptation
- Presence of comorbid conditions + health of residual bowel and blood flow are important prognostic factors for patients following massive enterectomy
- Plasma citrulline concentration (indicator of bowel mass) may be useful predictor of nutrition autonomy
  - 20 μmol/L (sensitivity, 92%; specificity, 90%) for distinguishing children who gained independence from total parenteral nutrition (TPN)

❖ Medical Management

- Limited Ileal Resection (< 100 cm)
  - Cholestyramine (2-4 g with meals) or colestipol (1-2g with meals) to manage bile acid malabsorption + diarrhea
  - Fat malabsorption:
    - Low fat (40g) diet (improved diarrhea + improved Ca^{2+}, Mg^{2+} + Zinc absorption)
    - Supplement with MCT for fat calories
  - Calcium (800-1500 mg daily) + Vitamin D 400-800 IU daily
  - Magnesium: oral +/- IV replacement; can have deficiency despite normal Mg levels as Mg is intracellular
  - Vitamin B12: unable to perform Schilling test; 1 mg IM monthly for life if suspected (oral and nasal preparations available)
  - Water soluble vitamins, carbohydrate and protein not compromised
- Extensive ileal resection (post-op)
  - TPN + NPO (nothing per OS [mouth])
  - Monitor: weight, volume status, extended lytes
  - PPI + H2RA's to suppress hypergastrinemia (+ limit volume loss)
  - Enteral tube feed → oral feeding in late post-operative phase
- Extensive Small Intestinal Resection and Partial Colectomy
  - PPI + H2RA's to suppress hypergastrinemia (+ limit volume loss)
  - Anti-diarrheal agents (next slide); take 1 hour before meals
    - Most studies show stomal output improvement up to 50% (positive water/lyte balance rarely achieved)
    - Octreotide usually not necessary unless proximal jejunostomy
      - Decreases splanchnic protein synthesis (reducing post-resection intestinal adaption)
      - Increased risk of cholelithiasis
  - Glucose polymer-based ORS
    - 2.5 g table salt, 1.5 g KCl, 2.5 g $NaHCO_3$-, 1.5g table sugar in 1L water
    - Glucose and sodium absorbed by same active transport mechanism. Glucose supports Na/water absorption; sodium not as readily absorbed from isotonic/hypotonic solutions (in proximal jejunum)
    - ORS not as critical if colon intact as long as sufficient sodium present
    - Glucose addition not helpful if significant jejunal resection (glucose does not enhance ileal water absorption)

- Anti-diarrheal/anti-motility agents

Therapeutic Agents Used to Decrease Intestinal Transit and Diarrheal Volume

Agent	Dosage
− Anti-diarrheal Agents	
▪ Loperamide*	4-6 mg qid
▪ Diphenoxylate-atropine*	2.5-5 mg qid
▪ Codeine phosphate*	15-30 mg bid to qid
▪ Tincture of opium	0.6 mL (2.5 mg) bid to qid
− Acid Reducing Agents	
▪ Ranitidine	300 mg bid
▪ Omeprazole	40 mg bid
▪ Octreotide	50-100 µg SC bid
▪ Clonidine	0.3 mg transcutaneous q1 wk

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- Extensive Small Intestinal Resection and Partial Colectomy (Diet)
  - Fat absorption compromised > carb or nitrogen
  - Encourage ↑ intake (up to 2-3x pre-op)
  - Small portions throughout the day (separation of liquid and solid portions of meals impractical)
  - ↑ fecal volume → discomfort (counterbalanced by normal eating habits and less TPN dependence)
  - Colon in continuity
    - High-complex carbohydrate diet / oxalate restricted diet

Vitamin and Mineral Requirements* in Patients with Short Bowel Syndrome

Micronutrient	Requirement
− Vitamin A	10,000-50,000 units daily*
− Vitamin B12	1000 µg SC monthly for patients with terminal ileal resection or disease
− Vitamin C	200 mg daily
− Vitamin D	50,000 units of 1.25(OH2)-D3 twice daily
− Vitamin E	30 IU daily
− Vitamin K	10 mg weekly
− Calcium	1000-1500 mg daily
− Magnesium	
− Iron	As needed
− Selenium	60-150 µg daily
− Zinc	220-440 mg daily (sulfate or gluconate form)
− Bicarbonate	As needed

Note: The table lists rough guidelines only, Vitamin and mineral supplementation must be monitored routinely and tailored to the individual patient, because relative absorption and requirements can vary. Supplements may be taken orally unless otherwise indicated.

Abbreviations: IU, international units; SC, subcutaneous

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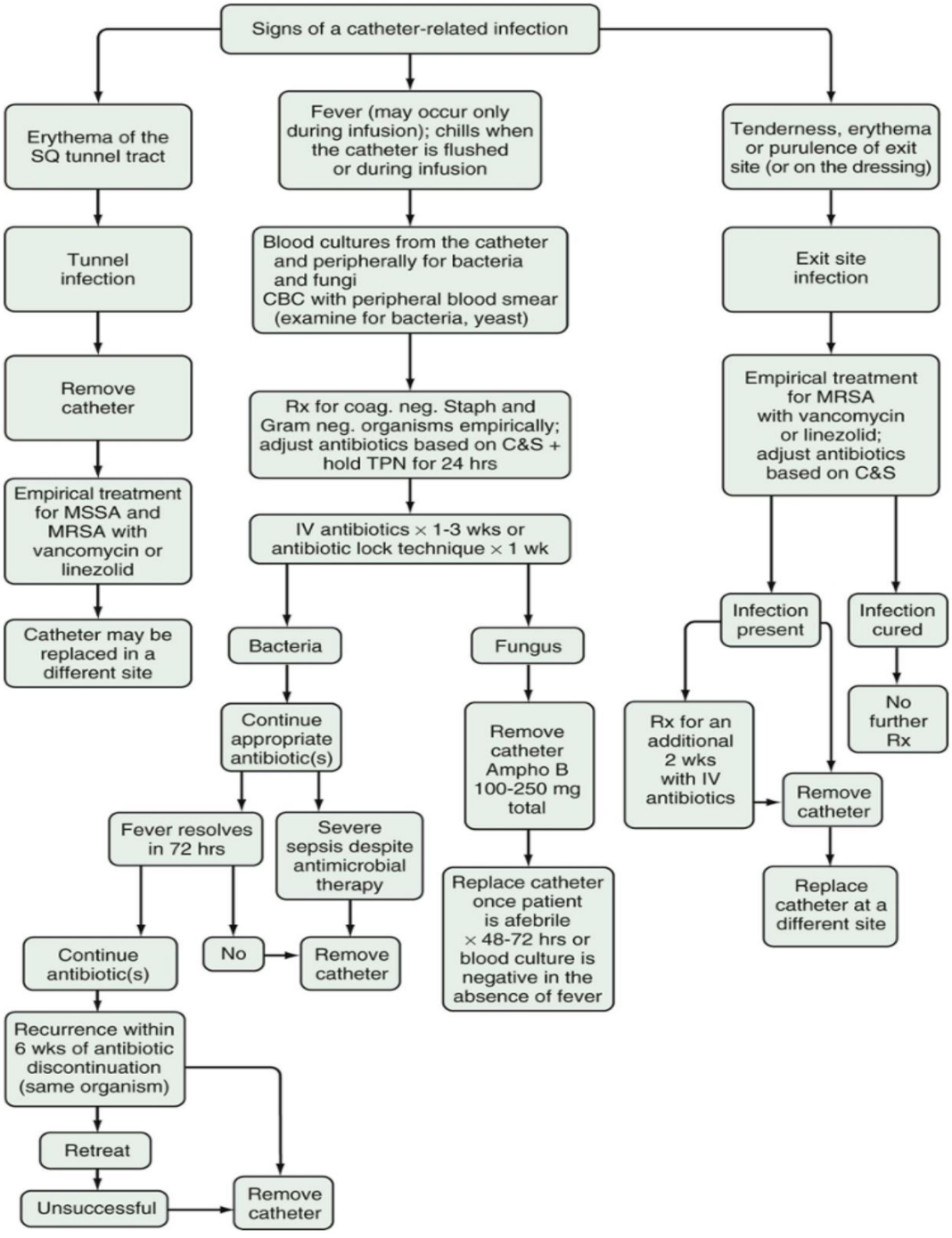
- Home Parental Nutrition (HPN)
  - Infused over 10-12 h period (overnight) + gradual 30-60 min taper (to avoid hypoglycemia)
  - (In US), patient must require TPN x 3 mon + failed enteral support with fat malabsorption
  - PICC line can be used for short term (< 6 mon); otherwise require tunneled catheter; TPN delivered in 1-2 wk batches (refrigerated)
  - Patient instructions:
    - TPN indications
    - Catheter care + dressings
    - TPN solution preparation
    - Acute complications (air embolism, hypoglycemia, infection)
  - Monitor for micronutrient deficiency (especially if TPN < 5 nights/wk)

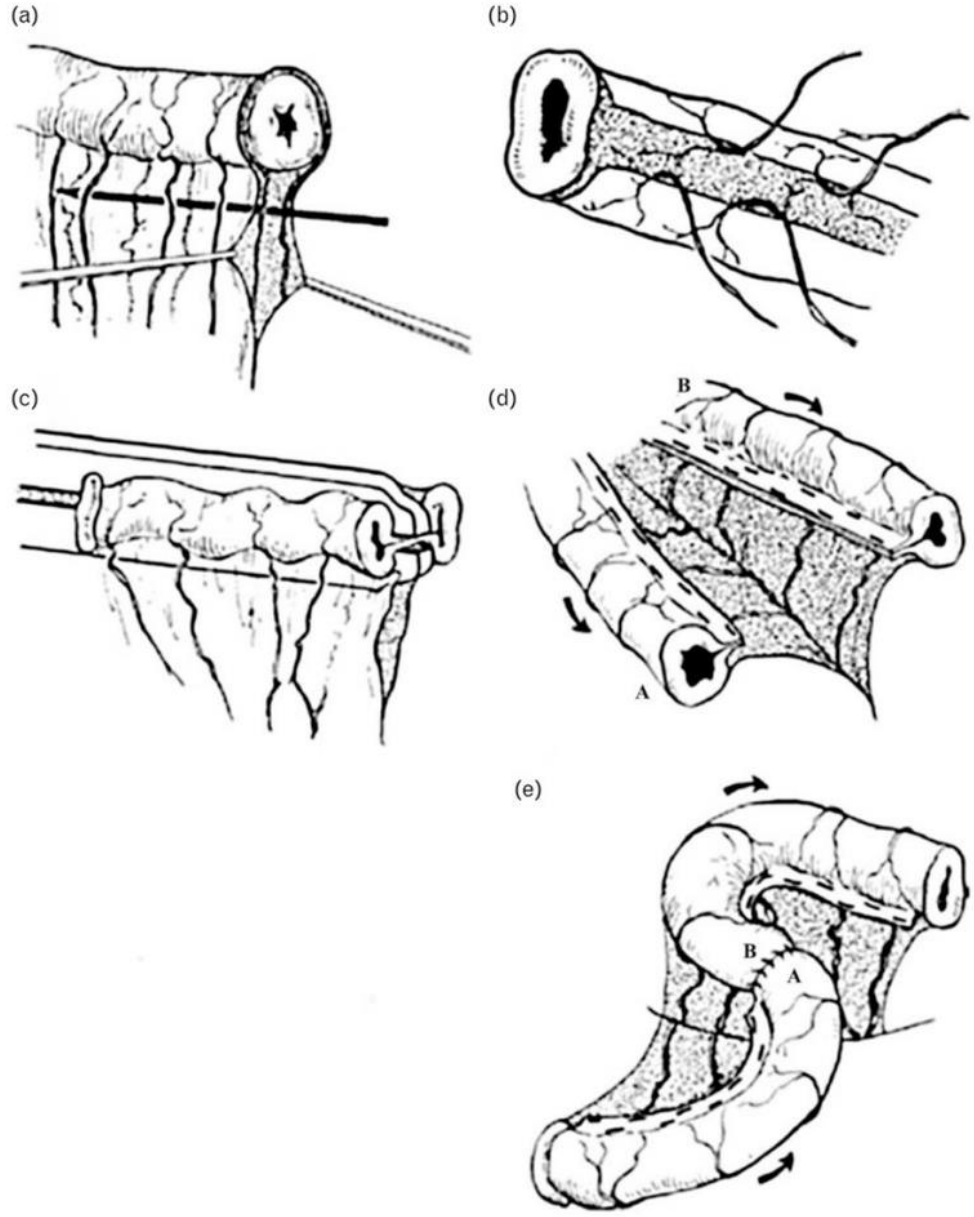
Algorithm of Diagnosis and Management of Catheter-related Infection



Printed with permission: Buchman AL. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 106 (Figure 106.5).

- Complications
  - Gallstones: decreased bile acid secretion, altered bile composition
  - Liver disease (cholestasis, steatosis, steatohepatitis)
    - >50% of TPN patients after 5 yr; defined as:
      - Grade 2 fibrosis/cirrhosis or 1 of the following:
        - Total bilirubin > 60 µmol/L > 1 mon
        - Ascites, portal hypertension (PH), hepatic encephalopathy (HE), liver failure + factor V < 50%
  - Calcium oxalate kidney stones
    - Long chain fatty acids (LCFAs) compete with oxalate to bind with Ca^{2+} in colon → ↑ absorption and stone formation
      - Monitor urine oxalate secretion, consider oral Ca citrate
  - D-lactic acidosis
    - Only in patients with preserved colon, and overfeeding of carbohydrates
    - Malabsorbed carbohydrate metabolized by colonic bacteria to SCFA and lactate → lowers colonic pH → Bacteroides sp. + gram- anaerobes produce D-lactate → absorbed
    - Clinical: AGMA + nystagmus, ophthalmoplegia, ataxia, confusion + inappropriate behaviour (usually suspected of inebriation with normal alcohol levels); treat with sodium bicarbonate
  - Others
    - Bone disease
    - Memory deficits
    - Neurologic abnormalities
    - Renal dysfunction
  - Surgical Management
    - Reanastomosis of residual small bowel to residual colon
      - Low mortality/morbidity, allows enhanced energy absorption
    - Intestinal Lengthening Procedures:
      - LILT/Bianchi procedure: dilated/dysfunctional bowel divided into 2 hemiloops and anastomosed end-end (last resort procedure); no data on effectiveness

Bianchi procedure or LILT



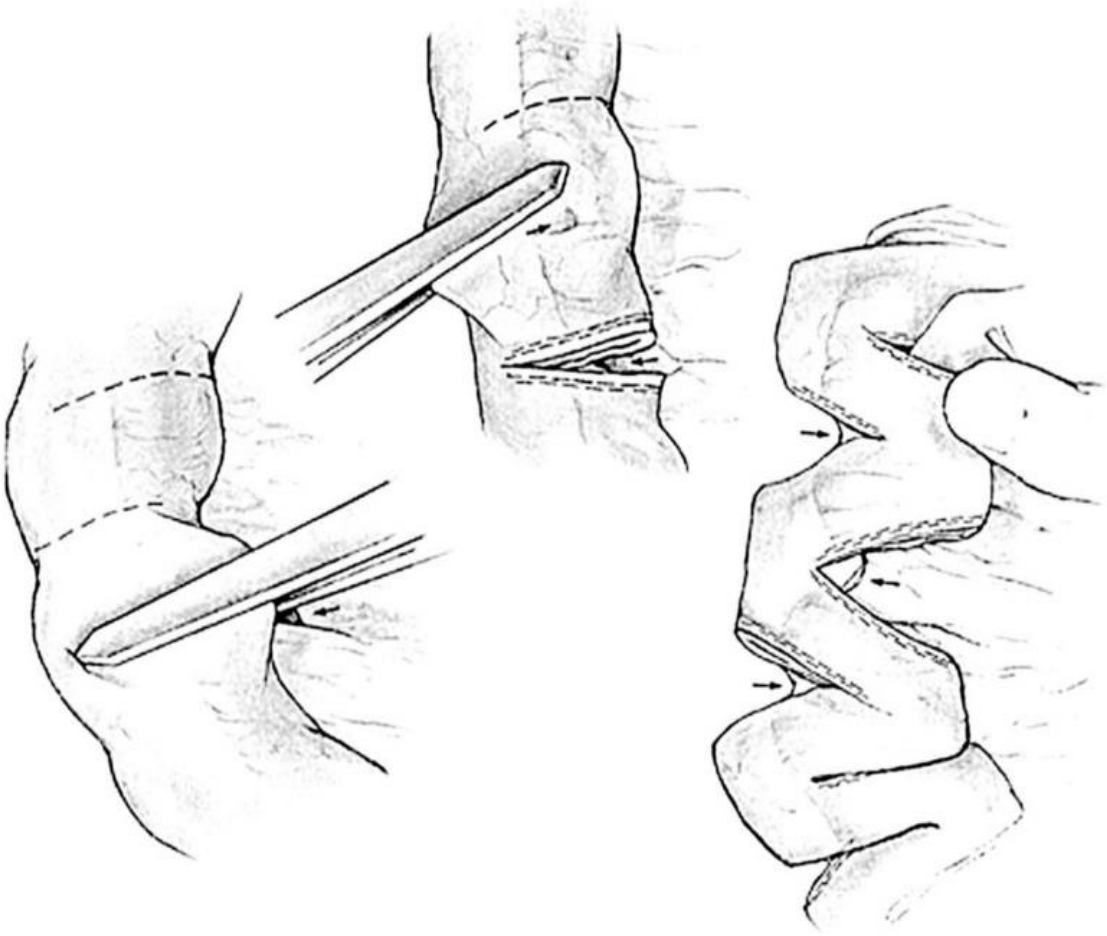
(a)separating the two leaves of the mesentery of the isolated small bowel segment. (b) Creating a funnel on the mesenteric site for dividing the small bowel. (c), (d) Separating the small bowel by introducing a surgical stapler. This can also be done by cutting the bowel half. (e) The two bowel loops are then anastomosed together in an isoperistaltic manner.

Abbreviation: ILT, Longitudinal Intestinal Lengthening

Source: van Praagh JB, et al. Curr Opin Organ Transplant. 2022;27(2):112-118.

- Serial Transverse Enteroplasty (STEP)
  - Intestinal tapering procedure, linear surgical stapler applied along intestinal mesenteric border to incompletely divide intestine
  - Nutrients channeled through longer but narrower intestine (improved absorption by up to 50% after 21 mon, ↓ risk of SIBO)

Schematic view of STEP

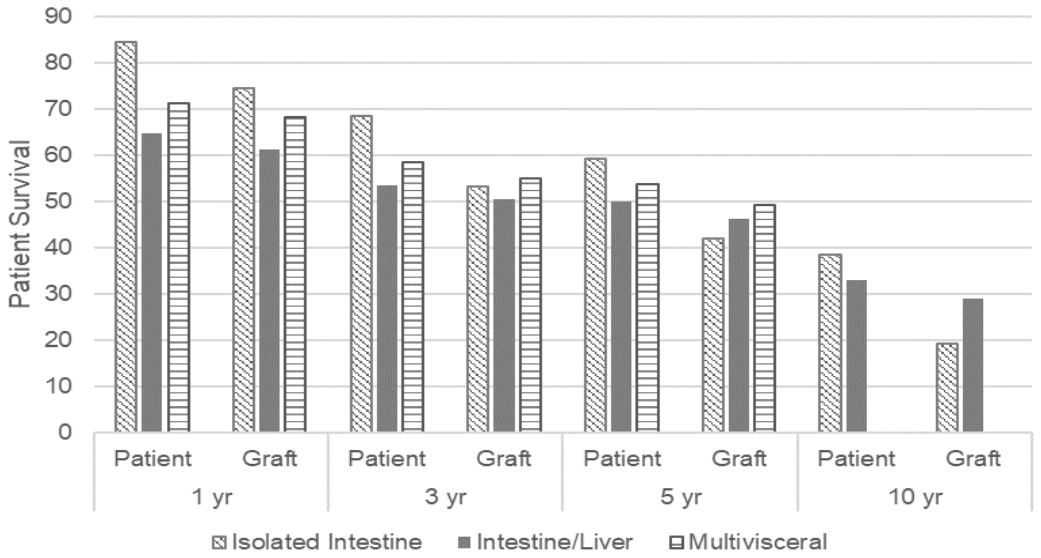


Perpendicular to the longitudinal axis, a stapler line is made preserving a 2 cm luminal diameter. After multiple staples, the bowel is lengthened

Abbreviation: STEP, Serial Transverse Enteroplasty

Source: van Praagh JB, et al. Curr Opin Organ Transplant. 2022;27(2):112-118.

Surgical Management



Adapted from: Buchman AL. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 106.

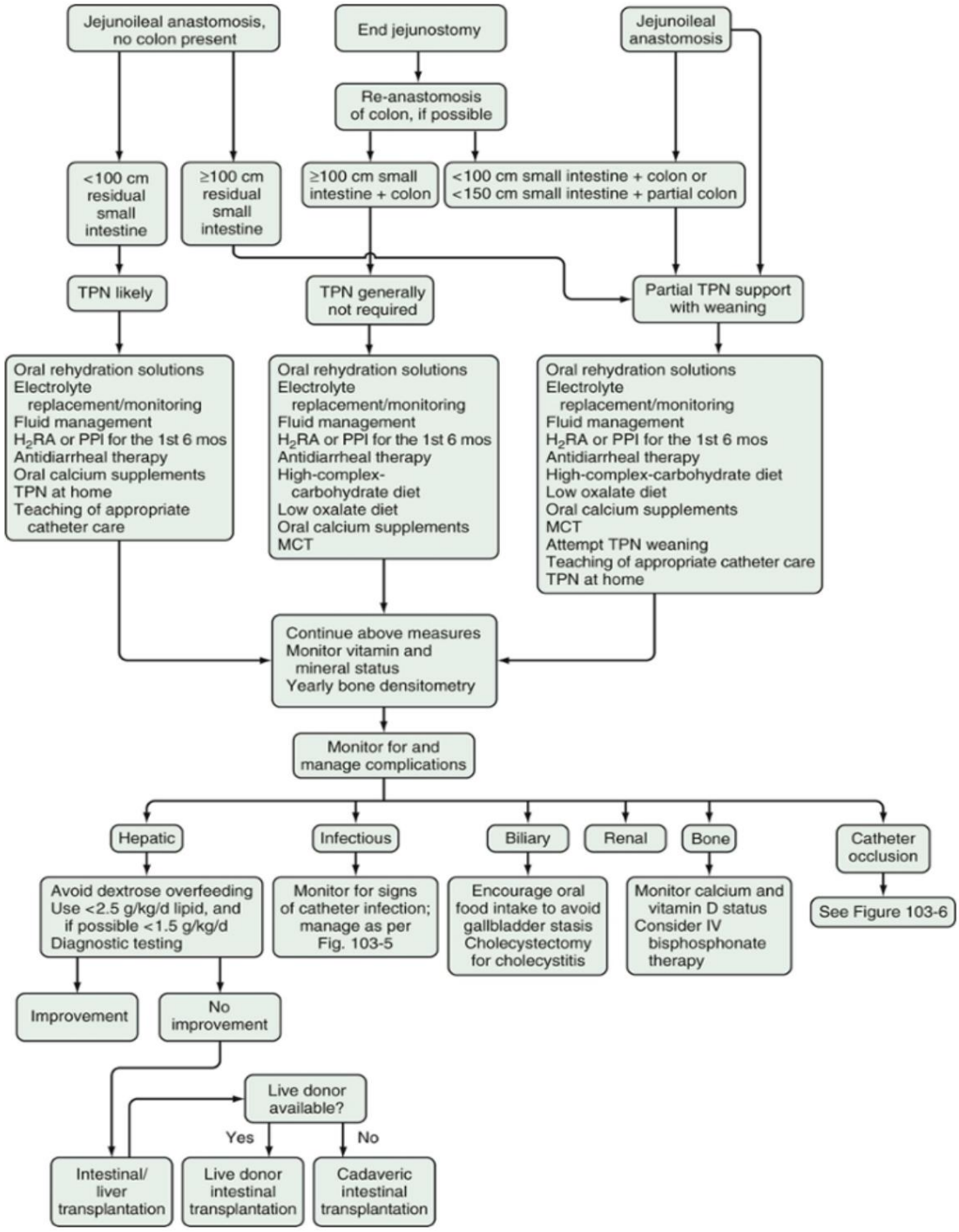
- Pharmacologic Enhancement of Bowel Adaption
  - Growth hormone (GH) / L-glutamine:
    - Two placebo controlled failed to show any beneficial effect on absorption
    - Two other studies showed marginal improvement in fluid/nutrient retention
    - Double blind RCT of growth hormone (GH) in 41 TPN patients showed improved TPN requirements (~ 1 night/wk)
  - GLP-2 (glucagon-like-peptide-2; teduglutide): a/w increased villus height, fluid absorption and energy/nitrogen absorption
    - Double blind RCT
      - Significant reduction in TPN requirements (generally 1-2 nights per wk)
      - Few subjects weaned (long term studies pending)

➢ Prognosis

- Prognosis determined by type + extent of resection + underlying disease
  - Limited intestinal resection → excellent prognosis with management of malabsorption
- Survival probability
  - 2 yr, 86%
  - 5 yr, 75%
- TPN dependence
  - 2 yr, 49%
  - 5 yr, 45%

  (bowel length < 100 cm highly predictive of permanent failure and lifelong TPN)

SBS Management Algorithm



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Abbreviations: bid, twice a day; Ca^{2+}, calcium; CCK, cholecystokinin; CHO, carbohydrate; Cl^{-}, chloride; CRP, C-reactive protein; GH, growth hormone; GI, gastrointestinal; GLP-1/2, glucagon-like peptide-1/2; H2RA, histamine-2 receptor antagonists; HPN, home parenteral nutrition; IM, intramuscular; LCFA, long-chain fatty acid; MELD, Model for End-Stage Liver Disease; Mg^{2+}, magnesium; min, minute; Na^{+}, sodium; NPO, nothing by mouth; ORS, oral rehydration solution, PPIs, proton pump inhibitors; PYY, peptide YY; qid, four times a day; SBS, short bowel syndrome; SCFA, short-chain fatty acids; TPN, total parenteral nutrition; US, ultrasound; VEGF, vascular endothelial growth factor; wk, week

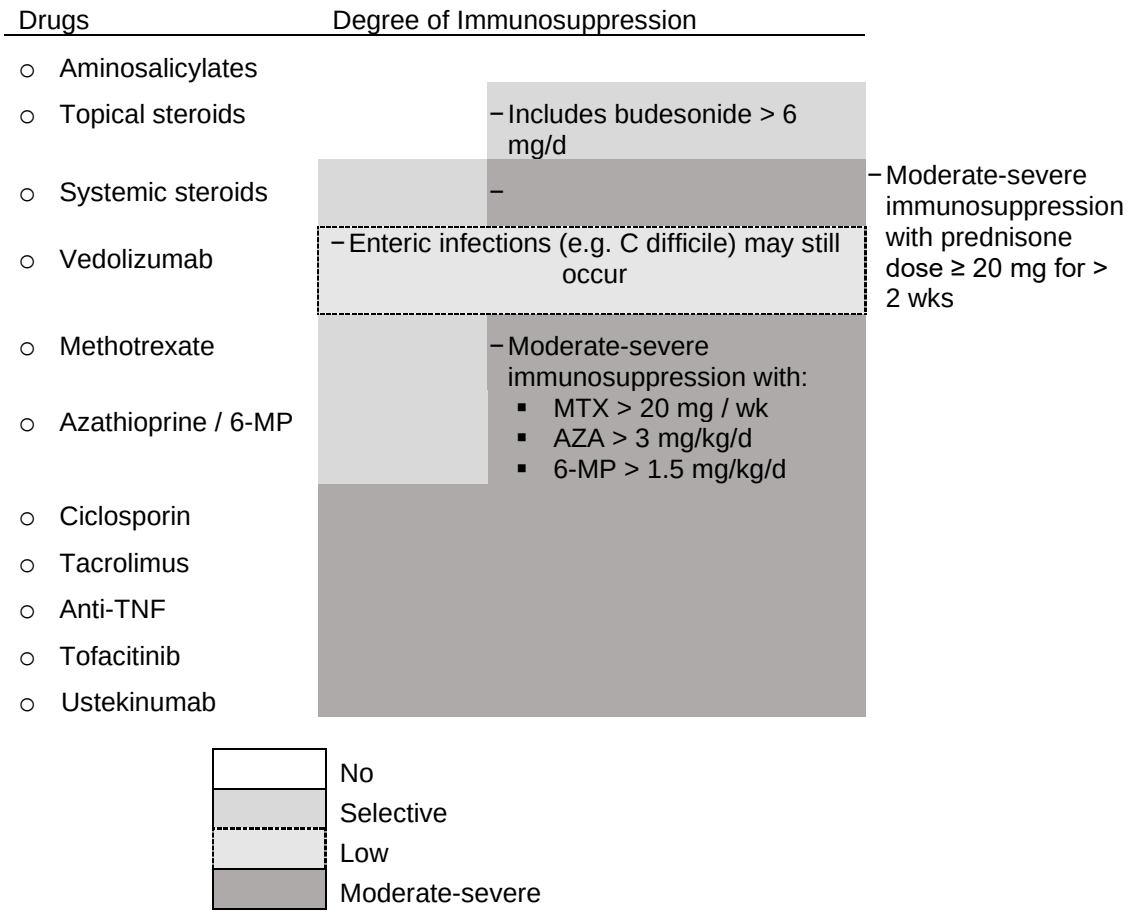
PREVENTION, DIAGNOSIS, AND MANAGEMENT OF INFECTIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Navneet Natt

Kucharzik T, et al. European Crohn and Colitis Organization (ECCO). J Crohns Colitis 2021;15(6):879-913

- Risk factors for opportunistic infections in IBD
  - >65 yr (over 20x ↑ risk)
  - Malnutrition
  - Immunodeficiency (e.g. HIV)
  - Comorbidity (e.g. diabetes mellitus)
  - Ongoing IBD activity
  - Use of immunosuppressive medications (combination therapy > steroids, thiopurines, or anti-TNF monotherapy)

- Drugs used in IBD, and their degree of Risk for Immunosuppression



Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine, MTX, methotrexate; TNF, tumour necrosis factor

Adapted from: Kucharzik T, et al. European Crohn and Colitis Organization (ECCO). J Crohns Colitis 2021;15(6):879-913 (Table 1)

ECCO Statement 2.1

- At risk for opportunistic infections are
  - IBD patients treated with immunosuppressive agents, particularly in combination (EL1)
- Further predictive factors are
  - Active disease
  - Comorbidities
  - Malnutrition
  - Obese body mass index (BMI)
  - Old age
  - Parenteral nutrition

ECCO Statement 3.1

- Do serological screening for hepatitis A, B, C, HIV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella zoster virus (VZV), and measles virus [in the absence of documented past infection or vaccination for the latter two] for all IBD patients at time of diagnosis [EL4] and especially before/during immunosuppressive treatment [EL1].
- Do a Pap smear for human papillomavirus screening [EL1]

- Hepatitis A Virus (HAV) Infection
  - Vaccinate for HAV before starting immunosuppressive therapy in non-immune patients
  - Give post-exposure prophylaxis with Hep A vaccine plus immunoglobulin (0.1 mL/kg) within 14 days of exposure for unvaccinated, immunosuppressed patients

- Hepatitis B Virus (HBV) Infection
  - All patients with IBD should be vaccinated against Hepatitis B
    - Check Hepatitis B surface antibody levels to confirm response to vaccination
    - Further doses may need to be administered to target anti-HBs IgG >10 IU/L
  - Patients with chronic Hepatitis B [HBsAg-positive] are at ↑ risk of reactivation with long term prednisone, thiopurine, or anti-TNF use (47.4% reactivation rate in those not receiving prophylaxis vs. 7% in those receiving prophylaxis)
    - Start prophylaxis 2 wk before introduction of immunosuppressant
      - Entecavir or tenofovir
    - Continue for at least 12 mon after immunosuppressant is withdrawn
    - Check liver enzymes, liver function tests, and HBV DNA level every 3-6 mon during prophylaxis and 12 mon after discontinuation
  - Prophylactic treatment with antivirals is not recommended in patients with IBD and previous Hepatitis B infection (cAb +, sAg -)

- Hepatitis C Virus (HCV) Infection

ECCO Statement 3.6

- Treat IBD patients with HCV in accordance with national and international guidelines [EL5].
  - Closely monitor these patients for disease exacerbation when they are treated with direct-acting antiviral agents [DAAs] [EL5]

- Hepatitis E Virus (HEV) Infection
  - Acute HEV infection is usually mild and self-limiting In immunocompetent patients
  - Diagnose acute infection with nucleic acid amplification testing (NAAT)
  - HEV E genotype 3 can progress to chronic infection in immunosuppressed individuals
  - Treatable with Ribavirin x 3 wks
    - Severe acute hepatitis E infection
    - Persistent viraemia > 3 mon (poses risk of chronic infection)

- Herpes Simplex Virus (HSV)
  - Ask patients if they have a history of HSV infection before starting immunosuppressive therapy
  - Consider routine prophylaxis to suppress HSV replication should be considered for patients with frequent recurrent IBD attacks, who are already taking intermittent suppressive antiviral therapy, or both:
    - Acyclovir 400 mg bid
    - Valacyclovir 500 mg daily, or
    - Famciclovir 250 mg bid

- Varicella Zoster Virus (VZV)
  - A significant ↑ risk for the development of symptomatic VZV reactivation with:
    - ↑ age
    - Immunosuppressive therapy
  - All IBD patients would benefit from vaccination against zoster if non-immune, but
    - Studies of vaccination against VZV in the IBD population have involved patients aged ≥50 yr
    - ECCO 2021
      - Recombinant herpes zoster vaccine [RZV] is the preferred vaccine for patients with IBD disease, given its efficacy and safety
    - If RZV not available, use a live zoster vaccine [ZVL] in immunocompetent patients ≥50 yr
    - Give 4 wk before starting immunosuppressive therapy of moderate-severe potency

- Cytomegalovirus (CMV)
  - Test patients with refractory for CMV colitis
    - Concurrent CMV colitis ↑ risk of
      - Toxic megacolon
      - Colectomy
      - Flare of disease
      - Rescue therapy needed
  - Diagnosis
    - Blood-based CMV tests
      - Specific, high
      - Sensitivity, poor
    - Take colonic biopsies for diagnosis for CMV colitis
      - Take multiple biopsies from the base and edge of ulcers (if present)
    - If no ulcers
      - Take multiple biopsies from left and right colon (at least 11 in UC and 16 in CD gives 80% probability of CMV detection)
      - Tissue should be sent for immunohistochemistry (IHC), and possibly for tissue PCR (no cut-off levels established)
  - Treatment
    - Give IV ganciclovir 5 mg/kg BID x 5–10 days then
      - Valganciclovir 900 mg daily for 2–3 wk
    - Use foscarnet
      - Ganciclovir intolerance / resistance
      - Monitor serum electrolytes and creatinine
    - Common side effects
      - Neutropenia
      - Thrombocytopenia

- Epstein-Barr Virus (EBV)
  - >95% of all adults are EBV seropositive (EBV IgG +)
    - Due to childhood or adolescent exposure to the virus
  - ↑ risk of lymphoma
    - Hemophagocytic lymphohistiocytosis (HLH) following primary EBV infection in immunosuppressed IBD patients (especially in those receiving thiopurines)
  - ECCO 2021: EBV-IgG negative individuals should be carefully considered for thiopurines (given the ↑ risk of lymphoma with primary EBV infection)

- Influenza
  - Influenza vaccination is safe in IBD patients
    - Not associated with risk of flare
  - All IBD patients on immunosuppression should receive annual flu vaccine, but note that
    - Immunosuppressive therapy may reduce the response to vaccination
      - Stop methotrexate discontinuation for 2 wk after vaccination (may be effective in rheumatoid arthritis patients, but unknown if this applies to IBD)
      - Timing of infusion of infliximab does **not** affect degree of serologic response

- Human Papilloma Virus (HPV)

ECCO Statement 3.17

- Treat IBD patients with HCV in accordance with national and international guidelines [EL5].
  - Closely monitor these patients for disease exacerbation when they are treated with direct-acting antiviral agents [DAAs] [EL5]

ECCO Statement 3.16

- Do prophylactic HPV vaccination for both young female and young male patients with IBD [EL2]

- Immunosuppressive therapy during viral infection

ECCO Statement 3.14

- Stop immunosuppressive therapy in
  - Severe cases of varicella infection
  - Disseminated HSV and VZV
  - Symptomatic infectious mononucleosis
  - EBV-related mucocutaneous ulceration, and
  - Severe influenza [EL4]
- Immunosuppressive therapy should be withheld in cases of measles [EL5]

ECCO Statement 3.15

- Use appropriate antiviral treatment in immunosuppressed IBD patients with an ongoing infection
  - HSV
  - Influenza
  - VZV [EL4]

- COVID-19
  - Severe COVID-19 infection occurs with
    - ↑ age
    - Immunosuppression
  - If an IBD patient tests positive for COVID-19
    - The decision of whether to continue or hold immunosuppression should be made on a case-by-case basis given the ↑ risks of IBD relapse with severe COVID-19
  - ECCO supports vaccination against COVID-19 in patients with IBD

➢ Bacterial Infections

- Latent tuberculosis infection (LTBI)
  - Screen for latent TB prior to starting immunosuppression or up to 2 wk after starting
  - Modes of screening:
    - Chest X-Ray
    - Tuberculin Skin Test (TST) – ≥ 5 mm is considered to be a positive test
    - Interferon Gamma Release Assay (IGRA)
  - TST may be negative in patients
    - On corticosteroids for ≥1 mon, on thiopurines/methotrexate for ≥3 mon
    - On infliximab, or
    - During active IBD without immunosuppression
    - In patients with IBD, perform TST plus IGRA is used in addition to
  - Patients who test positive for LTBI should be treated and immunosuppressive therapy should be avoided for at least 1 mon after TB treatment has begun
    - Delay immunosuppression x 2 mon for active TB

- Suggested Latent Treatment Regimens in Canada

Drug	Schedule	Duration (mon)	Side Effects
First Line Regimens			
Rifampin (4R)	Daily	4	▪ Rash / Drug interactions
Rifapentine + isoniazid (3HP)	Weekly	3	▪ Flu-like effects, drug interactions
Second Line Regimen			
Isoniazid (q9 h)	Daily	6	▪ Hepatotoxicity, peripheral neuropathy
Alternative Regimen			
Isoniazid (q6 h)	Daily	6	▪ Hepatotoxicity, peripheral neuropathy
Isoniazid	Twice Weekly	9	▪ Hepatotoxicity, peripheral neuropathy
Isoniazid a+ Rifampin (q3 h)	Daily	3	▪ Hepatotoxicity, peripheral neuropathy

From: Canadian Tuberculosis Standards – 8th Edition – Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2022.

- Streptococcus Pneumoniae

ECCO Statement 5.1

- Give Pneumococcal vaccination for all patients with IBD [EL3]

- Legionella Pneumophila
  - Test immunosuppressed IBD patient with pneumonia for Legionella
  - If Legionella test is positive
    - Stop immunosuppressive therapy until resolution of active infection
- Salmonella & Listeria

ECCO Statement 5.3

- Patients receiving immunosuppressive agents are at ↑ risk / more severe infections with
  - Salmonella enteritidis and S. typhimurium [EL4], and
  - Systemic and central neurological infections with Listeria monocytogenes [EL4]
- The ↑ incidence of L. monocytogenes infections is in patients treated with anti-TNF agents compared with other immunosuppressive agents [EL4].
- Temporarily withheld immunosuppressive therapy should be until resolution of the active infection [EL5]

- Clostridium difficile infection (CDI)
  - IBD patients are 5x more likely to develop CDI than those without IBD (even in absence of traditional risk factors such as antibiotic use, hospitalization)
  - CDI results in both short- and long-term adverse outcomes in patients with IBD
  - Do screening for CDI in patients with IBD and a disease flare
    - Especially those receiving immunosuppression
  - ECCO recommends two step stool testing for CDI
    - Glutamate dehydrogenase antigen enzyme assay or NAAT and
    - Toxin assays
  - Do **not** use the endoscopic demonstration of pseudomembranes to diagnose CDI (since pseudomembranes are seen in 13% of all hospitalized patients [false-positive])

- Treatment
  - 1st line
    - Non-Severe CDI
      - Vancomycin 125 mg qid x 10 d, or
      - Fidaxomicin 200 mg bid x 10 d
    - Severe Infection
      - Vancomycin 500 mg qid plus Metronidazole 500 mg IV tid x 14 d
  - Recurrent CDI
    - Vancomycin 125 mg qid x 10 d (1st recurrence)
    - Fidaxomicin 200 mg bid x 10 d (1st recurrence)
    - Prolonged vancomycin taper

- Nocardia

ECCO Statement 5.7

- Patients receiving immunosuppressive therapy are at ↑ risk of systemic and cutaneous infections with Nocardia spp.
  - Particularly when treated with corticosteroids [EL4]
    - Although Nocardia spp. is a ubiquitous agent, the risk in IBD patients is low [EL5]

- Meningococcus

ECCO Statement 5.8

- Give Meningococcal vaccination to patients with IBD as per regional or national recommendations for the general population [EL5]

CYTOMEGALOVIRUS (CMV) IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD)

Navneet Natt

- CMV in the immunocompetent host
  - Majority of CMV infections are *asymptomatic* in immunocompetent children and adults
    - Primary infection → lifelong latent infection in the host → periodic reactivation
  - When symptoms develop
    - Typically, mild and non-life-threatening
      - Fever, malaise, fatigue, lymphadenopathy
      - Leukopenia, atypical lymphocytosis, transaminitis
  - Clinically significant disease almost *universally* occurs in individuals who are immunocompromised
    - HIV/AIDS, organ transplant recipients, cancer patients
  - Common site of infection
    - CNS
      - Encephalitis
      - Retinitis
    - CVS
      - Myocarditis
    - Lung
      - Pneumonitis
    - GI
      - Colitis
      - Hepatitis

➢ Immunobiology

  - Double-stranded DNA virus in the *Herpesviridae* family (HHV-5)
  - Seroprevalence of CMV in the general population, 40-100%
    - ↑ with age
    - Most common congenital infection
  - Transmitted through close contact with bodily fluids of infected patient (urine, stool, semen, vaginal secretions, blood, breastmilk, tears, saliva)
    - Vertical transmission possible via placenta, during
      - Active labour
      - Post-natal through breastfeeding
  - High risk groups for acquisition
    - Employees at daycares/schools
    - Healthcare workers
    - Recipients of blood product transfusions / stem cell transplantations
    - Sexually active individuals

- Pathogenesis
  - pH-independent fusion (fibroblasts)
  - Endocytosis (epithelial and endothelial cells)
  - Paxillin-mediated macropinocytosis (monocytes)
  - Fibroblast entry
  - Epithelial cell entry
  - Non-permissive myeloid cell entry
  - Innate immune system detects CMV glycoproteins through toll-like receptors (TLR)
    - Upregulation of IFN-α and IFN-β which activate
      - Dendritic cells (DCs)
      - Macrophages, and
    - Natural killer (NK) cells
      - NK cells directly cause lysis of viral-infected cells
      - Remain in circulation (providing lifelong immune surveillance)
  - Adaptive immune system
    - Activated by viral pathogens, host macrophages, and DCs
    - B lymphocytes secrete neutralizing antibodies against gB
      - gH glycoprotein
      - gH glycoprotein involved in cell surface attachment
    - CD8+ and CD4+ T-cells limit viral replication
  - Sequence
    - CMV enters host cells and replicates
    - CMV resides dormant in myeloid cells
    - Can cause active infection once differentiated
    - Macrophages and DCs activated by cytokines and viral pathogens → T-cell activation
    - Activated T cells
      - Directly lyse infected cells or
      - Block viral replication
    - Antibodies neutralize viral proteins

- CMV Evasion of Host Immune Defenses
  - In healthy individuals, a robust innate and adaptive immune response restricts human cytomegalovirus (HCMV) reactivation and replication.
  - HCMV counters this with an armoury of measures to disable all arms of the immune response.
  - Recognition by CD8+ T cells is limited by major histocompatibility complex (MHC) class I downregulation and prevention of antigen loading and presentation at the cell surface.
  - Similarly, MHC class II presentation to CD4+ T cells is prevented by similar strategies including the expression of a viral interleukin-10 (IL-10) homologue that promotes MHC class II downregulation.

- Loss of MHC class I can potentially activate natural killer cell recognition and killing according to the 'missing self hypothesis', thus HCMV promotes the expression of an HLA-E inhibitory receptor as well as numerous gene products that disable natural killer activating receptors and upregulate natural killer inhibitory receptors.
- The interferon response is disabled at multiple points of the viral life cycle. Specifically, HCMV gene products interfere with DNA sensing pathways to prevent activation including inhibitors of IFI16 (for example, pp65 and US28) and cGAS–STING (UL31 and pp71).
- Interferon signalling is also disabled via an interaction of IE72 with the signal transducer and activator of transcription (STAT) transcription factor.
- HCMV also modulates the bio-activity of cytokines through expression of β-chemokine receptors that bind and sequester host cytokines.
- Additionally, HCMV encodes numerous α-chemokines that mimic CXCL1 and CXCL2 activity to modulate the recruitment to, and activity of, immune cells at the site of infection.

- Reactivation of Latent CMV Infection
  - Stress or Inflammation
    ↓
    - Catecholamine production
    - Differentiation of CD34+ myeloid cells to macrophages and DCs
    - TNF-α and proinflammatory prostaglandin secretion
      ↓
      - Promote transcription of CMV Major Immediate Early (MIE) genes which drive viral replication

➢ Distinctions

- CMV infection
  - Detection of CMV replication (detection by nucleic acid testing (NAT), antigen testing, or viral culture)
    - In human body fluids or tissue
- CMV disease
  - Isolation of CMV virus, plus
  - Clinical signs/symptoms of end-organ disease
- CMV gastrointestinal disease
  - Upper and/or lower GI symptoms, plus
  - Macroscopic mucosal lesion, plus
  - Tissue isolation of CMV

➢ **CMV in Patients with IBD**

➢ Demography

- No difference in CMV seroprevalence between patients with IBD and healthy controls (69.6% vs. 51.8%; OR, 1.36, 95% CI, 0.45–4.14)
- CMV colitis is uncommon in IBD patients with inactive disease or mild-moderate disease activity but may be seen in
  - Ulcerative colitis (UC), ~10%
    - TNF-α production
  - Crohn disease, ~0-5%
    - Th1 mediated IFN-γ release
  - Acute severe colitis (prevalence, 10-17%)
  - Steroid refractory colitis (prevalence 25-36%)

- Reactivation in UC

	Mechanism of Action
○ Corticosteroids resistance	− ↑ ratio of GRβ/α − ↑ IL-6 / ↑ TNF-α − ↓ IL-5
○ Corticosteroid/immunosuppressant resistance	− ↓ mucosal immunity − ↓ NK activity
○ CMV infected monocytes	− ↑ damage / ↑ inflammation

➢ Clinical

- Same as IBD without CMV

➢ Laboratory

- Viral culture
  - Not helpful to determine if the CMV is
    - Pathogenic, or
    - An innocent bystander

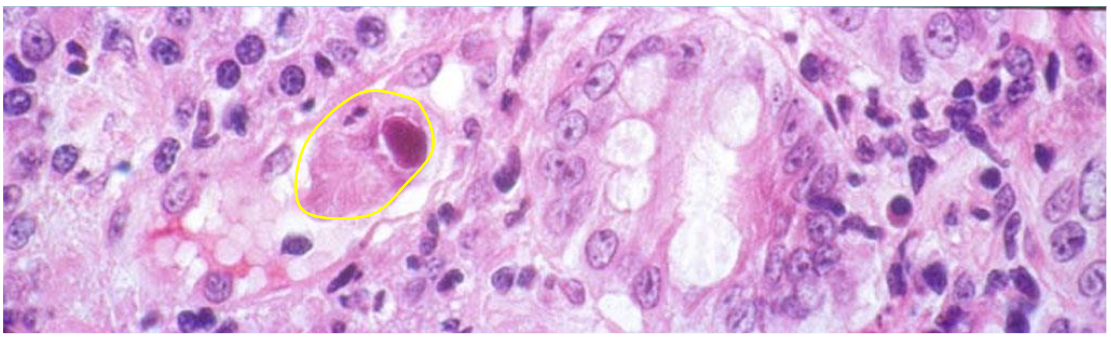
- Serology
  - CMV Antibodies
    - CMV Ab have limited utility in assessing for CMV infection in IBD
      - Negative CMV IgG may be able to rule out concurrent CMV colitis
    - CMV IgG
      - Patient with previous exposure to CMV
      - Positive in > 60% of IBD patients
    - CMV IgM
      - Positive in recent infection
      - Negative 3-12 mon following primary infection regardless of latency

- CMV Antigen Test
  - Semi-quantitative test
  - Immunofluorescent antibodies specific to viral antigen pp65 bind to circulating WBCs in the blood
  - Performance
    - Sensitivity, 60-100%
    - Specificity 83-100%
- CMV Blood PCR
  - DNA amplification assay used to quantify CMV viral load in circulating WBCs
  - Results obtained rapidly with
    - Sensitivity, 65-100%
    - Specificity, 40-92%
  - Higher viral loads correlate to higher risk of symptomatic disease
    - No cut-off defined: >3–4 log10 copies/ml in transplant patients

- Although highly specific, no clear cut-off level has been defined for the CMV antigen test or CMV blood PCR test.
- These tests and they should not replace histopathologic tests to diagnose CMV colitis in IBD patients
  - "Blood-based tests may be considered in addition to tissue-based tests when considering cessation of immunosuppressive therapy" – ECCO 2021

➢ Histopathology of GI mucosal biopsy

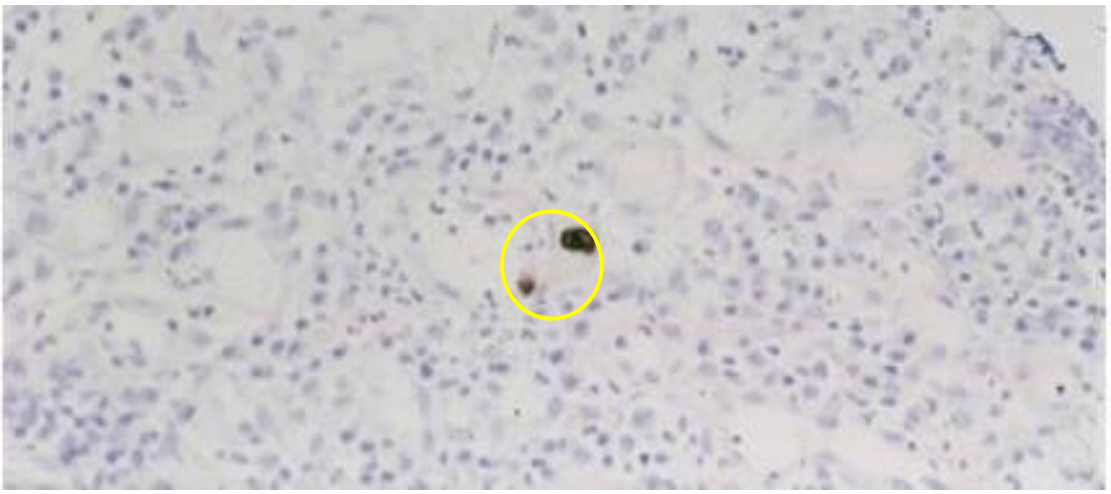
- Haematoxylin & Eosin (H&E) Stain
  - Large cytomegalic cells
  - Basophilic intranuclear inclusions surrounded by clear halo of cytoplasm
    - "Owl's eye" appearance
  - High false negative rate, with sensitivity as low as 10%
  - Highly specific for colonic CMV infection (specificity 92-100%)



Kindly provided by Professor Guito Tytgat, Netherlands

- Immunohistochemistry (IHC)
  - Monoclonal antibodies against pp65 viral antigen
  - Performance characteristics
    - Sensitivity 78-93%
    - Specificity 92-100%

CMV Infection



Kindly provided by Dr. Aducio Thiesen, University of Alberta

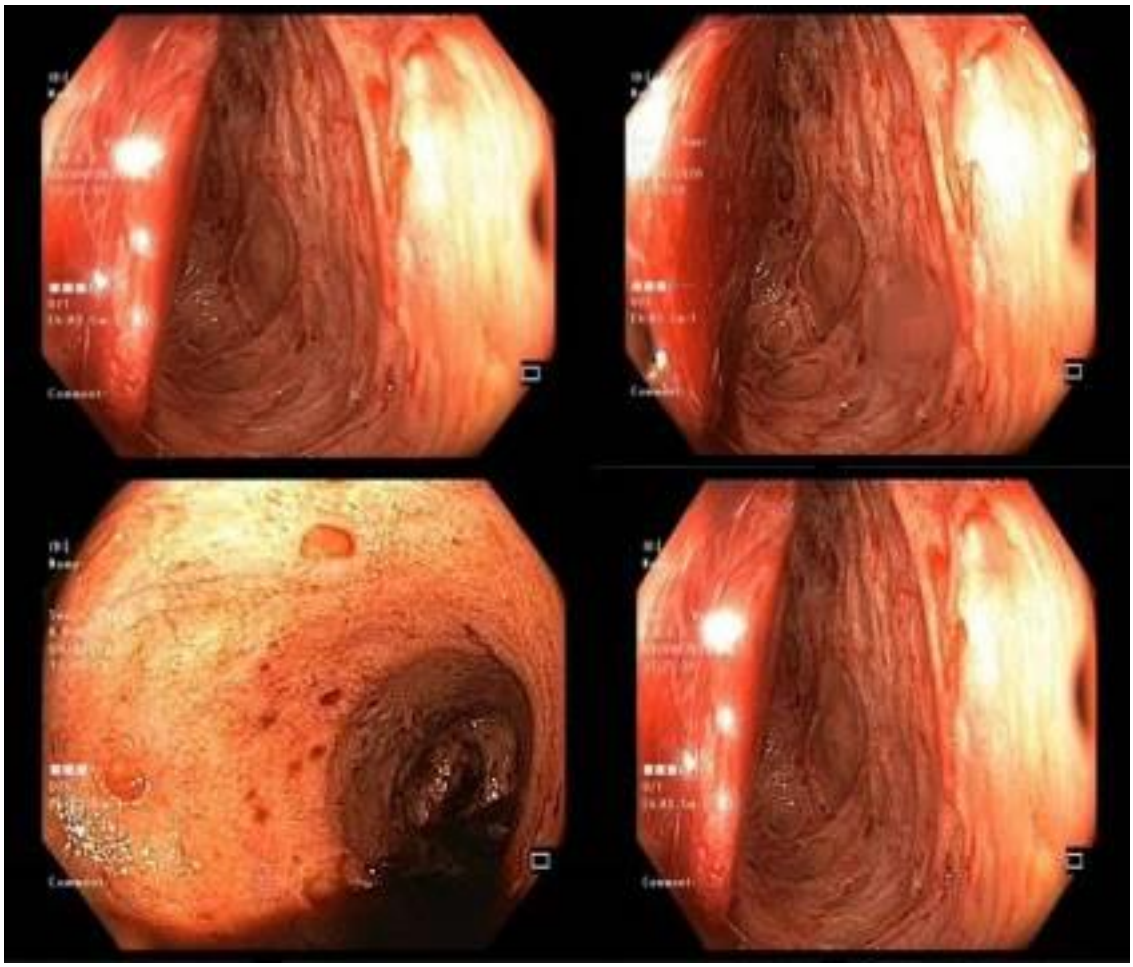
- Tissue Polymerase Chain Reaction (PCR)
  - Real-time DNA amplification assay used to quantify CMV DNA load within colonic cells
  - Performance characteristics
    - Highly sensitive (92-97%)
      - May be overly sensitive and detect mild CMV reactivation or latent disease with no clinical relevance
  - Using a higher viral load cut off may be able to predict clinically significant disease
    - Tissue CMV DNA >250 copies/mg tissue predicted resistance to steroids and three drug regimens (LR 4.3)

- Diagnosis using a combination of PCR, HE, IHC
  - Rate of surgery by test for CMV
    - PCR-, ~25%
    - PCR+, 20%
    - PCR+ plus IHC, 60%
    - PCR+ plus IHC plus HE, 80%

Adapted from: Johnson J, et al. Inflamm Bowel Dis 2018; 24(7): 1539-1546.

- Endoscopy
  - Irregular ulceration
  - Map-like appearance
  - Ulcerations with
    - Well-defined
    - Punched-out appearance, and
    - Longitudinal ulceration

CMV Infection



Source: Momayaz Sanat Z, et al. Arch Iran Med 2024; 27(5):277-286 (Figure 1)

- Increasing the yield of CMV biopsies taken during endoscopy
  - Take biopsies from
    - Inflamed mucosa, not normal tissue
    - Base and edge of ulcer
    - Both left (L) and right (R) colon
      - CMV may be detected exclusively from right colonic biopsies in ~7% of patients with UC and ~29% of patients with CD (so biopsy both L and R-side of colon)
- The more biopsies the better
  - Take
    - ≥ 11 biopsies in UC, and
    - ≥ 16 biopsies in CD to achieve 80% probability of having at least 1 positive biopsy

➢ Suggested Diagnostic Algorithm

- Colonoscopy in severe IBD to assess for CMV colitis
- Take
  - Examine for colonic ulcers
  - Endoscopic biopsies of inflamed mucosa
- Perform
  - H&E Stain
  - Immunohistochemistry (IHC)
  - Tissue polymerase chain reaction (PCR)
- Important results
  - Intracellular / intranuclear inclusion bodies on H&E and/or positive IHC on histology
  - Tissue CMV DNA more than 250 copies/mg tissue
    - Tissue CMV DNA
      - > 2.5 $\log_{10}$ copies/mg of tissue
      - > 5500 copies/µg DNA
  - Tissue CMV IHC-positive cells (per biopsy section)
    - > 10 cells
    - ≥ 5 cells
    - > 2 cells

Abbreviations: CMV, cytomegalovirus; H&E, haematoxylin and eosin IHC, immunohistochemistry; PCR, polymerase chain reaction

➢ Treatment

- Anti-viral therapy superior to non antiviral therapy (OR, 0.20; 95% CI, [0.08, 0.49])
  - ↓ risk of colectomy following antiviral treatment of steroid anti-viral treatment of steroid-refractory H&E/IHC+ UC

- ECCO 2021 Guideline Recommendations

Statement 3.9

- Concurrent CMV colitis worsens the prognosis of active IBD
  - Patients with refractory IBD should be tested for CMV colitis [EL3], especially if they are not responding to immunosuppressive therapy [EL2]

Statement 3.10

- Immunohistochemistry [IHC], possibly tissue polymerase chain reaction [PCR], or both
  - Essential for confirming active CMV infection [colitis] in IBD and should be the standard tests [EL2]
    - The findings and potential interventions should be discussed in the clinical content.

Statement 3.11

- In general, immunosuppressive therapy should not be discontinued in IBD patients with intestinal CMV reactivation
  - Corticosteroids should be tapered [EL4]
  - Antiviral therapy should be considered in steroid-refractory IBD patients with CMV colitis [EL3]
  - Discontinuation of immunosuppressive therapy is recommended in symptomatic disseminated CMV infection [EL4]

- BSG 2019 Guideline Recommendations

Statement 76

- Patients with moderate to severe colitis, particularly those with corticosteroid-refractory disease
  - Should have colonic biopsies to look for cytomegalovirus disease by
    - H&E staining, and preferably also by
    - Immunohistochemistry or quantitative tissue PCR (GRADE: weak recommendation, low-quality evidence. Agreement 93%)

➢ Summary

- Those with steroid-refractory disease and high CMV viral density seem to benefit the most from anti-CMV therapy in patients with IBD, however
  - The interpretation of results limited by retrospective study designs, small sample sizes, and varying definitions of CMV colitis

COLON

COLONIC MOTILITY AND FECAL INCONTINENCE

Cassandra Townsend

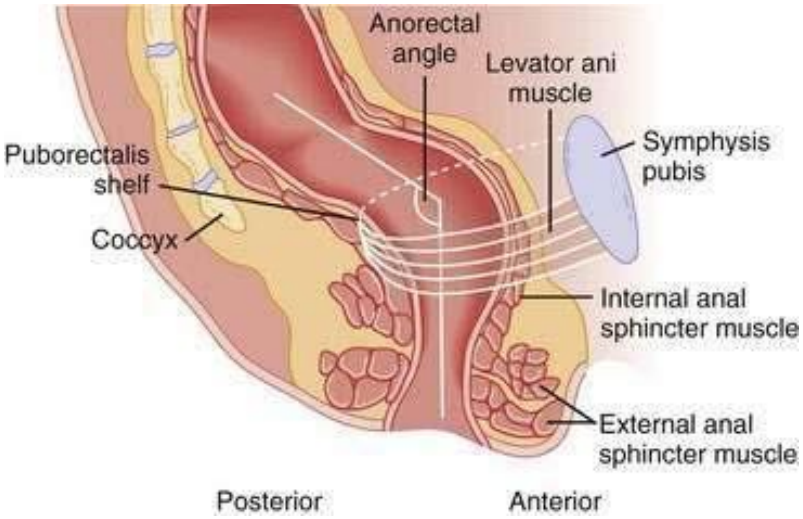
Fecal Incontinence

- Definition
  - Involuntary passage of fecal matter through the anus or inability to control the discharge of bowel contents

- Demography
  - Higher prevalence in middle-aged women, older adults and nursing home residents
  - Some patients may not seek care due to embarrassment
    - Persons with incontinence were 6.8 times as likely to miss work or school and missed an average of 50 work or school per yr compared with those without incontinence or other functional GI symptoms

- Pathophysiology
  - Structurally and functionally intact anorectal unit is essential for maintaining normal continence of bowel contents
    - Rectum
      - Hollow muscular tube composed of a continuous layer of longitudinal muscle that links with underlying circular muscle
      - Serves as a reservoir for stool and pump for emptying stool
    - Anus
      - Muscular tube, 2-4 cm in length that at rest forms an angle with the axis of the rectum
      - At rest the anorectal angle is approximately 90 degrees, with voluntary squeeze the angle becomes more acute, about 70 degrees and during defecation the angle becomes obtuse, about 110-130 degrees
      - Anal sphincter consists of two muscular components
        - Internal anal sphincter: 0.3- to 0.5-cm thick expansion of the circular smooth muscle layer of the rectum
          - Slow twitch, fatigue resistant smooth muscle and generates constant mechanical activity
          - Contributes to 70-85% of resting anal sphincter pressure, but decreases after sudden distention (40%) of rectum and following constant rectal distention (65%)
          - Remainder of pressure is provided by EAS or puborectalis or both
        - External anal sphincter: 0.6- to 1.0-cm thick expansion of the levator ani muscles
          - Reinforces tonic activity of IAS
      - Helped by the puborectalis muscle, forms a flap like valve that creates a forward pull and reinforces the anorectal angle
        - Anal tissue also helps ensure adequate closure (10-20% of resting anal pressure)

- Normal Defecation



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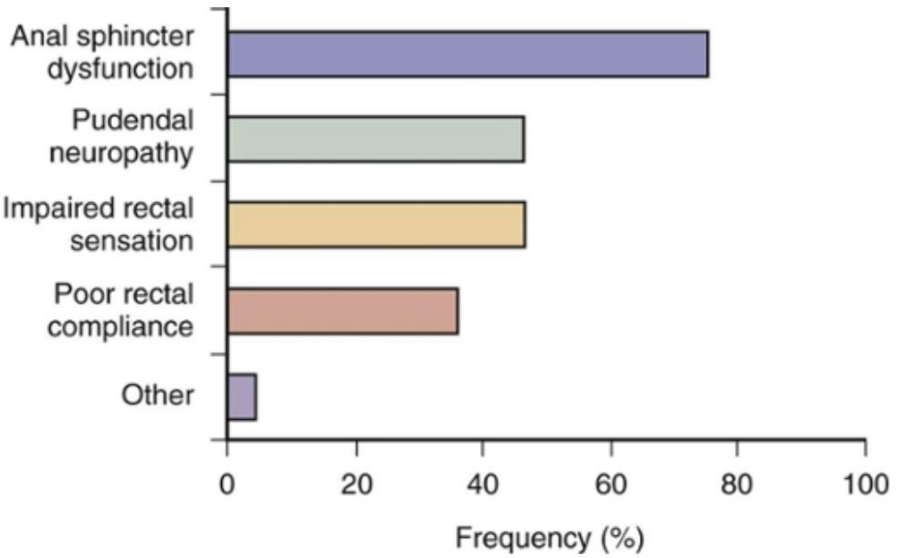
- Nerve Innervation
  - Anorectum is richly innervated by sensory, motor, and autonomic nerves and by the enteric nervous system.
    - The principal nerve to the anorectum is the pudendal nerve, which arises from the second, third, and fourth sacral nerves (S2, S3, S4), innervates the EAS, and subserves sensory and motor function.
  - The sensation of rectal distention is most likely transmitted along the S2, S3, and S4 parasympathetic nerves. These nerve fibres travel along the pelvic splanchnic nerves and are independent of the pudendal nerve.
  - Process by which humans perceive stool contents in rectum is incompletely understood but balloon distention is perceived in the rectum. Involved in maintaining continence. Sensory conditioning can improve incontinence symptoms.
  - The sensation of rectal distention is most likely transmitted via the parasympathetic nervi erigentes along the S2, S3, and S4 splanchnic nerves.
  - If parasympathetic innervation is absent, rectal filling is perceived only as a vague sensation of discomfort. Even persons with paraplegia or sacral neuronal lesions may retain some degree of sensory function, but almost no sensation is felt if lesions occur in the higher spine.
  - Also, may be sensation in IAS that helps to determine rectal fullness
    - Likely role is to discriminate between stool and flatus
  - Rectal distention is associated with a fall in anal resting pressure known as the rectoanal inhibitory reflex. The amplitude and duration of this relaxation increases with the volume of rectal distention.

- This reflex is mediated by the myenteric plexus and is present in patients in whom the hypogastric nerves have been transected and in those with a spinal cord lesion. The reflex is absent after transection of the rectum, but it may recover.
- Although the rectoanal inhibitory reflex may facilitate discharge of flatus, rectal distention is also associated with a rectoanal contractile response, a subconscious reflex effort to prevent release of rectal contents such as flatus
- This response involves contraction of the EAS and is mediated by the pelvic splanchnic and pudendal nerves. The amplitude and duration of the rectoanal contractile reflex also increases with rectal distention, up to a maximum volume of 30 mL. Abrupt increases in intra-abdominal pressure, as caused by coughing or laughing, are associated with an increase in anal sphincter pressure. A number of mechanisms, including reflex contraction of the puborectalis, may be involved.

- Multiple Mechanisms

Relative Frequencies of The Common Mechanisms That Lead to Fecal Incontinence



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Mechanism	Causes	Pathophysiology
Abnormal Anorectal or Pelvic Floor Structures		
Anal sphincter muscles	Hemorrhoidectomy, neuropathy, obstetric injury	Sphincter weakness, loss of sampling reflex
Puborectalis muscle	Aging, excessive perineal descent, trauma	Obtuse anorectal angle, sphincter weakness
Pudendal nerve	Excessive straining, obstetric or surgical injury, perineal descent	Sphincter weakness, sensory loss, impaired reflexes
Nervous system, spinal cord, autonomic nervous system	Avulsion injury, spine surgery, diabetes mellitus, head injury, multiple sclerosis, spinal cord injury, stroke	Loss of sensation, impaired reflexes, secondary myopathy, loss of accommodation
Rectum	Aging, IBD, IBS, prolapse, radiation	Loss of accommodation, loss of sensation, hypersensitivity

- Anal Sphincter Muscles
  - Disruption of external anal sphincter (EAS) or internal anal sphincter (IAS)
    - Most commonly related to obstetric trauma
      - More likely to have incontinence following sphincter tear during delivery
      - Episiotomy is a risk factor for anal sphincter dysfunction
    - Aging
      - Atrophy of anal sphincter with low estrogen state
      - Pudendal nerve terminal motor latency

- Nervous System Injury
  - Neuropathic injury is often sustained during childbirth, probably as a result of stretching of the nerves during elongation of the birth canal or direct trauma during passage of the fetal head.
  - Nerve damage is more likely to occur when the fetal head is large, the second stage of labor is prolonged, or forceps are applied, especially with a high forceps delivery or prolonged labor.

Abnormal Anorectal or Pelvic Floor Function		
Impaired anorectal sensation	Autonomic nervous system disorders, central nervous system disorders, obstetric injury	Loss of stool awareness, rectoanal agnosia
Fecal impaction	Dyssynergic defecation	Fecal retention with overflow, impaired sensation
Altered Stool Characteristics		
Increased volume and loose consistency	Drugs, bile salt malabsorption, infection, IBD, IBS, laxatives, metabolic disorders	Diarrhea and urgency, rapid stool transport, impaired accommodation
Hard stools, retention	Drugs, dyssynergia	Fecal retention with overflow

    - Intact sensation helps distinguish between formed stool, liquid feces and flatus
        - Impaired rectal sensation may lead to excessive accumulation of stool, thereby causing fecal impaction, megarectum (extreme dilatation of the rectum), and fecal overflow.
        - An intact sampling reflex allows an individual to choose whether to discharge or retain rectal contents.
        - Conversely, an impaired sampling reflex may predispose a subject to incontinence. The role of the sampling reflex in maintaining continence, however, remains unclear.
    - Causes: neurologic damage due to multiple sclerosis, diabetes mellitus, and spinal cord injury, analgesics (opioids), antidepressants

- Dyssynergic Defecation
    - In some patients, particularly older adults, prolonged retention of stool in the rectum or incomplete evacuation may lead to seepage of stool or staining of undergarments.
        - Most of these patients show obstructive or dyssynergic defecation, and many of them also exhibit impaired rectal sensation, whereby anal sphincter and pudendal nerve function is intact, but the ability to evacuate a simulated stool is impaired.
    - Fecal impaction may also cause prolonged relaxation of the IAS, thereby allowing liquid stool to flow around impacted stool and escape through the anal canal

- Descending Perineum Syndrome
    - In women with long-standing constipation and a history of excessive straining for many years (perhaps even without prior childbirth), excessive straining may lead to progressive denervation of the pelvic floor muscles.

- Most of these patients demonstrate excessive perineal descent and sphincter weakness that may lead to rectal prolapse, but
  - Fecal incontinence is not an inevitable consequence. Whether or not incontinence develops will depend on the state of the pelvic floor and the strength of the sphincter muscles.

- Abnormal Anorectal or Pelvic Floor Function
  - ↓ anorectal sensation
    - Autonomic nervous system disorders
    - Central nervous system disorders
    - Obstetric injury
    - ↓ stool awareness
    - Rectoanal agnosia
  - Feal Impaction
    - Dyssynergic defecation
    - Fecal retention with overflow
    - ↓ sensation
- Altered Stool Characteristics
  - ↑ volume and looseness
    - Drugs
    - Bile salt malabsorption
    - Infection
    - IBD
    - IBS
    - Laxatives
    - Metabolic disorders
    - Diarrhea/urgency
    - Rapid stool transport
    - Accommodation
  - Hard stools retention
    - Drugs
    - Dyssynergia
    - Fecal retention with overflow
- Miscellaneous
  - Physical mobility / cognitive function
    - Aging
    - Dementia
    - Disability
    - Multifactorial changes
  - Psychosis
    - Willful soiling
    - Multifactorial changes
  - Drugs
    - Anticholinergics
    - Antidepressants
    - Caffeine
    - Laxatives
    - Muscle relaxants
    - Constipation
    - Altered sensation
    - Constipation
    - Relaxation of sphincter tone
    - Diarrhea
  - Food intolerance
    - Malabsorption of
      - Fructose
      - Lactose
      - Sorbitol
    - Diarrhea
    - Flatus

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- Evaluation – History
  - Onset and precipitating event(s)
  - Duration and timing
  - Severity
  - Stool consistency and rectal urgency
  - History of fecal impaction
  - Coexisting problems (e.g., diarrhea, IBD)
  - Drugs, caffeine, diet
  - Past history
    - Back surgery
    - Diabetes mellitus
    - Neurologic disorders
    - Spine surgery
    - Urinary incontinence
  - Clinical subtypes
    - Fecal seepage
    - Passive or urge incontinence
  - Obstetric history
    - Use of forceps
    - Teara
    - Presentation of the infant
    - Repairs

- Circumstances surrounding incontinence
  - Passive incontinence, the involuntary discharge of fecal matter or flatus without any awareness.
    - This pattern suggests a loss of perception or impaired rectoanal reflexes, with or without sphincter dysfunction.
  - Urge incontinence, the discharge of fecal matter or flatus despite active attempts to retain these contents.
    - Predominant causes of this pattern are disruption of sphincter function and a decrease in rectal capacity to retain stool.
  - Fecal seepage, the undesired leakage of stool, often after a bowel movement, with otherwise normal continence and evacuation.
    - This condition results primarily from incomplete evacuation of stool or impaired rectal sensation. Sphincter function and pudendal nerve function are mostly intact.

➢ Quantifying Degree of Incontinence

- Cleveland Clinic Grading System
  - 7 parameters:
    - the character of the anal discharge as (1) solid, (2) liquid, or (3) flatus;
    - (4) the degree of alterations in lifestyle;
    - The need to (5) wear a pad or (6) take antidiarrheal medication; and
    - (7) the ability to defer defecation.
    - The total score ranges from 0 (continent) to 24 (severe incontinence). As noted earlier, however, clinical features alone are insufficient to define the pathophysiology.

− Incontinence for solid stool	0	1	2	3	4
− Incontinence for liquid stool	0	1	2	3	4
− Incontinence for gas	0	1	2	3	4
− Alteration in lifestyle	0	1	2	3	4
− Need to wear pad or plug				No 0	Yes 2
− Taking constipation medicines				0	2
− Lack of ability to defer defecation for 15 min				0	4

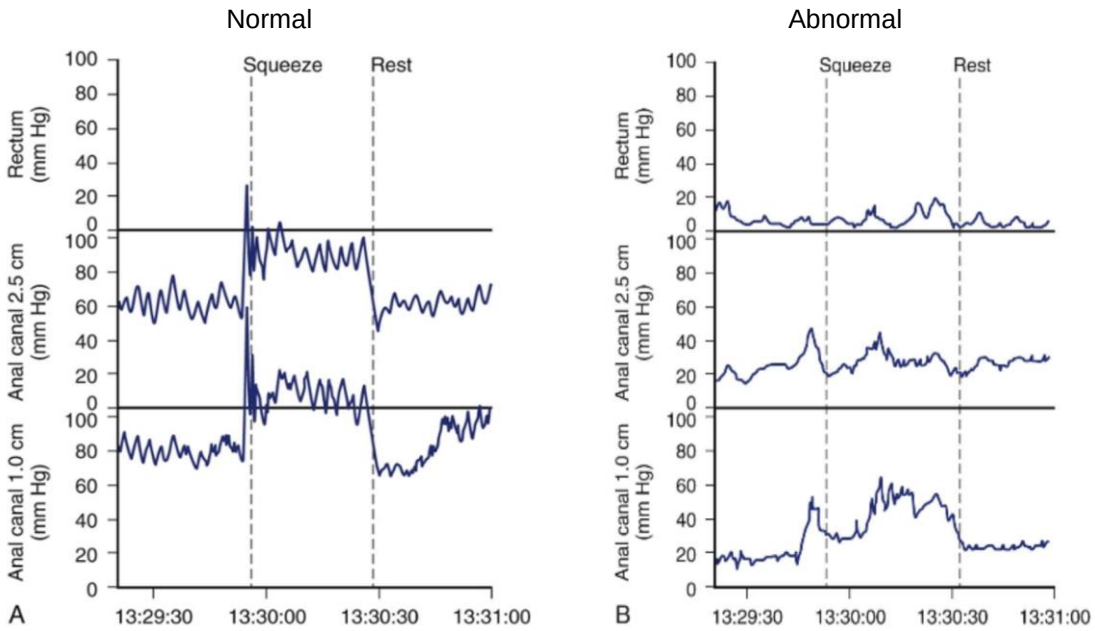
- Other Questionnaires
  - The use of validated questionnaires such as the symptom checklist 90-R (SCL-90-R) and short form 36 (SF-36) surveys may provide additional information regarding psychosocial issues and the impact of fecal incontinence on the patient's quality of life. A fecal incontinence severity index has been widely accepted as a useful clinical assessment tool.

- Physical Examination
  - Complete physical, including neurological exam
  - Perineal inspection
    - On inspection, the presence of fecal matter, prolapsed hemorrhoids, dermatitis, scars, skin excoriations, or a gaping anus and the absence of perianal creases may be noted.
    - An outward bulge that exceeds 3 cm is usually defined as excessive perineal descent
    - Perianal sensation should be checked.
      - The anocutaneous reflex examines the integrity of the connections between the sensory nerves and skin; the intermediate neurons in spinal cord segments S2, S3, and S4; and the motor innervation of the external anal sphincter.
    - This reflex can be assessed by gently stroking the perianal skin with a cotton bud in each perianal quadrant.
      - A normal response consists of a brisk contraction of the external anal sphincter ("anal wink").
      - An impaired or absent anocutaneous reflex suggests either afferent or efferent neuronal injury

- DRE
  - Resting tone, length of anal canal, strength of the puborectalis sling, acuteness of the anorectal angle, strength of anal sphincter squeeze, and elevation of the perineum during voluntary squeeze.
  - The presence of a rectocele or impacted stool may be noted.

➢ Diagnostic Testing

- Initial testing is incontinence associated with diarrhea?
  - Colonoscopy to exclude mucosal disease
  - Biochemical: thyroid dysfunction, DM, cholecystectomy
- Defining underlying mechanism
  - Anorectal Manometry
    - Anorectal manometry is a useful method for assessing IAS and EAS pressures as well as rectal sensation, rectoanal reflexes, and rectal compliance



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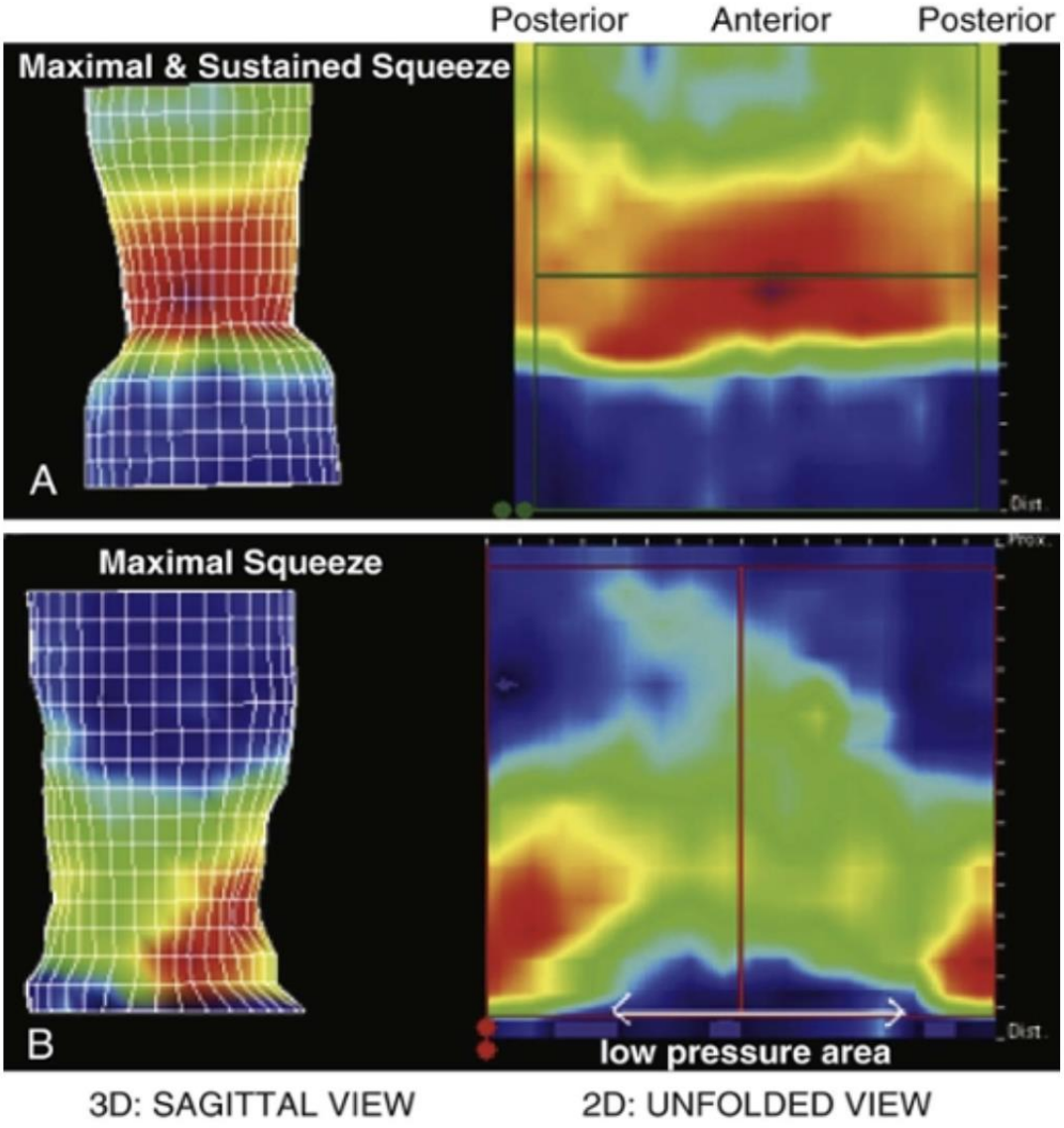
Squeeze and resting pressures are weak



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- Interpretation
  - Resting anal sphincter pressure predominantly represents IAS function, and voluntary anal squeeze pressure represents EAS and puborectalis function.
  - The duration of sustained squeeze pressure provides an index of sphincter muscle fatigue.
  - The ability of the EAS to contract reflexively can be assessed during abrupt increases in intra-abdominal pressure, as when the patient coughs. This reflex response causes the anal sphincter pressure to rise above that of the rectal pressure to preserve continence.
    - The response may be triggered by receptors in the pelvic floor and mediated through a spinal reflex arc.
    - In patients with a spinal cord lesion above the conus medullaris, this reflex response is preserved even though voluntary squeeze may be absent, whereas
      - In patients with a lesion of the cauda equina or sacral plexus, both the reflex and voluntary squeeze responses are absent.

- Rectal Sensory Testing
  - Rectal balloon distention with air or water can be used to assess sensory responses and compliance of the rectal wall.
    - By distending a balloon in the rectum with incremental volumes, the thresholds for first perception, first desire to defecate, and urgent desire to defecate can be assessed. A higher threshold for sensory perception indicates reduced rectal sensitivity.

- Imaging the Anal Canal
  - Anal endosonography
    - Assessment of EAS and IAS thickness and structural integrity and can detect scarring, loss of muscle tissue, and other local pathology
    - Higher frequency (10- to 15-mHz) probes and 3D reconstruction of the anal sphincter that provide improved delineation of the sphincter complex have become available
  - MRI
    - Endoanal MRI can provide superior imaging with excellent spatial resolution, particularly for defining the anatomy of the EAS.
    - The addition of dynamic pelvic MRI using fast imaging sequences or MRI colpocystography, which involves filling the rectum with ultrasound gel as a contact agent and having the patient evacuate while lying inside the magnet, may define the anorectal anatomy more precisely.
  - Defecography
    - Defecography uses fluoroscopic techniques to provide morphologic information about the rectum and anal canal. It is used to assess the anorectal angle, measure pelvic floor descent and length of anal canal, and detect the presence of a rectocele, rectal prolapse, or mucosal intussusception.
    - Abnormalities in the anorectal angle is not hugely helpful, may be seen in asymptomatic or symptomatic patients.
    - Although defecography can confirm the occurrence of incontinence at rest or during coughing, it is most useful for demonstrating rectal prolapse or poor rectal evacuation

- Balloon Expulsion Test
  - Normal patients can expel a 50-mL water-filled balloon or a silicone-filled artificial stool from the rectum in less than 1 min.
  - Most patients with fecal incontinence have little or no difficulty with evacuation, but patients with fecal seepage and many older persons with fecal incontinence secondary to fecal impaction demonstrate impaired evacuation.
    - In these patients, a balloon expulsion test may help identify coexisting dyssynergia or a lack of coordination between the abdominal, pelvic floor, and anal sphincter muscles during defecation

- Neurophysiologic Testing
  - Electrical recording of the muscle activity from the anal sphincter (EMG) is a useful technique for identifying sphincter injury as well as denervation-reinnervation potentials that can indicate neuropathy

- Saline Infusion Test
  - The saline infusion test assesses the overall capacity of the defecation unit to maintain continence during conditions that simulate diarrhea.
  - With the patient lying on the bed, a 2-mm plastic tube is introduced about 10 cm into the rectum and taped in position.
    - Next, the patient is transferred to a commode.
      - The tube is connected to an infusion pump, and 800 mL of warm saline (37°C) is infused into the rectum at a rate of 60 mL/min.
  - The patient is instructed to hold the liquid for as long as possible.
    - The volume of saline infused at the onset of first leak (defined as a leak of at least 15 mL) and the total volume retained at the end of infusion are recorded.
      - Most normal patients should retain most of the infused volume without leakage, whereas patients with fecal incontinence or patients with impaired rectal compliance, such as those with ulcerative colitis, leak at much lower volumes.

➢ Approach to Treatment of Fecal Incontinence (DRE/Manometry)

- Correct underlying / associated disease
  - ↓ rectal sensation
  - ↓ expansion (balloon)
  - ↓ pressure

  }
  - Pelvic floor exercise
  - Consider
    - Anal imaging
    - EMG
  - Pelvic floor exercise (evacuation disorder)

- Treatment – ACG Guidelines
  - Recommendations for nonsurgical treatments
    - Gastroenterologists and other providers should manage patients with FI using education, dietary modifications, skin care, and pharmacologic agents to modify stool delivery and liquidity before diagnostic testing, particularly when symptoms are mild and not bothersome (strong recommendation, moderate quality of evidence).
    - Gastroenterologists and other providers should prescribe antidiarrheal agents for FI in patients with diarrhea (strong recommendation, low quality of evidence).
    - Pelvic floor rehabilitative techniques are effective and superior to pelvic floor exercises alone in patients with FI who do **not** respond to conservative measures (strong recommendation, moderate quality of evidence).
  - Recommendations for minimally invasive procedures
    - Minimally invasive procedures such as injectable anal bulking agents may have a role in patients with FI who do **not** respond to conservative therapy (weak recommendation, moderate-quality of evidence).
    - There is insufficient evidence to recommend radiofrequency ablation treatment to the anal sphincter (SECCA) at this time (no recommendation, insufficient evidence
  - Recommendations for surgical treatment
    - Sacral nerve stimulation should be considered in patients with FI who do **not** respond to conservative therapy (strong recommendation, moderate quality of evidence).
    - Anal sphincteroplasty should be considered in patients with FI who do **not** respond to conservative therapy and who have an anatomic sphincter defect (weak recommendation, low quality of evidence).
    - Dynamic graciloplasty and artificial anal sphincter, where avail- able, may possibly allow the occasional patient with FI to avoid colostomy (weak recommendation, insufficient evidence).
    - Colostomy is a last resort procedure that can markedly improve the quality of life in a patient with severe or intractable FI (strong recommendation, low quality of evidence).

References: Sleisenger and Fordtran's and ACG 2014 – Management of Benign Anorectal Disorders

- Colonic Motility
  - Each day, 1200 to 1500 mL of ileal effluent enter the colon, 200 to 400 mL of which are finally excreted as stool.
  - The colon mixes its contents to facilitate transmural exchange of water, electrolytes, and short-chain fatty acids and, in doing so, stores stool for extended periods.
  - The mixing process involves rhythmic to-and-fro motions, together with short stepwise movements of contents, resulting in an overall net aboral flow rate that averages 1 cm per hour.

- Colon Anatomy
  - The outer longitudinal smooth muscle layer forms three thick, cord-like structures called the teniae coli, which are spaced evenly around the circumference of the colon.
    - Between the teniae, the longitudinal smooth muscle is much thinner, allowing the wall to bulge noticeably.

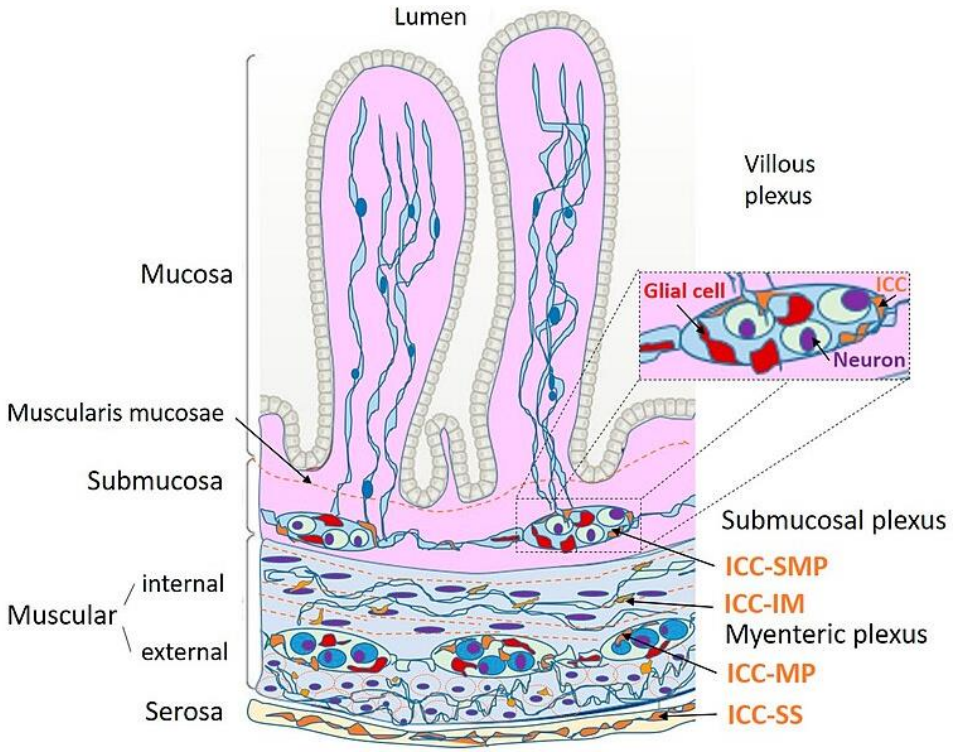
- Irregularly spaced circumferential constrictions pinch the colon into a series of pockets called haustra that give the colon a sacculated appearance for much of its length.
- The teniae fuse to form a continuous outer longitudinal smooth muscle layer at the rectosigmoid junction.
  - The longitudinal layer then continues down to the distal margin of the anal canal, insinuating itself between the internal and external anal sphincters.

- Colonic Smooth Muscle
  - Two types of rhythmic myoelectrical activity
    - Slow waves
      - Produced by major pacemaker region is located at the submucosal border or the circular muscle
      - Larger amplitude slower myogenic oscillations
      - Will see phasic pressure waves on manometry as a result of slow wave activity
      - Frequency 2-4 per min and propagate over short distances in the colon
      - Complex interactions occur as waves coming from different initiation sites collide, leading to mixing of contents with slow overall propulsion.
    - Myenteric potential oscillations
      - Small-amplitude rapid oscillations
      - Frequency 12-20 per min
      - Originate at the plane of the myenteric plexus
    - The currents produced by pacemaker cells at the submucosal and myenteric borders decay as they spread through the thickness of the circular muscle layer.
      - Cells in the middle of the circular smooth muscle layer display complex spontaneous electrical activity consisting of a mixture of MPOs and slow waves, with superimposed smooth muscle action potentials.
  - Enteric neural activity
    - Generates motor output that is superimposed on the myogenic activity
    - Function:
      - Augment phasic myogenic contractions
      - Generate powerful patterned contractions of much longer duration than those produced by slow waves
        - These contractions can propagate for long distances along the colon and are known as propagating sequences or mass movements

- Colonic Longitudinal Muscle
  - The longitudinal muscle probably acts in synergy with the circular muscle, preventing excessive lengthening when the circular muscle contracts.
    - It may also contribute to propulsion by pulling the colon over its contents so that circular muscle contractions gain more purchase

- Important Cells in Colon
  - Ion channels
    - High-threshold voltage-operated calcium channels (L-type calcium channels) do play a crucial role in colonic muscle contractility

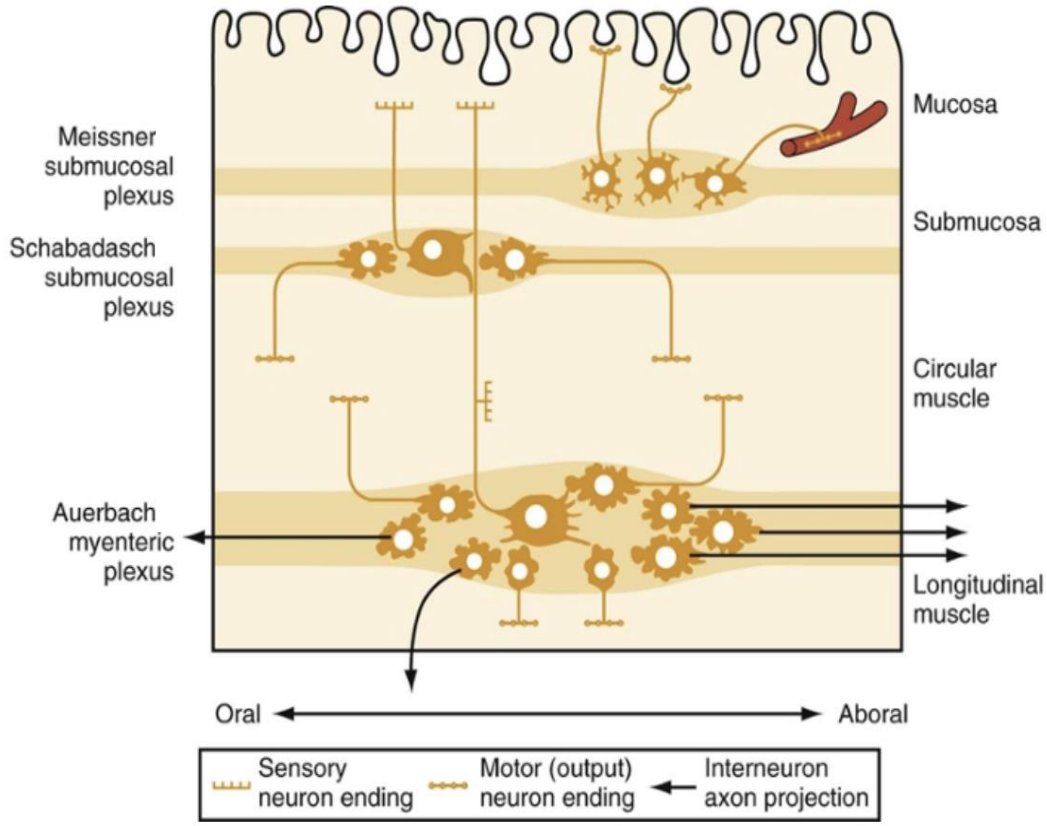
- Interstitial Cells of Cajal
  - Two important roles:
    - control of myogenic activity
    - mediating or amplifying the effects of motor neurons on the smooth muscle apparatus
  - Three types in humans (named by location)
    - ICC in the plane of the myenteric plexus (ICCMY),
      - Probably pacemakers for the MPOs
    - ICC near the submucosal plexus (ICCSM),
      - Pacemakers for slow waves
    - Intramuscular ICC located between the circular and the longitudinal muscle layers (ICCIM)
      - integrating non-neuronal pacemaker activity (Ach and NO) and neuronal inputs to smooth muscle



- Organization of interstitial cells of Cajal (ICC) at submucosal and myenteric plexuses in the digestive tube.
  - There are three principal cells represented in plexuses: neurons, glial cells, and the ICCs. Some prolongations end into mucosa. ICC-SMP: ICC of submucosal plexus; ICC-MP: ICC of myenteric plexus; ICC-IM: ICC intramuscular at internal and external muscular; ICC-SS: ICC of serosa.

Source: López-Pingarrón L, et al. Curr. Issues Mol Biol 2023; 45: 3552-3572 (Figure 1)

- Innervation of the Colon
  - Enteric Nervous System (autonomic NS)
    - Modulated by sympathetic, parasympathetic, and extrinsic afferent pathways
    - The nerve cell bodies of the ENS are located in plexuses of myenteric ganglia (Auerbach plexus) that lie between the longitudinal and the circular muscle layers of the muscularis externa, or in the submucosal ganglia that lie between the muscle and mucosa
  - Submucosal Plexus (two networks)
    - Meissner plexus
      - Lies closer to the mucosa
    - Schabadasch plexus
      - Adjacent to circular muscle



Printed with permission: Bass LM and Wershil BK. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 98 (Figure 98.4).

➢ Enteric Nervous System (ENS)

- Primary Afferent
  - Much of the motor and secretory activity of the intestine can be conceptualized as a series of reflexes evoked by mechanical or chemical stimuli.
    - These reflexes involve activation of enteric primary afferent neurons, integration by interneurons, and execution of appropriate responses by motor neurons.
  - The first neurons in these reflex circuits are primary afferent neurons (sometimes called "sensory" neurons, although they do **not** give rise to conscious sensation).
    - These neurons are located in both myenteric and submucosal plexuses and characteristically have several long axonal processes.
    - Some primary afferent neurons fire action potentials in response to stretch or tension in the bowel wall
      - Others are activated by chemical or mechanical stimuli of the mucosa.
    - These mucosal stimuli probably work at least in part by activating specialized enteroendocrine cells (e.g., serotonin-containing enterochromaffin cells) in the mucosal epithelium.
  - The enteric primary afferent neurons then release synaptic transmitters, such as ACh or tachykinins or other peptides, to excite other classes of enteric neurons in nearby ganglia.
    - Enteric primary afferent neurons also make excitatory synaptic contacts onto other neurons of their own class, so that they fire as coordinated assemblies.

- Motor Neurons
  - Excitatory motor neurons synthesize ACh, which they release from their varicose axons in the smooth muscle layers; some also release the tachykinin peptides substance P and neurokinin A, which also excite smooth muscle.
    - Typically, axons of excitatory motor neurons project either directly to the smooth muscle close to their cell bodies or orad for up to 10 mm.
    - Once in the smooth muscle layers, the axons turn and run parallel to the smooth muscle fibres for several millimeters; they branch extensively and form many small varicosities, or transmitter release sites, closely associated with ICCIM and fibroblast-like cells.
  - Inhibitory motor neurons are typically slightly larger than excitatory motor neurons, and there are fewer of them. They also have short dendrites and a single axon, but unlike excitatory motor neurons, they project aborally to the smooth muscle layer for distances of 1 to 15 mm in the human colon.
    - Once the axon reaches the smooth muscle, it branches extensively to form multiple varicose release sites.
      - Inhibitory motor neurons release a cocktail of transmitters that inhibit smooth muscle cells, including NO, adenosine triphosphate (ATP or a related compound like NADH), and peptides like vasoactive intestinal polypeptide (VIP) and pituitary adenyl cyclase-activating peptide (PACAP).
      - The varicose transmitter release sites of inhibitory motor neurons are also associated with ICCIM, as are the release sites of excitatory motor neurons.

- Inhibitory motor neurons are usually tonically active, modulating the ongoing contractile activity of the colonic circular smooth muscle.
  - Inhibitory motor neurons are particularly important in relaxing sphincteric muscles in the ileocecal junction and the internal anal sphincter.

- Interneurons
  - Some of these interneurons are involved in spreading descending inhibition along the colon, but others are likely to be involved in the propagation of migratory contractions.

- Sympathetic Innervation
  - The major sympathetic innervation of the proximal colon arises from the inferior mesenteric ganglion and projects through the lumbar colonic nerves to the ascending and transverse colon.
  - A small number of sympathetic neurons in the celiac and superior mesenteric ganglia, in the paravertebral chain ganglia, and in the pelvic plexus ganglia also project to the colon.
  - These neurons receive a powerful cholinergic drive from preganglionic nerve cell bodies in the intermediolateral column of the thoracolumbar spinal cord (principally segments L2-L5).
  - This is a major pathway by which the central nervous system modifies bowel activity, such as during exercise.
  - Another target for sympathetic axons is the circuitry of the submucosal plexus (largely Meissner plexus) involved in controlling epithelial secretion.
  - Hence, these pathways inhibit colonic motor activity, reduce blood flow, and inhibit secretion to limit water loss from the body during times of sympathetic activation.

- Parasympathetic Innervation
  - The colon receives parasympathetic innervation from both the vagus nerve and pathways in the sacral spinal cord.
    - Branches of the vagus nerve reach the prevertebral ganglia (superior hypogastric plexus) and then run with sympathetic axons to the cecum and the ascending and transverse colon.
  - The distal colon is largely supplied by sacral parasympathetic axons via the pelvic nerves (pelvic splanchnic nerves).
    - Some of these cholinergic spinal efferent neurons synapse first onto nerve cell bodies in the pelvic plexus (inferior hypogastric plexus), and others project directly to the colon.
  - From their point of entry into the colon, many of the axons run in an orad direction and form thick trunks called shunt fascicles.
  - Parasympathetic axons project to the enteric ganglia in the colon, where they make excitatory cholinergic synapses onto enteric nerve cell bodies.
  - Sacral parasympathetic pathways play an important role in increasing the propulsive activity of the distal colon before defecation.
    - They are probably also involved in triggering the sequences of propagating complexes that start in the transverse and ascending colon up to an hour before defecation.

- Extrinsic Afferent Pathways
  - Sensation from the colon is mediated by primary afferent neurons with cell bodies outside the bowel wall. Vagal afferent neurons with nerve cell bodies located in the nodose ganglia project to the proximal colon and run with the vagal efferent parasympathetic pathways.
    - Currently, their exact role in reflex control and sensation is not clear, but they are unlikely to be involved in the transmission of pain sensation from the colon.
  - The entire colon also is innervated by spinal primary afferent neurons with nerve cell bodies in the lumbar dorsal root ganglia.
    - Lumbar spinal afferents project along the lumbar splanchnic nerves, through the prevertebral inferior mesenteric ganglion, and through the lumbar colonic nerves to the colon, where they terminate in sensory endings in the mesentery, muscular layers, and mucosa throughout the entire colon and rectum.
      - In addition, a population of spinal afferents with cell bodies in the sacral dorsal root ganglia projects along the pelvic nerves to the colon and traverses the pelvic plexus en route.
  - In summary, sacral afferent and efferent (parasympathetic) pathways run in parallel and connect the distal bowel with neural circuitry in the sacral spinal cord via pelvic and rectal nerves.
    - The important role of these pathways in both rectal sensation and generating the enhanced motility required for defecation is clearly demonstrated by the effects of nerve lesions at several levels.
      - Thus, severing of peripheral nerves and distal spinal cord injury can lead to loss of rectal sensation and to severely impaired defecatory ability.

- Anorectal innervation
  - The internal sphincter directly receives a powerful inhibitory innervation from intrinsic enteric inhibitory motor neurons and also extrinsic input from lumbar sympathetic and sacral parasympathetic nerves that project via the pelvic plexus ganglia.
  - The external anal sphincter and other pelvic floor muscles are innervated through the pudendal nerve (S3-S4) by motor neurons with cell bodies in the spinal cord.
    - The external sphincter and surrounding connective tissue also receive a sensory innervation via the pudendal nerves.
  - In contrast, the rectum and proximal anal canal are richly supplied with sensory receptors of pelvic nerve origin that respond to rectal stretch and the composition of the intraluminal contents.
    - These receptors are important for detecting rectal filling, triggering sensations of urgency, facilitating rectal accommodation, and differentiating the composition (stool or gas) of rectal content

- Relationships among Cellular Events, Pressure, and Flow
  - The mechanical state of intestinal muscle is described by the plot of changes in stress against strain; the slope is referred to as compliance.
    - When muscle is activated by either excitatory enteric neuronal input or depolarizing myogenic mechanisms, it tends to generate tension, shorten, or both.

- This means that the stress/strain relationship becomes steeper, and compliance is decreased. How much it can shorten is determined by the resistance of the contents.
  - However, passive viscoelastic properties of the intestine, including stress relaxation, creep, and hysteresis, make this analysis complex.
- Changes in compliance reflect the extent to which the bowel wall can stretch to accommodate contents.

- Colonic and Anorectal Motor Patterns
  - Non-propagating
    - Mixing function – low amplitude contractions that propagate over short distances (< 9 cm)
    - 2-4 cycles per min
    - More common in distal colon
  - Propagating motor patterns
    - High amplitude propagating sequences
      - Strong activation of enteric excitatory motor neurons
      - Propagate towards the anus
    - Low-amplitude propagating sequences are also recorded in the colon and can be further classified as antegrade (aboral) or retrograde (orad)
    - More commonly in proximal colon
  - Rectal Motor Complexes/Periodic rectal motor activity
    - Periodic contractile activity
    - 15-60 mm Hg
    - More prevalent during sleep
    - Inhibited during defecation – braking mechanism to keep rectum empty

- Regulation of Colonic Filling and Transit
  - Ileocecal Junction
    - Fasting:
      - Cecal filling is slow and erratic, chyme is retained in distal ileum for prolonged periods
    - Filling slows as the cecum is distended
  - Relationship between Colonic Motor Patterns and Flow
    - Emptying of proximal colon accelerates when wall tone is increased (activates propulsive movements)
      - Has higher amplitude propagating events to move content towards the distal colon
    - The distal colon displays a high frequency of short-extent retrograde propagating pressure waves.
      - Helps with mixing and absorption of water, salts and electrolytes

- Defecation
  - Preparatory phase (1 h before defecation)
    - High-amplitude propagating pressure waves occur in a characteristic sequence
    - First ones start in the proximal colon, with each successive sequence originating slightly more distal than the preceding one – no conscious sensation, just propel contents distally

- Each successive propagating sequence originates from a site proximal to the preceding one
- Each sequence also tends to run for a slightly longer distance and has a higher amplitude than its predecessor
- The final sequences generate the forces necessary to fill and distend the rectum with semisolid fecal matter.
- As the distal sigmoid and rectum are distended, specialized low-threshold sacral spinal afferent mechanoreceptors are activated.
- These mechanoreceptors then give rise to the defecatory urge, prompting the expulsive phase in which the anorectum comes into play.
  - This is assisted by activation of sacral parasympathetic pathways to the distal bowel.

- Rectal Motility
  - When stool or gas enters the rectum, the rectal wall is stretched, thereby activating an enteric descending inhibitory reflex that causes transient relaxation of the internal anal sphincter. Simultaneously, an extrinsic reflex pathway is activated, leading to a brief contraction of the external anal sphincter that preserves continence.
    - Recto-anal inhibitory reflex can be demonstrated and tested by balloon distention of the rectum – reflects integrity of enteric neural pathways
      - Absent in Hirschsprung disease
  - A large-volume rectal distention causes an internal sphincter relaxation of longer duration that is registered consciously. Often an extra voluntary contraction of the external anal sphincter is needed to maintain continence while the person decides how best to deal with the intraluminal content (stool or gas)
    - Can temporarily store contents in sigmoid (retrograde propulsion) until timing is appropriate
    - When appropriate, rectal distention by stool stimulates complete relaxation of the internal anal sphincter via enteric reflexes, and the stool moves into the upper anal canal, heightening the sense of urge. Postural changes and straining facilitate this process in several ways. Sitting or squatting causes descent of the anorectal junction, and straining produces further rectal descent.
    - At this point, if the person wishes to proceed to expel stool, the external anal sphincter is relaxed voluntarily. At the same time, the puborectalis muscle is relaxed (further increasing the anorectal angle), the levator ani muscles contract, the perineum descends further, and stool is funneled into the anal canal and expelled by increasing strain-induced intrarectal pressure
  - Rectal distention also has negative feedback effects on the proximal bowel and inhibits gastric emptying, slows small bowel transit, reduces the frequency of proximal colonic propagating pressure waves, and delays colonic transit.

- Modulators of Colonic Motility
  - Physiologic
    - Eating
    - Exercise
    - Sleep (motility increases with lighter stages fo sleep)
    - Stress

- Pharmacologic
  - Laxatives
    - Bisacodyl and Chenodeoxycholic acid – activates afferent nerve fibres and stimulates high amplitude colonic propagating movements
  - Colchicine
    - Accelerates colonic transit time
  - Lubiprostone
    - ↑ intestinal chloride secretion
  - Serotonin antagonists – ↓ colonic activity
  - Serotonin agonists – ↑ colonic activity
  - Opiates
- Non-pharmacologic
  - Probiotics
  - Electrical stimulation. - S3 stimulation alters motor pathways in patients with slow transit constipation and fecal incontinence
  - Acupuncture

- Disorders of Colonic Motility
  - Constipation
    - Reduction in the overall number of high-amplitude propagating pressure waves, but the overall number of propagating pressure waves of all magnitudes is often normal or increased.
  - Diarrhea
    - Early and rapid transit through the ascending and transverse colon
  - IBS
    - No specific pattern
    - Possibly related to afferent hypersensitivity with variable colonic motor function

FECAL INCONTINENCE

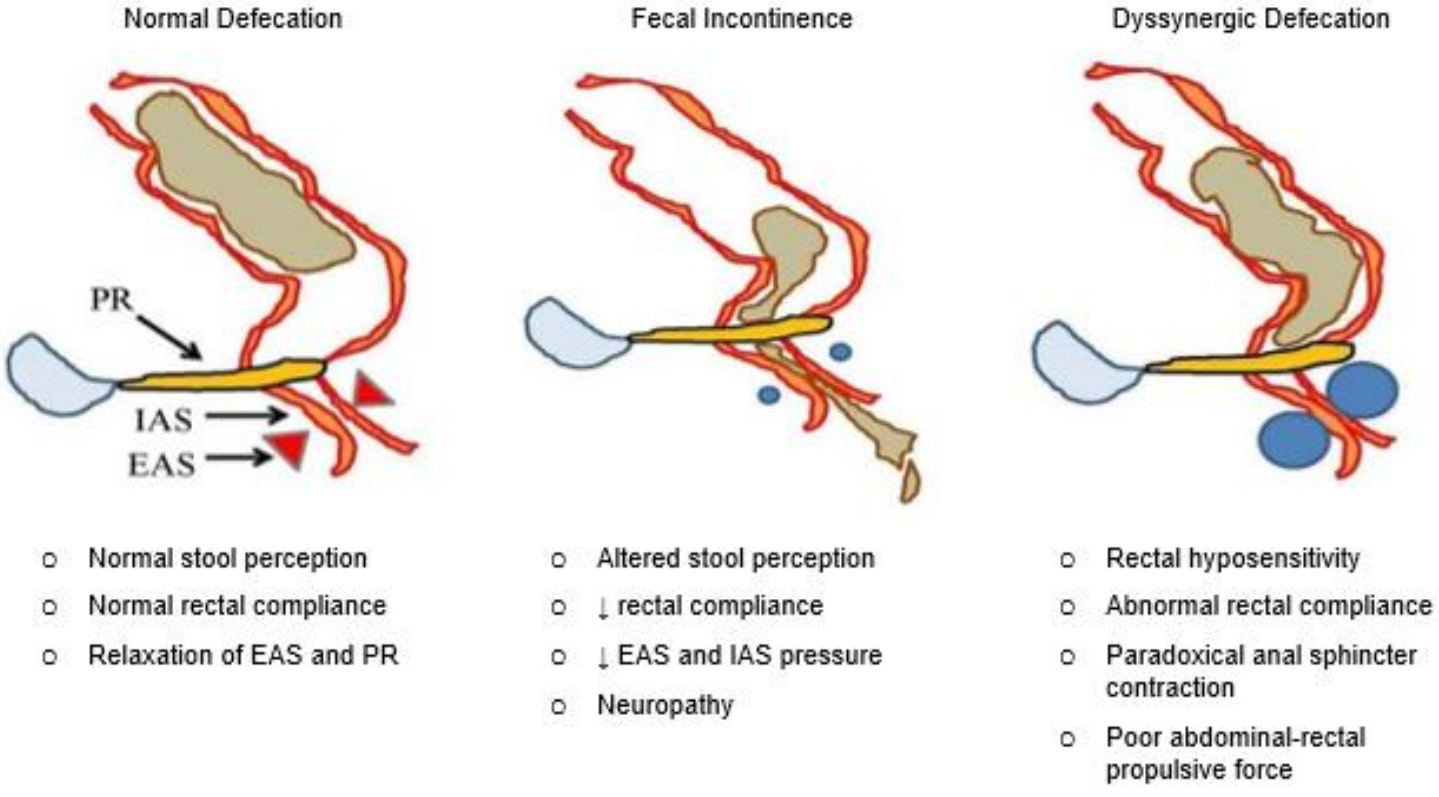
Keith McIntosh

- Definition
  - Fecal incontinence is a syndrome that involves recurrent unintentional passage of fecal material (and often gas) for > 1 mon
  - It is serious and embarrassing.

- Demography
  - ~3% general population (weekly FI) and 6% of women
  - Greater in the elderly – 15% and up to 50% of institutionalized residents
  - One third of women over 65 yr olds experience incontinence at least once/yr.
  - Profound effect on quality of life for those affected.

- Bowel Control
  - Continence is maintained by:
    - Mental function
    - Stool volume & consistency
    - Rectal sensation
    - Rectal storage capacity
    - Anal sphincter function
    - Anorectal angle (puborectalis m.)

- Normal defecation and physiological disruptions that underlie fecal incontinence and dyssynergic defecation



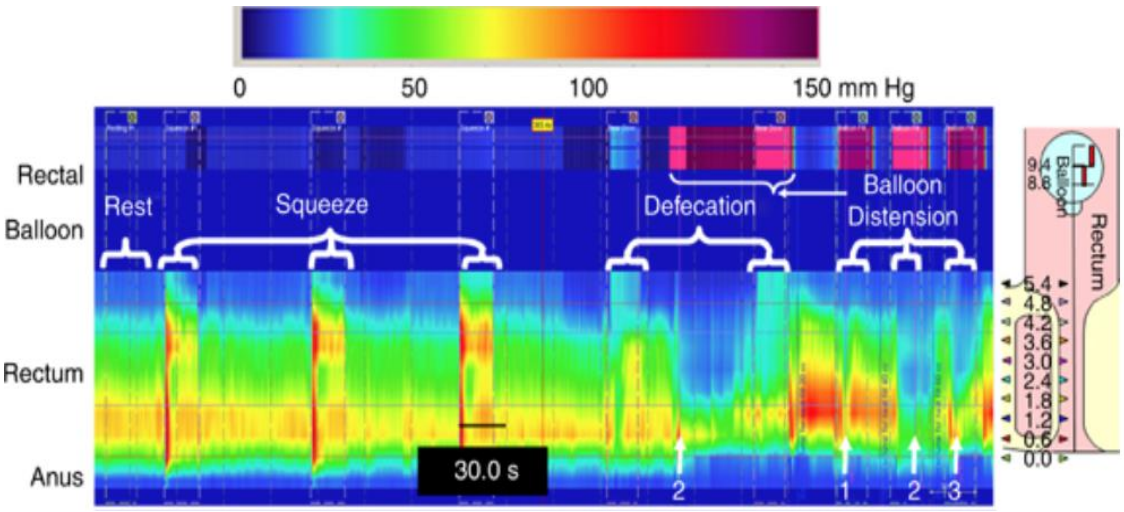
Abbreviations: EAS, external anal sphincter; IAS, internal anal sphincter; PR, puborectalis muscle.

Source: Lee YY. Front Med (Lausanne) 2014; 1:5.

- Classification of Fecal Incontinence
  - Myogenic Deficit
    - Obstetric misadventure (23% multigravidas)
    - Iatrogenic/post-surgical: hemorrhoidectomy, anal dilation, fistula surgery, Botox for fissures
    - Trauma: impalement injury, non-consensual anal intercourse
    - Rectal prolapse
  - Neurogenic Deficit
    - Post-operative: gynecological surgery, radical prostatectomy
    - Spinal cord injury (trauma, surgery)
    - Radiation
    - Neurologic disorder: diabetes, MS, stroke, etc.
  - Combined myogenic/neurogenic
    - Obstetric misadventure
    - Radiation
    - Connective tissue disorders
  - Overflow
  - Behavioural (children, institutionalized, dementia, willful soiling)
  - Idiopathic

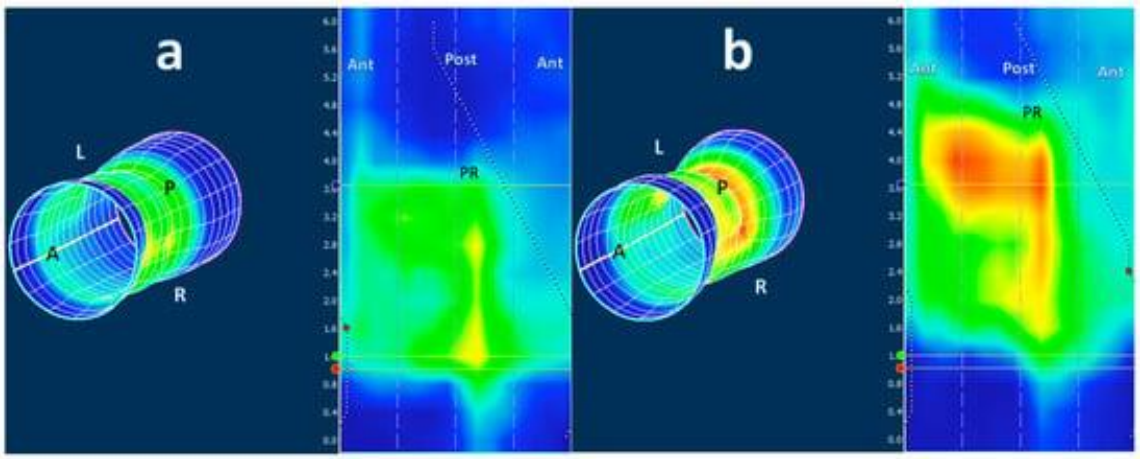
- Evaluation
  - Flexible Sigmoidoscopy / Colonoscopy
  - Anorectal Manometry
    - Indications
      - Fecal incontinence
      - Chronic refractory constipation
      - Suspected Hirschsprung Disease
    - Resting anal sphincter pressure (internal sphincter tone)
    - Augmented (squeeze) sphincter pressure (external sphincter contribution- pudendal nerve S2, S3, S4)
    - Intra-rectal balloon distension (sensory threshold and rectoanal inhibitory reflex)

High Resolution Rectal Manometry



Printed with permission: Noelting J, et al. Am J Gastroenterology 107(10): 1530-1536. (Figure 1).

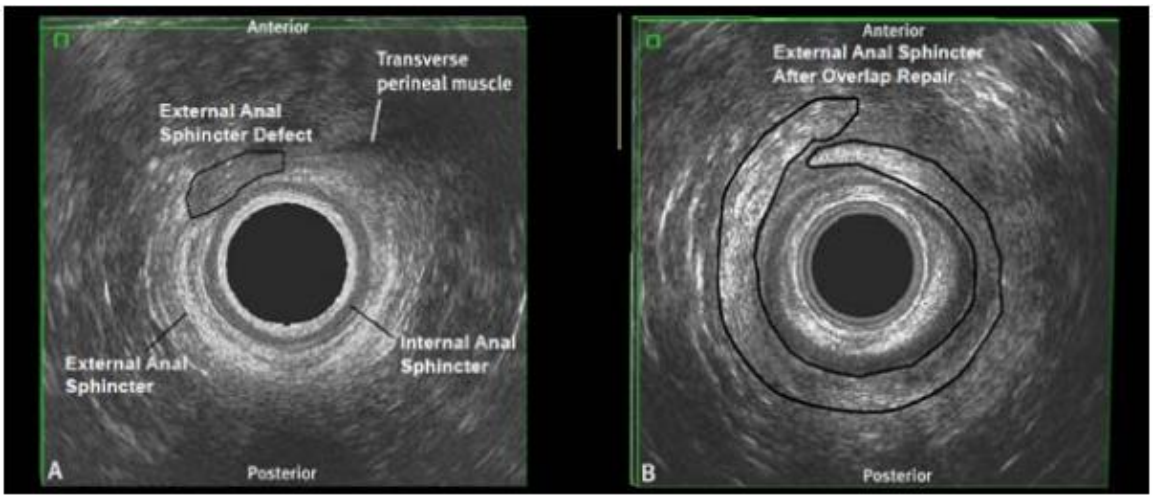
Pressure Profile in 2D and 3D High-Resolution Anorectal Manometry (45-yr-old male with fecal incontinence)



(a) Low anal resting pressure and (b) signs of reduced contractility, particularly on the anterior side (shown in blue), characterized by a diminished ability of the IAS muscles to generate a coordinated contraction. Legend: The puborectal muscle (PR) is seen in the middle of the 2D profile. ATN = anterior, POST = posterior, L = left, R = right. The white line in the cylinder is 'cut' and unrolled to obtain the 2D image, so that the anterior is on both sides (ANT) of the 2D image.

Source: Justin Y. van Oostendorp JY, et al. Diagnostics 2023, 13(16), 2657

- Endorectal Ultrasound / MRI



(A) A preoperative endoanal ultrasound scan showing an external anal sphincter defect at 12 o'clock
(B) A postoperative endoanal ultrasound scan showing an "overlapping" repair of the external anal sphincter

Printed with permission: Abbott D, et al. BMJ 2010; 341: c3414 (Figure 3)

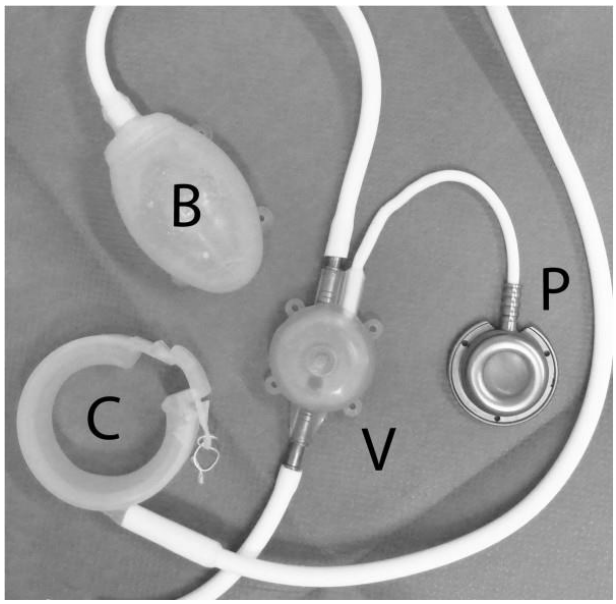
- EMG

➢ Management of Fecal Incontinence
  - Rule out fecal impaction
  - Treat underlying diarrhea
  - Patients with mental dysfunction or physical disability may benefit from a regular defecation program
  - Anal sphincter tightening Kegel exercises +/- biofeedback (40-80% response)

➢ Medical Treatments
  - Bulking agents (psyllium)
  - Loperamide (anti-diarrheal and increased anal sphincter tone)
  - Amitriptyline
  - Phenylephrine (alpha 1 adrenergic agonist) – ↑ anal sphincter tone

- Local Treatments
  - Anal Plugs
  - Dextranomer-Hyaluronic Acid (Solesta®) injections
- Surgical Treatments
  - Sphincteroplasty (anal sphincter plication) 70-80% success rate with myogenic FI
  - Gracilis/gluteus muscle transposition
  - Artificial sphincter device
  - Sacral Nerve Stimulation
  - Colostomy

Components of the soft anal band system ®



Abbreviations: B, balloon / activator; C, cuff ring; P, calibration port, V, valve

Source: Goos M, et al. BMC Surg. 2013;13:45.

- Professional Role
  - Sensitivity regarding the problem
  - Keep patients' dignity in mind during the work-up
  - Strict confidentiality of communications
  - Minimize patient embarrassment during investigations

IRRITABLE BOWEL SYNDROME

Yifan Han

- GI Heritage Moments
  - Likely first described sometime in the 1800s
  - W. Osler in 1892 – mucous colitis.
    - Mucorrea, abdominal colic, normal colonic epithelium.
    - Patients were hysterical, hypochondriac, depressed.
  - Jordan and Kiefer in 1929 – irritable colon
    - A colonic neuromuscular disturbance in 30% of outpatient GI cases.
    - Abdominal pain and disordered defecation.
  - Peters and Bargen in 1944 - irritable bowel syndrome
  - Rome working group in 1986-1989 – the most common classification system used today.
- Demography
  - Global prevalence ~11%
    - Varies by country.
    - In Canada, 9-22%
      - Highest in Atlantic provinces
      - Lowest in Quebec
  - Likely among the top 3 most common chronic GI conditions.
  - Higher rates in women than men (OR 1.67)
  - Higher rates in people < 50 yr (OR 0.75)
- Pathophysiology

- Visceral hypersensitivity
  - ↓ visceral pain thresholds (rectal ballon inflation)
    - Note, pain threshold to non-visceral stimuli was the same as non-IBS patients.
      - This suggests ↑ sensitivity is limited to visceral afferent pathways.
  - Level of the nervous system patients with IBS
    - fMRI volume of cortical activity response to rectal distension device was higher in.
  - Ketamine (NMDA) infusion blunts esophageal hypersensitivity.
  - Colonic biopsies
    - ↑ levels of serotonin.
  - Aptly named a “disorder of the gut brain interaction”
- Intestinal inflammation
  - ↑ lymphocytic infiltration of the
    - Colonic mucosa, and
    - Myenteric ganglions
  - ↑ mast cells in small and large intestinal biopsies.
  - ↑ IL-6, IL-8, TNF-alpha in baseline serum of patients with IBS.

- Motility
  - ↑ frequency/irregularity of colonic luminal contractions.
  - ↑ transit time in IBS-C.
  - ↑ colonic transit speed which correlates as to with abdominal symptoms to
    - Cholecystokinin (CCK) in IBS-D
    - Meal ingestion and
  - IV neostigmine improves transit time and abdominal symptoms in IBS, as compared with health controls.

Abbreviations: IBS-C- IBS with diarrhea; IBS-D, IBS with diarrhea

- Post-infectious
  - ↑ IBS-like symptoms (28% vs 10%) than persons who did not have gastroenteritis (cohort study on 2069 patients after exposure to contaminated water with 904 cases of gastroenteritis)
  - In patients with IBS, and persons ↑ positive bile acid malabsorption scans often cited an inciting gastroenteritis episode (case series studies)
    - ↑ lymphocytes and serotonin-containing enteroendocrine cells after enteric infection.

- Altered fecal flora
  - Different bacterial population by DNA sequencing in IBS patients compared with healthy controls.
  - Various probiotics can improve gastrointestinal symptoms but
    - Does not alter gut flora.
  - Inoculations of rats with fecal microbiota from IBS patients ↑ visceral hypersensitivity.

- Small intestinal bacterial overgrowth (SIBO)
  - ↑ positive glucose breath test in IBS patients.
    - Treatment to normalize breath test results leads to resolution of IBS symptoms in IBS patients.
  - However
    - Similar number of organisms via jejunal aspirate
    - Perhaps, antibiotics ↓ IBS symptoms through
      - Improvement of motility, and
      - Microbiota makeup (rather than SIBO alone)

- Food sensitivity
  - Immune
    - ↑ skin prick positivity in IBS patients.
    - Eliminating foods with patient-specific IgG elevations ↓ gastrointestinal symptoms

- Non-immune
  - ↑ intestinal permeability
    - FODMAPs
    - Gluten (non-celiac IBS patients)
  - ↑ inflammation
    - FODMAPs

- Genetics
  - Having a parent with IBS in an independent predictor of IBS
    - This could be social learning influencing development of IBS, or possibly genetics
  - Twin studies are inconclusive

- Psychosocial
  - ↑ history of sexual/physical abuse in women with functional disorders than those with organic disorders.
    - Correlation between ongoing abuse and IBS diagnosis, but
      - Correlation is less strong once controlled for “neuroticism”.

➢ Diagnosis:

- History
  - Rome IV criteria
    - Recurrent abdominal pain on average, at least 1 day/wk in the last 3 mon, associated with 2 or more of the following:
      - Related to defecation
      - Associated with a change in frequency of stool
      - Associated with a change in form (appearance) of stool
    - Criteria fulfilled for the last 3 mon with symptom onset at least 6 mon prior to diagnosis.
  - Look for the presence of alarm features
    - GI bleeding (hematochezia/melena)
    - Unintentional weight loss
    - Onset after age 45/50 yr
    - Anemia
    - Family history of IBD, colorectal cancer
  - The finding of alarm features is not always useful to determine whether IBS should have a colonoscopy
    - In 559 patients seen for colonoscopy, who meet Rome criteria for IBS
      - 28% of IBS patients with alarm features had organic disease vs. 15% in patients without alarm features, however
    - In study of 200 patients with IBS – 70% had red flag features:
      - 64% had colonoscopy
        - 10 patients had non-advanced adenomas
        - 1 had non-IBD colitis
      - 37% had CRP – 8 had positive values, 0 got diagnosed with IBD.
      - 36% had C. Diff testing – 0 positive.
      - 48% had celiac serologies – 0 positive.

- Physical examination
  - Inspection
    - ↑ lumbar lordosis
  - Abdominal palpation, look for
    - Masses
    - Cachexia
    - Carnett sign
  - Digital rectal examination (DRE), look for
    - Pelvic floor dyssynergy
    - Puborectalis tenderness
    - It is uncertain just how useful physical examination is in the patient with suspected IBS
  - Blood
    - For everyone
      - CBC
      - CRP
      - Celiac serologies plus IgA concentration
      - Possibly thyroid stimulating hormone (TSH), controversial, but certainly with symptoms suggestive of thyroid dysfunction
    - Do **not** do food sensitivity testing
  - Stool
    - Fecal calprotectin – everyone/diarrhea
    - Stool culture/ova & parasite /C. difficile
      - If patient has diarrhea
  - Abdominal imaging
    - Ultrasound in post-menopausal women
  - Colonoscopy
    - Alarm features
  - Anorectal manometry
    - Consider if patient has refractory constipation, or other clinical evidence of defecation disorder.

➢ Natural history

  - Chronic fluctuating disease.
    - Temporal relationship between chronic life stressors and severity of gastrointestinal symptoms.
    - Over time, 12-38% have improved symptoms, 30-50% have unchanged symptoms, 2-18% have worse symptoms.
    - 17-55% of patients who initially have IBS, do **not** report IBS symptoms 1-12 yrs later.
    - For post-infectious IBS
      - 43% will recover within 6 yr

➢ Treatment

- Dietary
  - Low FODMAPs diet
    - FODMAPS →
      - ↑ GI water secretion, and
      - Fermentation

      } ↑ gas / ↑ distention
    - Improves global symptoms including
      - Pain, and
      - Bloating.
    - Three stage method (Ideally with assistance of GI dietician)
      - Substitute foods with high FODMAPs. (6-8 wk to allow for symptom improvement)
      - Re-introduce of high FODMAPs foods (to determine acceptability of individual foods.
      - Maintenance phase using personalized diet.
  - Fibre, soluble
    - Soluble fibre improves in IBS symptoms (RR, 0.87)
      - Psyllium can improve diarrhea or constipation.
      - Low adverse effects.
    - Insoluble fibres lead to colonic fermentation → ↑ bloating (does not improve IBS symptoms)
  - Probiotics
    - Concept of use of probiotics supported by the importance of gut microbiome in IBS.
      - Many varieties of probiotics and are none individually rigorously studied.
- Exercise
  - Exercise has general health benefits
    - In RTC of 102 patients, 20-60 min of moderate/vigorous activity 3-5x per wk was compared to maintenance of baseline activity for 12 wk:
      - Physical activity arm had ↑ improvement in IBS symptom severity, compared with baseline (43% vs 26%)
      - ↓ worsening of IBS symptoms (8% vs 23%)
- Psychotherapy
  - Gut directed psychotherapies
    - Cognitive behavior therapy (CBT) / hypnotherapy.
      - Variety of techniques
        - Relaxation
        - Cognitive reframing of negative thoughts
        - Exposure
        - Decreasing helplessness.
      - Alters cognitive and affective pathways that modulate the perception of enteric signals.
      - As effective as low FODMAP diet (RCT level evidence)
      - Durable results.
      - Virtually no adverse events.
      - If significant mental health comorbidities – refer to mental health specialist.

- Pharmacology
  - Pain
    - Antispasmodics (low level of evidence)
      - Hyoscine/scopolamine (Buscopan®)
      - Dicyclomine (Bentyl®)
      - Pinaverium (Dicetel®)

      – Antimuscarinic
      – Calcium channel blocker
    - Peppermint oil
      - Various formulations available (enteric coated, non coated)
      - Blocks calcium channels
        - Possibly modulates voltage channels
        - Anti-microbial
        - Anti-inflammatory effects
      - Has effects from esophagus to large intestine, and gall bladder.
    - SSRIs
      - Citalopram/fluoxetine most often recommended.
        - ↓ transit time / ↑ transit
    - Tricyclic antidepressants (TCAs)
      - Amitriptyline
      - Desipramine
      - Imipramine
      - Nortriptyline
      - Start at low doses, gradually ↑ dose as needed
      - Modulates norepinephrine/dopaminergic receptors
        - ↓ perception of pain
        - ↓ transit time

        May be preferable in IBS-D patients
      - Minor adverse events (AEs)
        - Dry mouth
        - Dizziness
        - Insomnia/drowsiness.
      - No serious adverse events in most studies at IBS doses.
  - Constipation
    - Peg-based osmotic laxatives
      - ↑ frequency of bowel movements
      - Does not improve pain/bloating.
      - No guideline recommendation in Canada/US
      - Minor AEs short- and long-term
    - Linaclotide (Constella®) & Plecanatide (Trulance®)
      - Guanylate cyclase-C agonists
      - 290 µg daily & 3 mg daily
      - Symptom improvement typically by day 7
      - Usually stopped after 4-12 wk if not beneficial
      - Mechanism of action
        - ↑ bicarbonate/chloride secretion into lumen → ↑ peristalsis,
        - Most common side effect is diarrhea (overall well tolerated)

- Tenapanor (Ibsrela®)
  - Sodium/hydrogen exchanger 3 inhibitor
  - 50 mg bid
  - Symptom improvement typically by day 7. Stop after 4 wk if not beneficial
  - Mechanism of action
    - ↓ absorption of Na and PO_4
    - ↑ intestinal fluid volume
    - ↓ transit time
  - Most common side effect is diarrhea.
- Tegaserod – Not available in Canada
  - Serotonin agonist initiates peristalsis.
  - Second line in women < 65 yr, ≤ cardiovascular (CV) risk factors.
  - Initial RCTs on mostly women.
  - AEs
    - Diarrhea
    - ↑ possibly CV events
- Lubiprostone – Not available in Canada
  - Prostaglandin E1 analogue activates chloride channels in intestinal epithelial cells → ↑ intestinal secretion and ↑ peristalsis.

- Diarrhea
  - Loperamide
    - ↓ diarrhea but does not ↓ IBS related pain.
  - Bile acid (BA) sequestrants
    - Colestipol, cholestyramine, Colesevelam
    - ↑ rates of cholecystectomy / C4 (high in bile acid malabsorption [BAM]) in patients with IBS
    - BA sequestrants bind bile acids →
      - ↓ water and electrolyte secretion into the lumen
      - ↓ diarrhea
    - BAM / ↑ BA acids in lumen → ↑ colonic secretion of Ci-/HCO3- (diarrhea)
    - ↓ severe IBS symptoms in very small open-label study
    - Limited ability to test for BAM in Canada (SeHCAT scan, stool bile acid C4 concentration in blood)
    - Adverse effects
      - Bloating
      - Constipation
      - Flatulence
  - Rifaximin (Zaxine®)
    - Antibiotics
    - Acute in GI lumen 550 mg tid for14 days
    - Repeat courses may be necessary
    - Mechanism of action
      - Possibly corrects abnormal microbiome in IBS
      - Improves global symptoms, bloating, diarrhea
    - AEs
      - Nausea, fatigue, edema, dizziness, abdominal pain
      - Number needed to harm (NNH) = 8971

- Eluxadoline (Viberzi®)
  - Mixed peripheral opioid agonist/antagonist
  - 75-100 mg bid
  - ↑ abdominal pain and ↑ firming of bowel movements
  - AEs
    - Constipation
    - Nausea
    - Rare episodes of pancreatitis
    - Sphincter of Oddi dysfunction
  - Contraindicated
    - History of pancreatitis
    - Cholecystectomy
    - Alcohol use ≥ 3/day / alcohol use disorder
- Alosetron – Not available in Canada.
  - Serotonin antagonist
  - ↓ intestinal transit (↑ transit time)
  - Recommended as second line in women.
  - 4 mg to 8 mg tis did not significantly improved pain / stool texture after 12 wk
- AEs: ↑ risk of
  - Constipations with complications
  - Death
  - Ischemic colitis

➢ Summary

- IBS is a very common condition in Canada.
- Pathophysiology is complex.
- Use Rome IV criteria to diagnose and to classify suspected cases
  - Then proceed with workup determined by presence/absence of alarm clinical suspicion and alarm symptoms.
- Spectrum of evidence-based and non-evidence-based treatments.

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VASCULAR LESIONS OF THE GASTROINTESTINAL TRACT

Navneet Natt

Primary Vascular Lesions

- Colonic Angioectasias

➢ Demography
  - Most common vascular abnormality of the GI tract
  - Most common cause of LGIB in patients > 60 yr

➢ Definition
  - Tortuous dilated submucosal blood vessels that are acquired with aging

➢ Pathogenesis
  - Muscular contraction of colon → transient episodes of increased pressure → partial intermittent obstruction of submucosal veins as they pierce the muscularis layer
  - Leads to dilatation of the submucosal vein and venules/capillaries that drain into it
  - As capillaries dilate, they lose their pre-capillary sphincter tone, giving rise to small AV fistulas
  - Alternative theory = ↑ VEGF (vascular endothelial growth factor) / VEGF-receptors stimulates angiogenesis, especially in hypoxic states

➢ Clinical
  - Usually presents with recurrent low-grade bleeding, but can present with massive lower GI hemorrhage
  - Presentation varies from asymptomatic iron deficiency anemia to
    - Melena
    - Maroon stools, or
    - Bright red blood per rectum (BRBPR) depending on rate of bleeding
  - Bleeding stops spontaneously in 90% of patients
  - AEs may be found incidentally in ~3% of non-bleeding patients undergoing colonoscopy
  - Associated Conditions
    - Heyde Syndrome (aortic stenosis, AEs plus lower GI bleeding)
      - ↑ shear stress → disruption of Von Willebrand protein (VWP) → cleavage of VWP → disrupts primary hemostasis
      - Pre-existing AEs more likely to bleed
      - Bleeding usually resolves post-AVR
    - LVAD-associated GI bleeding secondary to angiodysplasia
      - Similar mechanism of bleeding secondary to acquired VWD

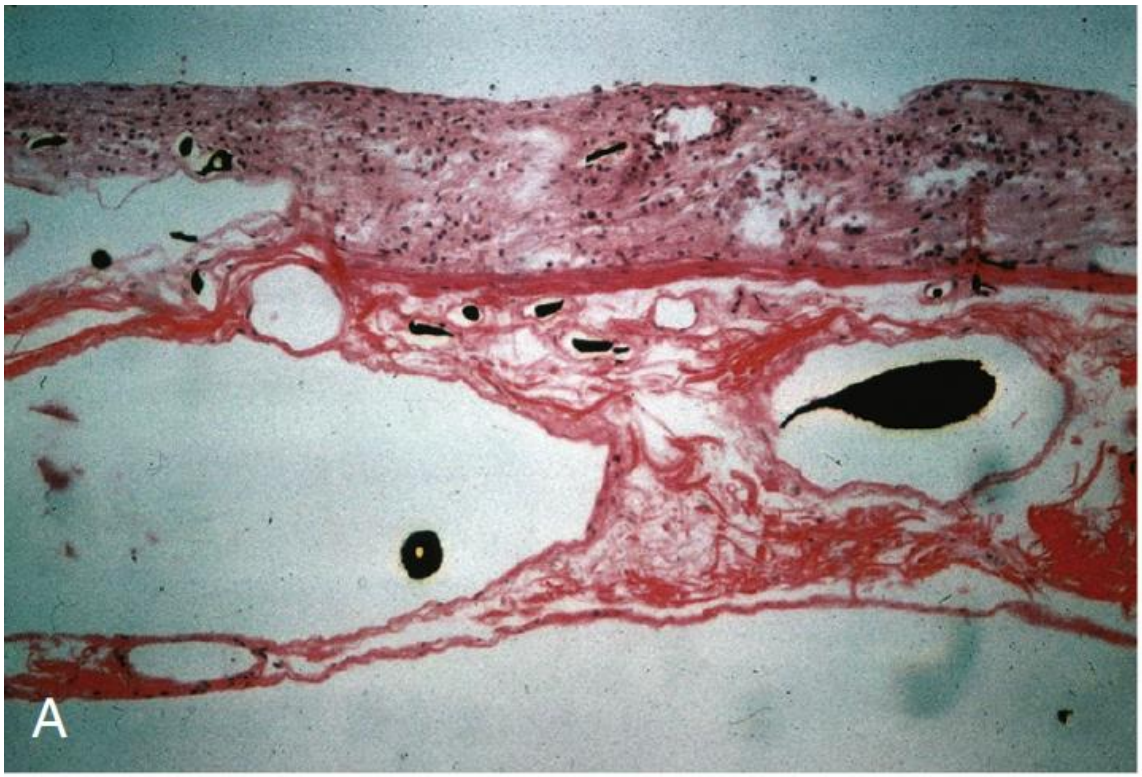
"In a patient being studied for GI bleeding, in whom the site of active bleeding is unproven, the only basis for determining that an identified AE or diverticulum is responsible is the indirect evidence provided by the patient's course after ablation or resection of the suspected lesion."

- Diagnosis
  - Colonoscopy
    - Main means of diagnosis
    - False-negative colonoscopy
  - ↑ appearance of vascular lesions may be diminished by hypotension, anemia, or cool water lavage which will vasoconstrict the vessels
  - Angiography can be used to identify actively bleeding AE
    - An early-filling vein
    - Dilated, tortuous vein
    - Densely opacified
    - Slow emptying
    - A vascular tuft

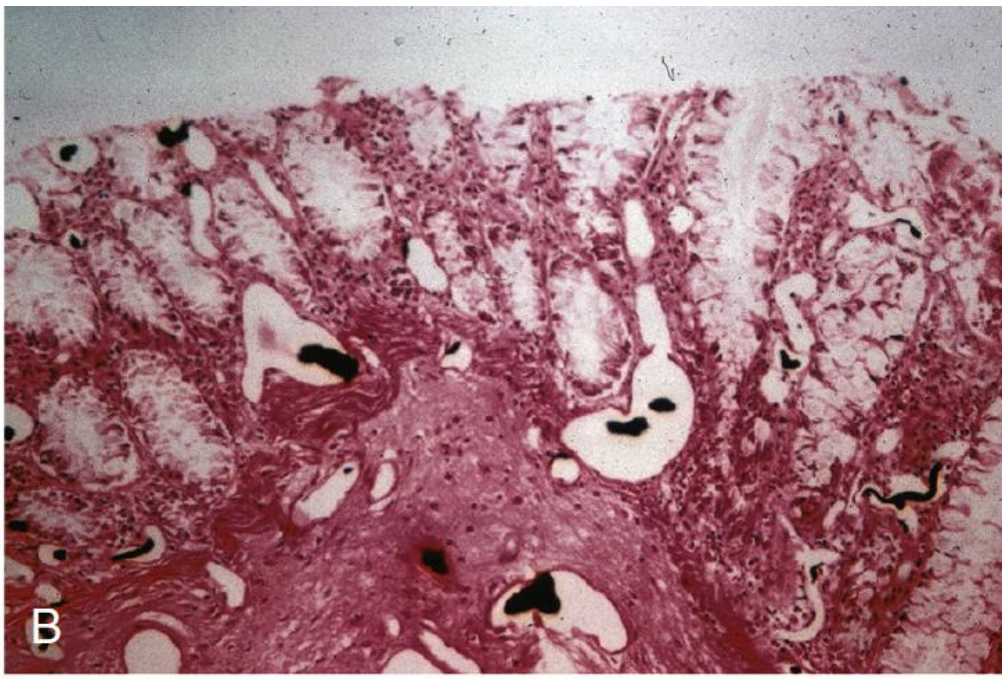
- Lesions that may be confused with AE on Endoscopy
  - Colitides
    - IBD
    - Infectious
    - Ischemic
    - Radiation
  - Neoplasm
    - Adenomatous polyps
    - Leukemic infiltration
    - Lymphoma
  - Non-neoplastic polyps
    - Hyperplastic
    - Lymphoid
  - Non-vascular lesions
    - Trauma
  - Vascular lesions
    - Angiomas
    - Arteriovenous malformations
    - Phlebectasia
    - Spider telangiectasias
    - Telangiectasias
    - Varices
    - Venous stars

- Histopathology
  - Definitive identification involves histologic examination
    - Involves injecting the colonic cells with silicone rubber and immersing the specimen in methyl salicylate for 24 h
  - Features
    - Early changes = dilated submucosal vein
    - Initially distorted vessels seen to involve the muscularis mucosa and later stages, go on to involve the mucosa
    - Thin-walled distorted venules, arterioles, and/or capillaries
    - Loss of prearteriolar sphincter function may give rise to small acquired AV fistulas
    - More common in RUQ (side of colon)

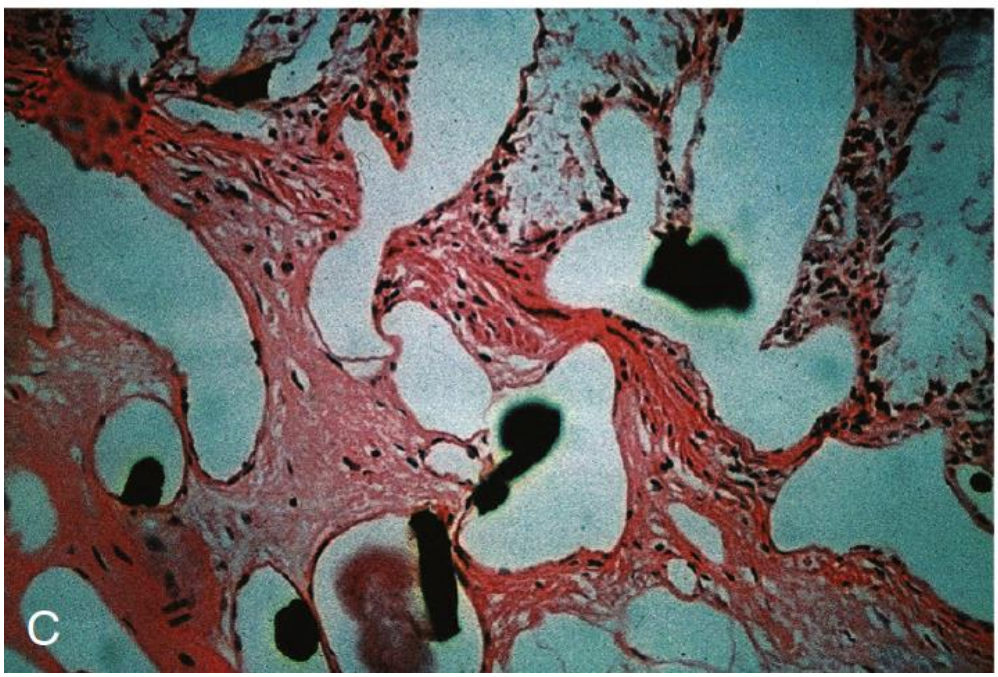
Large distended veins in submucosa



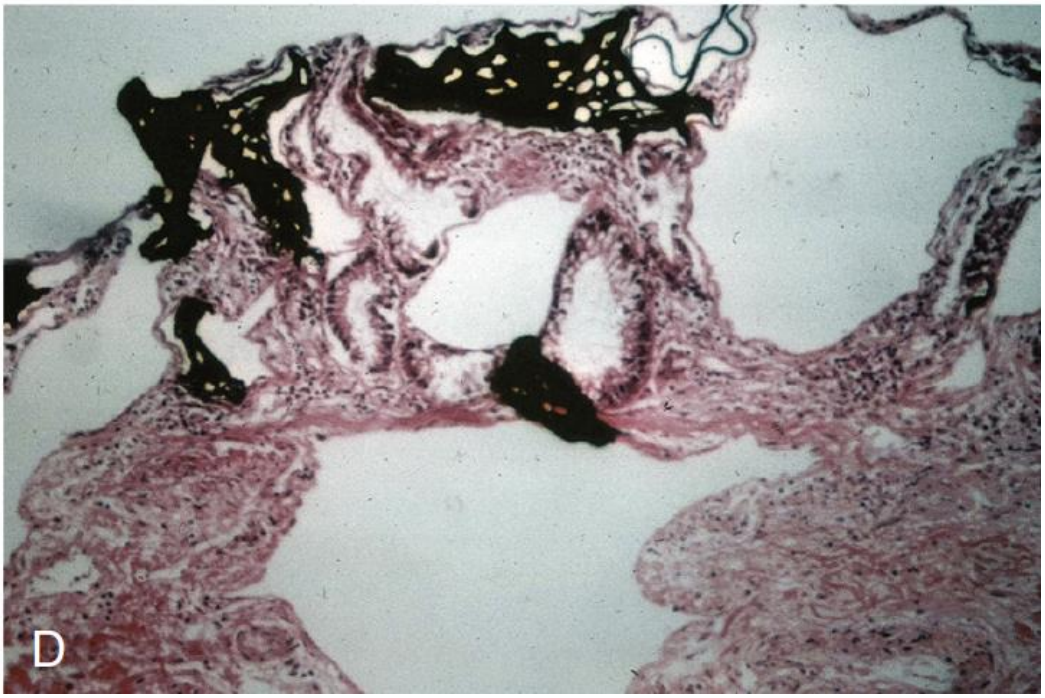
Dilated tortuous veins in the submucosa extend into the mucosa



Ectatic vessels start to extend into and disrupt the mucosa



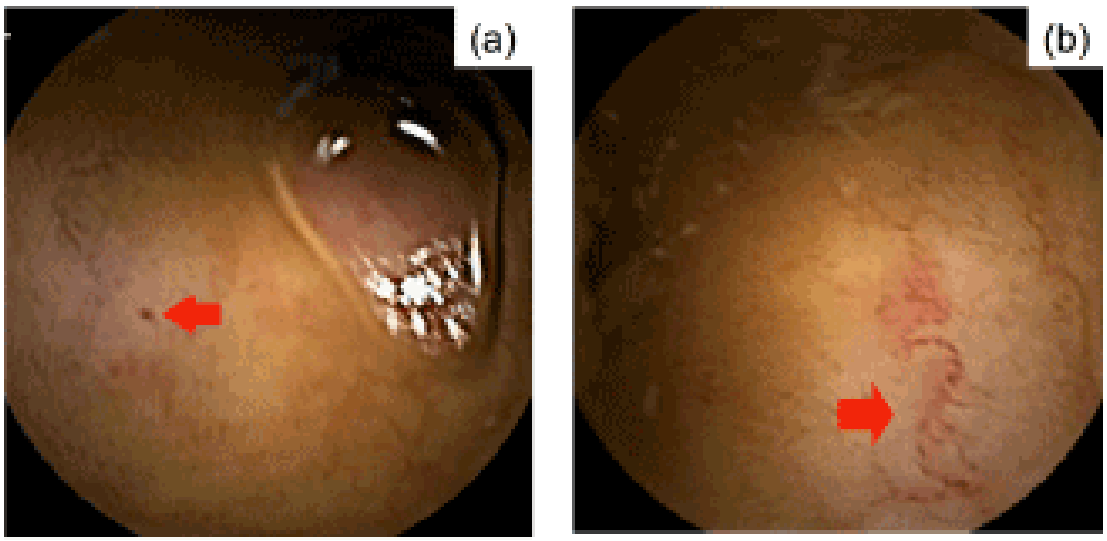
Mucosa replaced by ectatic vessels



Printed with permission: Kwah J and Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 38, page 563 (Figure 38.4).

- Endoscopy
  - Usually in cecum or ascending colon
  - 10% of patients may have similar lesions in small bowel
    - Multiple > solitary lesions
    - <10 mm in diameter
  - Coral reef-like pattern of small vessels is seen early on in the development of AE

Colonic Angiectasias (AEs)



Capsule endoscopy
a) Red spot,
b) Angioectasias

Source: Yokota T, et al. Gastroenterol Hepatol Endosc 2016: doi: 10.15761/GHE.1000113

- Treatment
  - Non-bleeding AEs
    - No therapy indicated
  - Bleeding AEs
    - ABC's of supportive care, hypotensive, bleeding
  - Systemic therapy
    - Somatostatin analogs / Octreotide
      - Mechanism of action
        - ↓ splanchnic blood flow
        - ↓ angiogenesis
        - ↑ platelet aggregation
        - Pooled OR for bleeding cessation 14.5 (95%CI 5.9-36) in a meta-analysis of 4 cohort studies
    - Other pharmacotherapies
      - Anti-angiogenic therapies (thalidomide, bevacizumab, and lenalidomide)
      - Procoagulants estrogens (with progestin)

- Angiodysplasia (AD)

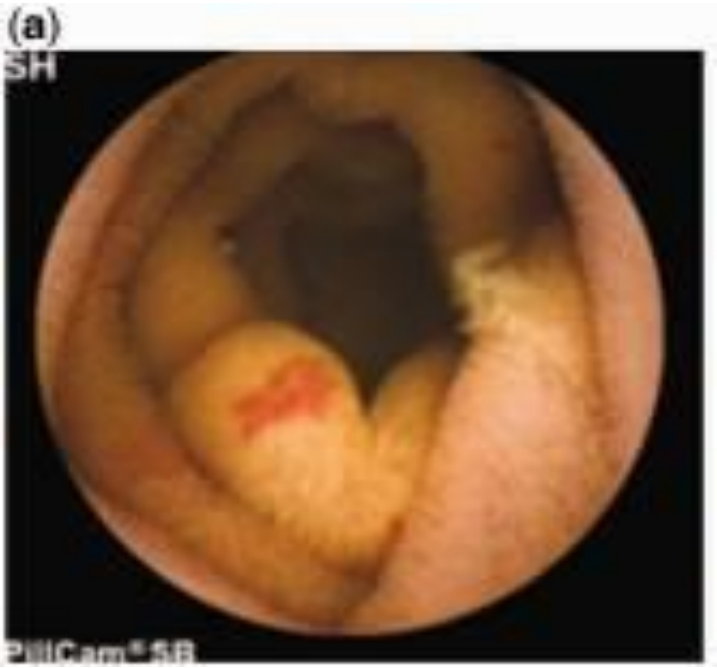
➢ Definition

  - Abnormal tortuous vessels in stomach, small bowel, and colon

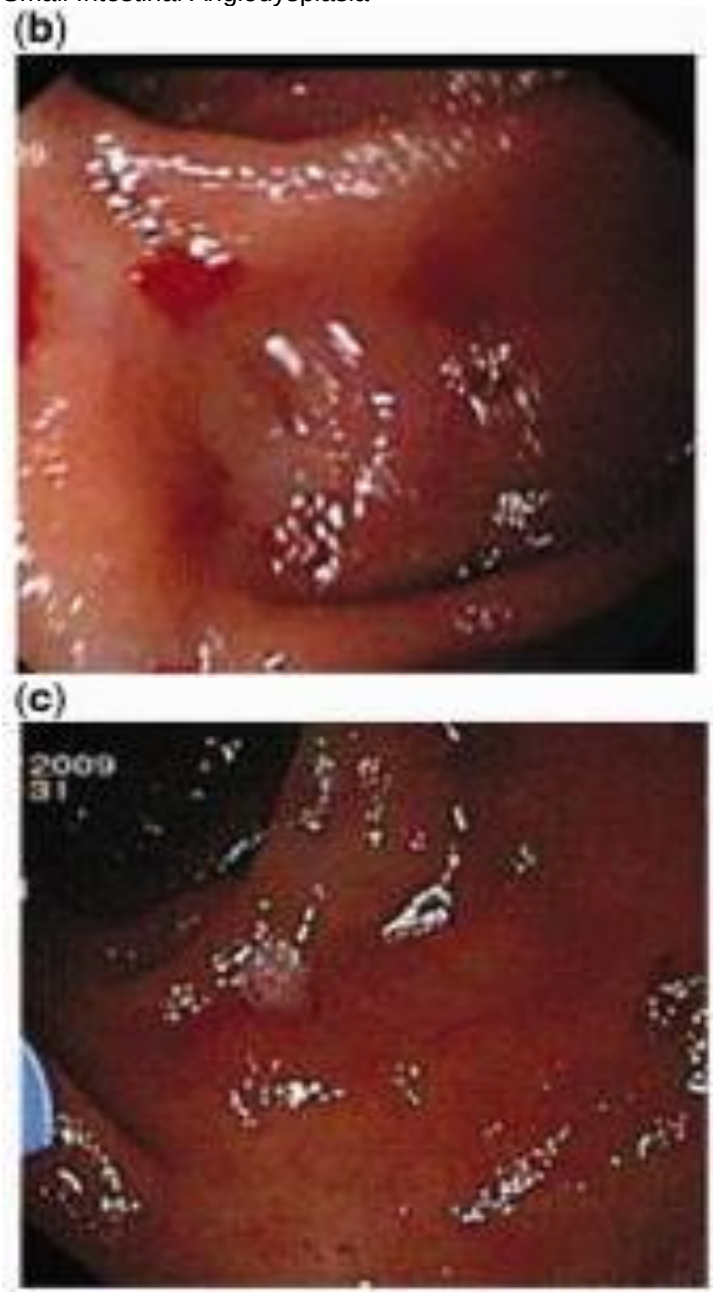
➢ Diagnosis

  - Esophagogastroduodenoscopy (EGD)
  - Video capsule endoscopy (VCE)
    - Diagnostic yield = 67% in overt small bowel bleeding
  - Enteroscopy (single or double balloon enteroscopy) can be used to provide diagnosis / endoscopic therapy
    - Higher yield when performed after a positive video capsule study (75% vs. 28% after negative video capsule)

Small Intestinal Angiodysplasia



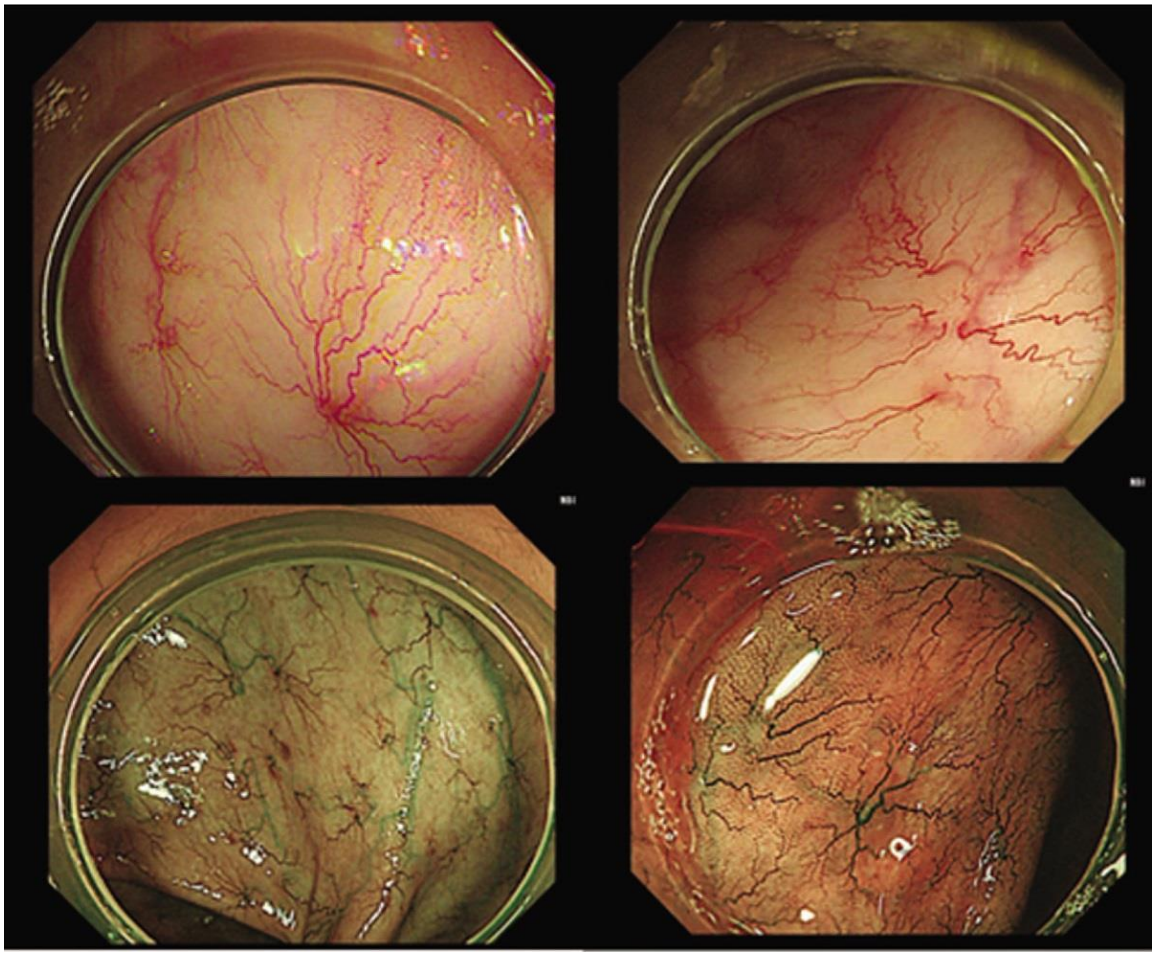
Small Intestinal Angiodysplasia



Patient of small bowel bleeding due to angiodysplasia in jejunum
a: Capsule endoscopy: angiodysplasia in jejunum;
b: Enteroscopy: angiodysplasia in jejunum;
c: Argon plasma coagulation (APC) of angiodysplasia

Source: Gunjan D, et al. Gastroenterol Rep (Oxf) 2014; 2(4):262-75 (Figure 1)

Colonic Angiodysplasia



- In colonoscopy, segments of the whole colon and the varicose veins showed multiple flaky spider-like telangiectasia changes. The blood vessels were radially distributed and converged in the center.

Source: Li, J-A, et al. Medicine 2020; 99(34): p e21106 (Figure 1)

- Treatment
  - Enteroscopy
  - Pharmacotherapy
    - APC
      - Rate of re-bleeding is 46% at 3 yr
    - Octreotide
    - (Thalidomide)

    } ↓ re-bleeding / ↓ transfusion requirements for refractory bleeding

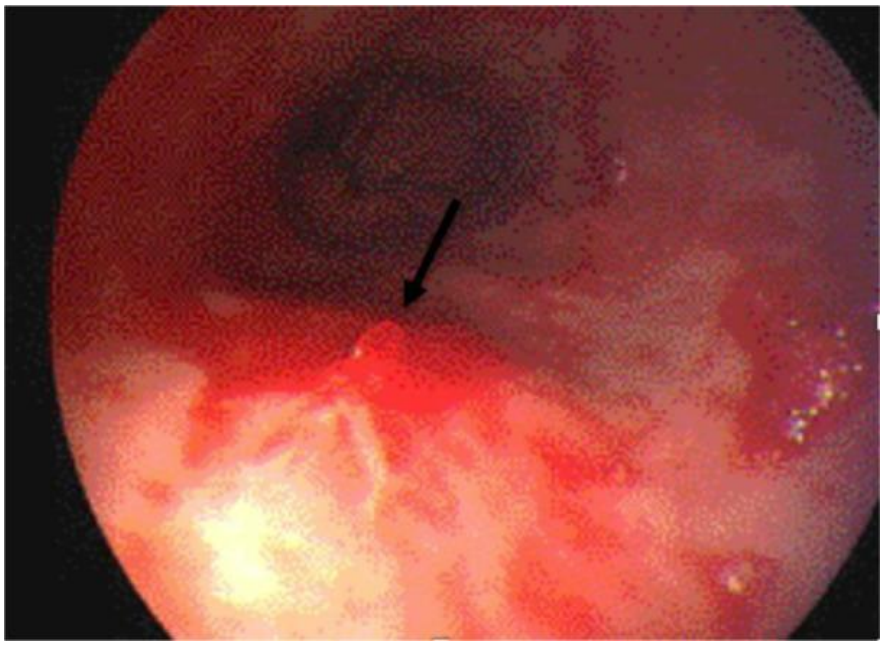
- Dieulafoy Lesion

➢ Demography
  - M >> F
  - Mean age of presentation, 52 yr

➢ Definition
  - Large calibre submucosal artery
    - Can be found anywhere along the GI tract from esophagus to rectum

➢ Endoscopically
  - Looks like an isolated protruding vessel surrounded by normal mucosa
  - Most common site of bleeding 6 cm distal to gastroesophageal junction
  - May be difficult to visualize endoscopically during active UGIB
    - Mesenteric angiography can be used to localize site of bleeding

Endoscopic findings of Dieulafoy lesions in the gastrointestinal tract



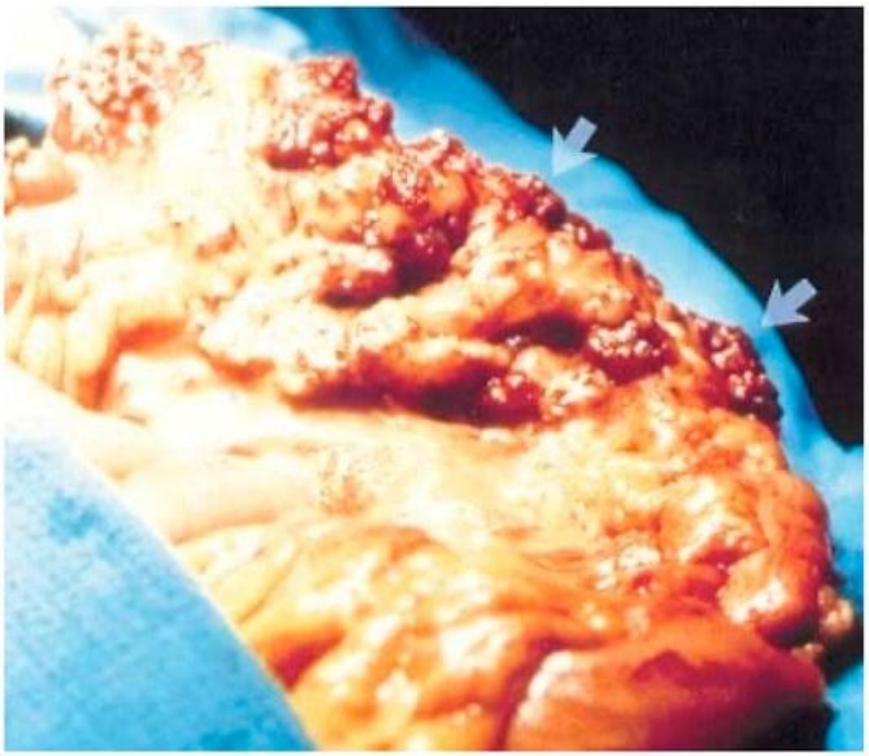
  - Profuse pulsatile bleeding at the gastric fundus with an adherent clot

Source: Al-Busaidi A, et al. EXCLI J 2023; 22:862-866 (Figure 1)

- Clinical
  - Presents with massive bleed once the mucosa erodes away, exposing the arterial wall
- Treatment
  - Combination therapy > monotherapy
    - Successful hemostasis in 95% of cases
  - Choices
    - Argon plasma coagulation (APC)
    - Heater probe
    - Hemoclips
    - Injection
    - Ligation
    - Over-the-scope clips

- Hemangioma

Cavernous Hemangioma of a Descending Colon



Source: Vlad RM, et al. Diagnostics 2024; 14(3):310 (Figure 4)

- Demography
  - Second most common vascular lesion of the colon
- Definition
  - Focal collection of blood vessels (veins, capillaries, or mixed) in the submucosal connective tissue
- Clinical
  - Usually slow bleeding
    - Melena or occult blood loss with anemia, but though large cavernous hemangiomas of rectum can present with brisk lower GI bleeding (LGIB)
- Diagnosis:
  - Endoscopy
    - Usually a few millimetres to 2 cm
    - Solitary or multiple
    - May be diffused
  - CT/MRI
  - EUS
    - Can identify extent of invasion into surrounding structures
  - Angiography
    - Rarely required
- Treatment
  - Small solitary hemangiomas
    - Endoscopic ablation
  - Larger lesions or multiple
    - Surgical resection

- Diffuse Intestinal Hemangiomatosis

- Site
  - Numerous synchronous cavernous hemangiomas in stomach, small bowel, and colon
  - Extraintestinal hemangiomas of the skin, head, and neck frequently co-exist
- Prevention
  - Usually in childhood
  - Complications
    - Anemia
    - Bleeding
    - Intussusception

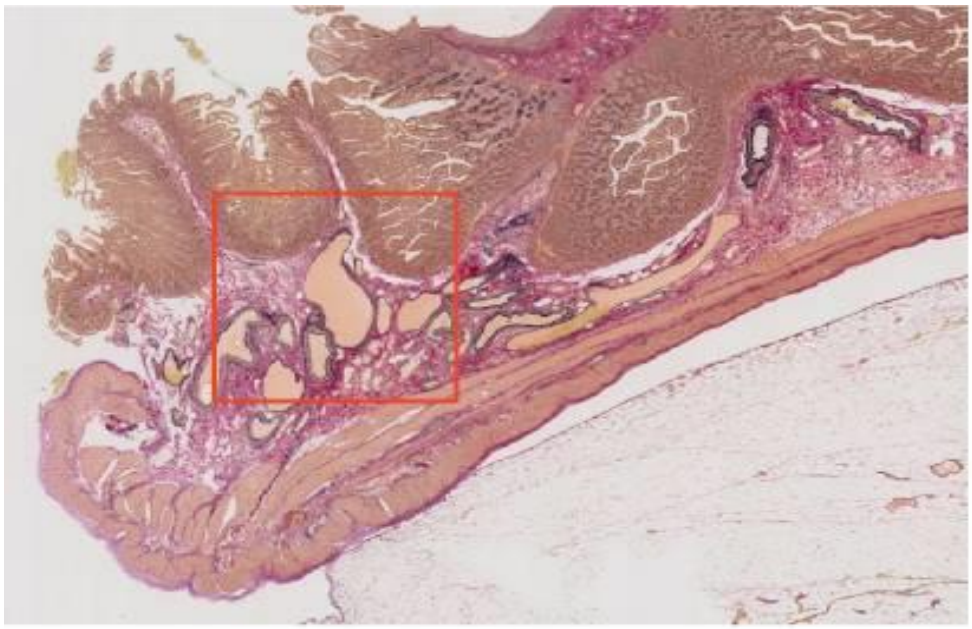
- Treatment
  - Definitive treatment
    - Surgery
  - VEGF inhibitors
    - Used to treat hemangioblastomas in the setting of Von Hippel Lindau Disease (by inhibiting angiogenesis)
      - There may be role for these agents in treating other benign hemangiomas

- Congenital Arteriovenous Malformations (AVMs)

- Definition
  - Development anomalies communications between the submucosal artery and vein

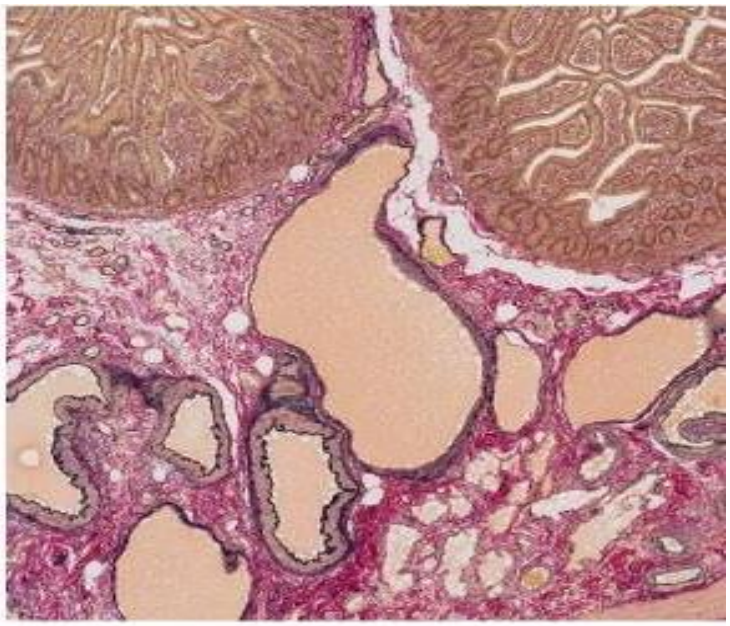
- Pathology
  - Arteries dilated and atrophic
    - Veins become tortuous and thick-walled

Congenital Arteriovenous Malformations (AVMs)



(a)

Congenital Arteriovenous Malformations (AVMs)



(b)

Elastica van Gieson staining revealed tortuous, dilated veins and arteries in the submucosal layer. The image in the right panel is a magnified view of the red box in the left panel. (a) ×magnifying glass imaging and (b) ×40.

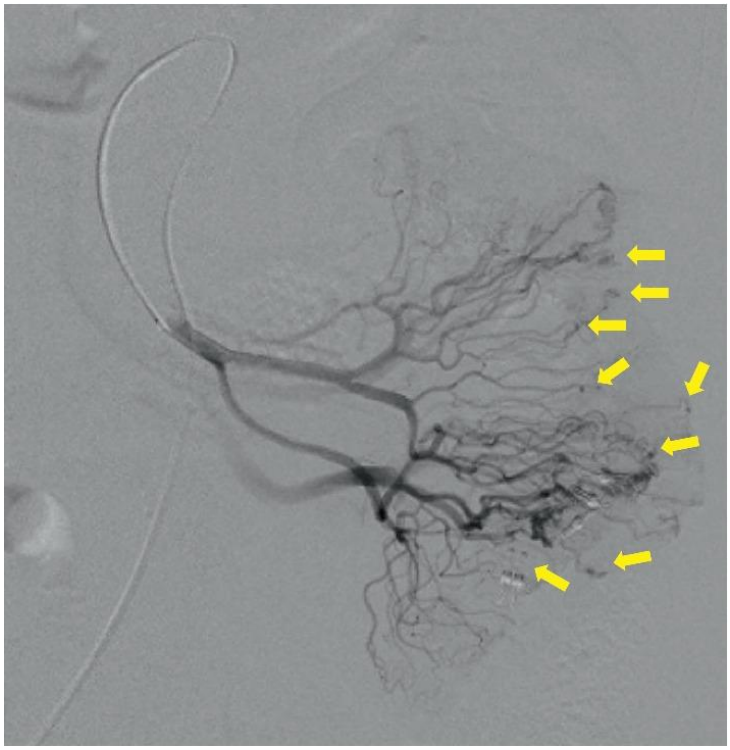
Source: Hirakawa M, et al. Case Rep Med 2019; 2019:2046857 (Figure 5)

- Risk factors
  - Atherosclerosis (95%)
  - Age > 60
  - Collage vascular diseases (e.g., Ehlers-Danlos disease)
  - Hypertension
  - Male gender
  - Smoking
  - White race

- Clinical
  - Sudden onset of abdominal/back pain)
    - Aneurysmal rupture
  - Most commonly ruptures into retroperitoneum
  - Rarely massive GI bleeding may present if aneurysm ruptures into D3/D4
    - Endoscopy would be most sensitive test to diagnose this

- Diagnosis
  - Angiography
    - Early-filling vein is hallmark
    - Prominent dilated SMA
    - Dilated SMV / portal vein with early filling
    - Small ectatic vessels supplying the bowel

Multiple Arteriovenous Malformations



Selective angiography: multifocal niduses were detected in the jejunum and were supplied by the second jejunal arteries (yellow arrows).

Source: Hirakawa M, et al. Case Rep Med 2019; 2019:2046857 (Figure 3)

- Treatment
  - Large AVMs with significant bleeding
    - Resection of involved segment of bowel

❖ Aneurysm

- Abdominal Aortic Aneurysm (AAA)

➢ Clinical

- Risk of rupture increases with AAA size (1% if 4.0-4.9 cm, and 11% if 5.0-5.9 cm)
  - Screening
    - One-time abdominal ultrasound (US) in men ages 65-80 yr with smoking history (sensitivity, 95-100%; specificity, 100%)
    - If AAA enlarged, perform serial US q6-12 mon to monitor growth rate

➢ Diagnosis

- CT angiography (CTA, gold standard) or MR angiography (MRA)

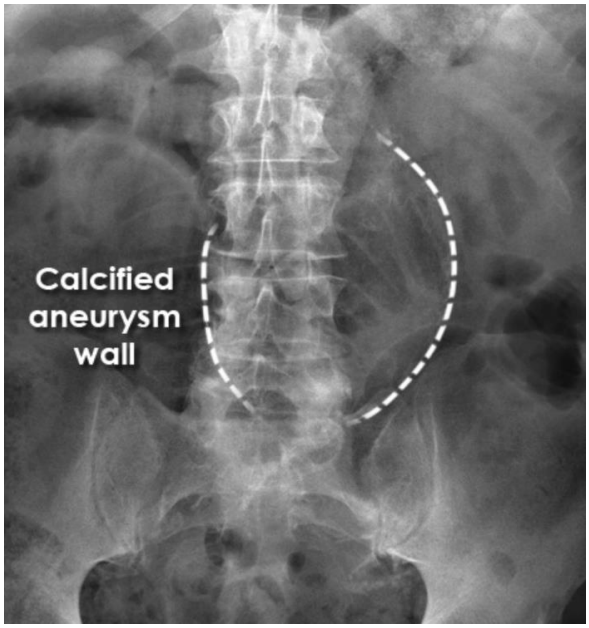
➢ Treatment

- Surgical (open or endovascular repair)
  - Rupture
  - Asymptomatic patients with AAA > 5.5 cm
  - Refer earlier high risk persons (e.g. familial aortopathy, connective tissue disease, rapid rate of growth >0.5 cm/yr)

➢ Screening

- US, 65-74 yr
- CAN, 80 yr

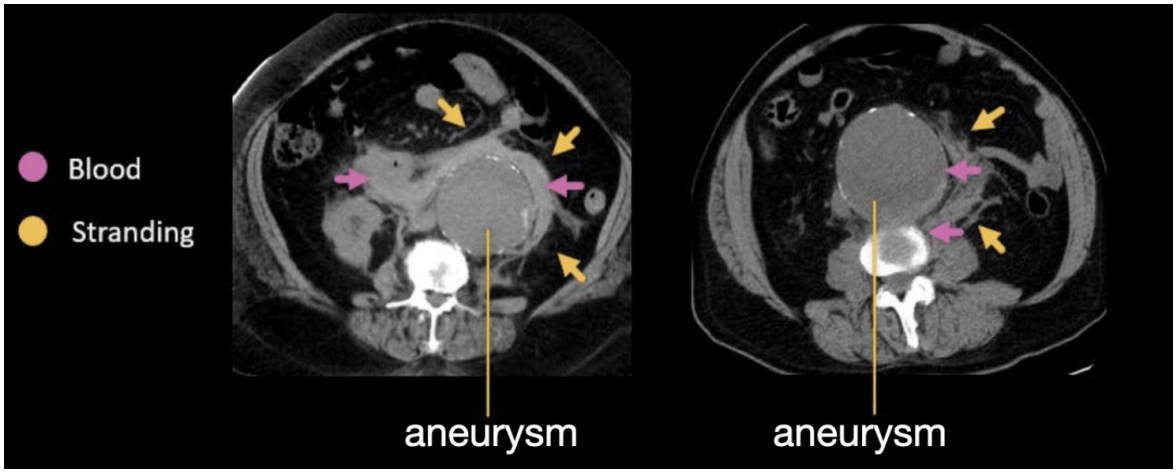
Abdominal Aortic Aneurysm (AAA)



- AAA may be visible on abdominal plain film as soft tissue mass with peripheral calcifications but not sufficiently sensitive to diagnose

Available from: https://www.radiologymasterclass.co.uk/gallery/abdo/abdominal_xray_calcification/aaa

CT of Abdominal Aortic Aneurysm



Source: Hartung MP and Cadogan M. Abdominal CT: aortic aneurysm. Life In the Fast Lane. May 22, 2023. Available from: https://litfl.com/abdominal-ct-aortic-aneurysm/

- Splanchnic Artery Aneurysms (SAA)

➢ Definition

- Includes aneurysms of the
  - Celiac axis
  - Splenic artery
  - Superior mesenteric artery (SMA)
  - Inferior mesenteric artery (IMA), and
  - Their branches
- Usually asymptomatic, detected incidentally on imaging

➢ Clinical

- Risk of rupture of SAA is 25%
  - Symptoms including:
    - Abdominal pain
    - Bruit
    - GI bleeding (if aneurysm erodes into the GI lumen)

➢ Diagnosis

- CTA, MRA, or splanchnic angiography

➢ Treatment options

- Embolization
- Endovascular stenting
- Surgical repair

- Splenic Artery Aneurysm

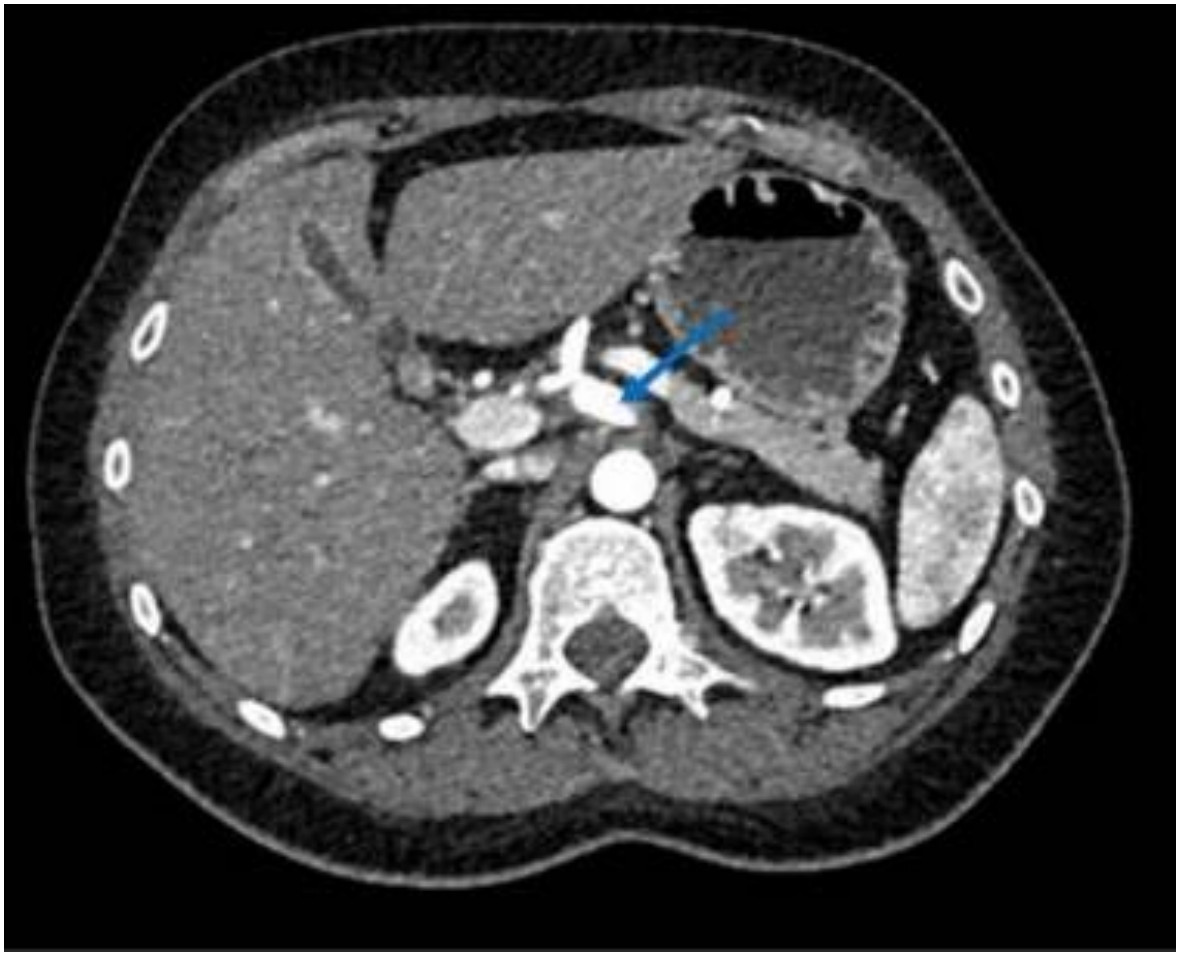
➢ Introduction
  - Typically, saccular
  - F>>M
  - More common in pregnancy (estrogen affects the elastic tunica media)

➢ Clinical
  - Risk of aneurysmal rupture, < 2%)
    - Except in pregnancy
  - Rupture → quiescent period where patient is hemodynamically stable as bleeding is confined to the lesser sac → shock/diffuse abdominal pain as bleeding overflows into the peritoneum
  - Symptoms
    - LUQ/epigastric pain, radiates to left shoulder

➢ Causes/Associations
  - Common
    - Atherosclerosis
    - Portal hypertension (HTN)
  - Less common
    - Ehlers-Danlos syndrome
    - Fibromuscular dysplasia
    - Polyarteritis nodosa
    - Septic emboli
    - Splenic arterial dissection
    - Systemic HTN
    - Systemic lupus erythematosus (SLE)

➢ Treatment
  - Surgical resection
    - Symptoms
    - SAA > 2 cm
    - Pregnancy (any size of SAA)
    - Rupture (urgent splenectomy)
  - Embolization
    - Aneurysm in setting of portal HTN
    - Aneurysm 1-2 cm → monitor CT/MRI q1 yr

- Celiac Artery Aneurysm



Dissection flap inside the coeliac artery aneurysm is pointed by blue arrow.

Printed with permission: Castelhano R, et al. BMJ Case Rep 2021;14(4): e240533 (Figure 3)

- Demography
  - Patients will often have synchronous aneurysms in other sites
  - Lifetime risk of rupture = 6%

- Causes/Associations
  - Atherosclerosis
  - Dissection
  - Infection (syphilis, TB)
  - Takayasu Arteritis
  - Trauma
- Clinical
  - Usually asymptomatic
  - Symptoms mimic pancreatitis (due to esophageal compression)
- Treatment
  - Refer for repair when > 2.5 cm
    - Open surgical repair
    - Ligation and aortohepatic bypass or aortic reimplantation
  - Ruptured aneurysm
    - Ligation
    - Percutaneous transcatheter embolization

- Superior Mesenteric Artery Aneurysm

- Demography
  - Rare
- Causes/Associations
  - Atherosclerosis
  - Biliary disease
  - Neurofibromatosis
  - Pancreatitis
  - Polyarteritis nodosa (PAN)
  - Septic emboli
  - Trauma
- Clinical
  - Symptomatic in 90%
    - Abdominal pain
    - GI bleeding
    - Up to 50% present with rupture
    - Complication of intestinal ischemia (secondary to downstream thrombus or dissection of SMA)

- Treatment
  - Symptoms in persons of ↓ surgical risk
  - Choices
    - Aneurysmectomy
    - Transcatheter embolization, or
    - Endovascular stenting
  - Persons with asymptomatic aneurysm < 2.5 cm

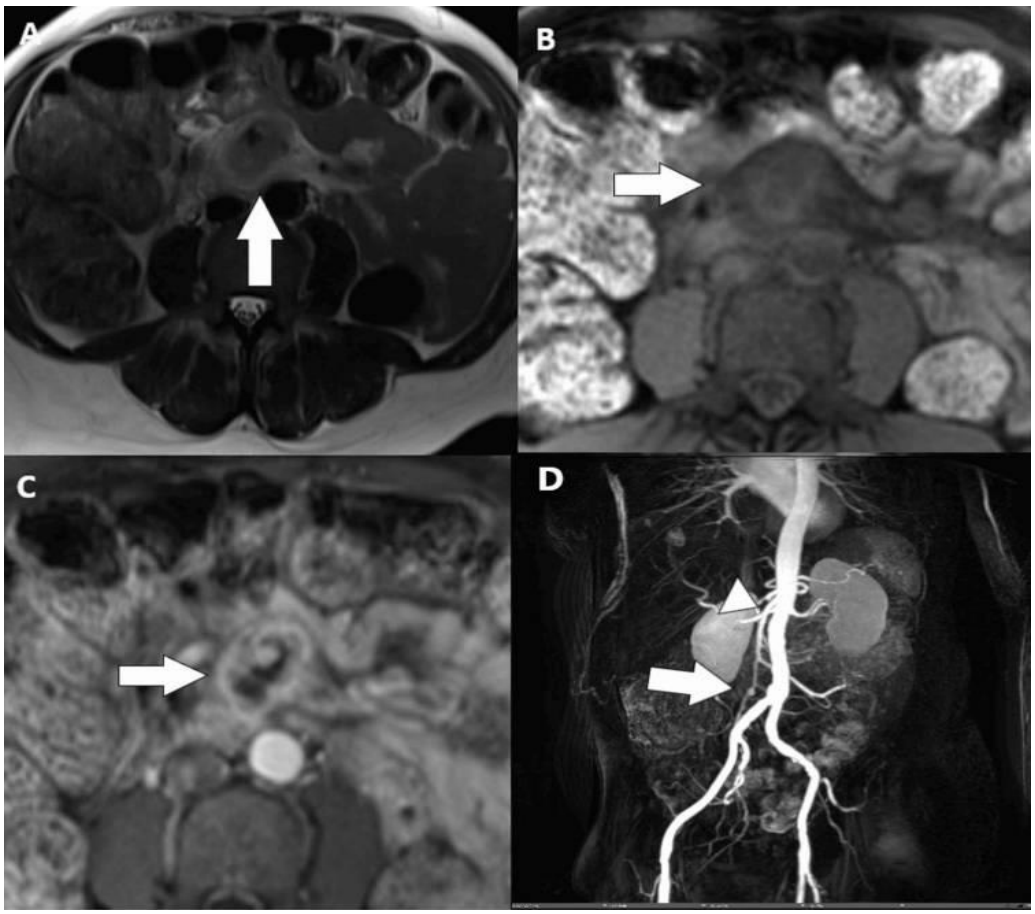
- Mycotic Aneurysm

- Definition
  - Infected aneurysm with lobular or saccular appearance

- Causes/associations
  - Most commonly caused by septic emboli in setting of endocarditis in the setting of endocarditis
  - Site
    - Celiac > SMA > IMA
  - Danger
    - Can rapidly expand and rupture
  - Risk factors
    - Intravenous drug use (IVDU)
    - Diabetes mellitus (DM)
    - Immunosuppression
      - Staphylococcus & salmonella are most common implicated organisms
      - Celiac > SMA > IMA

- Diagnosis
  - CTA
  - MRA

Mycotic Aneurysm of the Superior Mesenteric Artery



- A. MRI of the abdomen and pelvis.
  - Single-shot fast spin-echo sequence.
  - The arrow demonstrates wall thickening and stranding of the SMA.
- B. Precontrast VIBE sequence at the level of the mycotic aneurysm.
  - The arrow reveals mural edema.
- C. Postcontrast VIBE sequence.
  - The arrow denotes circumferential enhancement of the SMA wall.
- D. Coronal postcontrast VIBE MIP demonstrates
  - normal-caliber proximal SMA (arrowhead) with
  - foci of luminal dilation (arrow) and
  - narrowing of the involved SMA,
    - additional aneurysm of the arterial system within the abdomen or pelvis.

Abbreviations: MRI: magnetic resonance imaging; SMA: superior mesenteric artery; VIBE: volumetric interpolated breath-hold examination; MIP: maximum intensity projection

Source: Vulasala SS, et al. Cureus. 2024; 16(2): e54004. (Figure 2)

- Treatment
  - Surgical resection with vascular reconstruction
    - Post-operative IV antibiotics for 6 wk
    - Lifelong suppressive antibiotics po to ↓ risk of prosthetic graft infection

- Paraprosthetic Enteric and Aortoenteric Fistulas

- Risk factors
  - Previous aneurysmectomy / vascular prosthesis insertion (risk of fistula formation between the graft & adjacent bowel, aka secondary aortoenteric fistula)
    - ~ 1%
    - Mean interval post-surgery, 44 mon
  - Rarely occurs without previous surgery, ~ 0.05%

- Site
  - Most commonly occurs between D3/D4 and infrarenal abdominal aorta

- Risk factors
  - Infection
  - Malignancy
  - Radiation
  - Trauma

- Diagnosis
  - CT
  - EGD

- Treatment
  - Surgical repair

❖ Vascular Lesions Associated with Systemic Disorders or Manifestations

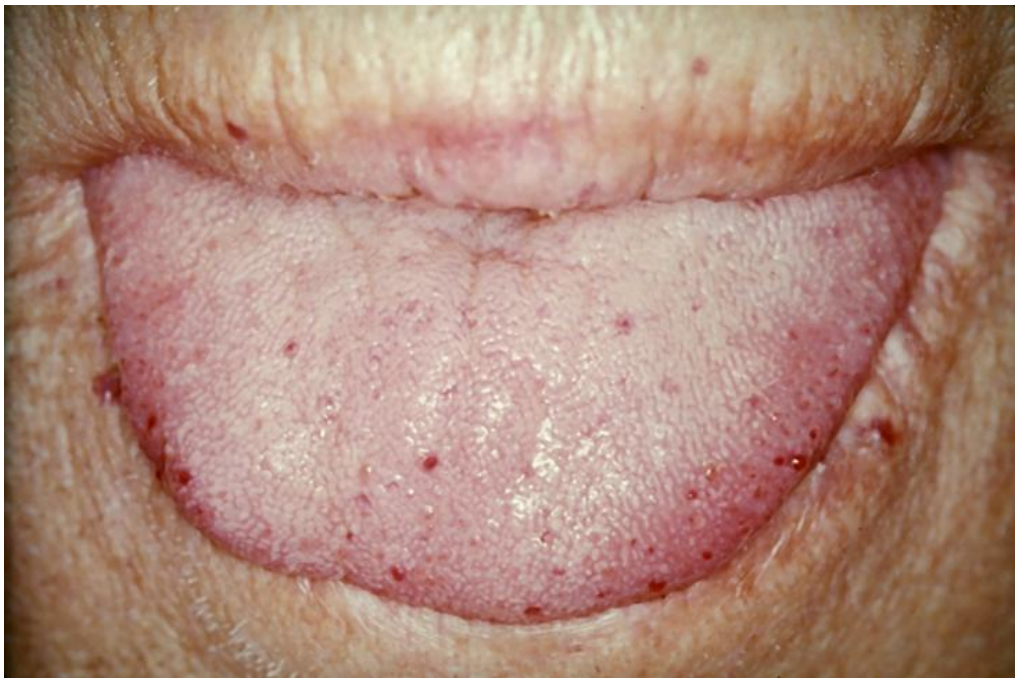
- Hereditary Hemorrhagic Telangiectasia (HHT); aka Osler Weber-Rendu (OWR) Syndrome

- Demography
  - Autosomal dominant
    - Lesions present in first few years of life

- Definition
  - Ectatic vessels
    - Without elastic lamina or muscular tissue in their wall w/ tendency to bleed
    - Telangiectasias of skin and mucosal membranes

- Clinical
  - Affects lips, oral cavity, nasopharynx, GI tract

Telangiectasias of Tongue



Source: https://commons.wikimedia.org/wiki/File:TongueTelang.JPG

  - Telangiectasias
    - Most common in
      - Stomach
      - Small bowel
    - Less frequent
      - Colon
  - Recurrent epistaxis and GI bleeding
  - Usually presents as melena
    - BRBPR / hematemesis are uncommon
    - If this is present, look for other causes

- Pathogenesis
  - Mutations of
    - ENG (Type 1 HHT), and
    - Activin gene (Type 2 HHT)

- Involvement of
  - Brain
  - Lungs
  - Liver
    - Encode receptors on vascular endothelium that help maintain vessel integrity
- Some HHT patients may have a SMAD4 gene mutation
  - Overlapping juvenile polyposis with risk of colorectal cancer
    - Requires screening colonoscopy

➢ Diagnosis
- CTA
- MRA
- Endoscopy (EGD, colonoscopy)

➢ Treatment
- Endoscopy during active bleeding (endoscopic hematostatic therapy (EHT)
  - Ablation with APC
- Pharmacotherapy (to ↓ bleeding & transfusion requirements)
  - Aminocaproic acid
  - Bevacizumab, IV (anti-VEGF Ab)
  - Estrogens
  - Surgical resection of involved bowel for failed EHT

• Blue Rubber Bleb Nevus Syndrome (BRBNS)

➢ Definition
- Vascular nevi plus intestinal lesions and GI bleeding

➢ Clinical
- Skin (face, eyes, trunk, limbs)
  - Blue raised 0.5-1 cm venous malformations
- Brain
- Heart
- Liver/spleen
- Bladder
- Genitourinary organs

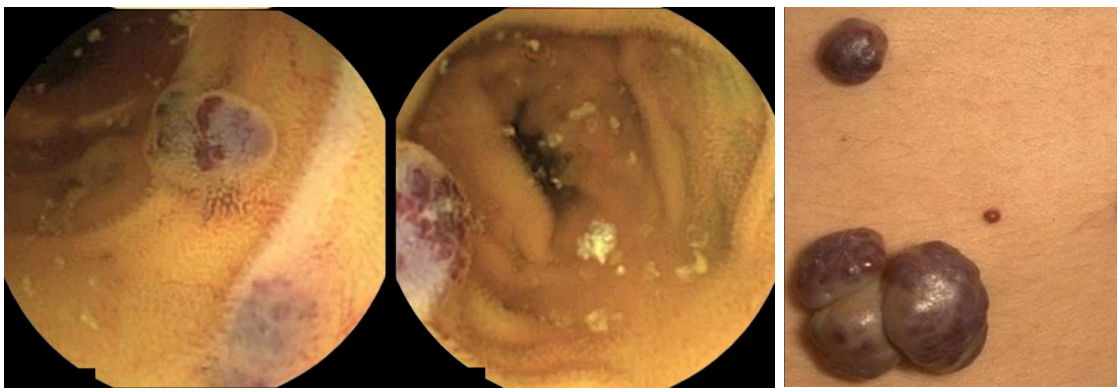
➢ Genetics
- Usually, sporadic somatic TEK gene mutation
  - May have autosomal dominant inheritance

- Diagnosis
  - Endoscopy (including video capsule endoscopy VCE small bowel lesions)
    - CT
    - MRI
- Treatment
  - Recurrent hemorrhage
    - Surgical resection of involved bowel
    - Endoscopy, but
      - Risk of perforation with APC (these lesions can involve full thickness of the bowel wall)

- Scleroderma

- Clinical
  - Telangiectasias
    - Usually seen in setting of CREST syndrome
  - Site
    - Most commonly
      - Face
      - Hands
      - Lips
      - Tongue
    - Less common
      - Stomach
      - Small bowel
      - Large bowel

Venous malformations in GI tract and on skin in BRBNS



Images from: https://litfl.com/blue-rubber-bleb-nevus-syndrome/

- Treatment
  - For clinically significant bleeding

- Klippel-Trenaunay (KTS) & Parkes Webber Syndrome (PVS)

- Demography
  - Rare congenital vascular disease

- Clinical
  - Triad
    - Vascular nevus on limb
    - Varicose veins
    - Hypertrophy of tissues in the affected limb (usually lower extremity)
  - Types
    - PWS
      - Same as KTS plus presence of AV fistulas
    - KTS
      - Capillary, venous, lymphatic abnormalities
  - Concurrent visceral lesions in
    - GI: liver, GI tract (20%)
    - GU: bladder, kidney
    - Heart

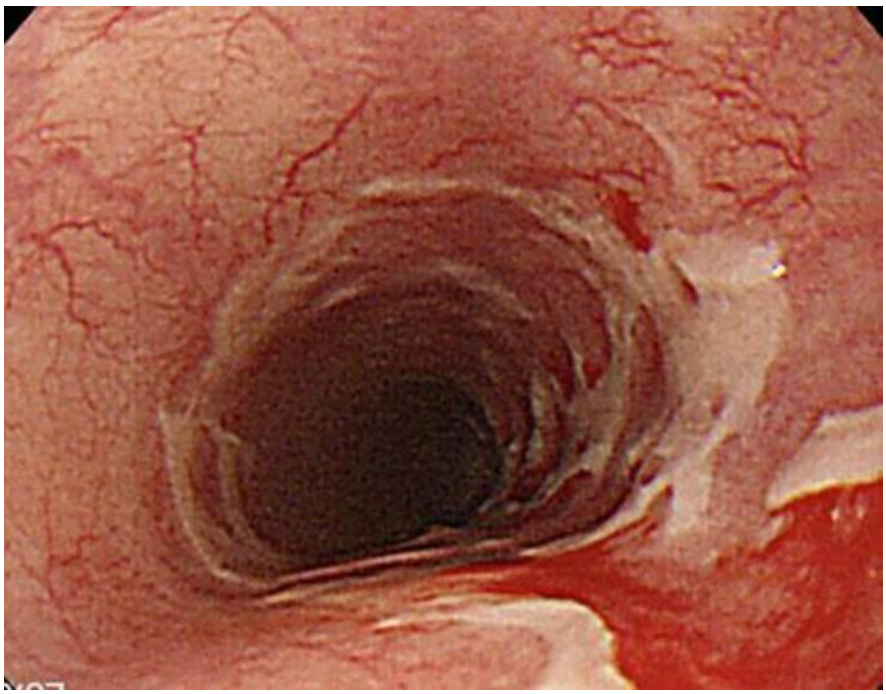
- Diagnosis
  - Physical examination
  - MRA
  - Angiography

- Radiation-induced mucosal injury

- Causes/Associations
  - Most commonly seen in rectosigmoid in patients who previously received pelvic radiation for prostate or cervical cancer
  - Radiation injury → endothelial proliferation → formation of vascular ectasias that are susceptible to bleeding

- Clinical
  - Bright red blood per rectum (BRBPR)

Radiation-induced mucosal injury



Source: Miura Y, et al. Case Rep Oncol. 2013; 6(2): 320–324.

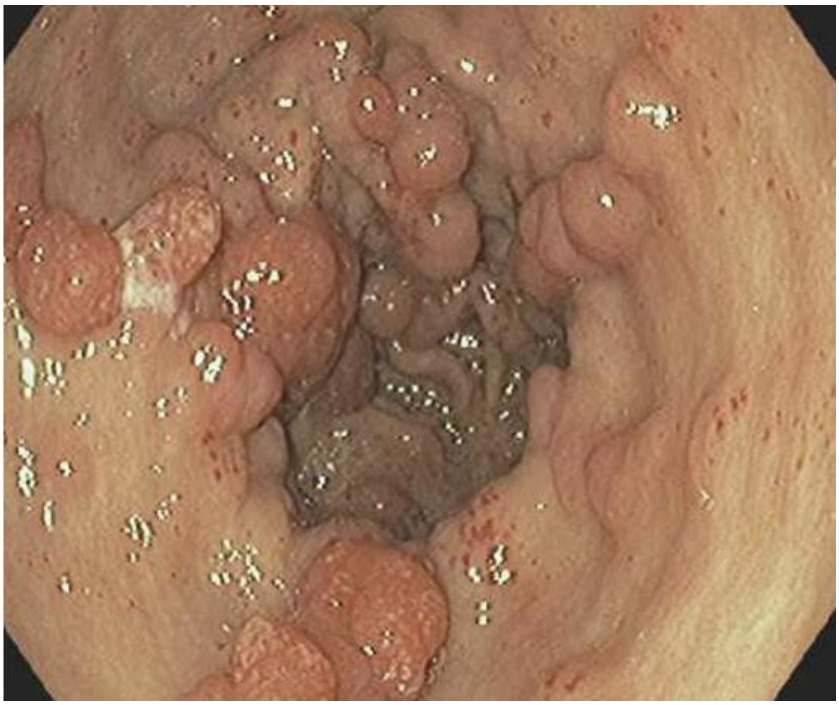
- Treatment
  - Pharmacological
    - 5-ASA
    - Formalin
    - Sucralfate enemas
  - Endoscopic hemostatic therapy (EHT)
  - APC

- Gastric Antral Vascular Ectasia (GAVE)

- Clinical
  - Presentation
    - Acute hemorrhage
    - Occult GI bleed
    - Iron deficiency anemia

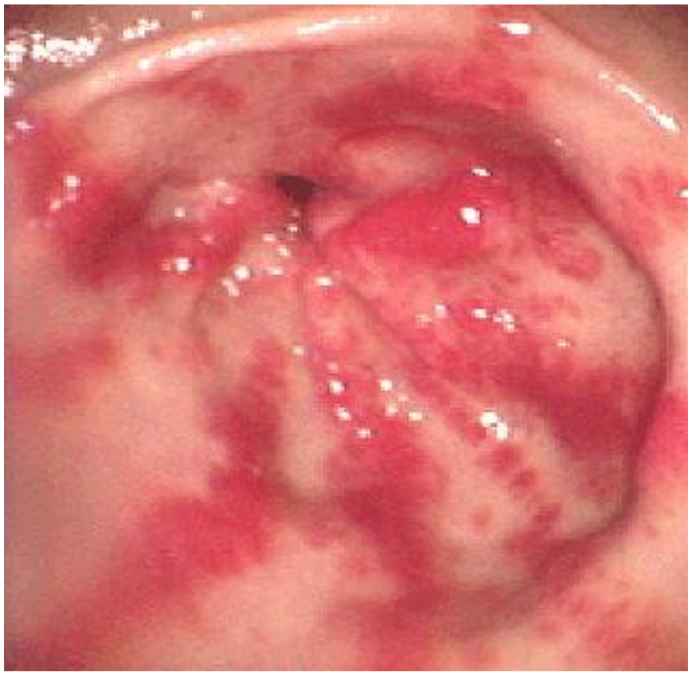
- Risk factors:
  - Cirrhosis / portal hypertension (PHT)
    - 40% of GAVE patients have underlying PHT - chronic kidney disease
  - Atrophic gastritis
  - Cardiac disease
  - Connective tissue disease
  - Post-bone marrow transplantation
- Endoscopy

Nodular GAVE



Source; Kudaravalli P, et al. Case Rep Med 2019; 2019: 1342368.

Classic Appearance of GAVE



Courtesy of Dr. Joanna C Walsh, Western University

- Histopathology
  - Tortuous dilated blood vessels in the gastric antrum
    - Radiate outwards from the pylorus
    - Papillary ectasia
    - Spindle cell proliferation
    - Lipohyalinosis
- Treatment
  - Pharmacologic therapy:
    - Estrogen-progestin
    - TXA
    - Thalidomide
  - Endoscopic therapy (mainstay of management)
    - APC → ↓ transfusion requirements and ↓ anemia
    - Band ligation
  - If APC not available consider
    - Band ligation
    - Endoscopic RFA
    - Cryotherapy
    - Cyanoacrylate spray

- Surgery
  - Portal HTN patients tend to be more treatment resistant
  - Resolution of GAVE post-liver transplant in those with portal HTN
- Antrectomy
  - For those who have failed pharmacologic and endoscopic treatment

- Portal Hypertensive Gastropathy (PHG)

➢ Demography

- Occurs in 20-98% of patients with portal HTN, depending on severity of portal pressures
- Affects the oxyntic mucosa in the gastric fundus and body

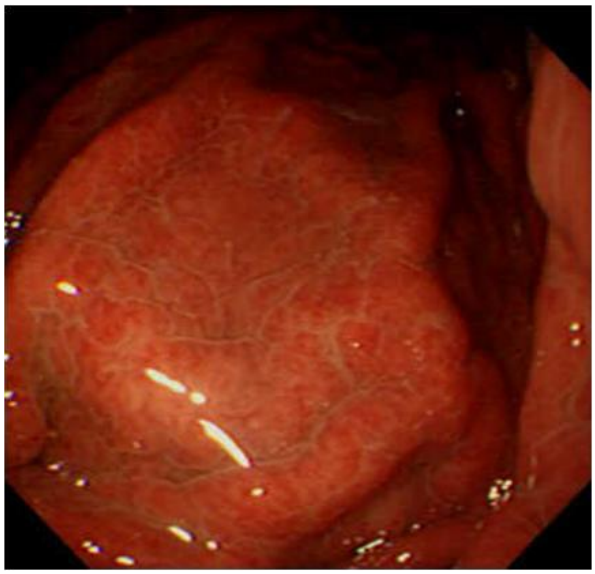
➢ Clinical

- Asymptomatic, or
- Present with
  - Chronic GI blood loss
  - Acute GI hemorrhage less common, <12%

➢ Endoscopy

- Mosiac or snake skin like appearance of gastric body / fundus
- May show spectrum of red spots
  - Small, faint red
  - Large, bright red
  - Hemorrhagic gastritis, diffuse

Portal Hypertensive Gastropathy (PHG)

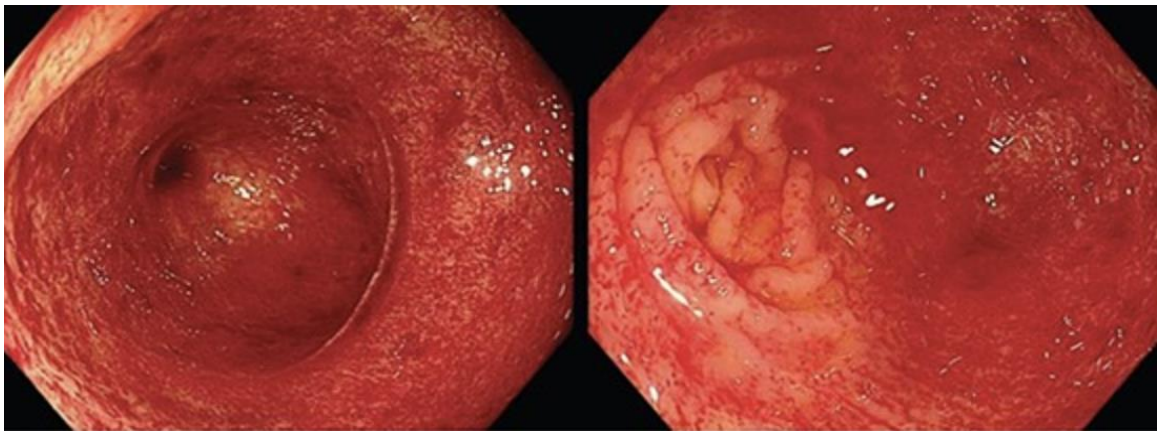


Courtesy of Dr. Joanna C Walsh, Western University

- Treatment
  - Prophylaxis
    - Non-selective beta blocker = 1st line
      - Rate of rebleeding at 12 mon (35% vs. vs. 62% placebo)
    - Refractory to NSBB
      - TIPS
  - Acute bleeding
    - Octreotide can be effective in setting of acute GIB

- Portal Hypertensive Colopathy
  - Colitis-like pattern, diffuse
  - Edema, mucosal
  - Tissue, friable
  - Varices, colorectal
  - Vascular ectasias

Portal Hypertensive Colopathy



Source: Sabat N and Schulze B. J Surg Case Rep 2023; ;2023(3): rjad114 (Figure 2)

- Portal Hypertensive Enteropathy
  - ↓ vascular pattern
  - Angioectasia
  - Edema, mucosal
  - Mosaic-like pattern
  - Polyps, inflammatory (small bowel)
  - Varices, small bowel

❖ Compression Syndromes

- Superior Mesenteric Artery (SMA) Syndrome

➢ Pathogenesis
  - Duodenal compression (D3) by SMA at the angle of the root of the SMA and the aorta (normal 45^{o} angle reduced to < 25^{o}) →gastric outlet obstruction

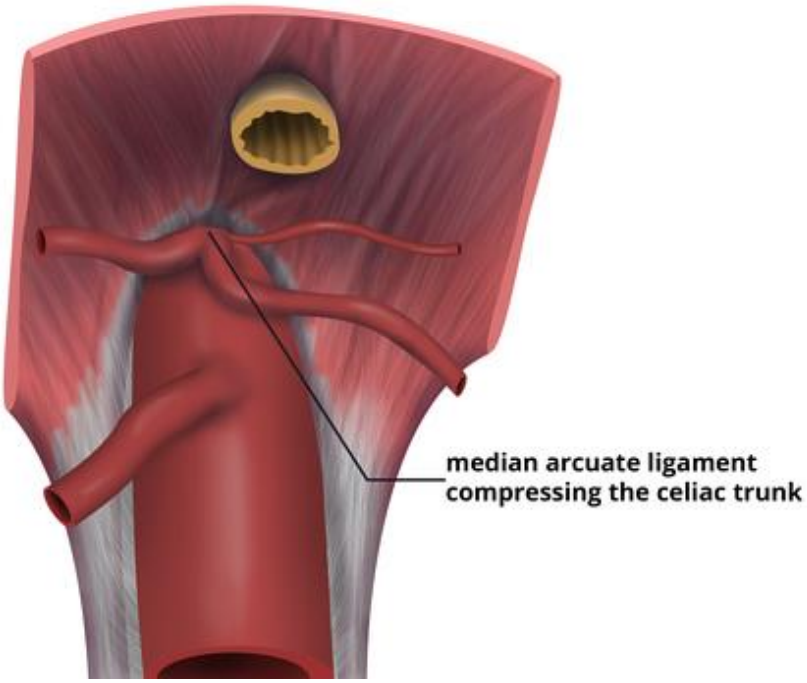
➢ Clinical
  - Nausea
  - Vomiting
  - Epigastric pain
  - Early satiety

➢ Risk factors
  - Anatomic abnormalities (high Ligament of Treitz or low SMA origin)
  - Immobilization
  - Rapid growth in children
  - Rapid weight loss

➢ Diagnosis
  - CTA or MRA
  - Barium studies
    - Cutoff at D3 with proximal dilation

➢ Treatment
  - Supportive
  - Restoration of weight loss
  - Surgery (rarely required)
    - Duodenojejunostomy

- Celiac Axis Compression Syndrome (CACS) (aka median arcuate ligament syndrome or Harjola syndrome)



Source: https://radiopaedia.org/articles/coeliac-artery-compression-syndrome

➢ Pathophysiology

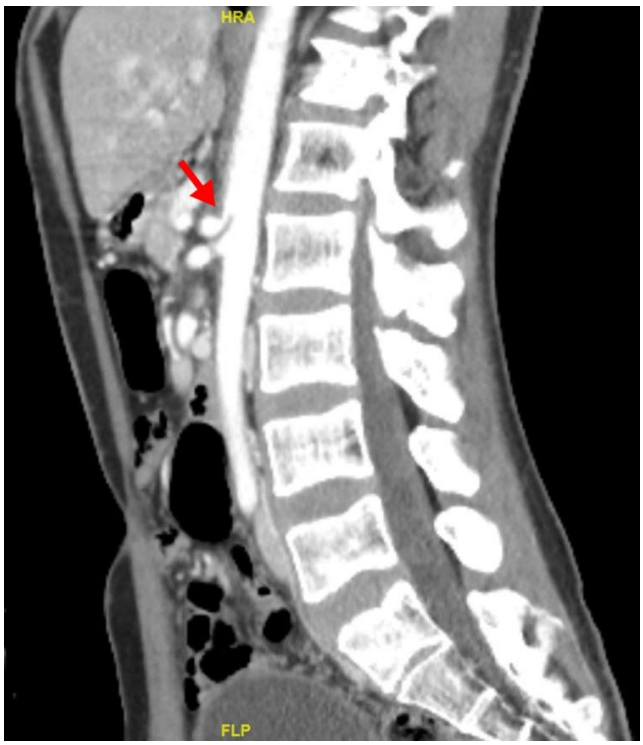
- Narrowing of celiac axis by the median arcuate ligament of the diaphragm → ischemia of the upper abdominal viscera resulting in the post-prandial pain, but
  - Any celiac compromise should be compensated by collateral flow from the SMA and IMA axis

➢ Clinical

- Post-prandial pain
- Epigastric bruit
  - ↑ intensity with
    - Deep expiration, or
    - ↑ compression
- Diarrhea
- Weight loss

- Diagnosis
  - CTA, MRA, EUS (best seen at end expiration)
  - Clinical significance of CACS is debated
  - Alternative theory
    - Pain due to ↑ pressure applied over the celiac ganglion (post-prandially when the celiac artery dilates to accommodate increased blood flow) → ↑ pain

Sagittal view with compression of celiac trunk



Computed tomography angiography of the abdomen demonstrated acute angle J-configuration of the takeoff of the celiac axis, with stenosis (red arrow) at its origin and focal post-stenotic dilatation.

Source: Ali H, et al. Cureus 2021; 13(7): e16175 (Figure 3)

- Treatment
  - Laparoscopic (or open) release of compression
    - Divide the fibres of the median arcuate ligament

COMPARISON OF PERFORMANCE OF METHODS FOR COLORECTAL CANCER: THE IMPACT OF THE ECLIPSE STUDY

Maytham Hussain

- Introduction:
  - Globally, colorectal cancer (CRC) is the third most common cancer
    - ~1.93 million new cases of CRC worldwide (2020), 935,000 deaths
    - This represents about 10% of all new cancer cases

    (Sung H, et al. CA Cancer J Clin 2021; 71(3):209-249)
  - The 5-yr survival rate for
    - Localized (early-stage) CRC ~90%, but it drops to around 14% metastatic disease, highlighting the importance of early detection
  - Survival rates for colorectal cancer are heavily dependent on the stage at diagnosis

    (Siegel RL, et al. CA Cancer J Clin. 2020; 70(3):145-164)
  - As of 2020, approximately ~70% of adults aged 50-75 were up to date with recommended colorectal cancer screening tests, including colonoscopy, FIT, and stool DNA tests
  - The participation rate for colonoscopy alone is around 60-65% among the eligible population
  - Colonoscopy remains the most used method, followed by stool-based tests like FIT.

    (Joseph DA, et al. MMWR Morb Mortal Wkly Rep 2020;69:253-259)
  - In Canada, the participation rate for colorectal cancer screening varies by province, but the national participation rate in the U.S (~55-65%)
    - Similar to the U.S., colonoscopy is widely used, but the FIT is also a common screening method
  - These participation rates indicate that screening programs are well-established in both countries, but
    - There is room for improvement, particularly in reaching those who are reluctant to undergo screening

    (Kalyta A; e al. Curr Oncol 2021, 28, 1558-1570)

- Tests for CRC screening
  - Blood
    - Cell-free DNA (cfDNA)
  - Stool
    - Fecal immune testing (FIT)
    - Fecal DNA
  - Endoscopy
    - Sigmoidoscopy
    - Colonoscopy
  - Diagnostic imaging
    - CT colography

- Fecal Immunochemical Test (FIT):
  - FIT detects hidden blood in the stool, which can be a sign of CRC
    - It is non-invasive and does not require
      - Dietary restrictions, or
      - Bowel preparation
    - FIT is effective at detecting CRC
      - Sensitivity, ~79% and
      - Specificity, ~94%

      (Lee JK, et al. Ann Intern Med 2014; 160(3): 171)
  - FIT has greater patient compliance compared to colonoscopy due to its non-invasive nature
  - Annual FIT testing is effective in reducing
    - CRC mortality by 50-60% when used as part of a regular screening program (Knudsen AB, et al. JAMA. 2016; 315(23): 2595-2609)

- Stool DNA Test (Cologuard):
  - Detects abnormal DNA and blood in the stool that may indicate the presence of CRC or advanced adenomas
    - Cologuard is a commonly used test in this category
    - Imperiale et al. (2014) reported that Cologuard has a sensitivity of 92% for detecting CRC vs 73% for FIT and 42% vs 24% with FIT for advanced precancerous lesions
      - Lower specificity (87%) vs 95% compared to FIT
  - The BLUE-C study published by Imperiale et al. (2024) for next-generation multitarget stool DNA test demonstrated that:
    - Sensitivity, 94% for CRC detection
      - Sensitivity for advanced pre-cancerous lesions (adenomas, SSA, large hyperplastic polyps at least 1 cm, high grade dysplasia and villous histology), 43%
    - Specificity for advanced neoplasia (both CRC or advanced pre-cancerous lesions), 91%
      - Still had a lower specificity compared to FIT

Source: Imperiale TF, et al. N Engl J Med 2014; 370(14):1287-97; Imperiale TF, et al. N Engl J Med 2024; 390(11):984-993.

- Cell-free DNA (cfDNA)
  - cfDNA refers to small fragments of DNA that are released into the bloodstream from normal and cancerous cells as they undergo apoptosis or necrosis
  - In cancer patients, a portion of cfDNA originates from tumour cells, referred to as circulating tumour DNA (ctDNA)
    - This ctDNA carries mutations and other genetic alterations specific to the tumour, such as CRC.

- cfDNA is collected through a simple blood draw
  - Minimally invasive procedure compared to traditional tissue biopsies
- Next-generation sequencing (NGS), or polymerase chain reaction (PCR), is used to analyze cfDNA in the blood
  - These methods detect
    - Genomic alterations
    - Aberrant methylation status, and
    - Fragmentomic patterns

- Cell-free DNA: **The Eclipse Trial** (Chung D, et al. N Engl J Med 2024; 390: 973-983)
  - The aim was to evaluate the performance of the cfDNA blood-based test (Shield, Guardant Health)
    - Observational, multicentre study at 265 U.S. sites
    - Inclusion criteria was patients aged 45-84 with an average risk of CRC undergoing a colonoscopy
    - Exclusion criteria were a history of cancer, a known diagnosis of inflammatory bowel disease, a hereditary predisposition to colorectal cancer, a history of colorectal cancer in a first-degree relative, and recent receipt of screening for colorectal cancer (colonoscopy within the preceding 9 yr, positive fecal immunohistochemical test [FIT] or fecal occult blood test within the preceding 6 mon, or completion of the multitarget stool DNA test or methylated Septin9 blood test within the preceding 3 yr)
    - A blood sample was drawn, and a colonoscopy was done within 60 days of enrollment
  - Coprimary Outcomes:
    - Sensitivity for Colorectal Cancer
      - Measured in participants aged 45-84, compared to the cfDNA test to colonoscopy
    - Specificity for Advanced Neoplasia: (colorectal cancer or advanced precancerous lesions) compared to colonoscopy
  - Secondary Outcome:
    - Sensitivity for Advanced Precancerous Lesions: detection of advanced adenomas (e.g., tubular adenomas ≥10 mm, adenomas with villous features, high-grade dysplasia, or carcinoma in situ) and sessile serrated lesions ≥10 mm
  - Enrollment Period: October 2019 to September 2022
  - Total Participants: 22,877 participants were enrolled
  - Colorectal Cancer Cases: 65 participants had colonoscopy-identified colorectal cancer
    - 48 (74%) confirmed to have stage I, II, or III disease
  - Clinical Validation Cohort:10,193 participants without colorectal cancer were
    - Randomly selected for the cohort
  - Final Analysis: 7,861 participants (~77%) met all criteria, had valid colonoscopy and cfDNA test results, and were included in the final analysis

- Mean age
  - 60 yr (range, 45 to 84 yr)
- Gender: 54% were women
- Race and ethnicity
  - 7% were Asian
  - 12% were Black or African American
  - 79% were White, and
  - 13% were Hispanic or Latino
- The demographic distribution closely mirrored the 2020 U.S. Census
- Overall sensitivity
  - 54 out of 65 participants (83%) with colonoscopy-detected colorectal cancer had a positive cfDNA test
  - Overall sensitivity of 83.1% (95% Confidence Interval [CI], 72.2 to 90.3)
- FDA acceptance: The lower boundary of the 95% CI exceeded the FDA's acceptance criterion of 65% for colorectal cancer screening tests
- Stage-specific sensitivity
  - Stage I: Sensitivity, 65% (95% CI, 41 to 83)
  - Stage II: Sensitivity,100% (95% CI, 78 to 100)
  - Stage III: Sensitivity, 100% (95% CI, 82 to 100)
  - Stage IV: Sensitivity,100% (95% CI, 72 to 100)
- Sensitivity increased with more advanced cancer stages
  - No substantial differences in sensitivity were observed based on
    - Tumour location
    - Histologic grade, or
    - Demographic characteristics
- Specificity for advanced neoplasia
  - ~90% of participants without any advanced colorectal identified on colonoscopy had a negative cfDNA test
  - 10% of these participants had a positive cfDNA test, indicating a specificity of ~90% (95% Confidence Interval [CI], 88.8 to 90.3) for advanced neoplasia
  - The lower boundary of the 95% CI exceeded the prespecified acceptance criterion of 85%
- Specificity for no neoplasia ~90% of participants who had a negative colonoscopy had a negative cfDNA test
  - 10% had a positive cfDNA test, indicating
    - A false positive rate of 10%, and a specificity for no neoplasia of 90% (95% CI, 89.0 to 90.7)
  - Age Correlation
    - Specificity for advanced neoplasia
    - Inversely correlated with age

- Sensitivity for advanced precancerous lesions
  - Among 1,116 participants with advanced precancerous lesions
  - cfDNA blood-based test was positive in 147 cases
  - Sensitivity of 13% (95% Confidence Interval [CI], 11.3 to 15.3) for detecting advanced precancerous lesions.
- Key points from ECLIPSE
  - The cfDNA blood-based test (Shield) showed an 83% sensitivity for detecting colorectal cancer in an average-risk screening population
  - The specificity for advanced neoplasia (including colorectal cancer and advanced precancerous lesions) was 90%
  - The sensitivity for detecting advanced precancerous lesions was 13%
  - The false positive rate of the cfDNA test was 10%, meaning 10% of patients without any neoplasia detected on colonoscopy had a positive cfDNA test
  - The sensitivity of the cfDNA test for colorectal cancer compares with other non-invasive tests like FIT (67%) and methylated Septin9 (68%), but is lower than multitarget stool DNA tests (94%)
  - Sensitivity for advanced precancerous lesions was lower than other tests, such as FIT (23%) and multitarget stool DNA tests (43%)

- Flexible Sigmoidoscopy:
  - Less invasive than a full colonoscopy
    - Does not require full bowel preparation and at times no sedation, but
    - Examines only the distal part of the colon is visualized
  - The UK Flexible Sigmoidoscopy Screening Trial (Atkin W, et al., 2017) showed that a single sigmoidoscopy reduced CRC incidence by 26% and mortality by 30% over 17 yrs of follow-up
  - Flexible sigmoidoscopy is less comprehensive than colonoscopy, as it does not examine the entire colon

Atkin W, et al. Lancet. 2017; 389(10076):1299-1311.

- Colonoscopy:
  - Colonoscopy is considered to be the gold standard for CRC screening
    - Colonoscopy is associated with a 68% ↓ CRC mortality by allowing for the detection, and removal of precancerous polyps (Nishihara R, et al. 2013)
    - Polypectomy during colonoscopy resulted in a 76-90% ↓ CRC incidence (The National Polyp Study, Winawer SJ, et al. 1993)
  - Individuals invited for colonoscopy screening had an 18% relative reduction in the risk of developing colorectal cancer over 10 yrs compared to those who did not receive the invitation, 0.98% vs. 1.20% incidence rates (Bretthauer M, et al. N Engl J Med. 2022; 387(17): 1547-1556.

- Despite ↓ CRC incidence, there was no statistically significant difference in CRC-specific mortality between the screened group and the control group (0.28% vs. 0.31%)
- All-cause mortality was virtually identical between the two groups, with no significant differences observed, however
  - Only 42% of those invited to undergo colonoscopy completed the screening, which is lower than the participation rates typically seen in the U.S. This lower adherence may have impacted the overall effectiveness observed in the study.
  - When focusing on those who did undergo the colonoscopy, the per-protocol analysis showed a more significant benefit
    - 31% ↓ CRC incidence, and
    - A 50% ↓ CRC-specific mortality
- This suggests that colonoscopy could be more effective than the overall trial results indicate, especially if screening adherence were higher.

Nishihara R, et al. N Engl J Med. 2013;369(12):1095-105
Winawer SJ, et al. N Engl J Med 1993; 329(27):1977-81
Bretthauer M, et al. N Engl J Med. 2022; 387(17): 1547-1556.

- CT Colonography (Virtual Colonoscopy):
  - CT colonography creates detailed images of the colon and rectum
  - Less invasive than traditional colonoscopy and does not require sedation
  - CT colonography is comparable to colonoscopy in detecting large polyps and cancers, with a sensitivity of 90% for detecting polyps larger than 10 mm
  - CT colonography is often recommended for patients who cannot undergo a traditional colonoscopy due to preference or either a prior failed or difficult procedure
  - However, if polyps are found, a traditional colonoscopy will subsequently be needed to remove them

Johnson CD, et al. N Engl J Med 2008; 359(26):2853.

	Screening Tool	Sensitivity for CRC	Specificity for CRC	Sensitivity for Advanced Pre-cancerous Lesion	Frequency of Screening	Invasiveness	Advantages	Disadvantages
○	Cell-free DNA (cfDNA) Blood Test	83%	90%	13%	q1-3 yr	-	– Non-invasive, – May improve adherence	▪ Lower sensitivity for pre-cancerous lesions ▪ Newer technology
○	Colonoscopy	95%	90%	High	q10 yr	+	– Gold standard – Can remove polyps	▪ Requires bowel prep, sedation, and recovery time
○	CT Colonoscopy (Virtual Colonoscopy)	90%	86-90%	Moderate	q5 yr	Minimally invasive	– Good sensitivity – Non-invasive	▪ Less effective for small polyps
○	Fecal Immuno-chemical Test (FIT)	67-79%	94-95%	Moderate	Annually	-	– Non-invasive, high specificity	▪ Lower sensitivity for polyps ▪ Requires annual testing
○	Stool DNA Test (e.g., Cologuard)	92%	87%	42%	q3 yr	-	– High sensitivity for CRC, non-invasive	▪ Lower specificity ▪ More false positive

- Discussion:
  - Non-invasive and easy to repeat for continuous monitoring
  - Provides a real-time snapshot of the genetic landscape of a tumour
  - Captures genetic heterogeneity and detects emerging mutations
  - Lower sensitivity for detecting early-stage cancers and precancerous lesions
  - May require sophisticated technology and bioinformatics tools for accurate analysis
  - Expensive, 500 to 1000 or more USD

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HEPATOBILIARY

MANAGEMENT OF ACUTE KIDNEY INJURY (AKI) IN PATIENTS WITH CIRRHOSIS (AGA, 2022)

Maytham Hussain

Flamm SL, et al. Clin Gastroenterol Hepatol 2022; 20: 2707-2716

- Diagnose acute kidney injury (AKI) when the serum creatinine (Cr_s) increases
  - 0.3 mg/dL (27 µmol/L) within 48 h, or
  - 50% from baseline
  - When ↓ urine output < 0.5 mL/kg/h for >6 h
- Preventive measures against the development of AKI in cirrhosis include
  - Avoidance of
    - Potentially nephrotoxic medications like nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Excessive or unmonitored diuretics or nonselective beta-blockade,
    - Large-volume paracentesis without albumin replacement, and
  - Counseling patients to avoid alcohol use
- Determine the cause of AKI
  - Hypovolemic
    - Volume responsive
    - Most common cause of AKI in patients with cirrhosis
  - Acute tubular necrosis
  - Hepatorenal syndrome with AKI (HRS-AKI)
    - A functional renal failure that persists despite volume repletion
  - HRS with acute kidney disease
    - A type of functional renal failure of <3 mon– duration in which criteria for HRS-AKI are not met; or
  - Postrenal
    - Rarely
- The specific type of AKI should be identified through a careful history, physical examination, blood biochemistry, urine microscopic examination, urine chemistry (NaD and urea) and selected urinary biomarkers, and renal ultrasound.
- Search for infection
  - A diagnostic paracentesis to evaluate for spontaneous bacterial peritonitis (SBP)
  - Blood and urine cultures
  - Chest radiographs
- There is no role for routine prophylactic antibiotics in patients with AKI
  - Broad-spectrum antibiotics should be started whenever infection is strongly suspected.
- When AKI is diagnosed
  - Stop diuretics and nonselective beta-blockers
  - NSAIDs discontinued
  - Precipitating cause of AKI treated
  - Fluid losses replaced, administering albumin 1 g/kg/d for 2 days if the Cr_s shows 2x↑ from baseline.
  - Measure urine output, vital signs, and when indicated
    - Echocardiography or
    - CVP (if there is a pre-existing central line) to monitor fluid status

- If Cr_s > 2x baseline despite these measures
  - Start treatment of HRS-AKI with albumin (1 g/kg IV) on day 1, followed by 20–40 g daily, plus
  - Vasoactive agents (terlipressin
  - If terlipressin is not available use
    - Octreotide plus midodrine; or
    - Norepinephrine (depending on institutional preferences) and
  - Continued either until 24 h following the return of Cr_s
    - To within 0.3 mg/dL of baseline for 2 consecutive days or
    - For a total of 14 days of therapy
- Give terlipressin as a bolus dose of 1 mg every 4–6 h (total 4–6 mg/d).
  - ↑ dose to a maximum of 2 mg every 4–6 h (total 8–12 mg/d)
    - If there is no ↓ Cr_s at day 3 of therapy by at least 25% compared to the baseline value, or
- Give terlipressin by continuous intravenous infusion at a ↓ starting dose of 2 mg/d, to ↓ ischemic side effects and
  - ↑ dose gradually every 24–48 h up to a maximum dose of 12 mg/d, or reversal of HRS.
- Do **not** use terlipressin in patients with a serum creatinine 5 mg/dL, or oxygen saturation of < 90%.
- Use oral midodrine at doses of 7.5 mg and titrated upward to 12.5 mg 3 tid with octreotide (start with 100 mg and titrate to 200 mg SC tid).
- Use norepinephrine as a continuous IV infusion at a starting dose of 0.5 mg/h
  - ↑ dose q4 h by 0.5 mg/h to a maximum of 3 mg/h
  - The goal of ↑ mean arterial pressure (MAP) by ±10 mm Hg and/or the urine output to >50 mL/h for at least 4 h.
- The risks of ischemic side effects of terlipressin and norepinephrine include
  - Angina pectoris and
  - Ischemia of fingers, skin, and intestine
  - ↓ side effects starting at the lowest dose and gradually titrating upward
- Closely monitored fluid status should be because of the risk of pulmonary edema with excessive use of albumin
- Indications for renal replacement therapy (RRT) may be used
  - AKI secondary to acute tubular necrosis
  - HRS-AKI in potential candidates for liver transplantation (that is, RRT should not be used in patients with HRS-AKI who are not candidates for liver transplantation)
  - AKI of uncertain etiology in which the need for RRT may be considered on an individual basis
- Do **not** use transjugular intrahepatic portosystemic shunts as a specific treatment of HRS-AKI.

- Liver transplantation is the most effective treatment for HRS-AKI.
  - Pharmacotherapy for HRSAKI before proceeding with liver transplantation may be associated with better post-liver transplantation outcomes.
  - Selected patients with HRS-AKI may require simultaneous liver kidney transplantation based on updated Organ Procurement and Transplantation Network listing criteria

- Acute Kidney Injury (AKI) in Patients with Cirrhosis

➢ Demography

- Traditionally, AKI has been defined by ↑ serum creatinine (Cr_s) levels
- AKI occurs in 47% of hospitalized patients with complications of cirrhosis and ~ 30% of outpatients with cirrhosis.
- The total hospitalization costs in the US related to AKI in cirrhosis is > $4 billion.
- AKI in cirrhosis patients is associated with a 7-fold ↑ morbidity and mortality as compared to those without AKI.
- Repeated episodes of AKI → ↑ risk of progressing to chronic kidney disease (CKD).

➢ Definition

- Cr_s and urine output are the most common measures of renal function
  - They may underestimate the severity of renal impairment in cirrhosis, due to
    - ↓ hepatic production of creatine
    - ↓ muscle mass
    - Female sex
    - Hyperbilirubinemia
- AKI is defined by the Kidney Disease: Improving Global Outcomes organization clinical practice guidelines as either:
  - ↑ Cr_s by 0.3 mg/dL (26.5 mmol/L) within 48 h
  - ↑ Cr_s to 1.5x from baseline presumed to have occurred within the previous 7 days, or
  - Urine volume < 0.5 mL/kg/h for 6 h
- When a baseline serum creatinine value within the previous 7 days is not available, the most recent serum creatinine value obtained within the previous 3 mon is used as baseline.
- Lower urine output, though associated with avid Na^+ and H_2O retention in cirrhosis
  - Also indicative of AKI when it falls < 0.5 mL/kg for more than 6 h.
  - This condition is associated with higher mortality compared to patients meeting only the serum creatinine criteria of AKI
- The diagnostic criteria for AKI identify patients at risk of
  - Longer hospital stays
  - ↑ multiorgan failure
  - ↑ number/duration of hospital stays
  - ↑ 30-day mortality

- Pathophysiology
  - Splanchnic vasodilator → ↓ effective arterial blood volume
  - ↓ effective arterial blood volume
  - Activation of systemic vasoconstrictor pathways such as
    - Renin-angiotensin-aldosterone system
    - Sympathetic nervous system
    - Arginine vasopressin → aims to ↑ effective arterial blood volume → ↑ renal sodium retention -→ ↓ solute-free water excretion, and renal vasoconstriction → ↓ kidney blood flow and ↓ function
- Causes/associations
  - AKI in cirrhosis
    - ↓ hypovolemia
    - Hepatorenal syndrome (HRS)
    - Acute tubular necrosis (ATN)
  - HRS, the most severe manifestation of renal impairment, is characterized by
    - ↓↓ glomerular filtration rate (GFR) due to intense renal arteriolar vasoconstriction, plus contributions from
      - Systemic inflammation
      - Adrenal dysfunction
      - Intra-abdominal hypertension
      - Hepatorenal reflex
- Laboratory
  - Hematuria and proteinuria are typically absent in HRS
  - Urine sediment is usually normal
- Diagnostic imaging
  - Renal ultrasonography is normal
- Histopathology
  - Kidney biopsy may show tubular injury despite the absence of renal damage criteria
- Types
  - Depending on the severity and duration of kidney injury, HRS can manifest as
    - HRS-AKI, representing acute renal function impairment, or HRS-non-AKI
    - Functional kidney injury lasting > 7 d, without other causes of kidney disease

➢ Diagnostic Criteria for Hepatorenal Syndrome (HRS) type 1 and type 2 (HRS-AKI and HRS-CKD)

- HRS type 1
  - Cirrhosis plus ascites
  - No shock
  - No response to stopping diuretics plus a 2-day volume challenge albumin 26% to 25%, using 1 g/kg per day
  - No current or recent use nephrotoxic drugs (e.g., contrast-dye, NSAIDs)
  - No structured damage
    - No proteinuria > 500 mg/d
    - No hematuria > 50 RBCs per hpf
    - Normal renal ultrasound
  - Serum creatinine (Cr_s)
    - Previously
      - 2x ↑ Cr_s to > 2.5 mg/dL within 2 wk
    - Current
      - ↑ Cr_s by ≥ 0.3 mg/dL within 48 h

- HRS type 2
  - Previously
    - ↑ Cr_s slowly to > 1.5 mg/dL
    - Not meeting previous criteria
  - Current
    - HRS-AKI
      - Baseline creatinine within the last 3 mon
      - ↑ Cr_s ≥ 1.5x (50% ↑) from baseline
      - No other cause for chronic renal disease, plus eGFR (estimated GFR) < 60 mL/min per 1.73 m^2 for < 3 mon
    - HRS-CKD
      - No other cause for renal disease, plus
      - eGFR < 60 mL/min per 1.73 m^2 for > 3 mon

Abbreviations: AKD, acute kidney disease; CKD, chronic kidney disease; Cr_s, serum creatinine; eGFR, estimated glomerular filtration rate; RBC, red blood cells

- Approach to Increasing Serum Creatinine (Cr) in Patients with Cirrhosis Acute Kidney Injury (AKI)
  - AKI-1a: Cr ≤ 1.5 mg/dL
    - Stop NSAIDs, NSBB, diuretics
    - Treat precipitating
      - Infection
      - ↓ plasma volume
  - AKI-1b: Cr > 1.5 mg/dL
    - As above, plus albumin, 1 g/kg for 2 d
    - No resolution: perform using biomarkers

- HRS
  - Albumin, plus
  - Vasoconstrictor
- ATN
  - Prolonged renal repalcement
- Initial management of AKI (↑ Cr_s >0.3 mg/dL in 48 h) is geared toward reversing risk factors.
- In patients with stage 1 AKI (↑ Cr_s >0.3 mg/dL but to <2 times baseline value)
  - Vasoconstrictor agents not currently indicated but may be evolving
  - ↑ Cr_s > 1.5mg/dL (Stage 1b), or to ≥2 times baseline value (stage 2; or
    - Stage 3 is when serum creatinine has increased >3 times baseline value) and remains above these levels despite risk factor management for 2 days, then vasoconstrictor agents are indicated provided patient meets HRS criteria
- The indications for RRT are also outlined. Complete response to therapy is defined as return of the Cr_s with treatment to <0.3 mg above baseline value – partial response is defined as reduction in serum creatinine but to >0.3 mg above baseline value.

∗Risk factor management involves holding diuretics, beta-blockers, and nephrotoxic drugs and discontinuing nonsteroidal anti-inflammatory drug [NSAID] agents); treating infections and other precipitating causes; and expanding plasma volume as required.

∗∗Careful monitoring for fluid overload is required when albumin is administered in patients with AKI because of the risk of pulmonary edema

- Management
  - Stop **all** intake of alcohol
  - Monitoring Cr_s / electrolytes in patients
    - On diuretics
    - Administer albumin infusion during therapeutic paracentesis
    - Provide antibiotics during episodes of gastrointestinal bleeding
    - Antibiotic prophylaxis for spontaneous bacterial peritonitis
    - Avoiding
      - Nonselective beta-blockers
      - Nephrotoxic medications like
        - Angiotensin-converting enzyme inhibitors
        - Angiotensin II receptor blockers, and
        - Nonsteroidal anti-inflammatory drugs
  - The effectiveness of long-term albumin infusion in preventing HRS is uncertain. While one study showed that long-term albumin administration reduced the likelihood of HRS development and improved 18-mon survival, another study failed to replicate these results.
  - Maintain serum albumin levels are maintained > 4 g/dL.
    - Monitor for
      - Volume overload, and
      - Life-threatening pulmonary edema

- Initial evaluation

➢ Clinical

- History: Inquire about the use of
  - Diuretics
  - Excess alcohol use
  - Lactulose
  - Nephrotoxic drugs
  - Nonselective beta-blockers
  - Radiographic contrast agents, and
  - Symptoms
    - Diarrhea
    - Hematemesis
    - Melena
    - Vomiting
- Physical signs
  - Focus on detecting
    - Infection
    - Volume status
    - Monitor for hepatic and extrahepatic organ failure
- Determine cause of AKI
  - Acute tubular necrosis
  - HRS-AKI
  - Hypovolemic AKI
- Urinalysis
  - Helps exclude structural renal diseases.
  - Stop all diuretics
  - Adjust lactulose to ↓ diarrhea severity, and a fluid challenge using albumin
- Significant
  - Give blood loss requires red cell transfusions to maintain hemoglobin levels
    - Use careful monitoring to avoid volume overload
  - Drugs

➢ Laboratory

- Blood
  - Serum creatinine (Cr_s)
  - Electrolytes urinalysis
  - Blood/urine and blood cultures, chest radiography, and diagnostic paracentesis (to exclude spontaneous bacterial peritonitis)
- Urine
  - Urinalysis
- Diagnostic Imaging
  - Chest x-ray
  - Ultrasound

  - Urinary sodium and urea excretion
    - A fractional excretion of sodium (FENa)
      - <1%, suggests prerenal causes
      - >1%, suggests structural causes like ATN
- Fractional excretion of urea (FEUrea) may better discriminate HRS from prerenal azotemia or ATN
- Biomarkers e.g., cystatin C, NGAL
  - Help estimate GFR and differentiate structural from functional renal diseases
    - NGAL performs better in distinguishing ATN from prerenal azotemia or HRS-AKI, with a cutoff value reported to predict mortality

❖ Pharmacological Treatment of HRS-AKI

- Albumin
  - Volume-expanding, anti-inflammatory, and other non-oncotic properties.
  - An intravenous albumin challenge involving 1 g per kilogram of body weight per day for 2 consecutive days, without improvement in Cr_s in patients meeting other diagnostic criteria, confirms the diagnosis of HRS-AKI.
  - Therapy for HRS-AKI typically involves administering albumin in a dose of 20–40 g/day, plus vasoconstrictors.
  - Albumin alone is not effective for managing HRS-AKI and must be combined with vasoconstrictors.
  - Higher total doses of albumin may improve 180-day survival, but
    - Excessive albumin administration can lead to respiratory failure, necessitating careful monitoring to prevent volume overload.
    - If albumin is unavailable
      - Crystalloids can be used as an alternative (albumin is preferred due to its superior efficacy)
- Vasoconstrictors
  - Splanchnic vasoconstrictors are the primary pharmacological treatment for HRS-AKI, aims to reverse splanchnic vasodilatation responsible for development of HRS.
  - Prompt initiation of vasoconstrictor therapy is crucial, as
    - Longer/higher pretreatment serum creatinine levels are linked with treatment failure
    - Vasoconstrictor agents (each exerting its effects through different mechanisms) include
      - Midodrine
      - Norepinephrine
      - Octreotide
      - Terlipressin
  - Terlipressin, administered intravenously in
    - Bolus IV q6 h for up to 14 days
    - Continuous infusion may offer similar efficacy with fewer side effects.

- Norepinephrine has
  - Shows promise in improving renal function but
  - Requires administration in an ICU setting due to monitoring requirements
- Midodrine and octreotide combination therapy
  - Slower/less effective compared to terlipressin, but

➢ Adverse effects

- CNS
  - Blurred vision
  - Headaches
- CVS
  - Cardiac arrhythmia
  - Ischemic complications
  - Palpitations
- RS
  - Respiratory side effects GI
- GI
  - Abdominal pain
  - Emesis
  - Nausea
- MSK
  - Back pain
- Skin
  - Rash
- General
  - Fatigue
- Monitoring for adverse effects and response to treatment is essential for HRS-AKI

- Renal replacement therapy (RRT)
  - Indications
    - Patients with HRS-AKI who are
      - Unresponsive to pharmacologic therapy and serves as a bridge to liver transplantation (LT), or
      - For managing volume overload, electrolyte imbalances, or uremia
  - Continuous RRT is preferred over intermittent RRT (due to ↓ fluid shifts and ↓ hemodynamic instability)
  - ~2/3 of patients with HRS-AKI who have
    - RRT before LT experience renal function recovery post-transplantation
    - Do RRT soon after decision for LT
    - Long teat time for RRT → ↑ risk of
      - No recovery of kidneys post-LT
      - ↑ need for renal transplantation

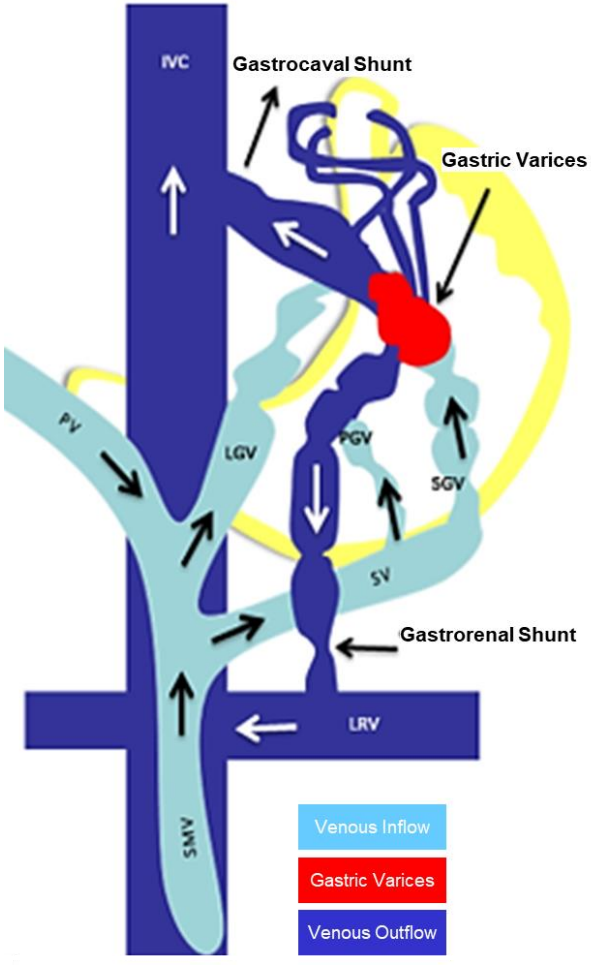
  - When LT not indicated, RRT indicated for
    - ATN
    - Idiopathic AKI
  - RRT may also be indicated for patients with other etiologies of AKI if they are LT candidates or may become candidates in the future.
  - In patients who are not LT candidates, RRT may be indicated for those with acute tubular necrosis (ATN) or in cases where the etiology of AKI is uncertain

- Transjugular intrahepatic portosystemic shunts (TIPS)
  - **Not** currently advised
  - Liver Transplantation

- Liver transplantation (LT)
  - The optimal treatment for HRS-AKI (because liver failure underlies the development of HRS-AKI, and
    - Is generally reversible with LT)
  - Many patients with HRS-AKI may have contraindications for LT, and the limited availability of donor organs may result in patients dying while awaiting transplantation
  - Patients with HRS-AKI may have worse pre-transplant prognosis compared to those with other causes of acute kidney injury, but the etiology of AKI is not factored into liver allocation prioritization in the Model for End-Stage Liver Disease (MELD) sodium-based system
  - There is concern that successful reversal of HRS-AKI with pharmacological therapy may ↓ Cr_s → ↓ MELD Na^+ prioritization for LT.
    - However, medical treatment should not be withheld due to these concerns, as effective management outweighs potential negative consequences
  - The duration of renal injury and the presence of acute tubular necrosis (ATN) impact negatively on the likelihood of renal recovery post-LT.
  - Terlipressin plus albumin ↓ requirement for LT, ↑ pre-transplantation survival, and ↓ risk of chronic renal disease after LT (in some but not all studies).
  - Renal function sometimes improves after LT
    - A significant proportion of patients remain dialysis-dependent, especially if they had chronic renal disease and required renal replacement therapy (RRT) prior to transplantation.
  - Selected patients with HRS-AKI may require simultaneous liver-kidney transplantation based on updated Organ Procurement and Transplantation Network listing criteria, which prioritize candidates with persistent renal dysfunction for combined transplantation
  - The implementation of the MELD scoring system for liver allocation led to a substantial ↑ simultaneous liver-kidney transplantation procedures, and
    - Current policy allows for high-priority registration for renal transplantation alone in patients with persistent renal dysfunction post-LT

ENDOHEPATOLOGY: INTERVENTIONAL RADIOLOGY AND ADVANCED ENDOSCOPY

Yousef Almahanna



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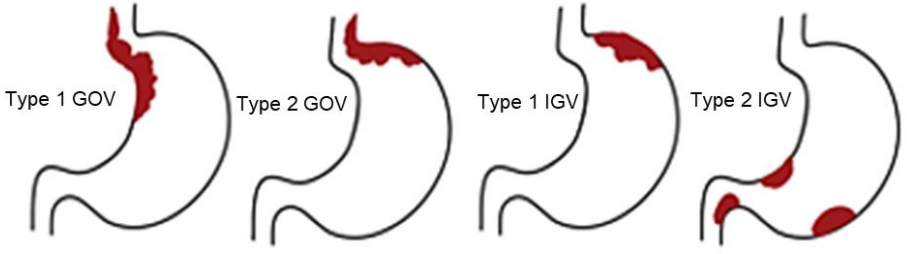
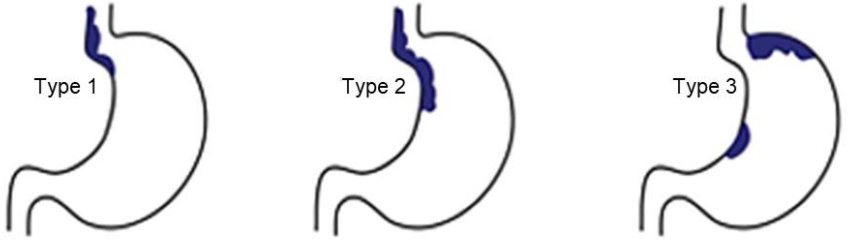
SARIN CLASSIFICATION

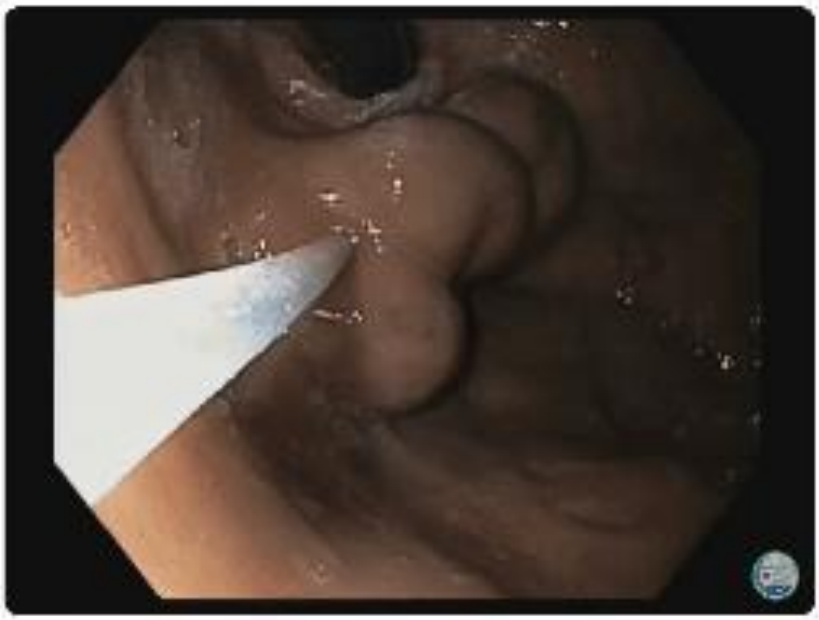


HOSKIN AND JOHNSON CLASSIFICATION



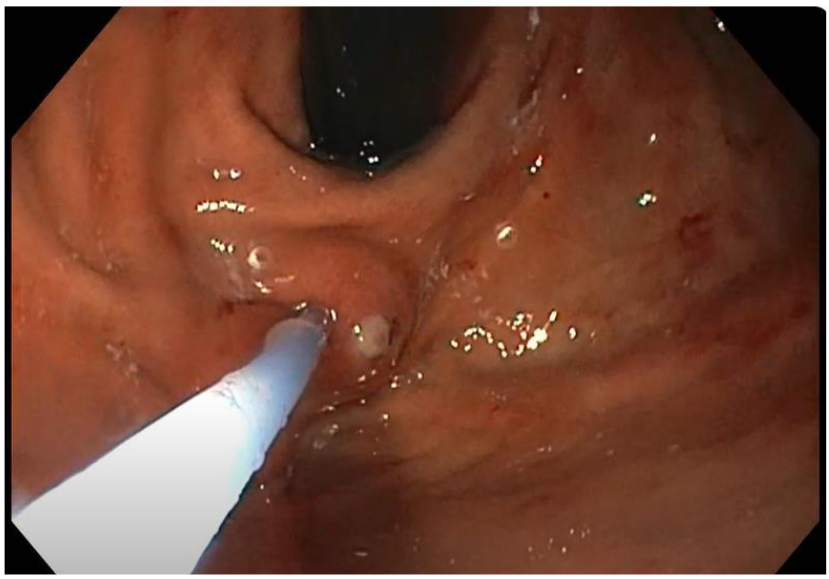
Source: Philips CA, et al. BMC Gastroenterol. 2020 Oct 30;20(1):361 (Figure 1)

Glue/Injection of Gastric Varix



Source: GLUE INJECTION OF GASTRIC VARIX Cyanoacrylate / Endocryl #BD_ENDOSCOPY - YouTube

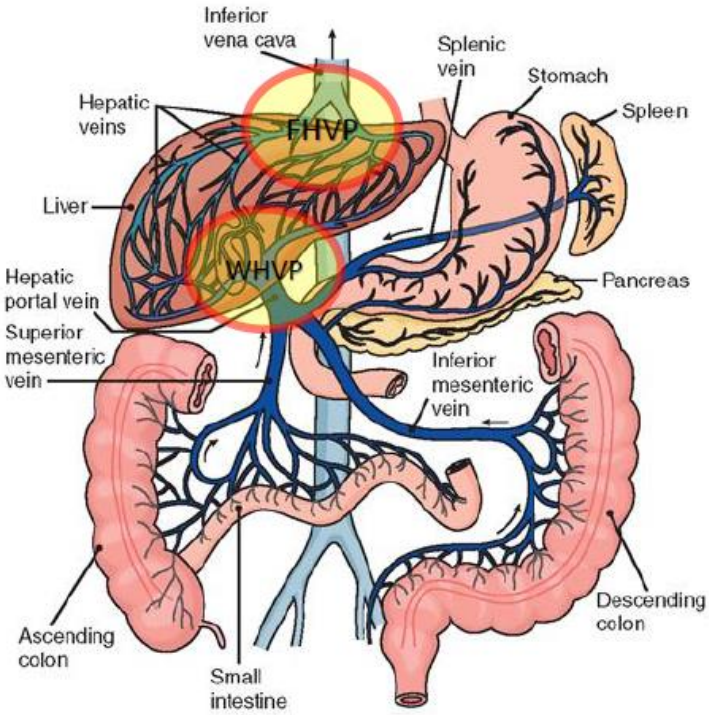
Glue/Injection of Gastric Varix



Source: EGD; Glue injection at bleeding IGV1 with white nipple sign. (youtube.com)

Portal Hypertension

- Definition
  - Increased pressure within the portal venous system.
  - It is determined by increased Hepatic venous pressure gradient (HVPG)
    - The difference in pressures between the portal venous pressure (WHVP = Wedge) and the free pressure within the inferior vena cava or the hepatic vein (FHVP = Free)
      - Note: normal WHVP ~5-10, normal FHVP ~ 1-5
  - Normally HVPG (≤ 5 mm Hg)
    - This pressure enables blood to flow through the liver into the systemic circulation.
      - Gradient of 6 mm Hg or more suggests the presence of portal hypertension in most cases.
      - When the pressure gradient is >10-12 mm Hg, portal hypertension becomes clinically significant.
  - Components for increased resistance:
    - Structural changes
      - Occur when there is distortion of the liver microcirculation
    - Dynamic changes, thought to be due to
      - ↑ production of vasoconstrictors (e.g., endothelins, angiotensin-II, norepinephrine, thromboxane A2), and
      - ↓ release of endothelial vasodilators (e.g., nitric oxide)



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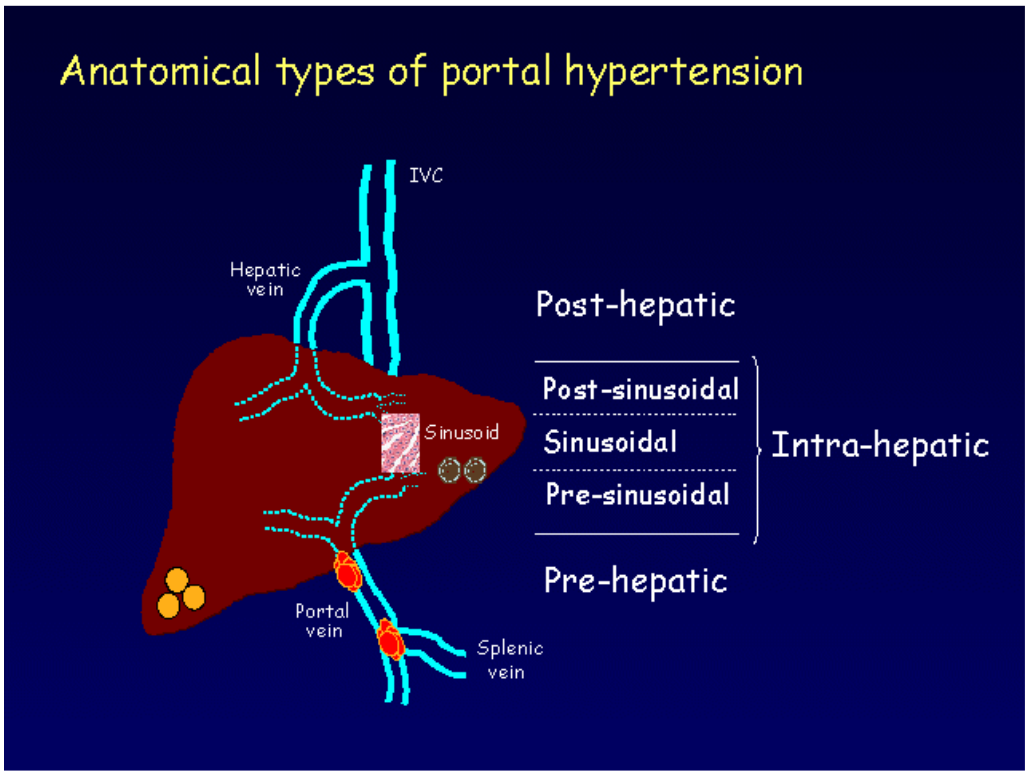
Let's think about

- Cirrhotic (most common)
  - Steatotic liver disease (ALD/MetALD/MASLD)
  - Viral: Chronic hepatitis C and B
  - Autoimmune: PBC, PSC, AI hepatitis
  - Hereditary hemochromatosis
  - Wilson disease
  - Alpha-1 antitrypsin deficiency
  - Celiac disease
  - Congestive hepatopathy
- Non-cirrhotic
  - Pre-hepatic
  - Intra-hepatic
  - Post-hepatic

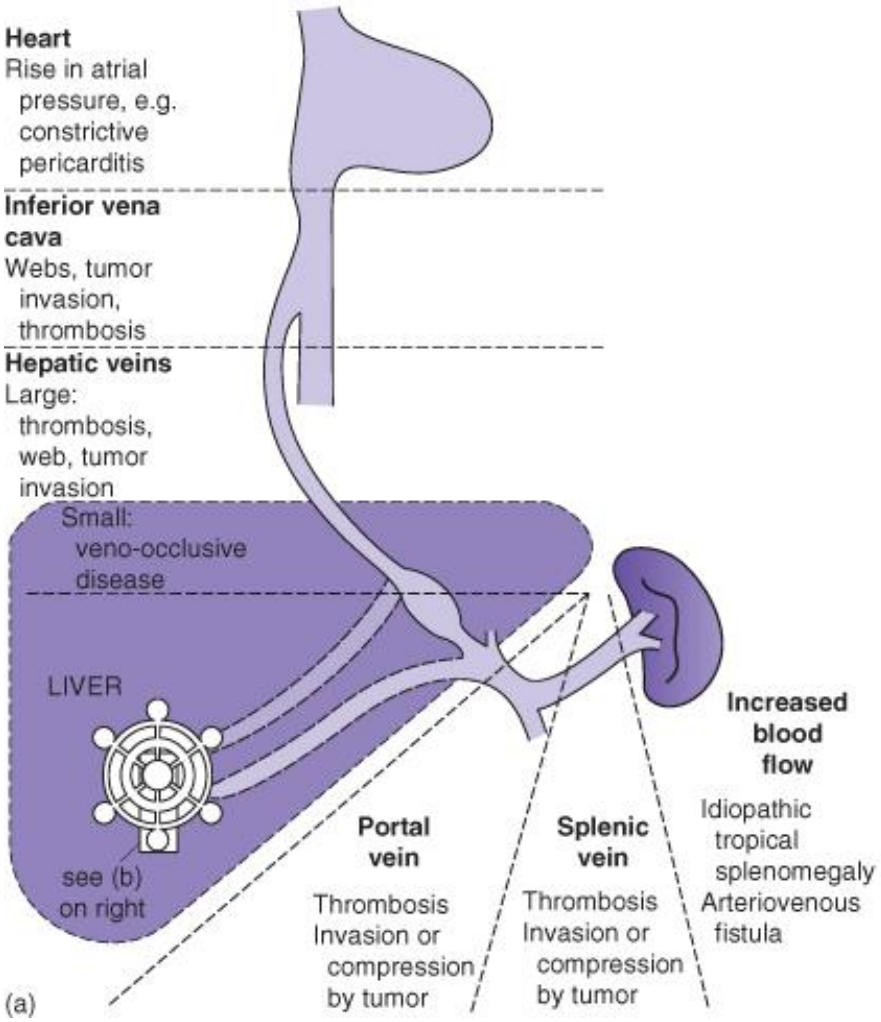


Source: https://www.ias.ac.in/public/Resources/meetings/annmeet/71am_talks/sksarin/img17.gif

- Non-Cirrhotic Portal Hypertension

A) Pre-hepatic

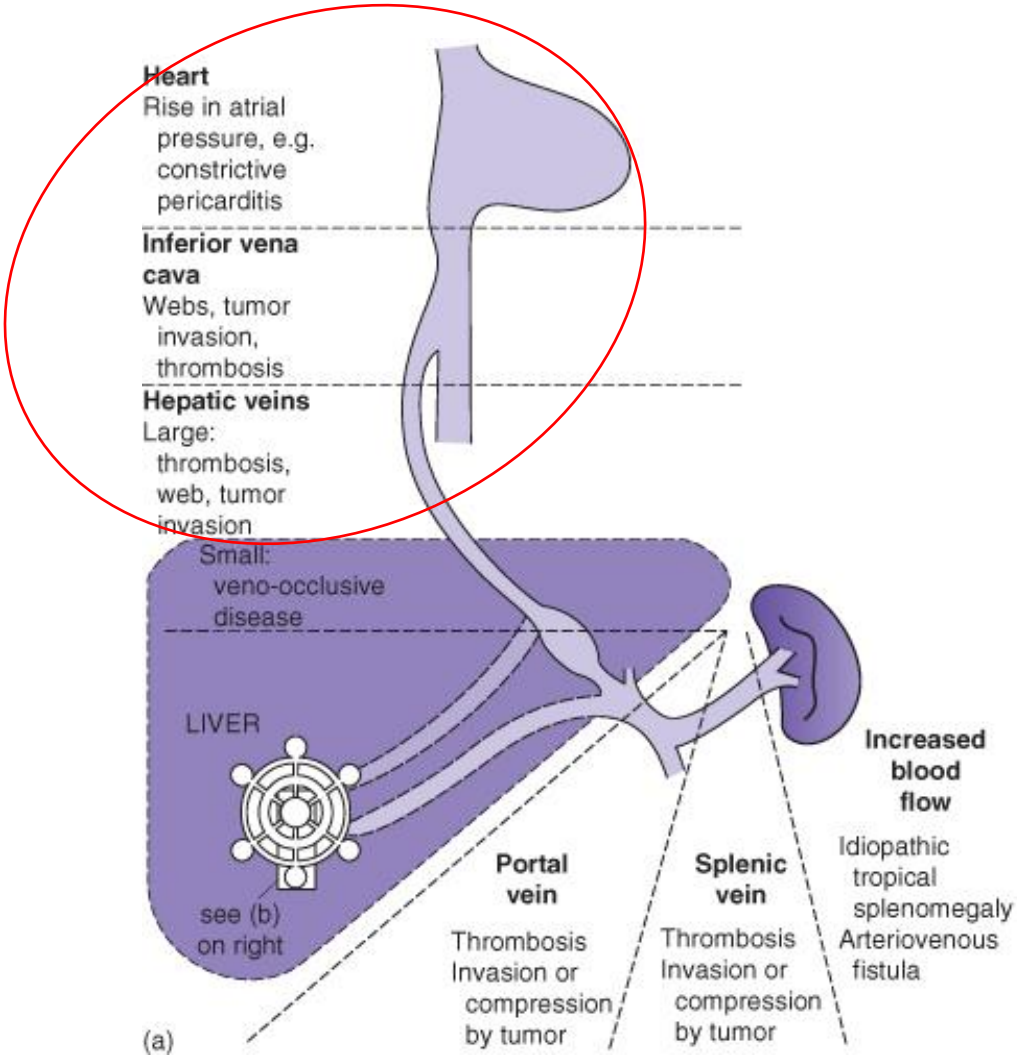
- Etiology:
  - Obstruction in portal vein or splenic vein
    - Portal vein thrombosis (clot or tumour)
    - Splenic vein thrombosis (clot or tumour)
  - Increased blood flow
    - Splenic AV Fistula (SAVF)
    - Splenomegaly & sequestration (e.g. lymphoma, Gaucher's disease)



Source: [Management of complications of portal hypertension in adults and children: variceal hemorrhage | Abdominal Key]

B) Post-hepatic

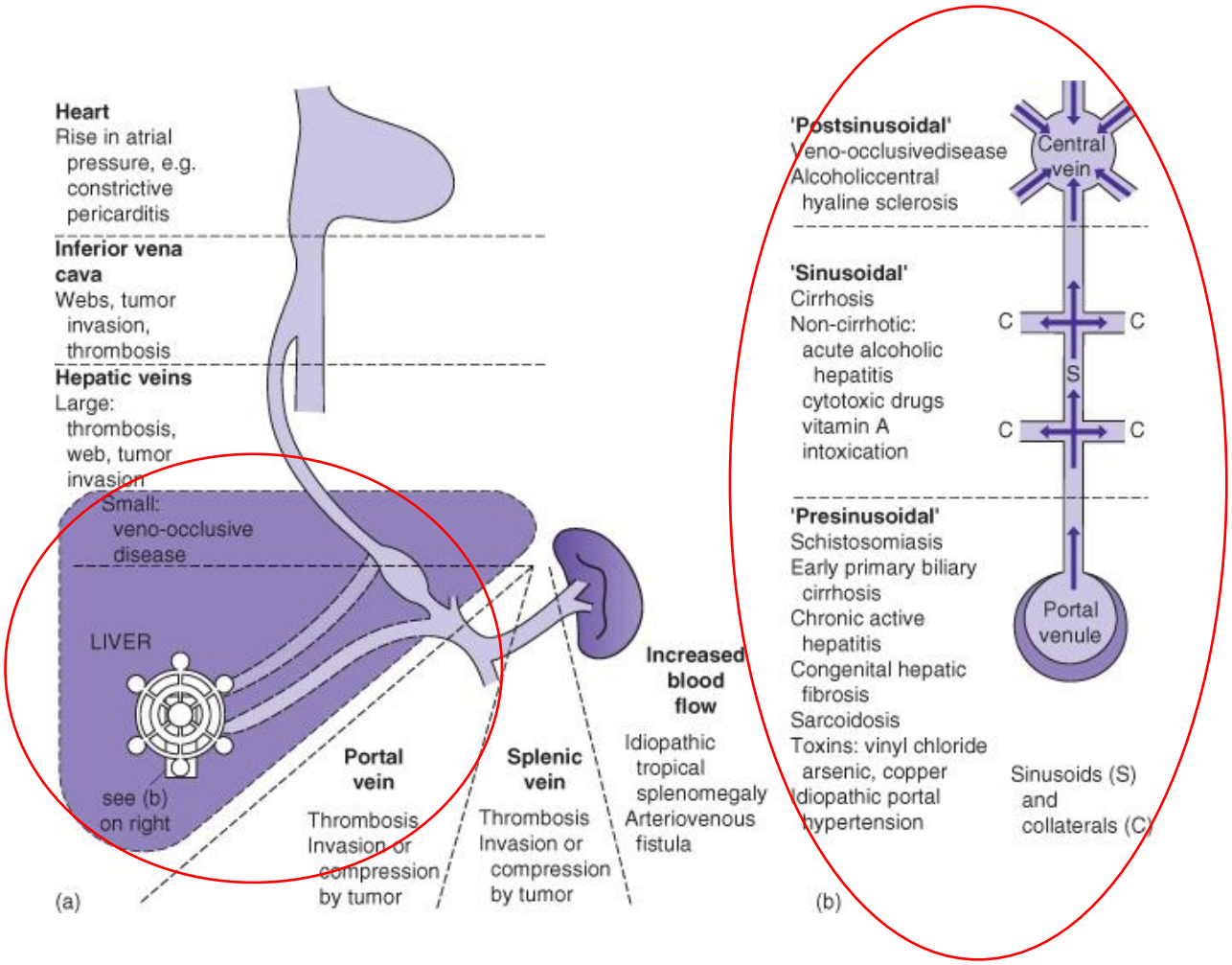
- Can be at the level of the
  - Heart
    - Constrictive pericarditis
  - Hepatic vein or inferior vena cava
    - Clot (as in Budd-Chiari syndrome)
    - Tumour thrombus



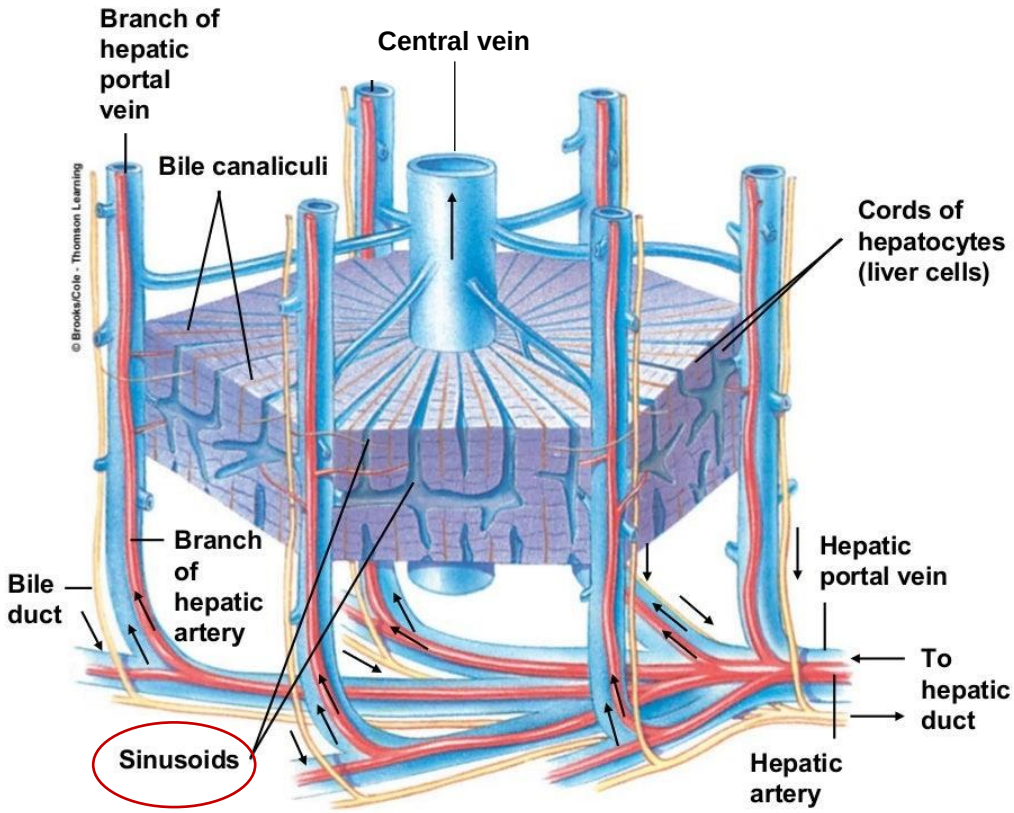
Source: [Management of complications of portal hypertension in adults and children: variceal hemorrhage | Abdominal Key]

C) Intra-hepatic

- Pre-sinusoidal
- Sinusoidal
- Post-sinusoidal

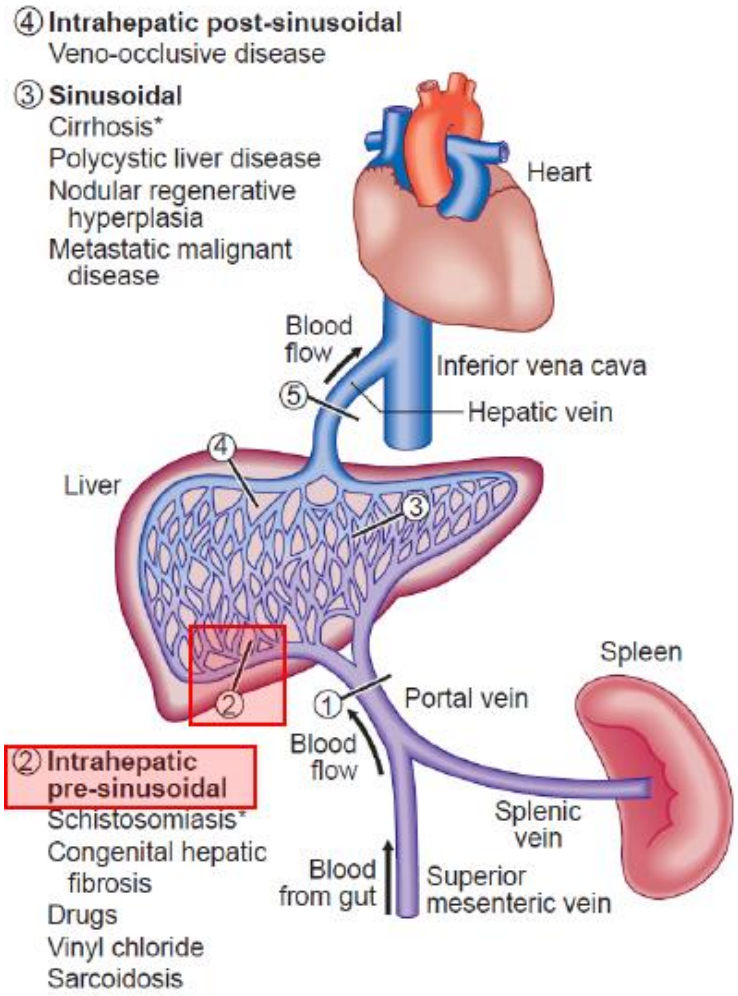


Source: [Management of complications of portal hypertension in adults and children: variceal hemorrhage | Abdominal Key]



Source: https://o.quizlet.com/MZ9qSgAu1LgnMzFucbc1eA.png

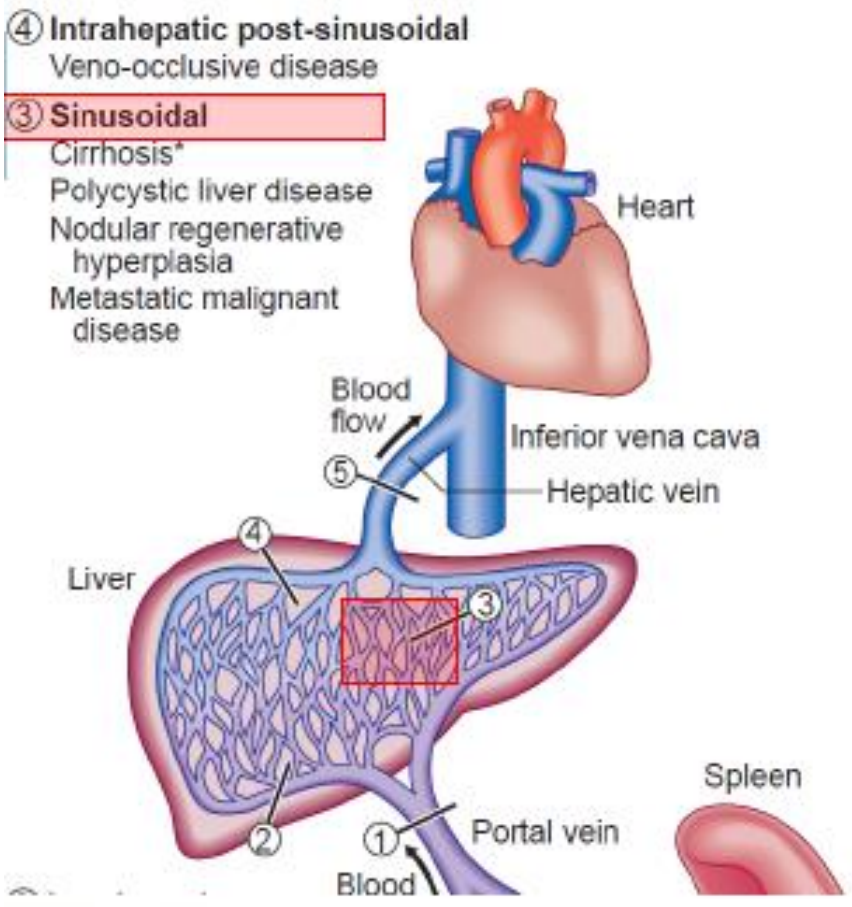
- **Pre-Sinusoidal**
  1. Developmental/congenital abnormalities
     - E.g., adult PCKD, congenital hepatic fibrosis, AV fistulas
  2. Biliary diseases
     - E.g., biliary cholangitis (PSC/PBC), AI cholangiopathy, toxic vinyl injury
  3. Neoplastic occlusion of intra-hepatic PV
     - E.g., lymphoma, epithelial malignancies (Cholangiocarcinoma, HCC), CLL
  4. Granulomatous disease
     - E.g., sarcoidosis, schistosomiasis
  5. Idiopathic non-cirrhotic PH (including focal nodular regenerative hyperplasia)



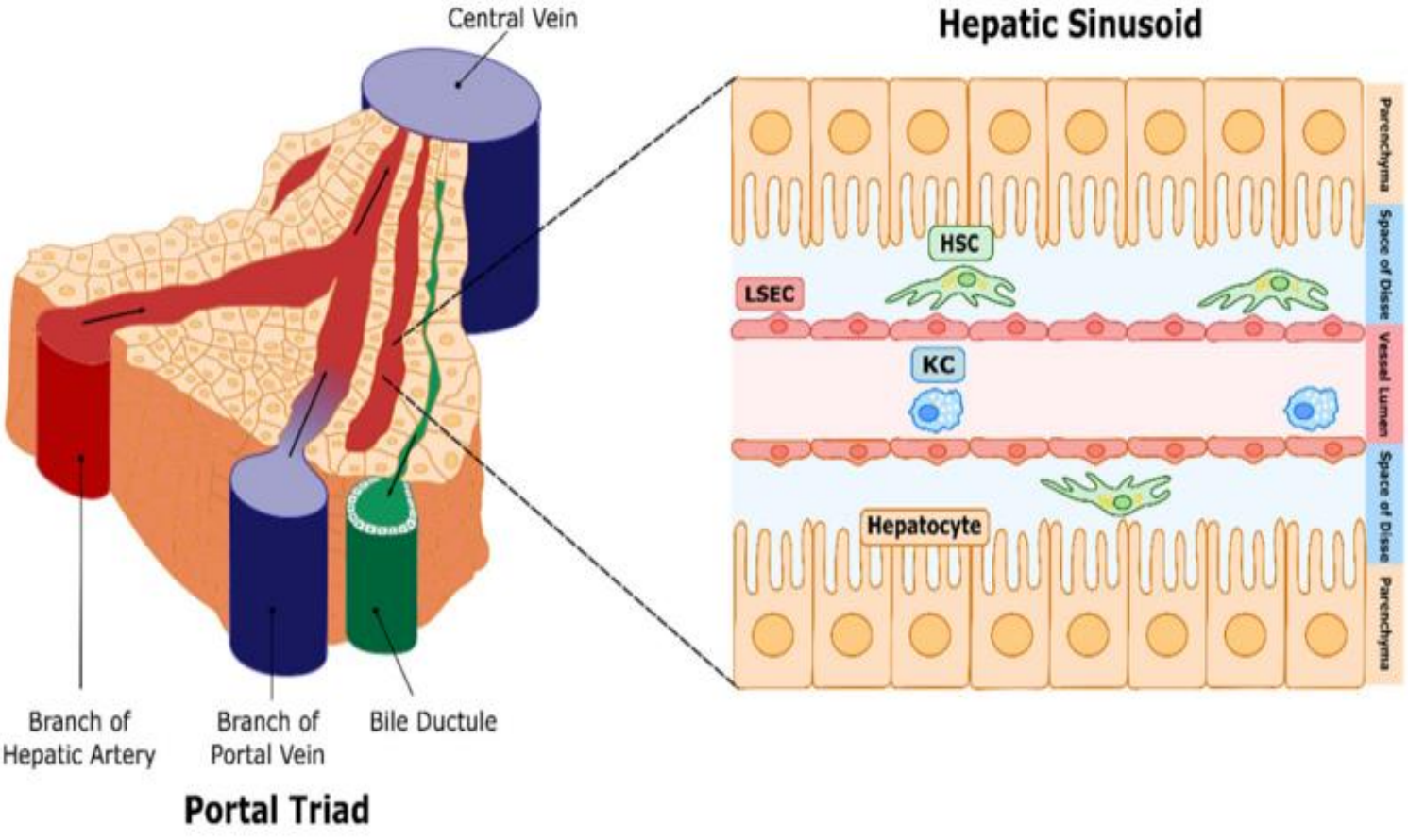
Source: https://www.grepmed.com/images/10522/diagnosis-causes-portalhypertension-differential-hepatology24

- Sinusoidal
  - Amyloidosis or light chain deposition in space of Disse
  - Fibrosis of Disse space
    - Metabolic/MASLD
    - Infectious: viral hepatitis, prior CMV, long term schistosomiasis, chronic Q fever
    - Drug induced (i.e., MXT, amiodarone, copper)

- Sinusoidal destruction
  - Secondary to acute hepatic injury
- Infiltrative diseases
  - Mastocytosis
  - Gaucher disease (deficiency of an enzyme called glucocerebrosidase)
- Compression of sinusoids by markedly hypertrophied hepatocytes from Microvascular steatosis
  - Acute fatty liver of pregnancy, Raye's syndrome, Drugs (salicylate, Valproate, Tetracyclines), inherited disorders of fatty acid metabolism, mitochondrial disease

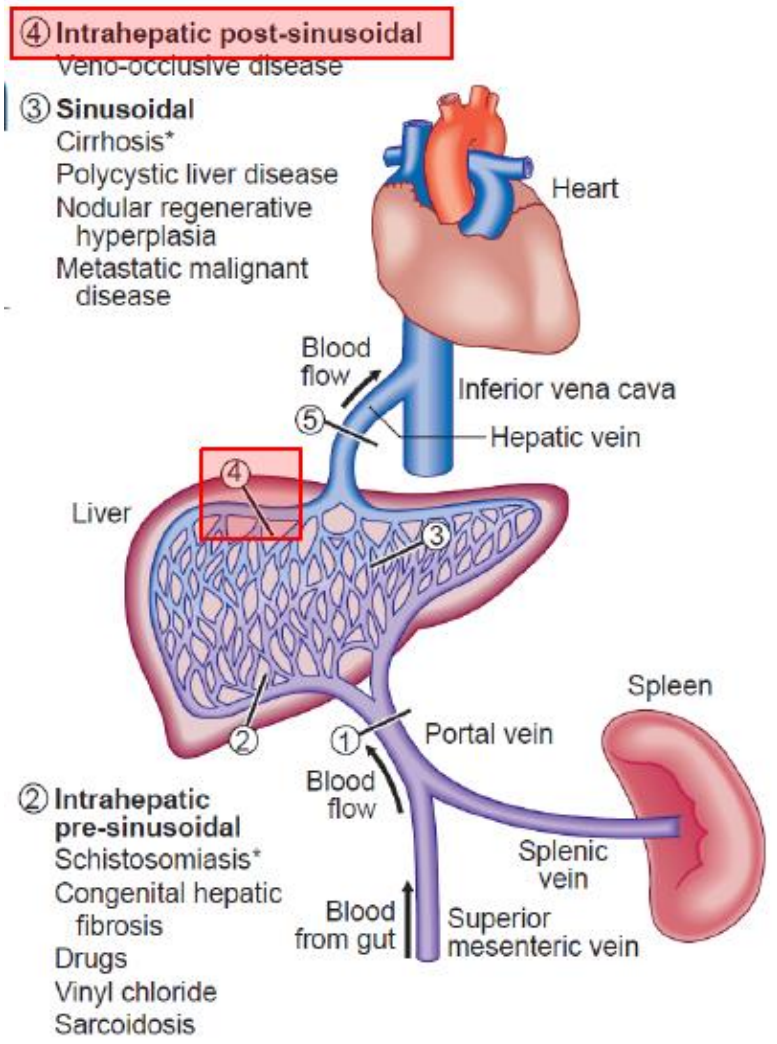


Source: https://www.grepmed.com/images/10522/diagnosis-causes-portalhypertension-differential-hepatology



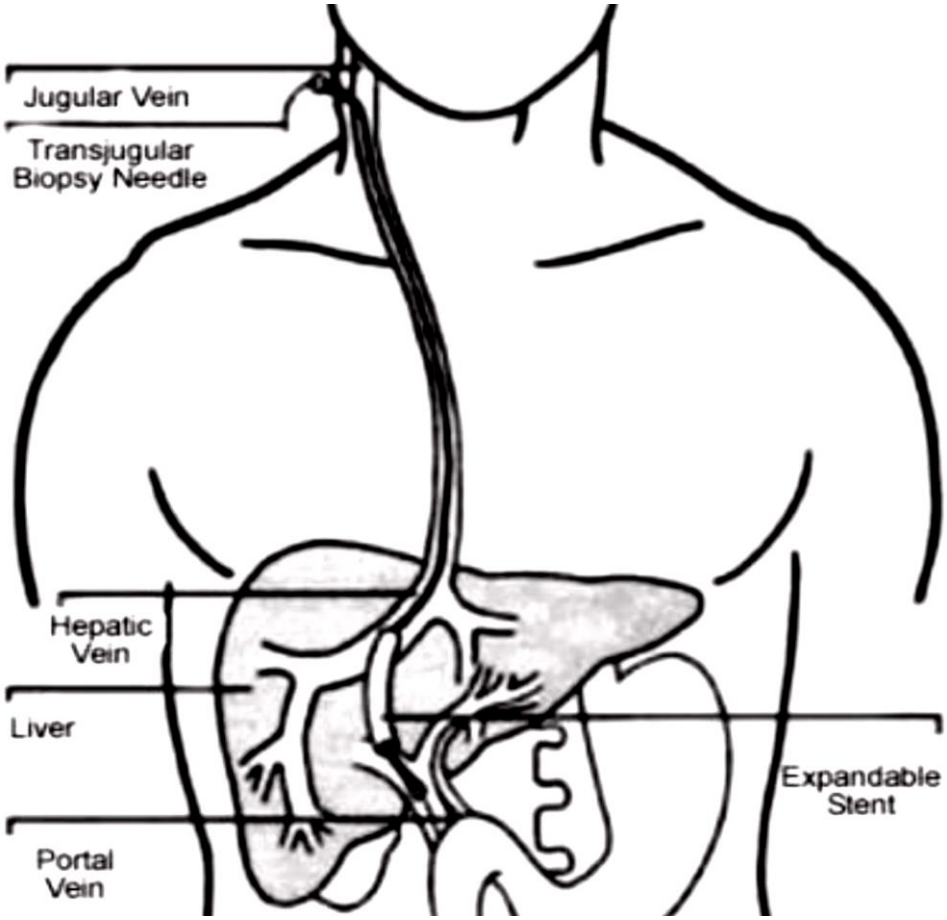
Source: Gibert-Ramos A, et al. Cancers 2021; 13(22):5719 (Figure 1)

- Post-Sinusoidal
    1. Sinusoidal obstruction syndrome (SOS)
    2. Phlebo-sclerosis of hepatic veins (E.g., EtOH related liver disease, Chronic radiation therapy, Hyper-Vitaminosis A)
    3. Primary vascular malignancies (e.g., angiosarcoma)
    4. Grandulomatous phlebitis (e.g., sarcoidosis, M. Avium)
    5. Lipogranulomas (e.g., mineral oil granuloma)

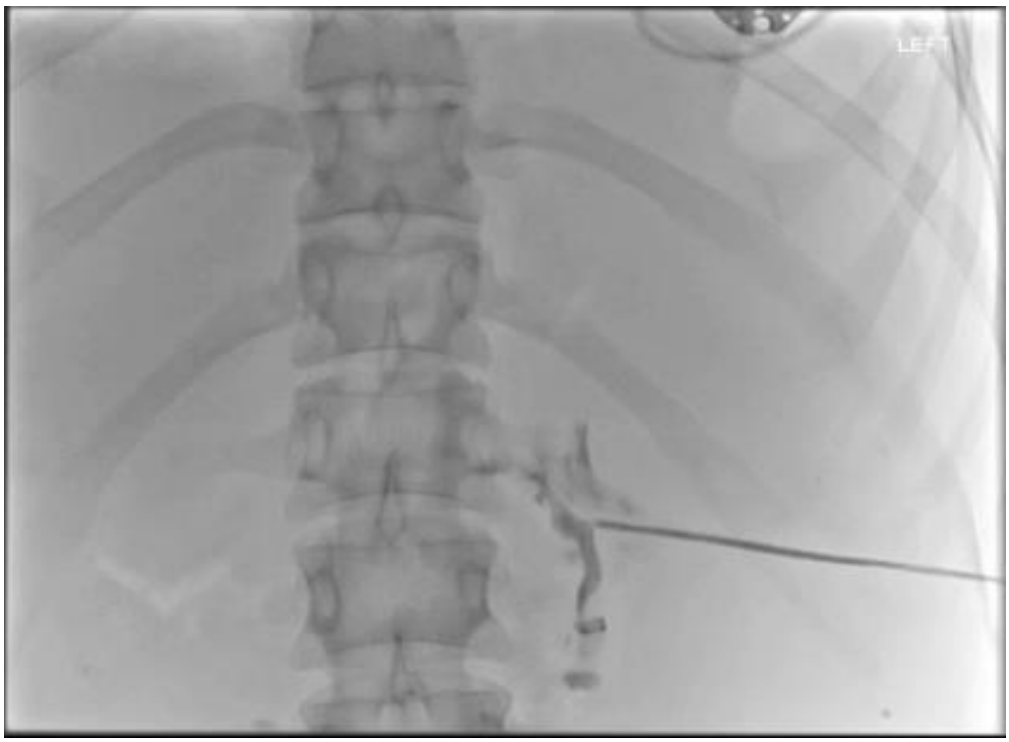


Source: https://www.grepmed.com/images/10522/diagnosis-causes-portalhypertension-differential-hepatology2626

- Triphasic CT Scan – Guided Liver Biopsy using Transjugular Approach
  - Repeat CT (triphasic)-Impression
    - No cirrhosis noted
    - Marked splenomegaly (20 cm) with new splenic infarct compared to the CT from 10 d ago.
    - The right hepatic vein is not visualized and is likely chronically thrombosed.
    - Non-visualization of the left and right portal veins, splenic vein and no normal appearing SMV.
      - Instead, there is a tangle of collaterals along the porta hepatis and in the SMV bed. There are large extensive gastric varices.



Budd-Chiari Syndrome



LHSC, 2024

- Budd-Chiari Syndrome

➢ Definition

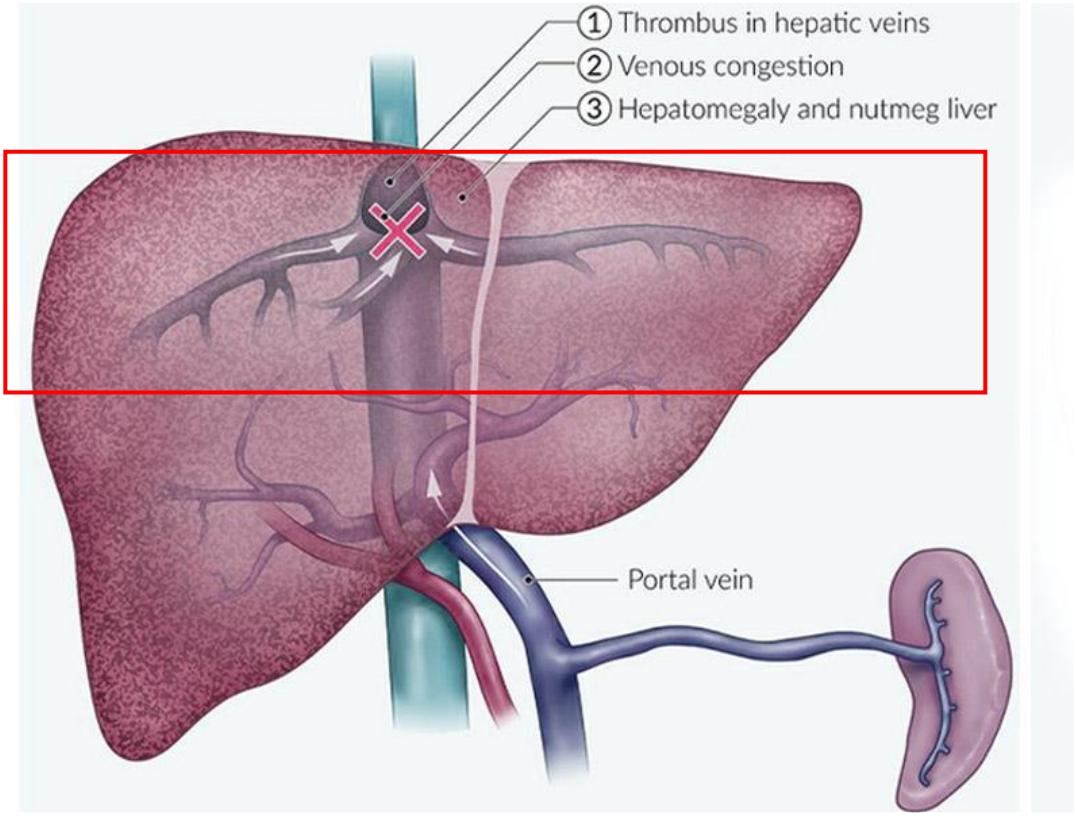
  - Hepatic venous outflow tract obstruction
    - Secondary to obstruction of the hepatic veins or terminal IVC

➢ Origin of name

  - George (Budd), a British internist, described three cases of hepatic vein thrombosis due to abscess-induced phlebitis in 1845
  - Hans (Chiari), an Austrian pathologist, added the first pathologic description of a liver with “obliterating endophlebitis of the hepatic veins” in 1899.

➢ Demography

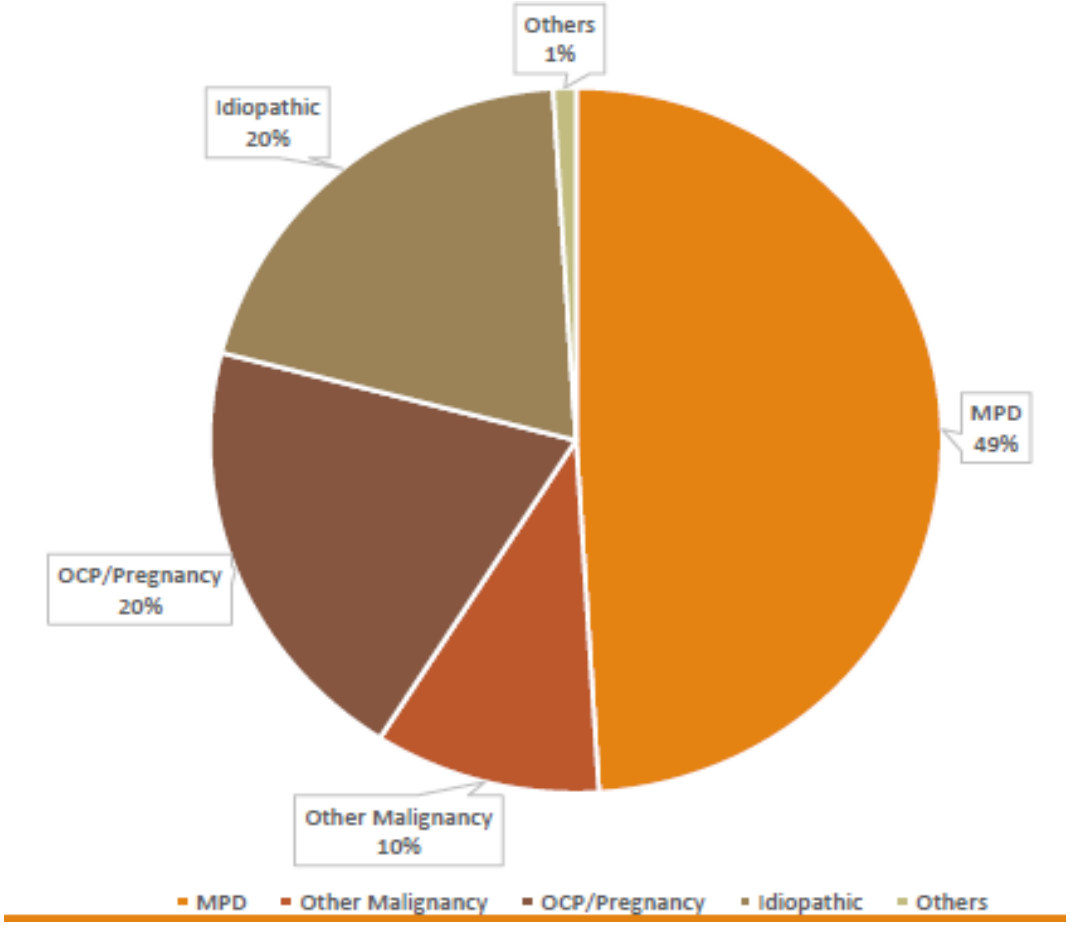
  - Rare disease. BCS occurs in 1/100,000of the general population worldwide.
  - Slight female predominance in the western world, but more in males in Asia.
  - Median age at diagnosis 38.



Source: https://arihantgastroenterologycentre.com/budd-chiari-syndrome-treatments-in-borivali-west-mumbai/

- Presentation:
  - Acutely (weeks)
    - Abdominal pain, intractable ascites and hepatomegaly.
    - Decreased hepatic flow cause ischemic coagulative necrosis and injury leading to liver dysfunction +/- liver failure.
  - Subacute (<3 mon)
    - Mild ascites& later lower limbs edema due to development of collaterals, vague abdominal discomfort(epigastric/RUQ).
  - Chronic
    - More chronic symptoms related to long-standing portal hypertension leading to cirrhosis.
  - Concurrent PVT is common:
    - Outflow tract obstruction> reduces the low-pressure portal venous inflow> leading to stasis (plus underlying hypercoagulable state)

- Etiology
  - Primary
    - Due to venous process.
  - Secondary
    - Due to compression or invasion of hepatic vein/IVC that originates outside veins.



- Most common cause
  - Almost ½ of the cases are secondary to myeloproliferative disorders

➢ Investigations

- For diagnosis:
  - US with Doppler:
    - Poor visualization for junction between HVs and IVC
    - Irregular and stenotic or dilated HVs
    - Spider web appearance in vicinity of hepatic vein ostia
    - Abnormal blood flow
    - Collaterals connected to hepatic veins
  - CT/MR used to confirm Dx and guide management/interventions:
    - Similar findings US + delayed/absent filling of the three major HVs, rapid clearance of contrast from caudate lobe
  - Liver biopsy
    - Not usually indicated unless
      - Unsure about diagnosis
      - Done when planning for TIPS (but risk of bleeding in the context of likely requiring anticoagulation afterwards)

- For underlying etiology
  - Hematological/myeloproliferative disorders investigations
    - Most commonly: MF, PV, ET, APLA
      - Check: JAK2 V617F mutation, Calreticulin gene mutations
      - Bone marrow biopsy
      - Anti-clotting factors: antithrombin, protein C, and protein S levels is warranted only if the prothrombin level is normal.
  - Systemic diseases/malignancies
    - IBD, CTD, Vasculitis, Sarcoidosis
    - HCC, RCC
  - Liver infections
    - Liver abscess, hydatid cyst
  - Hormonal factors:
    - Pregnancy or OCP use
  - PNH, Factor V Leiden deficiency
    - Flow cytometry

- Prothrombotic Factors for BCS
  - Acquired thrombophilia
    - Antiphospholipid syndrome
    - Behcet disease
    - Essential thrombocytosis
    - Hyperhomocysteinemia
    - Idiopathic myelofibrosis
    - JAK2 V617F mutation
    - Myeloproliferative disease
    - Paroxysmal nocturnal hemoglobinuria
    - Polycythemia vera
  - Inherited thrombophilia
    - Antithrombin deficiency
    - Factor V Leiden
    - MTHFR C677T mutation
    - PC deficiency
    - Protein S deficiency
    - Prothrombin gene G20210A
    - Thalassemia
  - Systemic factors
    - Behcet disease
    - Connective tissue disease
    - Inflammatory bowel disease
    - Sarcoidosis
    - Vasculitis
  - Hormonal factors
    - Pregnancy
    - Recent oral contraceptive use

➢ Management

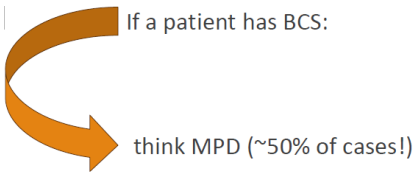
- All patients should receive anticoagulation
- Directed therapy to underlying cause.
- Other BCS directed treatments
  - Patients with PH should receive management similar to cirrhosis patients.
  - Consideration for angioplasty
  - If not controlled/refractory
    - TIPS> surgical portocaval shunt > LT

➢ Presentation and Diagnosis (ACG-ALF Guidelines [July 2023])

- Acute-to-subacute presentation
- Most common affects women in their fourth to fifth decades of life

- Often associated with hypercoagulable states
- Obstruction of hepatic venous outflow tract causes severe intrahepatic ischemia and massive hepatic necrosis
- Laboratory-predominantly hepatocellular liver injury pattern with marked transaminase elevation in the 1000s, and AST:ALT ratio often exceeds 1.
- Patient present with abdominal pain and ascites
- Etiology-specific management
  - In patients with BCS leading to ALF, TIPS in the preferred intervention in those who fail anticoagulation
  - In patients with BCS-induced ALF, we recommend heparin as initial therapy in the absence of contraindications to anti-coagulations
  - In patient with BCS-induced ALF, who do **not** respond to medical and therapeutic interventions, we recommend liver transplantation

- **Take Home Message**



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INDETERMINATE BILIARY STRICTURES (IDBS): DIAGNOSIS AND MANAGEMENT: ACG AND ASGE CLINICAL GUIDELINES (2023)

Saif Alnuaimi

Elmunzer BJ, et al. Am J Gastroenterol 2023;118(3):405-426.
Fujii-Lau LL, Gastrointest Endosc 2023; 98(5):694-712.

- Definition
  - A biliary stricture is an abnormal narrowing of the bile ducts, which form the drainage system for bile produced by the liver.
    - This narrowing can lead to clinically significant obstruction of bile flow, resulting in various symptoms and complications.

- Primary goals
  - Accurately diagnose the cause of the stricture (particularly to determine whether malignancy is present)
  - Restore the normal flow of bile into the intestinal lumen.
  - Achieving these goals differs depends on whether the stricture is
    - Extrahepatic (occurring in the bile ducts outside the liver)
    - Perihilar (located at the junction where bile ducts exit the liver)
  - Extrahepatic strictures
    - Endoscopic ultrasound (EUS)-guided tissue sampling is the standard diagnostic tool (high accuracy in obtaining biopsies)
    - The treatment of extrahepatic strictures is usually more straightforward, with procedures such as
      - Endoscopic drainage being relatively safe and effective.
    - This method is well-established and widely used
  - Perihilar strictures (located closer to the liver)
    - More challenging due to
      - The complexity of the anatomy, and
      - Difficulty in accessing the area
    - However, the treatment of perihilar strictures (especially malignant strictures) is
      - More complex
      - May involve advanced techniques and careful decision-making, and
      - More frequent complications
  - Recent research has provided
    - Clearer guidance on several aspects of diagnosing and treating biliary strictures, especially in terms of
    - Which methods and techniques are most effective for specific locations and types of strictures.
    - However, certain areas (particularly the management of perihilar strictures) remain controversial and require further investigation.

- Diagnostic Dilemma
  - Indeterminate Biliary Strictures (IDBS)
    - Biliary strictures of undetermined etiology from imaging and history, or
    - Non-diagnostic prior ERCP

- Diagnosing malignancy
  - Often requires multiple procedures
  - This results in
    - Delays in treatment → worse prognosis
    - ↑ patient anxiety, costs, potential for adverse events

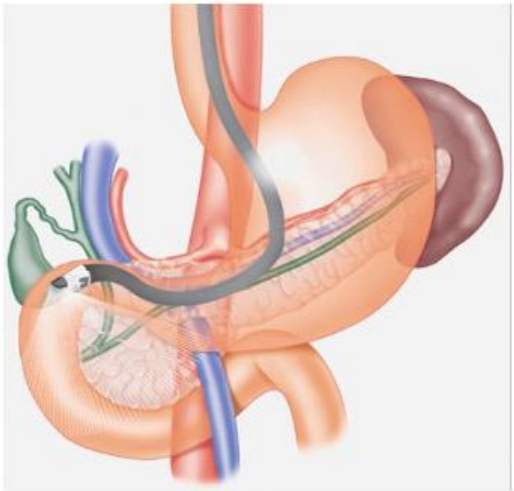
➢ Classification of Biliary lesions and strictures

- Malignant
  - Cholangiocarcinoma
  - Gallbladder cancer
  - Hepatocellular cancer
  - Metastatic disease
    - Breast
    - Colon

    *most common, often hilar (aka Klatskin tumour)
  - Pancreatic cancer
- Benign
  - Autoimmune cholangiopathy
  - Choledocholithiasis
  - Fibrotic stricture due to chronic pancreatitis
  - Post-operative stricture (including liver transplant)
  - Primary Sclerosing Cholangitis (PSC)

➢ Diagnosis: Endoscopic Evaluation and Sampling of IDBS

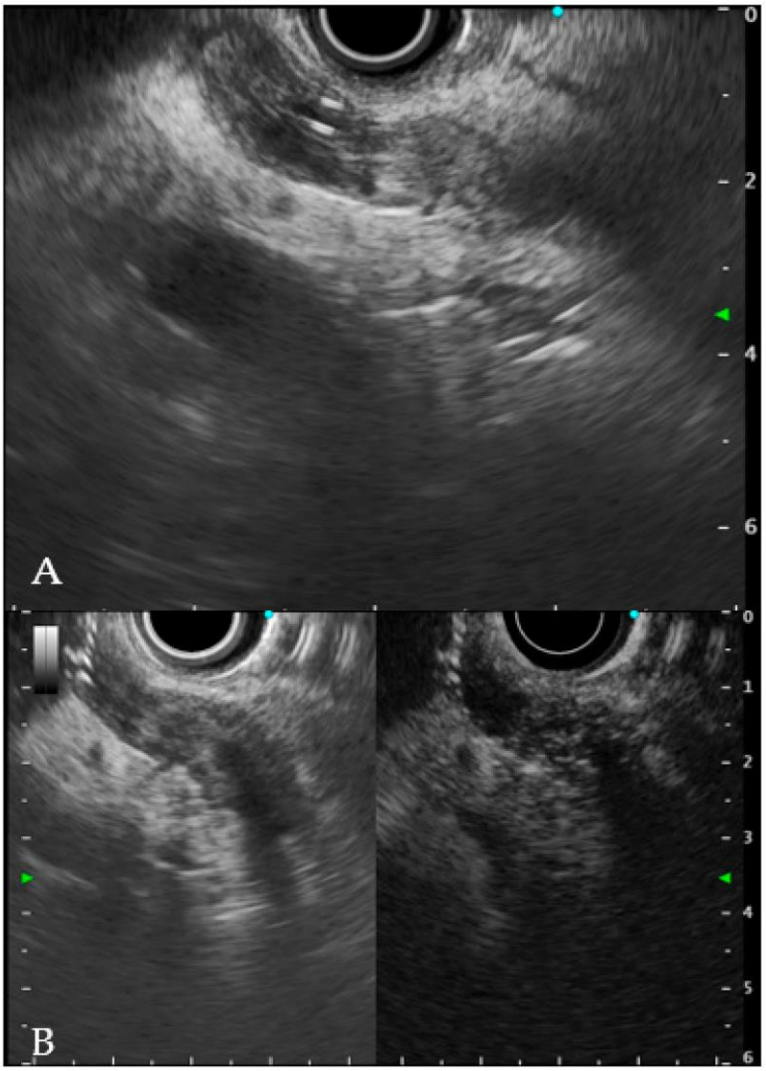
- Endoscopic Ultrasound (EUS)



- EUS Evaluation of Indeterminate Biliary Strictures

➢ Indications

  - Masses < 2 cm
  - To assess for possible lymph nodes or liver metastases
  - Chronic pancreatitis



  - EUS images of a distal malignant biliary stricture. (A) A small 1 cm hypoechoic mass was noted in the distal CBD traversed by a plastic biliary stent on EUS.
    - This lesion was not clearly observed in CT abdomen before EUS examination. (B) CE-EUS showed a hypoenhanced mass with fine tumour vessels.

Source: Siu W, et al. Gastroenterol Insights 2022; 13(2):192-205 (Figure 6)

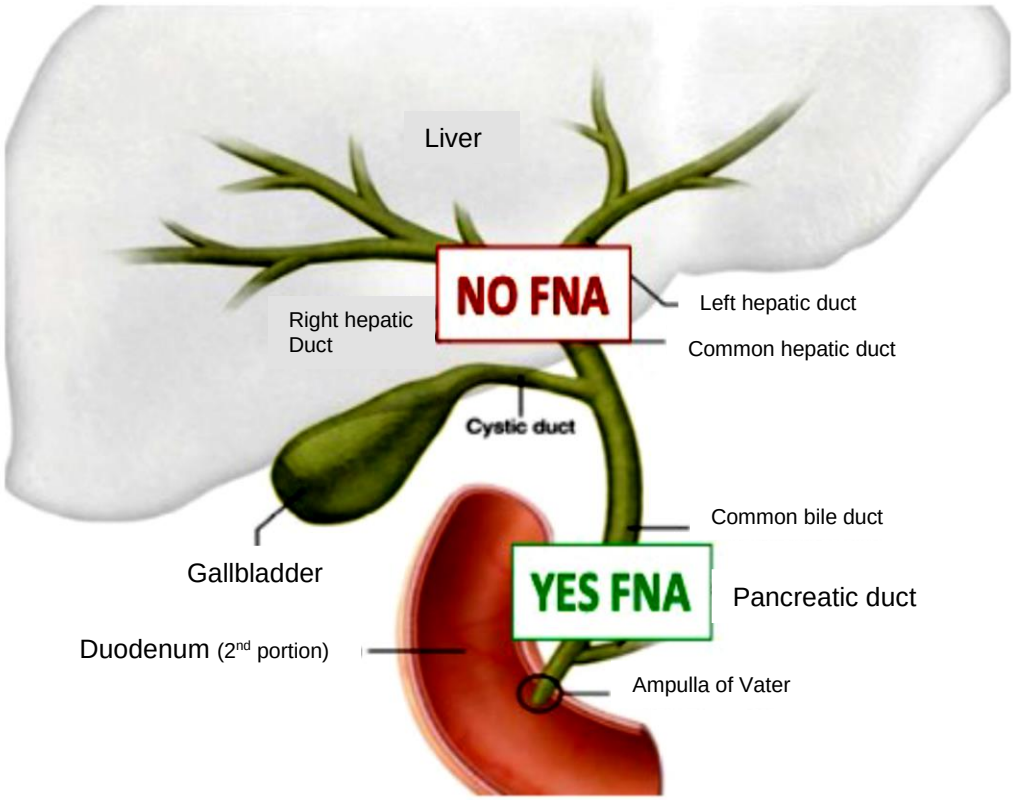
Byrne et al., Endoscopy 2004
DeWitt et al., GIE 2006
Eloubeidi et al., Clin Gastro Hepatol 2004
Fritscher-Ravens et al., Am J Gastro 2004
Lee et al., Am J Gastro 2004
Meara et al., Cytopathology 2006
Mohamadnejad et al., GIE 2011
Rosch et al., GIE 2004

➢ EUS Sampling

ASGE 2023 Guidelines:

- Indications
  - Distal IDBS
    - Wall thickening or mass)
    - EUS with FNA recommended
  - Hilar strictures
    - EUS to look for biliary masses, but
    - Would only FNA lymph nodes or liver metastases
  - Small risk of tumour seeding from FNA of *hilar lesions*
    - Do **not** use for most liver transplant protocols

- EUS + ERCP for IDBS
  - Superior for tissue in terms of tissue acquisition than EUS alone, or ERCP alone



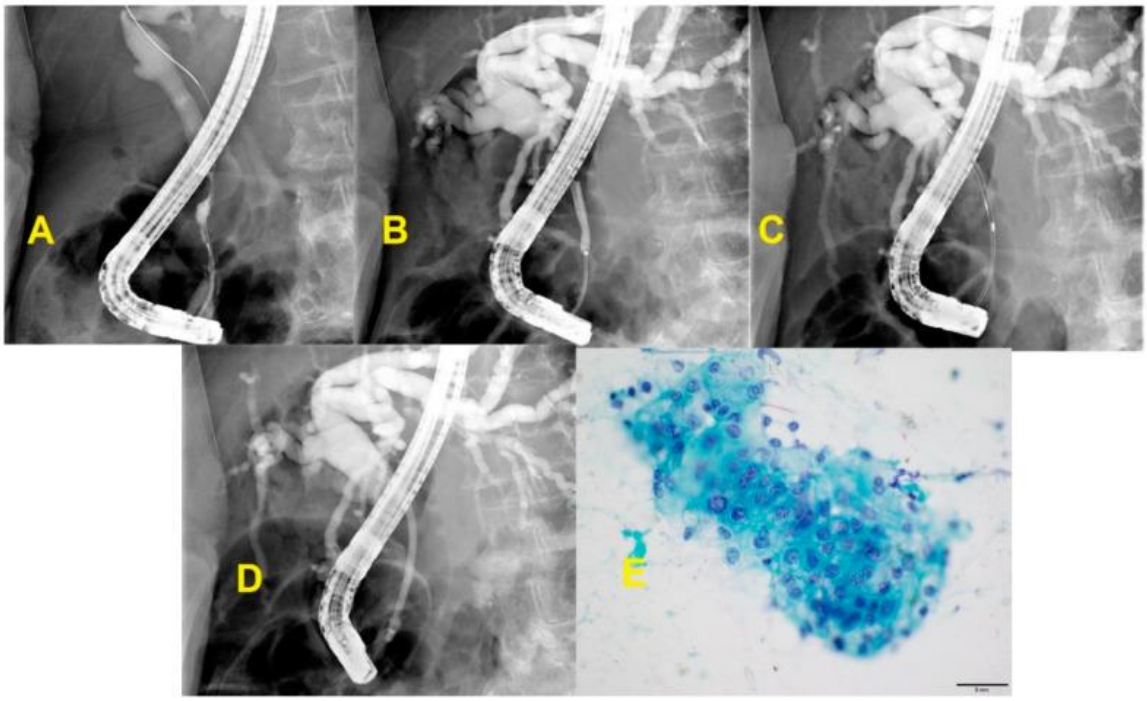
Fritscher-Ravens et al., Am J Gastro 2003
Abu-Hamda et al., Semin Liver Dis 2004
Nayar MK, et al. Hepatogastro 2011
Mohamadnejad et al., GIE 2011
Levy et al., Curr Opin Gastroenterol 2012
Fujii-Lau L, et al. GIE 2023

- Pooled Test Characteristics for tissue acquisition in EUS + ERCP and ERCP alone

Results	ERCP Alone	EUS Alone	EUS + ERCP
– Pooled diagnostic test characteristic			
▪ Sensitivity	0.61 (0.57-0.64)	0.74 (0.71-0.77)	0.88 (0.85-0.91)
▪ Specificity	0.99 (0.94-1)	0.88 (0.83-0.92)	0.99 (0.94-1)
– Positive likelihood ratio (PLR)	10.3 (4.2-25.23)	5.41 (3.07-9.51)	17.45 (7.13-42.67)
– Negative likelihood ratio (NLR)	0.43 (0.37-0.5)	0.28 (0.19-0.41)	0.15 (0.09-0.25)
– Diagnostic Odds Ratio (OR)	24.55 (9.22-65.4)	22.26 (10.49-47.25)	
– Summary receiver capacity characteristics (SROC)	0.7598	0.9128	0.9799

Adapted from: Fujii-Lau LL, Gastrointest Endosc 2023; 98(5):694-712 (Table 5)

ERCP with brushings and resultant cytology

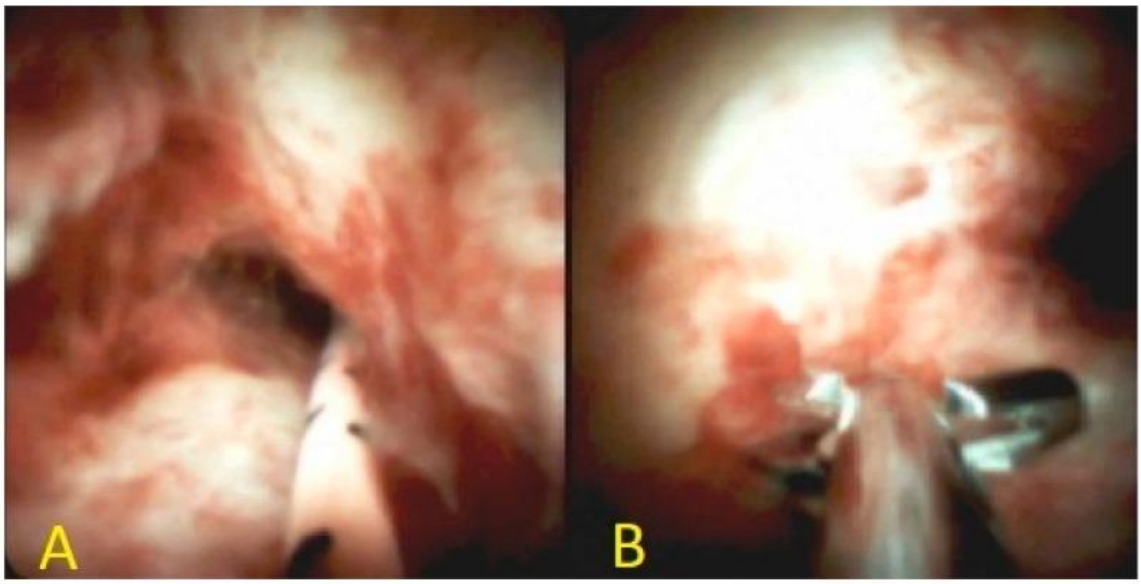


A: Cholangiography showing distal bile duct stricture with upstream ductal dilatation. B: Balloon dilation of distal bile duct stricture. C: Brushings obtained from distal bile duct stricture during ERCP. D: Plastic stent placed in bile duct across stricture for biliary drainage. E: Brush cytology showed biliary tract adenocarcinoma.

- The group shows loss of polarity, irregularly spaced nuclei. The nuclei are angulated and pointed with subtle grooves and folding. Small nucleoli are present in the cells (Papanicolaou stain).

Source: Dorrell R, et al. Diagnostics (Basel) 2020; 10(5):337 (Figure 6)

- ERCP Brush Cytology (BC) + Fluoroscopic Guided Biopsy (FGB) [ERCP-BC + FGP])
  - Superior tissue requisition for which BC + FGB than for BC alone, or FGB for the same “results” as for outcomes last as above EUS, ERCP, EUS+ERCP



A: Cholangioscopy revealing hilar stricture with irregular mucosa and neovascularization. B: Stricture sampling with SpyBite biopsy forceps.

Source: Dorrell R, et al. Diagnostics (Basel) 2020; 10(5):337 (Figure 7)

Pooled characteristics for brush cytology alone, fluoroscopic-guided biopsies alone, and brushing + biopsies

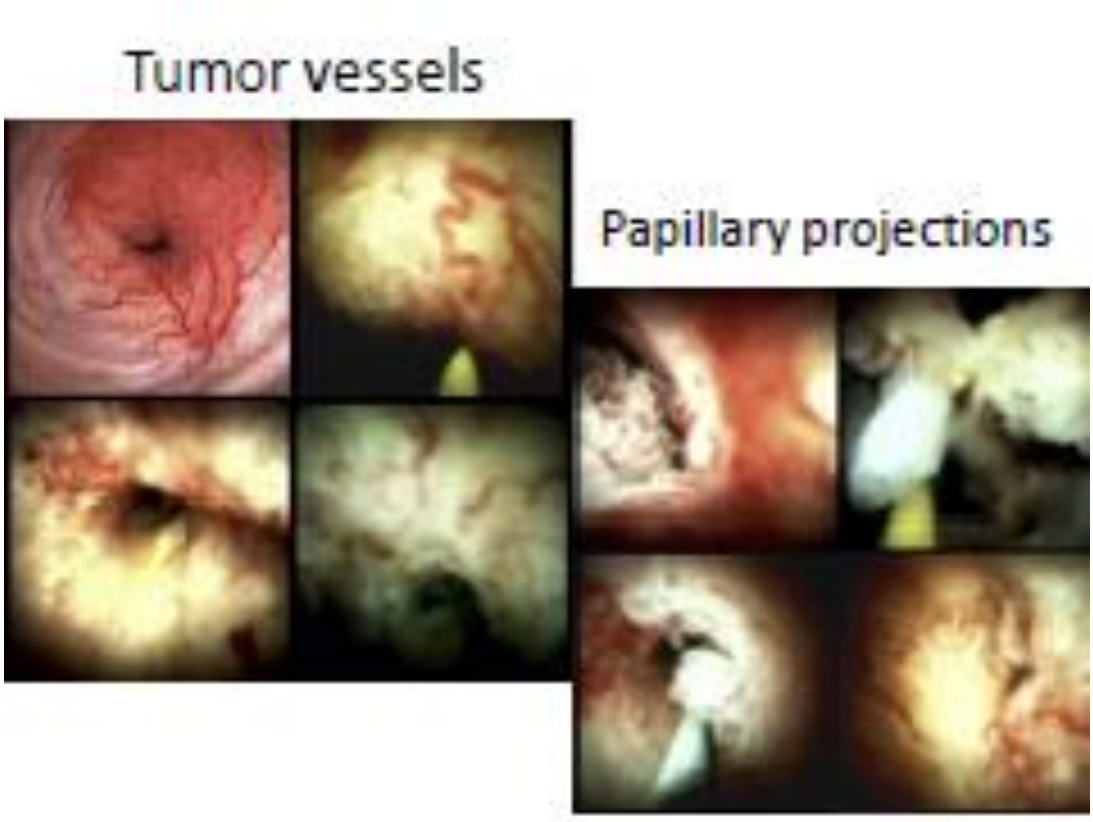
Results	Brush cytology alone (BC)	Fluoroscopic guided biopsies (FGB) alone	Biopsies + brushing (BC + FGB)
− Pooled diagnostic test characteristic (21 studies)			
▪ Sensitivity	0.43 (0.4-0.46)	0.52 (0.49-0.55)	0.66 (0.63-0.69)
▪ Specificity	0.99 (0.98-1)	0.97 (0.96-0.99)	0.97 (0.95-0.98)
▪ Positive (likelihood ratio)	13.79 (7.96-23.91)	10.25 (6.36-16.5)	11.91 (7.37-19.23)
▪ Negative likelihood ratio	0.6 (0.54-0.66)	0.51 (0.43-0.59)	0.38 (0.33-0.43)
▪ Diagnostic odds ratio	25.333 (14.05-45.67)	20.96 (12.42-35.4)	31.78 (18.59-54.35)
▪ Summary receiver capacity characteristics (SROC)	0.71	0.799	0.767
− Pooled adverse events (7 studies)			
▪ Adverse events	2 (n=503)	5 (n=518)	N/A

Adapted from: Fujii-Lau LL, Gastrointest Endosc 2023; 98(5):694-712 (Table 3)

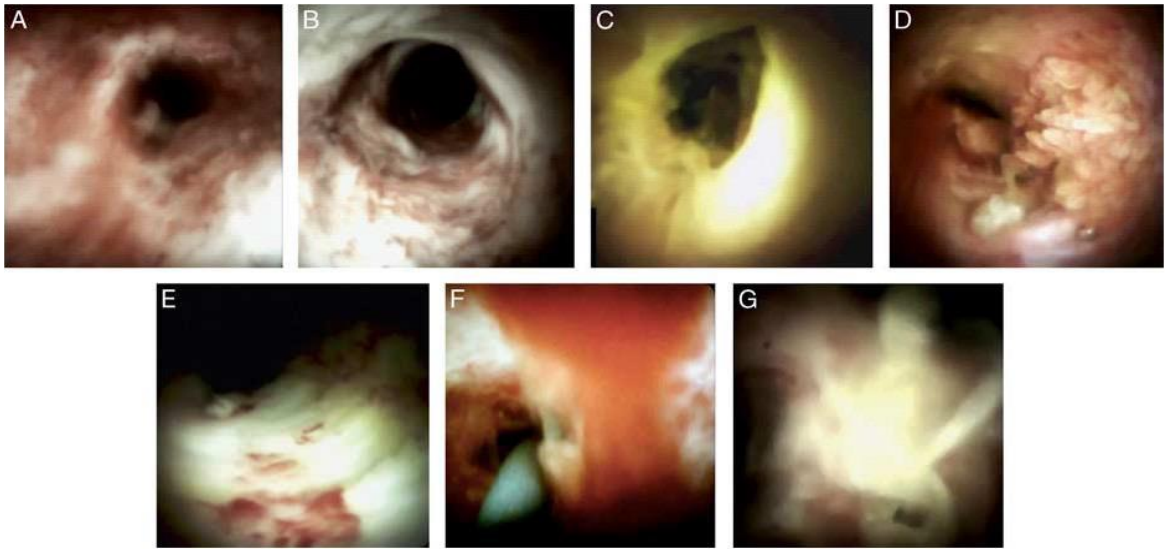
- ERCP with Cholangioscopy
  - Digital imaging with single operator cholangioscopes (DSOC)
    - Endoscopic visualization inside the bile duct
    - Directly visualized biopsies (DVB)
  - Difficulty evaluating distal strictures
  - Risk of bacteremia and need to give IV antibiotics

➢ Visual Criteria for Malignancy Visualized by Cholangioscope

If prior ERCP sampling negative → DSOC Visual Impression > 90% Sens, > 79% Spec, Accuracy > 89%



- Monaco Classification



Ulceration associated with malignancy
Accuracy 70%

Printed with permission: Kulpatcharapong S, et al. Endoscopy 2020; 52(03): 174-185 (Figure 1).

- Quality Important (Ways to Improve Diagnostic Accuracy)
  - ERCP + DSOC +DVB superior to ERCP alone done for the same “result outcomes risk”

Pooled test characteristics for ERCP with and without cholangioscopy

Result	ERCP without Cholangioscopy	ERCP + Cholangioscopy
− Pooled diagnostic test characteristic (13 studies)		
▪ Sensitivity	0.61 (0.57-0.66)	0.72 (0.66-0.77)
▪ Specificity	0.93 (0.91-0.96)	0.96 (0.92-0.98)
▪ Positive likelihood ratio	11.31 (3.42-37.35)	10.61 (6.57-17.12)
▪ Negative likelihood ratio	0.48 (0.39-0.6)	0.32 (0.22-0.46)
▪ Diagnostic odds ratio	23.21 (9.56-56.31)	59.72 (27.85-128.02)
▪ Summary receiver capacity characteristics (SROC)	0.7495	0.9689
− Pooled adverse events (3 studies		
▪ Adverse events	21 (total n = 72)	16 (total n = 81)

Adapted from: Fujii-Lau LL, Gastrointest Endosc 2023; 98(5):694-712 (Table 4)

  - Tissue Analysis
    - − Fluorescence In Situ Hybridization (FISH)
      - ▪ FISH + Cytology vs. cytology alone (Sensitivity 63% vs.35%; for malignancy (specificity 99%)
      - ▪ FISH and cholangioscopy biopsies for proximal strictures (76% vs. 48%)
    - − Next Generation Sequencing
      - ▪ BiliSeq + path dx: Sens 85%; Spec 99% for malignancy

  - AI and Cholangioscopy
    - − Artificial intelligence for diagnosing neoplasia on digital cholangioscopy: development and multicenter validation of a convolutional neural network model

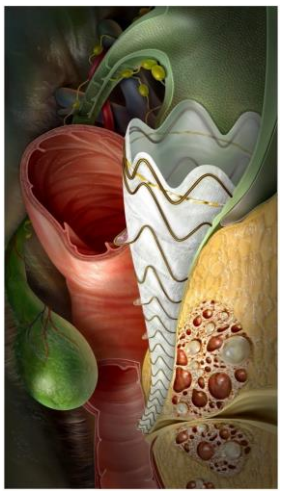
  - DSOC-based AI systems have higher accuracy than conventional ERCP biopsy and brush cytology.
    - − Software obtained higher diagnostic accuracy than 25% of the participant experts and 50% of the nonexperts.
    - − Is capable of performing detection in real time and on previously recorded videos.
    - − Can be applied as a second opinion tool for less experienced advanced endoscopists. (Marya NB, et al. GIE 2023, 97(2), 268-278)

➢ Treatment

- Benign biliary strictures
  - Balloon dilation
    ↓
  - Placement of the maximal number of plastic stents
    ↓
  - Repeat ERCP every so often with stent stacking
    ↓
  - Continue until “fluoroscopic resolution” of the stricture, 6-12 mon

Costamagna G, et al. Endoscopy 2001; 33(4): 317-22.
Costamagna G, et al. Gastrointest Endosc. 2010;72(3):551-7.

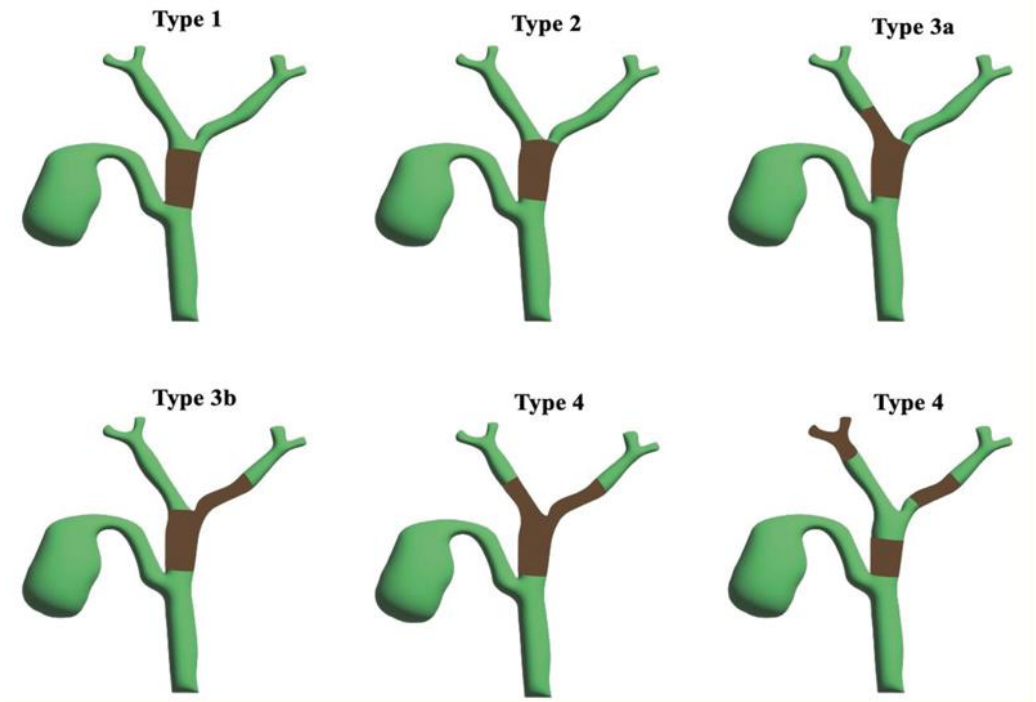
- Fully covered metal stents (SEMS) for benign bile duct stricture (BBDS)



  - Similar
    - Stricture resolution
    - Recurrence
    - Adverse events
  - Allows for
    - Fewer ERCPs with FcSEMS (at least one less)
    - More useful for important caveats
      - Cystic duct
      - Proximity to hilum
      - PEP
      - PHT

Cote et al. JAMA 2016
Ramachandani et al. Gastro 2022
Kaffes et al. Ther Adv Gastroenerol 2014
Haapamaki et al. Endoscopy 2015
Tal et al. GIE 2017

- Bismuth Classification of Hilar Strictures



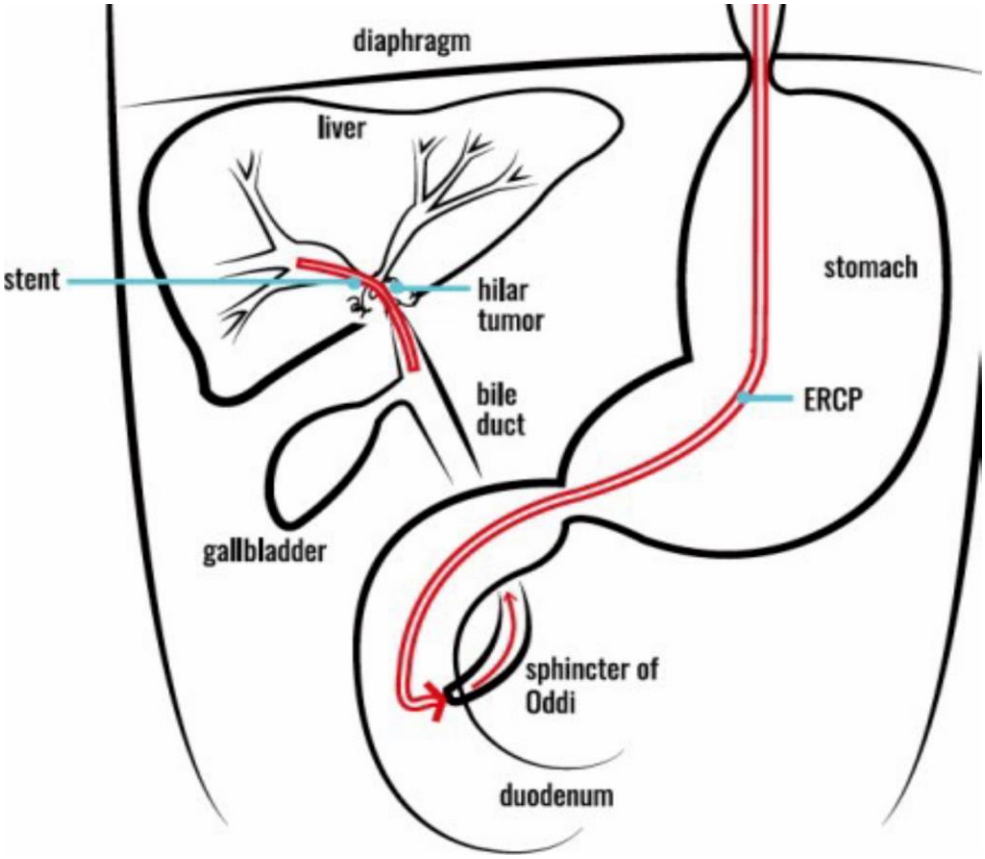
Source: Louise L and Arumugam R. J Gastrointest Abdominal Radiol 2023; 06(03): 212 – 226 (Figure 7)

Types	Description
1	○ Tumour involves the common hepatic duct, and − Spares the bifurcation of the right and left hepatic ducts
2	○ Tumour involves the common hepatic duct, and − Extends to the bifurcation
3a	○ Tumour involves the common hepatic duct, and bifurcation, and − Extends into the tertiary branches of the right hepatic duct
3b	○ Tumours involves the common hepatic duct, bifurcation, and − Extend into the tertiary branches of the left hepatic duct
4	○ Tumour involves the common hepatic duct, bifurcation, and − Extends into the tertiary branches of both the right and left hepatic ducts and Multicentric tumour

- Therapeutic consideration
  - Drainage
  - Unilateral vs. bilateral drainage
  - ERCP or PTC
  - Plastic vs. metallic stents
  - Adjuvant intraductal therapies

➢ Treatment

- ERCP
  - Generally favoured
    - High success rates for other types of obstruction
    - Safer than percutaneous transhepatic cholangiography (PTC)
    - More comprehensive tissue sampling
    - Avoids external tubes



- Percutaneous transhepatic cholangiography (PTC)
  - PTC >> ERCP* (observational data)
  - Recommended for
    - Bismuth 3 & 4 strictures**
  - ~40% pivot to PTC after ERCP***

*Paik et al. GIE 2009, Moole et al. Can J Gastro Hep 2016, Hameed et al. HPB 2016
**Rerknimitr et al. J Gastroenterol Hepatol 2013
***Wiggers et al. Endoscopy 2015

- Two available RCTs
  - Pre-op ERCP vs. PTBD for resectable cholangiocarcinoma (CCA)
    - 54 pts (terminated)
    - No difference in severe complications
    - >> mortality in percutaneous transhepatic biliary drainage (PTBD) group
    - 50% of ERCP patient required PTBD after ERCP
  - ERCP vs. PTBD for unresectable gallbladder (GB) cancer
    - 54 patients
    - PTBD:
      - >success
      - > quality of life (QoL)
      - < complications
    - No difference in mortality

Coelen et al. Lancet GH 2018
Saluja et al. CGH 2008

Take Home Points: Approach to IDBS

- TWO IS ALWAYS BETTER THAN JUST ONE!
  - EUS with ERCP
    - Look for small masses, nodes, liver metastasis → FNA distal lesions but don't FNA hilar strictures/masses
  - ERCP with BC + FGB
  - ERCP + cholangioscopy + directed visual biopsies
    - Especially for hilar strictures
    - Consider on index ERCP to make diagnosis earlier
- If negative sampling →
  - Repeat attempt
  - Workup benign causes multi-disciplinary discussion

- Chronic Pancreatitis as a Cause of Stricture:
  - Chronic inflammation leading to benign strictures is detected
  - Always a challenge to differentiating benign from malignant strictures.
  - Stent Types and Management:
    - Role of plastic vs. fully covered metallic stents.
    - Risk of stent migration or shearing during removal.
    - Important: do periodic stent exchange to prevent complications like cholangitis

ACUTE LIVER FAILURE: ACG GUIDELINES 2023

Alvi Islam

Shingina A, et al. Am J Gastroenterol 2023; 118(7): 1128-1153

- Overview of guidelines
  - Guideline provides evidence-based recommendations for ALF management.
    - General Management (Expert opinion)
    - System specific (5 Recommendations)
    - Etiology specific (4 recommendations)
    - Liver transplant prognostication (1 recommendation)
  - Intended for a wide range of medical professionals including hepatologists, gastroenterologists, and emergency responders.
  - Focus on improving patient outcomes and standardizing treatment protocols.
- GRADE Methodology Overview
  - Risk of bias
  - Evidence of publication bias
  - Heterogeneity
  - Directness of evidence

10 recommendations + Key concepts (Expert opinion)

System specific:

- CNS
- Coagulopathy
- Infection
- Hemodynamics
- Renal failure

Etiology specific

- APAP
- Non-APAP
- HBV
- Mushroom poisoining

Abbreviations: APAP, N-acetyl-p-amino-phenol; CNS, central nervous system

- Definition (ALF)
  - Severe liver impairment, leading to multi-organ dysfunction, in patients without pre-existing liver disease
    - Exceptions: Autoimmune hepatitis (AIH), Budd Chiari syndrome, Wilsons disease
    - < 26 wk duration
    - Coagulopathy (INR > 1.5) and hepatic encephalopathy (HE)
  - Remember the definition
    - Acute liver failure is different from
      - Acute-on-chronic liver failure (ACLF)
      - Decompensated cirrhosis

- Pathophysiology
  - Understanding the pathophysiology is essential for effective management.
  - Early recognition and intervention can significantly impact survival outcomes.

- Clinical
  - Systemic
    - Catabolic state
    - High energy expenditure
    - Immunosuppression
    - Systemic inflammatory response
  - Brain
    - Cerebral edema
    - Hepatic encephalopathy
    - Intracranial hypertension
    - Seizure
  - Heart
    - Hepatocardiac syndrome
    - High output state
    - Subclinical myocardial injury
  - Lung
    - Acute lung injury
    - Acute respiratory distress syndrome (ARDS)
    - Hepatopulmonary syndrome (HPS)
  - Liver
    - Coagulopathy
    - Hyperammonemia
    - Hypoglycemia
    - Lactic acidosis
  - Pancreas
    - Pancreatitis

- Bone marrow
  - Anemia
  - Frequent suppression
  - Thrombocytopenia
- Kidney and adrenals
  - Electrolyte abnormalities
  - Hepatoadrenal syndrome
  - Hepatorenal syndrome

- Rapidity of Onset: O'Grady Classification

Types of ALF	Time Frame	Examples
○ Hyperacute	< 7 d	− Acetaminophen − Hepatitis A, E − Ischemic injury
○ Acute	7-21 d	− Hepatitis B
○ Subacute	> 21 d and < 26 wk	− Non-acetaminophen DILI

  - Beware ↑ risks
    - Hyperacute
      - Cerebral edema
    - Subacute
      - Death

Abbreviations: ALF, acute liver failure; DILI, drug-induced liver injury

Adapted from: Shingina A, et al. Am J Gastroenterol 2023; 118(7): 1128-1153 (Table 4)

➢ Demography
- Varies geographically
- Rare- Prevalence, 1-6/10^6 annually (in North America [NA])
  - Most common causes in NA and Europe
    - Cryptogenic/ Idiopathic
    - DILI
    - Viral Hepatitis
  - Less common causes
    - Acetaminophen
    - Autoimmune hepatitis
    - Ischemic
    - Malignant infiltration
    - Mushroom poisoning
    - Pregnancy related
    - Thrombotic (Budd Chiari)
    - Wilson disease

➢ Treatment

- General
  - Distinguish between ALF vs ACLF/Decompensated Cirrhosis
  - Perform comprehensive history and physical examination, focusing on
    - Timeline of precipitants
    - Use of medications, and
    - Risk factors
  - If alcohol induced liver disease is suspected
    - Measure biomarkers
      - ETG
      - PETH
  - Key concepts
    - All patients with suspected ALF should be referred early for consultation by hepatology or gastroenterology
    - Patients with grade 2 HE should be promptly transferred to ICU, and
      - Intubation should be considered for Grade 3 and 4

- Central Nervous System (CNS) Management
  - Early CRRT
    - ↓ ammonia (NH_3) levels and
    - Improves neurological outcomes in ALF patients (Larsen FS, et al. Am J Gastroenterol 2001; 96(3): 906-912)
    - ↓ intracranial pressure, and
    - ↓ cerebral edema in patients with acetaminophen-induced ALF (Bower WA, et al. Hepatology 2007; 45(1): 147-156)
      - Prevents cerebral edema by managing hyperammonemia.
  - Early intervention associated with ↓ mortality and ↑ transplant-free survival.

Abbreviation: CRRT, continuous renal replacement therapy

Recommendation

- Perform early CRRT for management of hyperammonemia in patients with ALF and grade 2 or higher encephalopathy
  - Even in the absence of conventional RRT indications." (GRADE: Conditional, Strength: very low)

- Coagulopathy
  - Routine correction of coagulopathy in non-bleeding ALF patients
    - Does **not** improve outcomes and may increase the risk of complications (Harrison PM and Wendon J. J Hepatol 2012; 56(3): 782-787)
  - INR does **not** correlate with bleeding risk in ALF patients.
  - A conservative, evidence-based approach to managing coagulopathy reduces unnecessary interventions.
    - Routine correction should be avoided unless there's a clear clinical need.
    - Focus on individualized management based on patient-specific factors.

Recommendation

- Do **not** routinely correct coagulopathy in patients with ALF who have
  - Active bleeding, or
  - Impending high-risk procedure

(GRADE: conditional, strength: very low)

- Infection Management
  - Prophylactic antibiotic use in ALF patients
    - ↓ incidence of bloodstream infections, or
    - 21 day mortality

(Stravitz RT, et al. Liver Transplantation 2009; 15(8): 997-1005)

  - Routine prophylactic antibiotics
    - Can lead to resistance and unnecessary side effects
    - No efficacy in ↓ infection rates or ↓ mortality.
  - Targeted antibiotic use based on clinical evidence of infection is more effective.

Recommendation

- Do **not** routinely give prophylactic antimicrobial agents in patients with ALF (no improvement in either rate of bloodstream infection or 21-day mortality) (GRADE: conditional, strength: low)

- Hemodynamics – Fluid Resuscitation
  - Norepinephrine is effective as the first-line vasopressor in managing hypotension in ALF patients, showing better outcomes in maintaining hemodynamic stability (Harrison PM and Wendon J. J Hepatol 2012; 56(3): 782-787)
    - Norepinephrine is particularly effective when fluid resuscitation alone is insufficient to maintain blood pressure.

- Maintaining adequate perfusion to vital organs is crucial to preventing organ failure.
- Early and appropriate use of norepinephrine is essential to prevent the progression to multi-organ failure.

Recommendation

- Use norepinephrine as the first-line vasopressor for hypotension refractory to fluid resuscitation in patients with ALF (GRADE: Strong, Strength: Moderate)

- Hemodynamics – Vasopressin
  - Adding vasopressin to norepinephrine ↑ blood pressure control in ALF patients with refractory hypotension (Bower WA, et al. Hepatology 2007; 45(1): 147-156)
    - Vasopressin works synergistically with norepinephrine to achieve better hemodynamic stability.
    - This combination is particularly effective when norepinephrine alone is insufficient.
    - Continuous monitoring and reassessment are essential to manage side effects and ensure efficacy.

Recommendation

- Adding vasopressin as a secondary agent in patients with ALF with hypotension not responsive to norepinephrine." (Conditional, low)

- N-acetyl cysteine (NAC) in Acetaminophen-Induced ALF
  - Early administration of N-acetylcysteine (NAC) ↓ liver injury and ↑ survival rates in patients with acetaminophen-induced ALF (Bower WA, et al. Hepatology 2007; 45(1): 147-156)
  - NAC works by replenishing glutathione stores, thereby protecting the liver from further damage.
  - Earlier intervention of NAC administration a better achieves better outcomes.
  - Continuous monitoring of liver function and NAC levels is necessary to optimize treatment.

Recommendation

- Use early administration of NAC in patients with suspected acetaminophen toxicity (Strong, Low)

- Non-Acetaminophen ALF
  - NAC is also be beneficial in non-acetaminophen-related ALF, though the evidence is less robust compared to acetaminophen-induced ALF (Stravitz RT, et al. Liver Transplantation 2009; 15(8): 997-1005)
    - NAC's antioxidant properties may help ↓ liver injury in various forms of ALF, not just those caused by acetaminophen.
    - Early initiation of NAC in non-APAP ALF can potentially improve liver function and patient outcomes.
  - Again, as in acetaminophen ALF, monitoring and adjusting treatment based on the patient's response is essential.

Recommendation

  - Use early NAC in patients with non-APAP ALF (Strong, moderate)

- Hepatitis B Reactivation
  - Early antiviral therapy in Hepatitis B-induced ALF can significantly reduce viral load and improve patient outcomes (Bernuau J, et al. J Viral Hepatitis 2002; 9(2), 174-181)
  - Antiviral therapy, particularly with agents like entecavir or tenofovir, helps control the viral replication in acute Hepatitis B exacerbations.
    - Early initiation of antiviral therapy is associated with
      - ↑ survival rates, and
      - ↓ need for liver transplantation.
  - Monitoring viral load and liver function is essential to guide ongoing therapy.

Recommendation

  - Start antiviral therapy in patients with ALF due to reactivation of HBV (Strong, low)

- Mushroom Poisoning in ALF
  - Early administration of silibinin IV improves outcomes in patients with ALF due to Amanita mushroom poisoning (Tait PA, et al. Br J Clin Pharmacol 2006; 62(3), 446-448)
  - Silibinin acts as a hepatoprotective agent
    - ↓ uptake of toxins by the liver cells
  - IV Penicillin G has also been used as an alternative (silibinin is generally preferred when available)
  - Early treatment is crucial to prevent severe liver damage and improve survival rates.

Recommendation

  - Use IV silibinin as soon as possible in patients with ALF due to mushroom poisoning
    - IV penicillin G may be used if IV silibinin is unavailable (conditional, very low)

- Liver Transplantation and Prognostic Models
  - King's College Criteria (KCC) and the MELD score have been validated as effective prognostic tools in determining the need for liver transplantation in ALF patients (O'Grady JG, et al. Hepatology 1989; 10(2): 163-170).
  - The KCC criteria are based on arterial pH, INR, and creatinine levels.
  - The MELD score is calculated using bilirubin, INR, and creatinine levels
    - Give an objective measure of liver disease severity.
    - KCC and MELD identify patients at high risk of poor outcomes (prognosis) who may benefit from early referral for liver transplantation.
  - Continuous reassessment is necessary to ensure timely and appropriate decision-making.

Recommendation

  - Use either the KCC criteria or the MELD score for prognostication in patients with ALF
    - Patients who meet the KCC criteria or presenting with a MELD score >25 are at high risk of poor outcomes (Conditional, low).

- When to Perform a Liver Biopsy
  - Liver biopsy
    - Exclude infiltrative disease and malignancy in ALF patients, providing crucial information for management decisions (Jalan R, et al. J Hepatol 2002; 36(3), 329-336)
    - Identify patients who may have contraindications for liver transplantation, thus guiding treatment plans.
  - Consider biopsy when non-invasive methods are inconclusive, or when specific diagnostic information is needed.
  - The decision to biopsy should weigh the risks of the procedure against the potential diagnostic benefits.

- Summary of ALF Management Guidelines
  - Comprehensive management of ALF involves a multidisciplinary approach tailored to the patient's specific needs.
  - Early intervention across all affected systems—CNS, coagulation, infection, hemodynamics, and renal function—is crucial to improving outcomes.
  - Guidelines emphasize evidence-based practices supported by robust studies to optimize patient care.
  - Ongoing research and adaptation of these protocols are essential for continuing to improve survival rates and quality of life for ALF patients.

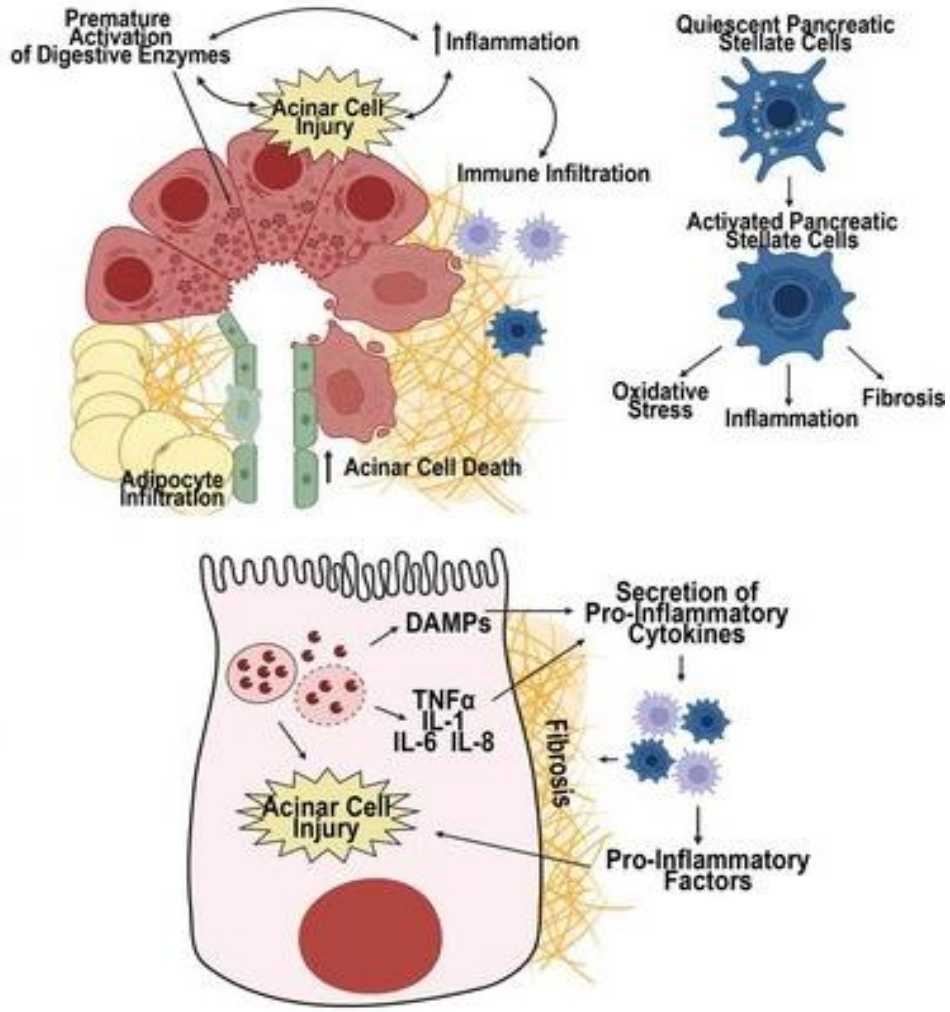
PANCREAS

CHRONIC PANCREATITIS

Pavithra Parthasarathy

Chronic Pancreatitis

- Overview



  - Chronic pancreatitis describes prolonged inflammation caused by a variety of factors, including recurrent severe acute pancreatitis.
    - Similar to acute pancreatitis, acinar cell injury drives expression of pro-inflammatory cytokines that promotes immune infiltration.
    - Unlike acute pancreatitis, macrophages make up the majority of the immune landscape in chronic pancreatitis cases.
    - In addition to immune infiltration, chronic inflammation and cellular stress causes pancreatic stellate cells to activate, causing increased oxidative stress, inflammation and fibrosis that cumulative increase acinar cell death and, in some cases, promote adipocyte infiltration.

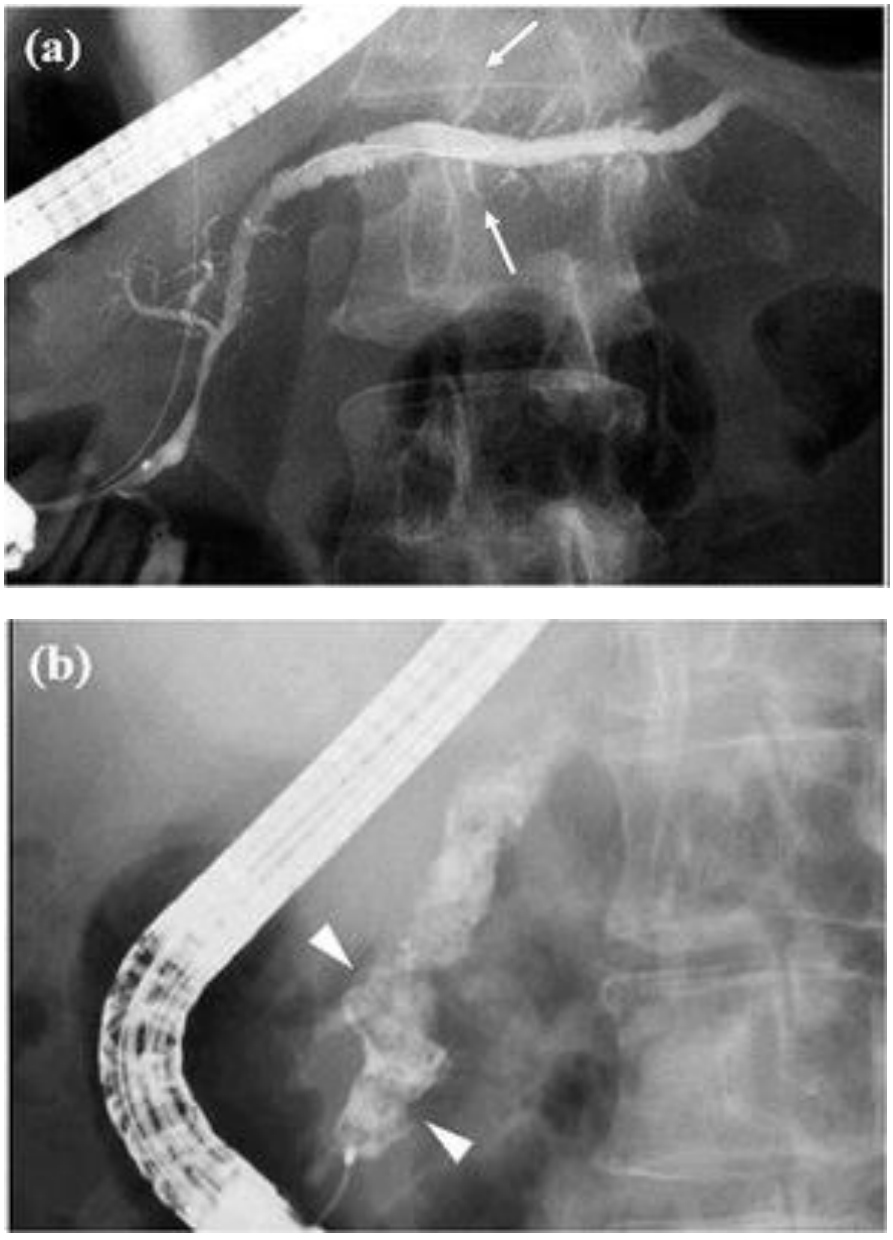
Source: Lilly AC, et al. Cell. Mol. Life Sci 2023; 80: 206 https://doi.org/10.1007/s00018-023-04855-z

- Sequalae of long-standing pancreatic injury resulting from a destructive, inflammatory conditions; irreversible morphologic change
- Histology changes
  - Fibrosis and distortion of normal architecture
  - Loss of normal acinar cells and islet cells
  - Inflammatory cell infiltrates
- Symptoms/signs
  - Abdominal pain
  - Maldigestion
  - Exocrine/endocrine insufficiency
- Clinical diagnosis
  - Combination of clinical, functional, morphologic, histologic features
- Multiple scoring systems and classifications, no unified singular system at present

➢ Diagnostic Imaging Modalities

- ACG Clinical Guideline: Chronic Pancreatitis (2020)
- CT/MRI as first-line for diagnosis of CP. EUS only if diagnosis is in question after cross-sectional imaging (strong recommendation, low quality of evidence)
- Secretin-enhanced MRCP if no clarity with cross-sectional imaging/EUS and clinical suspicion is still high (conditional recommendation, low quality of evidence)
- Histological examination is gold standard for high-risk patients with clinical and functional evidence of CP (where imaging modalities are inconclusive) (conditional recommendation, very low quality of evidence)
- Major complications of chronic pancreatitis include
  - Calcification
  - Dilate ducts
  - Dilated common bile duct
  - Gastric varices
  - Pancreatic parenchymal atrophy
  - Pseudocysts
  - Splenic vein thrombosis

ERP in Chronic Pancreatitis



- Endoscopic retrograde pancreatography findings of Cambridge classification for chronic pancreatitis:
  - (a) Abnormal branches
  - (b) Intraductal filling defects or calculi

Source: Yamamiya, A., et al. DEN Open, 3: e164. https://doi.org/10.1002/deo2.164

- Mildly dilated duct with
  - Side branch dilatation
  - Small intrapancreatic duct stones
- Severe chronic pancreatitis
  - Markedly dilated main pancreatic duct
  - Numerous dilated side branches
  - Multiple intraductal pancreatic stones
- The diameters of the ducts are 2, 4, and 8 mm

- TIGAR-O (V2)

➢ Causes/Associations

- Autoimmune
- Genetic
- Idiopathic
- Obstructive
- Recurrent severe/acute pancreatitis
- Toxic-metabolic

- MANNHEIM – Severity Score

Clinical Features	Points
Patient report pain	
No pain without therapy (patient reports requiring no pain medication)	0
RAP (patient reports freedom from pain between attacks of acute pancreatitis)	1
No pain with therapy (patient reports freedom from pain with pain medication or endoscopic intervention	2
Intermittent pain (patient reports intermittent pain-free episodes, ▪ Either with or without therapy ▪ Possibly additional attacks of acute pancreatitis	3
Continuous pain (patient reports absence of pain-free episodes) ▪ Either with or without therapy ▪ Possibly additional attacks of acute pancreatitis	4

Clinical Features	Points
○ Pain control	
– No medication	0
– Use of non-opioid drugs or use of mild opioids (WHO step 1 or 2)	1
– Use of potent opioids (WHO step 3) or endoscopic intervention	2
○ Surgical intervention	
– Pancreatic surgical intervention for any reason	4
○ Exocrine intervention	
– Absence of exocrine insufficiency	0
– Presence of mild, moderate, or unproven exocrine insufficiency no requiring enzyme supplementation (including patient reports of intermittent diarrhea)	1
– Presence of proven exocrine insufficiency (according to exocrine function tests), or	2
– Presence of marked exocrine insufficiency defined as steatorrhea (> 7 g fat / 24 h), normalized, or	
– Markedly reduced by enzyme supplementation	
○ Endocrine insufficiency	
– Absence of DM	0
– Presence of DM	4
○ Morphological status on pancreatic imaging (according to the Cambridge classification)	
– Normal	0
– Equivocal	1
– Mild	2
– Moderate	3
– Marked	4
○ Severe organ complications	
– Absence of complications	0
– Presence of possibly reversible complications	2
– Presence of irreversible complications	4

Clinical Features	Points
○ Severe index severity level point range	
− M-ANNHEIM A	Minor 0-5 points
− M-ANNHEIM B	Increased 6-10 points
− M-ANNHEIM C	Advanced 11-15 points
− M-ANNHEIM D	Marked 16-20 points
− M-ANNHEIM E	Exacerbated > 20 points

- ○ M-ANNHEIM scoring system points are added together, and
  - − The sum is used to categorize a patient's disease according to the M-ANNHEIM system.

Abbreviations: DM, diabetes mellitus; M-ANNHEIM, pancreatitis with Multiple risk factors-Alcohol consumption, Nicotine consumption, Nutritional factors, Hereditary factors, Efferent duct factors, Immunological factors, Miscellaneous and rare metabolic factors; RAP, recurrent acute pancreatitis; WHO, World Health Organization

Adapted from: Gardner TB, et al. Am J Gastroenterol 2020; 115(3): 322-339 (Table 6).

- Other Classification Systems
  - ○ Rosemont classification – EUS-based criteria
  - ○ Mannheim classification – clinical criteria
  - ○ Ultrasound features
  - ○ Ultrasound and pancreatography
- Cambridge Classification System
  - ○ (Previously) most common classification system for severity of CP
  - ○ Done on EUS/ERCP/CT
  - ○ Limited by lack of integration of clinical and etiological factors

➢ Cambridge classification (pancreatic morphology in chronic pancreatitis)

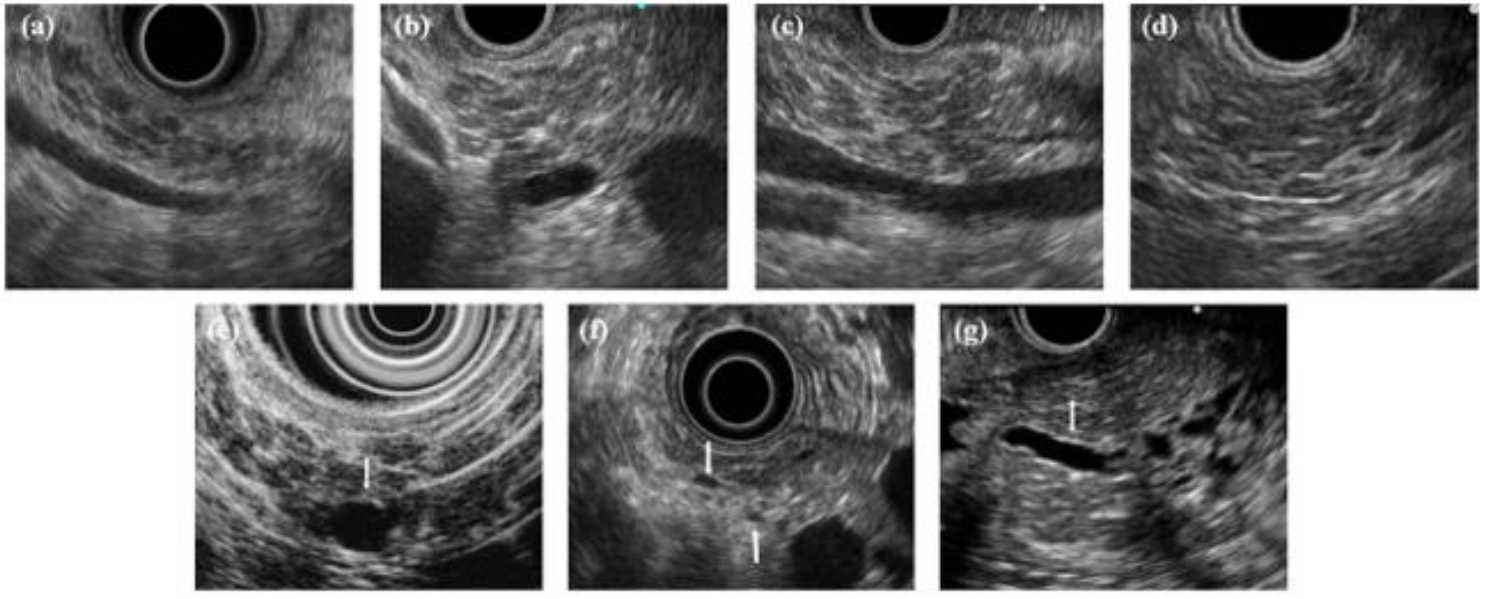
- Pancreatic morphology evaluated by ERCP

	Main Duct	Abdominal Side Branches	Additional Features
○ Normal	− Normal	None	
○ Equivocal	− Normal	< 3	
○ Mild changes	− Normal	≥ 3	
○ Moderate changes	− Abnormal	> 3	
○ Marked changes	− Abnormal	> 3	▪ One or more of the following − Filling defects − Irregularity − Large cavity − Obstruction − Severe dilatation

- Pancreatic morphology evaluated by computed tomography and ultrasound
  - ○ Normal
    - − Main pancreatic duct
      - ▪ < 2 mm
      - ▪ Normal gland size and shape
      - ▪ Homogenous parenchyma
  - ○ Equivocal
    - − One only of the following signs
      - ▪ Main pancreatic duct enlarged (between 2 and 4 mm)
      - ▪ Slight gland enlargement (up to 2 x normal)
      - ▪ Heterogeneous parenchyma, small cavities (<10 mm)
      - ▪ Irregular ducts, focal acute pancreatitis
      - ▪ Increased echogenicity of the main pancreatic duct wall
      - ▪ Irregular head / body contour
  - ○ Mild changes
    - − ≥ 2 of the above listed criteria
  - ○ Moderate changes
    - − As with mild changes (not differentiated)
  - ○ Marked changes
    - − As above, with one or more of the following
      - ▪ Large cavities (>10 mm)
      - ▪ Gross gland enlargement (>2× normal)
      - ▪ Intraductal filling defects or calculi
      - ▪ Duct obstruction
      - ▪ Structure or gross irregularity
      - ▪ Contiguous organ invasion
  - ○ The Cambridge classification established clear-cut criteria for the description of equivocal, mild, moderate, and severe changes of chronic pancreatitis using the imaging technique of ERCP.
    - − The Cambridge classification also categorized chronic pancreatitis according to pancreatic imaging findings on CT and abdominal US, similar to the grading of ERCP changes. However, the grading according to CT and US did not clearly differentiate between mild and moderate changes

Adapted from: Schneider A, et al. J Gastroenterology 2007; 42: 101–119 (Table 5).

- EUS for Chronic Pancreatitis: Rosemont Classification



Endoscopic ultrasound findings of Rosemont classification for chronic pancreatitis:

- (a) Lobularity with honeycombing
- (b) Lobularity without honeycombing
- (c) Hyperechoic foci without shadowing
- (d) Strands
- (e) Cysts
- (f) Dilated side branches
- (g) Hyperechoic main pancreatic duct margin

Source: Yamamiya, A., et al. DEN Open, 3: e164. https://doi.org/10.1002/deo2.164

- Chronic Pancreatitis Prognosis Score (COPPS)
  - Only prospectively validated tool to predict outcomes
  - Biochemical and clinical parameters
  - Newly developed, for grading and predicting severity of CP
  - Correlates with number of readmissions and combined length of hospital stays

Reference

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PANCREATIC CYSTS

Alan BR Thomson

Gonda TA, et al. N Eng J Med 2024; 394: 832-843

- Demography
  - From imaging studies, 2% to 15%
  - From autopsy studies, 50%
  - Prevalence
    - Asymptomatic, 2% to 14%
    - > 70 yr, 40%
    - Cysts > 2 cm, 0.8%
  - Risk of malignancy
    - Pancreatic cysts
      - 0.5% to 1.5% (depends upon type of cyst (e.g., mucinous, please see below)
    - Pancreatic duct adenocarcinoma (PDCA)
      - 15% of all PNCA arises from mucinous pancreatic cysts
    - Malignancy at time of imaging, 0.25%
    - Annual transformation rate to cancer, 0.24%
    - Considering just IPMNs
      - Overall risk of pancreatic duct adenocarcinoma (PDAC), 2.8%, 0.7% per yr
    - Considering high risk IPMNs (normal nodule, dilated MPD)

	Pooled Cumulative Incidence	
	Low Risk Group (HGD, PDCN)	High Risk Group
1	0.02%	2.0%
5	3.1%	9.8%
10	7.8%	~25%

Abbreviations: CEA, carcinogenic antigen; DI, diagnostic imaging; EUS-FNA, endoscopic ultrasound with fine-needle aspiration; F, female; HGD, high grade dysplasia; IPMNs, intraductal papillary mucinous neoplasms; M, male; MCNs, mucinous cystic neoplasia; PD, pancreatic duct; PDAC, pancreatic duct adenocarcinoma; PNGT, pancreatic neuroendocrine tumours; SCA, serous cystadenomas; SPNs, solid pseudopapillary neoplasia; YoA, years of age; yr, year

➢ Classification

Cyst Type	EUS Features	Fluid Appearance	Cytology	CEA	Amylase
○ SCA	- Microcystic, honeycombed, 20% macrocystic	▪ Thin, clear, some-times bloody	▪ Cuboidal cells clear glycogen-positive cytoplasm	Low	Low
○ MCN*	- Macrocystic	▪ Viscous, clear	▪ Mucin-rich fluid, columnar mucin-positive cells, with variable atypia	High	Low
○ IPMN*	- Duct dilation ▪ Main duct (MD – IPMN) ▪ Branch duct (BD – IPMN) ▪ Malignant potential MD >> BD – IPMN	▪ Viscous, clear	▪ Mucin-rich fluid, columnar mucin-positive cells, with variable atypia	High	High
○ PP	- Macrocystic, thick wall - Unilocular, internal debris	▪ Thin, dark, non-mucinous	▪ Inflammatory cells without evidence of mucin or epithelial cells	Variable	High
○ PET (cystic)	- Variable	▪ Variable, typically non-mucinous	▪ Small cells, scant cytoplasm, monomorphic nuclei	Uknown	Low
○ SPT	- Mixed solid and cystic	▪ Bloody	▪ Papillary structures, macrophages, myxoid stroma, monomorphic neoplastic cells	Low	Low
○ LEC	- Solid, heterogeneous - Subtle posterior enhancement	▪ Thick and milky, gray or frothy	▪ Anucleated squamous cells, lymphocytes	Variable	Low

Abbreviations: EUS: Endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm; LEC, lymphoepithelial cysts; MCN, mucinous cystic neoplasms; PD: Pancreatic duct; PET, pancreatic endocrine tumour; PP, pancreatic pseudocysts; SCA, serous cystadenoma; SPT, solid pseudopapillary tumours

- Types
  - Common
    - Classification of risk of malignancy
      - Low
        - Serous cystadenoma, pseudocyst
      - Intermediate
        - Small mucinous cysts
        - IPMNs, branched duct
      - High (high-grade dysplasia or invasive cancer)
  - Less common ~15 other rare type
  - Benign
    - Serous cystadenoma (SCNs)
    - Pseudocysts (PC)

    } 15% to 25% of all pancreatic cysts

Diagnostic Imaging Alert

- SCAs are usually microcystic, but a few may be macrocystic
  - When SCA is macrocystic, it may resemble IPMNs/MCNs, and so to distinguish it from IPMNs/MCNs, the cyst fluid must be assessed for CEA.

  - Malignant
    - Mucinous cystic neoplasms (MCNs)
    - Intraductal papillary mucinous neoplasms (IPMNs)

    } ~50%

    - Solid papillary tumours (SPTs)
    - Cystic neuroendocrine tumours (cNET)

    - Branched duct (1% - 38%)
    - Main duct
    - Mixed type

    } 33% - 85%

    } ↑ risk of ductal CA
    ↑ risk of pancreatic CA

MCQ Alert

- The explanation of associated PDCA with IPMN
  - Field defect → multifocality
    - PDCA
  - Separate from ↑ risk of pancreatic cancer

  - Pseudocysts-associated with acute/chronic pancreatitis
    - Uni-/multilocular
    - May be connected to main pancreatic duct

- Cystic endocrine neoplasms
  - Associated multiple endocrine neoplasia, 10%
  - Somatostatin receptors, 80%
- Poor prognosis, especially if
  - ↑ histological grade
  - Invasion, lymphovascular
  - Ui-67 (proliferation index) ≥ 3%

➢ Clinical

High Risk Characteristics for Mucinous Pancreatic Cysts

- Symptoms
  - Acute pancreatitis secondary to the cyst
  - Elevated serum CA19-9 when no benign cause for elevation is present
  - Jaundice secondary to the cyst
- Imaging findings
  - Mural nodule or solid component with the cyst or pancreatic parenchyma
  - Main pancreatic duct diameter of > 5 cm
  - Charge in main duct caliber with upstream atrophy
  - Size ≥ 3 cm
  - Increase in cyst size ≥ 3 mm/yr
- Cytology
  - High-grade dysplasia or pancreatic cancer

Adapted from: Elta GH, et al. Am J Gastroenterol 2018; 113: 464-479 (Table 3)

Recommendation

- Use caution when attributing symptoms to a pancreatic cysts
  - The majority of pancreatic cysts are symptomatic and the non-specific nature of symptoms requires clinical discernment (Conditional recommendation, very low quality of evidence)

➢ Causes/associations

- Acquired cysts
  - Central cavitary necrosis
  - Parasitic cyst
  - Pseudocyst
- Angiomatous cysts
- Congenital true cysts
  - Cystic fibrosis
  - Dermoid cysts
  - Polycystic disease
  - Von Hippel-Lindau disease

- Cystic neoplasms
  - Mucinous tumours
    - Mucinous cystadenoma (aka macrocystic adenoma) and cystadenocarcinoma
    - Intraductal mucin hypersecreting neoplasm (aka mucinous ductal ectasia)
  - Non-mucinous tumours
  - Serous cystadenoma (aka microcystic adenoma)
    - Papillary cystic tumour
    - Cystic cavitation of pancreatic adenocarcinoma or lymphoma
- Inflammatory
  - Abscess
  - Hydatid cyst
  - Pseudocysts
- Metastases, with cystic component
- Misdiagnosed nonpancreatic lesions
  - Choledochal cyst
  - Duodenal duplication cyst or diverticulum
  - Hypoechoic solid tumour
  - Lesser sac biloma
  - Lymphangioma
  - Mesenteric cyst
  - Splenic artery aneurysm

- Steps to classify for management purposes
  - Initial classification
    - Clinical
    - Diagnostic imaging
  - Diagnosis
    - Certain diagnosis (75%) – surveillance
    - Uncertain
      - EUS +/- fluid / fine-needle aspiration
      - Cytology
      - Genetics
    - Unspecified
      - Assume to be mucinous
    - High-risk
      - Surgery
  - Low risk
    - None of the following signs on MRI/CT
  - Intermediate
    - Pain, ↓ body weight

- High risk
  - Biliary obstruction
  - MRCP: main pancreatic duct > 10 mm
  - Solid nodule: ≥ 5 mm
  - Jaundice

  } PPV 56% to 89%

➢ Diagnostic Imaging

- MRI/MRCP

	CT	MRI	EUS
Performance characteristics			
− Cyst detection	20%	3%	
− Accuracy to distinguish			
▪ Benign from malignancy cysts	70-80%	~75%	
− Sensitivity to identify communication between MPD and cysts (distinguish IPMN from other types of cysts)			
MRI superiority			
− Sensitivity to			
▪ Detect cysts			86-96%
▪ Distinguish benign from malignant	70-80%	55-75%	86-96%
▪ Distinguish IPMN from other types of cysts (communication between cyst and MPD)	80%	96%	86-96%
− Better assent of internal morphology, e.g., mural nodule			
− MRI superior to CT scan			
▪ ↓ identification of calcification			
− Secretin-stimulated MRCP			
▪ Extra visualization of communication of cysts to MPD, 5%			

Dedicated MRI with MRCP is the imaging modality of choice for pancreatic cysts

- Combination of

Diagnostic Imaging (DI)	Diagnostic Accuracy	Predicting Malignancy
− PET/CT	94%	97%
− MDCT	77%	
− MR	87%	76%

- "A consensus statement be radiologist recommended is dedicated MRI with MRCP as the imaging modality of choice for pancreatic cysts"

- ERCP
  - Inferior to MRCP, EUS
    - Only role is for evaluation of MPD in IPMN

Recommendation(s)

- Magnetic resonance cholangiopancreatography (MRCP) is recommended as first-line investigation
  - Pancreatic protocol CT or EUS (endoscopic ultrasound) recommended if MRI/MRCP cannot be performed
- If cyst is considered to be “indeterminant”
  - Perform a second modality (e.g.,
  - EUS plus aspiration of cysts fluid

  (Conditional recommendation, very low quality of evidence)
- Caution
  - The performance characteristics of the MRI/MRCP, CT, EUS are poor in diagnosing
    - Types of cysts, 40% to 50%
    - Distinguishing benign from malignant, 55% to 75%

  (Conditional recommendation, very low quality of evidence)
- Criteria for
  - Regular surveillance (no high-risk characteristics)
    - Guided by size of cyst
  - ↑ frequency of surveillance
    - High risk characteristics

  (Conditional recommendation, very low quality of evidence)
- Pancreatitis
  - Cyst plus inflammation
- MPD, 5 to 10 mm
  - Diffuse dilation
  - Stricture, distal dilation / atrophy
- Cyst > 3 cm
  - ↑ size ≥ 20% / ≥ 2.5 mm /yr
- Mixed nodule < 5 mm
  - Contrast enhanced
- Septations
  - Enhanced

➢ Endoscopy

- Perform if clinical, diagnostic imaging is uncertain / equivocal

- Endoscopic ultrasound (EUS) +/- fluid or fine-needle aspiration
  - Indications
    - To help determine if intermediate risk from assessment with clinical and diagnostic imaging are supportive of high risk categorization
    - To help direct therapy
  - EUS is superior to MRI for
    - Determining if there is communication of cysts with ducts
    - Identifying small mixed nodes
    - Whether mucous is coming out of the “fish-mouth” papilla
    - Obtain fluid by fine needle aspiration (FNH)

- Endoscopic ultrasound, contrast-enhanced
  - Advantages
    - MPD dilation
    - Epithelial nodules

    } ↑ sensitivity vs. EUS alone
  - Prediction of advanced neoplasia

Performance Characteristics	AGA	Fukuoka
Sensitivity	28%	35%
Specificity	96%	94%

  - Features of AGA guidelines
    - Good
      - 60% ↓ unnecessary surgery
    - Bad
      - 5% of patients selected for surveillance had missed cancer
  - Contrast-enhanced EUS (CE-EUS)
    - Colour flow image microbubbles to detect ↑ vascularization in mural nodules
    - Detection of PDAC vs. focal pancreatitis, neuroendocrine tumour (NET)
      - Sensitivity, 94%
      - Specificity, 89%
      - Overall accuracy, 92%
  - Direct intracystic biopsy
  - Confocal laser-induced endomicroscopy (CLE)
    - Identifies villous epithelial pattern in IPMNs
  - MCN
    - Grey band with a thin dark line (mucin-producing epithelium with “interwoven” fibrous tissue”
  - SCN
    - Superficial vascular network (“necklace”) of subepithelial cells along wall of cyst
    - Production of SCN
      - 100% specific, 100% PPV!

Abbreviations: AGA, American Gastrointestinal Association; BD, branch duct; CEA, carcinoembryonic antigen; CE-EUS, contrast-enhanced endoscopic ultrasound; CLE, confocal laser-induced endomicroscopy; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; M, men; MD, main duct; MRI, magnetic resonance imaging; NPV, negative predictive value; PD, pancreatic duct; PPV, positive predictive value; W, women; yr, year

Inflammatory Pancreatic Fluid Collections (PFCs) **(**Muthusamy VR, et al. Gastrointestinal Endoscopy 2016; 83: 481-486)

- Define types of pancreatic fluid collections and their contrast-enhanced CT findings.

Term	Definition	Contrast-enhanced CT findings
○ Acute peripancreatic fluid collection (peri-PFC)	− Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. − This term applies only to areas of peripancreatic fluid seen within the first 4 wk after onset of interstitial edematous pancreatitis and without the features of a pseudocyst. − Multiple, homogenous collection of fluid − No wall to the collection of fluid − Retroperitoneal fascial planes are normal	▪ Homogeneous collection with fluid density ▪ Confined by normal peripancreatic fascial planes ▪ No definable wall encapsulating the collection ▪ Adjacent to the pancreas (no intrapancreatic extension)
○ Pancreatic pseudocyst	− An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. − This entity usually requires >4 wk after onset of interstitial edematous pancreatitis to mature. − PFCs arising from pancreatic and peripancreatic fluid − Persist > 4 wk − May develop necrotizing pancreatitis − Well-defined non-epithelial wall − Fluid rich in amylase/lipase	▪ Well circumscribed, usually round or oval homogeneous fluid density ▪ No non-liquid component ▪ Well-defined wall (completely encapsulated) ▪ Maturation usually requires >4 wk after onset of acute pancreatitis ▪ Occurs after interstitial edematous pancreatitis
○ Acute necrotic collection	− A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis − The necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues. − Multiple, loculated collections of fluid and necrotic debris (< 4 wk) − Occur in 20% of patients with acute pancreatitis (AP) − Often associated with disruption of the main pancreatic duct (MPD) − Secondary infection in 30%	▪ Occurs only in the setting of acute necrotizing pancreatitis ▪ Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in the course) ▪ No definable wall encapsulating the collection ▪ Can be intrapancreatic and/or extrapancreatic

Term	Definition	Contrast-enhanced CT findings
○ Walled-off necrosis	− A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. − This usually occurs >4 wk after the onset of necrotizing pancreatitis. − Collection of pancreatic / peripancreatic necrotic debris − Enhancing encapsulated wall (reactive tissue) − WON develops ≥ 4 wk after necrotizing pancreatitis − May become infected − Predicts severity and progression of pancreatic inflammation" − Diagnose by MRCP/MRI, EUS, contrast enhanced CT scan − Perform again before endoscopic drainage or surgery	▪ Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous) ▪ Well-defined wall (completely encapsulated) ▪ Intrapancreatic and/or extrapancreatic location ▪ Maturation usually requires 4 wk after onset of acute necrotizing pancreatitis

Adapted from: Muthusamy VR, et al. Gastrointest Endosc 2016; 83: 481-486 (Table 2).

➢ Diagnostic imaging and endoscopic / surgical drainage

- Give why MRCP / contrast enhanced CT and EUS should be reported before endoscopic / surgical drainage.
  - The differential will give several conditions which do **not** need to be drained (non-inflammatory fluid collection)
    - Cystic neoplasm
    - Duplication cyst
    - Pseudoaneurysm
  - Differentiating infected from non-infected necrosis
    - Infection most common at 2-4 wk
      - Fever
      - Gas bubbles on imaging
      - Clinical deterioration

- Give why EUS-FNA of WON not recommended to differentiate infected from non-infected WON.
  - False-negative rate high
  - ↑ risk of contamination (introduction of bacteria into previously sterile WON)

Recommendation(s)

- Drain all infected PFCs in patients who fail to improve with conservative management alone (Quality of evidence, high)
- Drain symptomatic sterile necrosis lasting more than 8 wk after the onset of acute pancreatitis (Quality of evidence, moderate)
- Routine FNA of PFCs is not required to diagnose infected necrosis (Quality of evidence, low)

➢ Treatment

Recommendation(s)

- Perform endoscopic drainage of PFCs only after sufficient exclusion of alternative diagnoses, such as cystic pancreatic neoplasms and pseudoaneurysms (Quality of evidence, high)
- Wait for maturation of the cyst wall of PFCs before endoscopic intervention (Quality of evidence, moderate)
- Drain symptomatic pancreatic pseudocysts (Quality of evidence, moderate)

- Acute peri-PFCs / ANCs
  - Do **not** usually require treatment
- Pseudocysts, WON-treated after 4 wk (encapsulation)
  - Treated after 4 wk (encapsulation)

▪ The later the timing of drainage, the better

Time (days) from hospital admission	Mortality rate
0-14	56%
14-29	26%
> 29	15% (P < 0.001)

- Pseudocysts, WON treated after 4 wk (encapsulation)
- Pseudocyst endoscopic (ERCP) drainage (transmural)
- Outcomes
  - Drainage successful, ~80% to 100%
  - Adverse events, ~5% to 15%
  - Recurrence, 18%
    - Better outcomes when transmural stent is combined with placement of nasocystic tube (NCT)

Recommendation(s)

- Drain rapidly enlarging pancreatic pseudocysts (Quality of evidence, low)
- Consider endoscopic drainage for initial therapy before surgical drainage of pancreatic pseudocysts (Quality of evidence, moderate)

- WON
  - Indications (after 8 wk)
    - Pain, refractory
    - Anorexia / ↓ weight
    - Obstruction
      - Stomach
      - Bile duct
    - Systemic illness
      - Peridrainage care
        - Antibiotics
        - CO_2 insufflation
        - Deep sedation
  - Comparison of endoscopic is surgical drainage: ↓ risk of
    - Inflammation
    - Multiple-organ failure (MOF), new onset
    - Fistulae

➢ Endoscopic Methods of Drainage of Pseudocysts

- Transmural
  - Make an endoscopically assisted women in wall of stomach / duodenum
    - Dilate puncture incision with a balloon
  - Insert ≥ 1 stents
    - Double-pigtailed
    - Plastic
    - Self-expandable metal stent (SEMS; lumen-apposing, covered)
    - SEMS plus plastic double pigtail

Recommendation(s)

- Perform endoscopic drainage of PFCs only with the availability of surgical and interventional radiology support (Quality of evidence, high)
- Use CO_2 when performing transmural drainage procedures (Quality of evidence, low)

SO YOU WANT TO BE A THERAPEUTIC ENDOSCOPIST!

- Give when it is recommended to use EUS-guidance for endoscopic drainage of PFCs.
  - When there is no compression / indentation of the lumen of the stomach or duodenum from the PDC to be drained endoscopically visible

Recommendation(s)

- Use EUS for transmural drainage of PFCs in the absence of a luminal bulge or when portal hypertension is suspected (Quality of evidence, high)
- Also, use for
  - PFC in unusual location
  - Varices which might complicate the procedure: "…prior failed direct endoscopic approach"

- Transpapillary
  - For pseudocysts which communicate with MPD, perform sphincterotomy and pass the stent towards the tail of the pancreas, placing the stent across any area of disruption of the MPD (↑ rate of successful drainage in pancreatis body / tail)
  - Adverse outcomes of transpapillary drainage
    - Parenchyma
    - Duct
    - Fluid
    - Post-ERCP pancreatitis
    - Stent-induced scarring
    - Slower / incomplete drainage
    - Infection

➢ Walled Off Necrosis (WON)

- Place 2 transmural plastic pigtail stents
  - Lumen opposing large-diameter metal stents nasocystic drainage (NOD)
  - If inadequate clinical benefit from NCD within 48-72 hours
    → endoscopic transmural necrosectomy (ETN)
    → repeat ETN q48-72 h as needed to remove all necrotic debris
- Outcomes
  - Success rate ~75%
  - Adverse events, 36%
  - Mortality, 6%
- Other methods
  - Combined endoscopic plus radiological drainage
  - Multiple transluminal gateway technique (MTGT)
    - Transmural tract for nasocystic lavage
    - Tract for drainage of necrotic debris

    } ↑ rate of clinical success vs. conventional single tracts, 92% vs. 52%

Recommendation

- Initial endoscopic transmural and/or percutaneous drainage of WON before consideration of endoscopic transmural necrosectomy or surgical drainage (Quality of evidence, high)

- After-procedure Care
  - Antibiotic prophylaxis
  - Repeat / follow-up CT scan at 4-6
  - Remove internal stents endoscopically when diagnostic imaging suggests resolution
  - In patient with chronic pancreatitis (CP)
    - Perform endoscopic therapy of any obstruction of the MPD
  - In patient with WON plus disconnected pancreatic duct syndrome / disruption of MPD
    - Insert long term indwelling transmural stent to ↓ risk of recurrence of PFC
    - Infection in site of transpapillary drainage may be resolved with
      - Conversion to a transmural approach
      - Exchange smaller for larger stent

- Adverse events of endoscopic therapy of PFCs
  - Pancreas
    - Infection
    - ↑ risk
      - Inadequate drainage of fluid / necrotic debris
    - Hemorrhage, obstruction, perforation (damage to MPC)
  - Stent
    - Migration
  - Patient
    - Aspiration, sedation complications, mortality

Pancreatic Neoplasms (Muthusamy VR, et al. Gastrointest Endosc 2016; 84: 1-9)

- Demography
  - Found incidentally in 2.5% persons by diagnostic imaging undertaken for other reasons incidence in persons ≥ 70 yr, 10%

- Types

- Neoplastic (epithelial)
  - Serous cystic neoplasms (SCNs) (16%)
  - Mucinous cystic neoplasms (MCNs) (20%)
  - Intraductal papillary mucinous neoplasms (IPMNs) (38%)

- Indeterminate Biliary Strictures Non-neoplastic
  - Pseudocysts
  - Other types of pancreatic tumours which may have cystic component
    - Neuroendocrine tumours (NET), cystic component (7%)
    - Pancreatic duct adenocarcinoma (PDAC)
    - Solid pseudopapillary neoplasms

- Endoscopy: Endoscopic Ultrasound
  - Do **not** use EUS to distinguish
    - Benign from malignant IPMN< or
    - Mucinous from non-mucinous pancreatic neoplasms
  - Do **not** use size of cysts to distinguish benign from malignant pancreatic cystic tumours
    - Of cystic lesion ≤ 2 cm
      - Malignant, 20%
      - Malignant potential, 45%

      } However, ~95% of these were symptomatic
  - Microcysts
    - Multiple small (< 3 cm) compartments within a cystic lesion suggests a serous cystic lesion
    - Accuracy 92% to 96%

- Pancreatitis
  - Atrophy
  - Calcifications
  - Change in echo texture

  } → Plain cysts → Septations
  → Plus, cysts with no → Solid components

  } Pseudocyst
    - Sensitivity, 94%
    - Specificity, 85%

- Distinguish intracystic mucus from epithelial nodule
  - Intracystic mucus
    - RIM
      - Smooth, well-defined
    - Centre
      - Hyperechoic
      - Hypoechoic
  - Epithelial nodules
    - RIM
      - Poorly defined
    - Centre
      - Hyperechoic
- Predictors of malignant vs. benign IPMN
  - Cyst > 3 cm
  - Enhancing solid component in cyst
  - MPD walls thickened
  - Enhancing solid component in cyst
- Worrisome features
  - MPD
    - 5-9 mm
    - Sudden change in diameter of duct
  - Parenchyma
    - Atrophy upstream to duct
  - Peripancreatic lymphadenopathy

- Contrast enhanced EUS
  - Assess ↑ vascularity

Recommendation

- ERCP, pancreatoscopy, and intraductal US may be helpful in the diagnosis and characterization of suspected main duct IPMNs (Quality of evidence: low)

- EUS plus FNA
  - Perform cystological / histological examination of
    - Aspirated solid material
    - Regional lymph nodes
  - Performance characteristics of cytology to distinguish mucinous from neuromucinous pancreatic cysts
    - Sensitivity, 54% to 63%
    - Specificity, 88% to 93%

- Adverse events ~3%
  - Pancreatitis
  - Bleeding
  - Infection
- "…current ASGE guidelines suggest administration of antibiotics for 3 to 5 d after EUS-FNA of pancreatic cysts lesions

Recommendation(s)

- Administer of prophylactic antibiotics for patients undergoing EUS-FNA for the evaluation of cystic pancreatic neoplasms (Quality of evidence, low)
- Clues
  - Cuboid cells
    - Glycogen-ride → serous neoplasm
  - Histocytes
    - Macrophages, neutrophils → pseudocyst
  - Mucin
    - Mucinous neoplasm
- Use EUS-FNA of any pancreatic cystic lesion over 3 cm in diameter or when cross-sectional or EUS imaging confirms an epithelial nodule, dilated main pancreatic duct, or suspicious mass lesion (Quality of evidence, medium)
- EUS-FNA is optional in asymptomatic patients in whom cross-sectional imaging demonstrates a cyst <3 cm and without either a mass and/or epithelial nodule or associated dilated main pancreatic duct (Quality of evidence, low)

- New Endoscopic Techniques
  - Confocal laser endomicroscopy plus IV fluorescein
  - Cholangioscopy
  - Pancreatography

- ERCP **not** usually recommended, except if
  - Signs suggestive of
    - MPD IPMN
      - Mucus coming out of patulous pancreatic orifice (pathognomonic, seen in 20% to 55%)
    - Pancreaticoduodenal fistula, with mucous seen in IPMN with malignant invasion
  - Narrow MPD
    - Pancreatitis
    - PDAC
    - Pancreatic trauma

- Communication with MPD
  - IPMN
  - Pseudocyst
    - SCN
    - MCN

  } Rare

➢ Establish type of cyst

- Differentiating benign vs. malignant EUS
  - Sensitivity, 85% to 96%
  - Specificity, 30% to 99%
- Differentiating true solid cyst from mucin

	Mural Nodules	Mucin
– Border	▪ Poorly defined	▪ Well defined
– Echoic	▪ N/↑ centre	▪ ↓ centre

- Performance characteristics to distinguish IPMNs or MCNs from other types of cysts vary depending upon cut-off used for fluid measurements
- CEA in cystic fluid

	Cyst Fluid Cut-off	
	192 ng/mL	> 800 ng/mL, or < 5 ng/mL
– Sensitivity	63%	50%
– Specificity	95%	95%

  - ↑ amylase in cystic fluid < 250 IU/L excludes 98% of pseudocysts
  - Cytology
    - Sensitivity, 54% to 63%
    - Specificity, 88% to 93%
  - Genetic profiles, KRAS +/- GNAS mutation
    - Sensitivity, 84% to 96%
    - Specificity, 100%

➢ Establish HGD/PDAC

- CEA
  - Poor performance
    - Sensitivity, 65%
    - Specificity, 65%
- Cytology
  - Sensitivity, 65%
  - Specificity, 90%
- Endoscopic equipment
  - Cytology
    - Impaired brush

- Needle
  - Microbiopsy forcep
  - Confocal microscopy
    - Performance characteristics for
      - Distinguishing

	Sensitivity	Specificity
– SCAs from other types of cysts	59% to 69%	100%
– IPMNs/MCNs from other types of cysts		80%

Abbreviations: GNAS, guanine nucleotide-binding protein, KRAS, k-RAS 2 Kirstein rat sarcoma viral oncogene homology

Recommendation(s)

- EUS-FNA plus analysis of cyst fluid: indications
  - Cysts diagnosis which are not clear, or when type of cyst will change treatment
    - CEA (cyst fluid) to differentiate IPMNs/MCNs from other cysts
    - Do **not** do CEA or identify IPMNs/MCNs with high grade dysplasia/cancer

    (Conditional recommendation, very low quality of evidence)
  - Cytology of cyst fluid to determine if the cyst has high grade dysplasia/cancer when
    - "…imaging features alone are insufficient to warrant surgery

    (Conditional recommendation, very low quality of evidence)
  - Molecular markers
    - To identify IPMNs/MCNs when diagnosis is unclear
    - When making a diagnosis would change treatment

    (Conditional recommendation, very low quality of evidence)

- Pre-/intraoperative pancreaticoscopy
  - Outline direct margins for resection of selected areas

	SCNs	MCNs	IPMNs	PC	SPT	CEN
Sex	F	F	F, M		F	F, M
Age of diagnosis (decade)	5-7	4-6	5-7		2-3	
Single		+				
Multiple						
Site in pancreas						
– Head			+		+	
– Body			+		+	
– Tail			+		+	
Microcysts (honey comb)	+					
Well-demarcated					+	
Ovarian stroma		+				
Heterogenous					+	

	SCNs	MCNs	IPMNs	PC	SPT	CEN
○ Component						
− Solid	+					
− Cystic	+					
− Unilocular	+	+				
○ Calcification	+(*)	+(*)			+	
○ Central scar	+(*, 30%)					
○ Walls						
− Thick	+					+
− Enhancing						+
○ Functioning tumour						+ (15%)
○ High grade dysplasia, cancer	5-15%					
○ Metastases						
− Solid					+	
− Cystic	+	+	+		+	

* pathognomonic
** IPMNs are multifocal, occur throughout pancreas, and a derived from ductal cells

	MD	BD	M	SPT
○ Malignancy	33% - 85%	11% - 38%	33% - 85%	10% - 15%
− Pancreatic cancer	+	+	+	

	IPMN		
	Main Duct	Branched-duct	Mixed
○ Common	-	+	+
○ Main pancreatic duct dilated diffuse / segmental, branched duct	-	+	+
○ No cyst first-month papillary	+		
○ Single/unilocular; cluster		+	
○ Multifocal		2% - 10%	
○ Head		+	
○ Body		+	
○ Tail		+	

➤ Characteristics of pancreatic cystic lesions

	Pseudocyst	IPMN	Mucinous cystic neoplasm	Serous cystic neoplasm	Cystic endocrine neoplasm	Solid pseudopapillary neoplasm	Ductal adeno-carcinoma with cystic degeneration
Clinical features	History of moderate to severe pancreatitis	History of pancreatitis, abdominal pain, or found incidentally	Usually found incidentally but can cause abdominal pain and a palpable mass if large	Usually found incidentally but can cause abdominal pain and a palpable mass if large	May have clinical features of solid pancreatic endocrine neoplasm	Usually found incidentally; rarely causes abdominal discomfort	Presents with painless jaundice, abdominal/back pain or rarely pancreatitis
Morphology/ EUS findings	Anechoic, thick-walled, rare septations, regional inflammatory nodes may be seen	Dilated main pancreatic duct or side branches; may appear as a septated cyst; may have a solid component	Macrocystic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant	Microcystic with a "honeycomb" appearance; rarely has a macrocystic component; central calcification	Unilocular cyst occupies most of neoplasm	Solid and cystic components	Primarily solid mass with cystic spaces
Fluid characteristics	Thin, muddy-brown	Viscous or stringy, clear	Viscous or stringy, clear	Thin, clear to serosanguineous	Thin, clear	Bloody + necrotic debris	Bloody ± debris
Fluid chemistries	↑ amylase, low CEA	↑ amylase and CEA	↑ CEA, low amylase	↓ CEA and amylase	Variable	Variable	Variable
Cytology	Neutrophils, macrophages, histiocytes; negative staining for mucin	Mucinous columnar cells with variable atypia; fluid stains positive for mucin	Mucinous columnar cells with variable atypia; fluid stains positive for mucin	Cuboidal epithelium that stains positive for glycogen	Monomorphic endocrine tumour cells; stains positive for chroma granin and synaptophysin	Monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm; stains positive for vimentin and a-1-antitrypsin	Malignant adenocarcinoma may be seen, but varying degrees of atypia may be present in the specimen
Malignant potential	None	Yes	Yes	Almost none (rare reports)	Yes	Yes	Already present

Abbreviations: *IPMN*, Intraductal papillary mucinous neoplasm; *CEA*, carcinoembryonic antigen

Printed with permission: Muthusamy VR, et al. Gastrointest Endosc 2016; 84: 1-9 (Table 2).

➢ Laboratory

- Blood
  - ↑ CA19-9, new ↑ in glycated hemoglobin (Hg A1C; new onset of diabetes) of advanced neoplasia/cancer
  - Measurements on fluid obtained by endoscopic aspiration from a cyst
  - Cystic fluid
    - Amylase
      - ↑ PC, IPMN
      - ↓ MCN, SPT, CNGT
    - CEA
      - ↑ IPMN, mucinous cysts (MCN)
      - ↓ SCA (↓ CEA rules out mucinous cysts)
    - Glucose
      - ↑ SCA, PC to distinguish
      - ↓ MCN, IPMN (glucose in cyst fluid < 50 to 80 ng/mL, 90% to 94% to distinguish mucinous from non-mucinous cysts
  - Mucinous vs. non-mucinous
    - ↑ CEA
    - ↓ glucose

➢ DNA mutations

- SCN
  - VHL
    - Present in 20% to 50%
    - Specificity, 100%
- MCA, IPMN
  - KRAS
    - Sensitivity, 60% to 70%
    - Specificity, 95%
  - VHL plus KRAS+ or GNAS+
    - Specificity, ~99%
  - IPMN
    - GNAS present in 30% to 60%
    - Specificity, high
- mTOR (PIK3A, AKT), usually found with high-grade dysplasia/cancer
- SPT
  - CTNNB-
    - Specificity, high
- CNET
  - MEN1
    - Specificity, high

➢ Histopathology

In the context of a pancreatic tumour and

- Patient – No pain or weight loss
- Tumour – Large, but no obstruction of biliary tree
- Blood test – ↑ LDH (lactate dehydrogenase)

- Give the most likely pathological diagnosis.
  - Only 1% of pancreatic tumours are lymphomas or extranodal non-Hodgkin lymphomas, and the typical patient-, tumour- and its characteristics are given above.

- Give "pathognomonic" findings which help to differentiate between the types of pancreatic cysts.
  - ERCP-mucus dripping from ampulla of Vater → IPMN
  - CT-central, sunburst calcification → serous cystadenoma

➢ Treatment

- Give the traditional therapeutic approach to the therapy of cystic lesions.

	Pseudocyst	Serous	Mucinous	Malignant
Head	Drain	Monitor	Monitor	Resect
Body	Drain	Monitor	Resect	Resect
Tail	Resect	Resect*	Resect*	Resect

  - Cyst fluid CGA < 3.1 mg/ml suggests serious cystadenomas, whereas CEA > 480 mg/ml suggest mucinous fluid

*Approach varies with risk of surgery

- Patient Fitness for Pancreatic Surgery
  - Predicting death from non-PDAC causes vs. PDAC
    - Charlson comorbidity index (CCI) at 5 yr, 78% of deaths not sue to IPMNs
      - Chance of non-IPMNs-related death at 3 yr CACI > 7
        - ↑ IIX median survival 43 mon
      - CACI may be useful to predict which patient would not likely to benefit from surgical resection of IPMN (would die from non-IPMN comorbidities)
    - Adult Comorbidity Evaluation 27 (ACE-27) score moderate/severe, plus age of patient at diagnosis may also predict when patient with IPMN more likely to die of their comorbidity than from the IPMN

- Ablation of Pancreatic Cysts
  - Alcohol +/- paclitaxel, or radiofrequency ablation → ↓ size of cyst, however
    - There is no evidence that ↓ size of IPMN/MCN reduces the risk of
      - Progression to HGD/PDAC
      - Development of PDAC in a patient of the pancreas away from the cyst

Recommendation(s)

- Asymptomatic cysts on initial investigation
  - Patients no fit for surgery
  - Pseudocysts on clinical history/initial investigation (which have very low risk of malignant transformation do **not** investigate extensively

  (Conditional recommendation, low quality of evidence)
  - Initial investigation suggests MCN/IPMNs in patient who is surgically fit offer cyst surveillance

  (Conditional recommendation, low quality of evidence)
- MRCP is the best diagnostic imaging modality for surveillance of pancreatic cysts
  - EUS is performed for surveillance when MRCP cannot be performed

  (Conditional recommendation, very low quality of evidence)

- Postsurgical resection
  - MSNs surgically resected MCNs (regardless of presence of dysplasia [even HGD])
    - Do **not** develop a new MCN in remainder of post-surgical pancreas, but
    - 25% risk of recurrence of original cancer
      - Surveillance for 5 yr
  - IPMNs high risk of recurrence of IPMNs including PDAC in remnant pancreas (10% to 65%)
    - Follow guidelines for PDAC (e.g., Tamera K, et al. Ann Surg 2014; 259: 360-368)
  - HDG resected
    - Recurrence 13% to 31%
    - Median time to recurrence, 19 to 47 mon
    - Surveillance (MRI/EUS) q6 mon
  - Low/intermediate grade dysplasia resected
    - Recurrence in 0% to 22%
    - Surveillance q2 yr
  - Solid-pseudopapillary neoplasm with negative margins
    - Recurrence in 4% within a median time of ~50 mon
    - Surveillance imaging q1yr for 5 yr

Recommendation(s)

- Patients with surgically resected benign cysts (e.g., SCA, pseudocyst), do **not** require post-operative surveillance or resected MCNs without cancer (Strong recommendation, low quality of evidence)
- Surveillance
  - IPMNs
    - Post-operative surveillance
  - Solid pseudopapillary
  - Neoplasm
    - Surveillance q1yr for ≥ 5 yr

    (Strong recommendation, very low quality of evidence)
- If patient becomes a non-surgical candidate
  - Stop surveillance (Strong recommendation, very low quality of evidence)
  - Assess patients > 75 yr for suitability for surgery (Conditional recommendation, very low quality of evidence)
- Also consider
  - Family history of pancreatic cancer
  - Selected genetic changes e.g., mTOR
  - Other high-risk factors e.g., age

- Multidisciplinary team
  - High risk (MCN, IPMN)
    - Surgical resection / minimally invasive procedures
      - If cyst is stable (< 20% / ↑ size/yr or growth < 2.5 mm/yr → ↓ frequency as per size of cyst q6 mon

❖ AGA Guidelines

Indication for EUS (≥ 2 of the following)	Indications for Surveillance
– Cyst size ≥ 3 cm	▪ < 3 cm
– Solid component	▪ No solid
– MOD dilated (no specific measurement)	▪ No MPD dilation
↓	↓
Surgery	MRI at 1 yr, then q2 yr x2 if concerning features develop → EUS-FNA

- Fukuoka guidelines for resection
  - All MCN / MD-IPMN, mixed
  - BD-IPMN
    - Symptoms obstructive jaundice from PCN at level of pancreas
    - Solid component, enhancing on diagnostic imaging
    - MPD > 10 mm
    - EUS-FNA cytology suspicious

Concern for Fukuoka Guidelines
- MPD > 6 mm, ↑ risk of malignancy, pooled or 7.27 (95%CI: 3.0-17.4)

  - Intermediate risk
    - Perform additional laboratory / diagnostic imaging to fully stratify risk
    - If highly likely to be intermediate risk segmental resection plus surveillance
    - MRCP / MRCP+EUS
    - MRCP, 6 mon x2, then q1yr
    - Surveillance
    - Surgery sometimes performed, with no need for further surveillance

- Image considerations (high risk cysts (IPMNs/MCNs) (↑ risk HGD/PDAC)
  - Size of IPMN cyst ≥ 3 cm
    - Surrogate for HGD/PDAC or for HGD/PDAC 2.97 (95%CI, 1.82-4.85); other data or 62.4 (95%CI, 30.8-126.3)
  - Rapid ↑ size of IPMN ≥ 3 mm/yr (range, 2 to 5 mm per yr)
    - Repeat MRI/EUS +/- EUS +/- FNA in 6 mon
  - Mural nodule / solid component OR 9.3 (95%CI, 5.3-16.1)
    - Patients with IPMNs, but not patients with MCNs are at risk of developing malignancy in the preventive parenchyma anatomically sperate from the cyst" (a "concomitant" PDAC; develops in 4% to 8% of persons with IPMNs
    - Implication: in patient with IPMN, and the rest of the pancreatic parenchyma
  - Main pancreatic duct (MPD) > 6 mm (dilation)
    - OR 7.25 (95%CI, 3.0-17.4) for HGD/PDAC
    - ↑ risk
      - HGD, ~60%
      - PDAC < ~44%
    - Suggestion of ACG Guideline Committee
      - "We recommend use of a consecutive duct diameter [of] > 5 mm
      - A sudden change in the caliber of the MPA is also of concern
    - Focal dilation/obstructing lesions

Serous Cystadenoma

- Laboratory
  - Cyst filed with clear, watery fluid (no mucin)
  - Cytology of fluid may show cuboidal cells with glycogen-rich cytoplasm.
- Diagnostic imaging
  - Body or tail of pancreas
  - Many tiny cysts
  - Fibrous septa
  - Honeycomb appearance
  - Scar with stellate appearance
  - Stellate scar may be calcified
  - Central. “sunburst” calcification (on CT scan)
  - No communication with pancreatic duct
- Prognosis
  - Rarely malignant (3%)

Mucinous Cystic Neoplasm (MCN)

- Laboratory
  - Thick mucus material (or blood)
  - Fluid in cyst
    - ↑ CEA
    - In benign MCN
  - Cytology shows
    - Adenocarcinoma cells
    - Columnar
- Diagnostic imaging
  - May be benign, but in individual patient assume to be malignant
  - Body or tail of pancreas
  - Thick wall
  - Occasional septa
  - Stroma (ovarium-like)
  - Mucinous epithelial cells with atypia

- No communication with pancreatic duct on ERCP/MRCP larger cysts with nodules in wall are more likely to be malignant than benign MCN.
- Lesions are never mutifocal, so once the single lesion is removed, surveillance is not necessary.

- Prognosis
  - 5-yr survival rate after resection of tumour, 30% to 63%

Intraductal Papillary Mucinous Neoplasms (IPMN)

- Definition
  - "…. Papillary neoplasms within the main pancreatic duct showing mucin hypersecretion that often leads to duct dilation and chronic obstructive pancreatitis.
  - Thick (viscous) mucous with ↑ CEA, ↑ amylase

- Demography
  - Male: female ratio: 1-2.4
  - Mean age of diagnosis
    - 65 yr

- Genetics
  - As compared with pancreatic adenocarcinoma
    - In IPMN there are more frequent molecular changes in SKT 11/LKB1 inactivation and PIK3CA mutation
    - Less frequent mutations in K-Ras and P53 tumour suppressor genes, P16 and DPC4
  - In IPMN, there is ↑ expression of
    - Fascin (an actin-bundling protein), methylated PPENK
    - Human telomerase reverse transcriptase

- Types
  - Main, branched or main plus branched (mixed) pancreatic ducts
  - Main duct IPMNs are more likely to become malignant and to grow faster: 63% develop HGD/cancer in 5 yrs, vs 15% for branched chain IPMNs

- Clinical
  - Symptoms arise from mucin distending involved pancreatic duct; (may see mucus extruding from ampulla on ERCP)
  - 5-yr survival rate after resection, > 75%
  - Main duct IPMN or branching chain IPMN > 3 cm are more likely to be malignant.

- Laboratory
  - Increased serum bilirubin predicts the presence of malignancy
  - ↑ CEA in 80-95% of IPMNs

- Give the significance of ↑ amylase concentration in the fluid aspirated from pancreatic cysts.
  - Amylase in a gut aspirate only signifies that the cyst which contained the fluid was in commutation with a pancreatic branch duct or main duct.

- Diagnostic imaging
  - MRI
  - CT
    - CT using pancreatic protocol (detects IPMN in 97% of cases)
  - MRCP
    - Breath-hold MRCP
    - MRCP with secretin (S-MRCP),
    - MRCP is superior to CT to demonstrate communication between ducts, and cyst morphology
  - EUS
  - ERCP
  - PET scanning sensitivity, 57-90%; specificity, 85-97%
  - Exclude pancreas divisum (MRCP, 100% accurate; CT, sensitivity 90%, specificity, 97%)

- Histopathology
  - Cytology
    - Columnar mucinous epithelial cells with variable atypia
  - Grape-like cluster of cysts, localized or diffuse dilation of main pancreatic duct, patulous ampulla of Vater
  - Lesions of main or bronchial pancreatic ducts, with proliferation of the mucinous epithelium leading to ductal and cystic dilation
  - 20-30% of IPMNs are multifocal, arising from a field defect in the entire pancreas that can cause multiple primary neoplasms.
  - Range histologically from benign, low grade (LGD), or high grade dysplasia to invasive cancer, with various grades of histology, probably being present with the same specimen

- Treatment
  - Chemotherapy
  - Cyst ablation with ethanol or paclitaxel (a chemotherapeutic agent which inhibits the disassembly of microtubules and induces apoptosis with complete resolution of cysts in 79%, may be reasonable for IPMNs with low risk of malignancy:
    - No symptoms
    - < 3 cm size
    - Main duct < 6 mm
    - No mural nodules, thickness or septations
  - Endoscopy
    - Nasogastric (NG) drain
    - Stent

- Give the pros and cons of nasogastric drains versus pancreatic stents.

Nasogastric Drain	Stent
Pros	
Flushing and fluoroscopy at any time	▪ Easy, quick, dislocation rare ▪ Not disabling, patients stay mobile, feel better
Cons	
Discomfort; easily dislocated; leads to immobilization of patients, nose-pain; flushing often futile and tedious, no direct control during flushing	▪ No flushing ▪ Control needs endoscopic session

Printed with permission: Giovannini M. Best Pract Res Clin Gastroenterol 2004; 18(1):183-200.

  - Surgery
    - Sendai guidelines for resection
    - After surgical resection, invasive > 40%, non-invasive > 70%; resections recur in a median of 20 mon, and 58% of these recurrences involve distal sites.

- Give the **Sendai Guidelines** for resection of IPMNs.
  - Symptomatic – All IPMN (MD- and BD – IPMN) with symptoms
  - Asymptomatic – All MD-IPMNs
    – BP-IPMNs > 3 cm
  - EUS – All IPMN with
    - Nodules
    - Thickening
  - CEA – > 192
  - Surveillance EUS, ERCP, MRCP (CT scan) – Enlargement on surveillance every 6-12 mon

An ↑ CEA > 192 in IPMN predicts future or present malignant degeneration.

Non-Inflammatory Pancreatic Cysts (Pancreatic Cystic Neoplasm [PCNs])
Phan J and Raman Muthusamy VR. Curr Gastroenterol Rep 2018; 20(7):32.

- Demography
  - Incidental findings in 3% to 20% of all abdominal CT/MRIs
  - Prevalence ↑ with age
  - W > M, except for IPMN
  - Risk of cyst seen on MRI becoming PDAC 0.24%
  - Malignant potential
    - Low: non-mucinous
      - Serous cystic neoplasms (SCNs)
      - Solid pseudopapillary epithelial neoplasms (SPEN)
    - High: mucinous
      - Mucinous cystic neoplasm (MCN)
      - Intraductal papillary mucinous neoplasms (IPMN)
  - Surgical
    - Morbidity and mortality, 30%

- Clinical
  - Asymptomatic or symptomatic e.g., jaundice (biliary obstruction)

- Diagnostic imaging (DI)
  - CT/MRI useful to demonstrate non-inflammatory pancreatic cysts
    - May not indication which type, or benign vs. malignant

- Typical DI features
  - SCN
    - Clusters
    - Microcysts
    - Central radiation
    - Stellate calcifications
  - Present in only 20% of SCNs
    - Multiple septations (accuracy for SCN > 90%)

➢ Endoscopy

- Endoscopic ultrasound (EUS)
  - Incremental diagnostic yield of EUS to CT scan, 19% to 36%
  - Sensitivity for detecting cysts < 1 cm EUS > CT
  - Presence of mural nodules
    - Diagnostic accuracy mucinous cysts (MCN/IPMN), 83%
    - Associated with dysplasia/cancer
- EUS plus FNA
  - Performance characteristics for detecting mural nodules
    - Sensitivity, 2x > CT
    - Specificity, 35% to 58%
    - EUS, 63%
    - EUS plus FNA (cytology plus fluid analysis), 86%
  - Identify cancer
    - Sensitivity, 30% to 63%
    - Specificity, 100%
- Septations
  - Multiple septations suggests SCN (accuracy > 90%)
- Fluid markers
- Carcinoembryonic (CEA) secreted by mucinous cells
  - CEA > 300 ng/mL predictive of MCN/IPMN
    - Sensitivity, 48%
    - Specificity, 98%
  - CEA < 5 ng/mL predictive of SCN/pseudocyst
    - PPV, 95%
    - Accuracy, 67%
- Limited use for CA124, CA72-4, CA19-9
- Amylase
  - Present if fluid in cyst arises from communication between cyst and main pancreatic duct (MPN), e.g., in IPMN
  - Amylase < 250 U/L rules out pseudocysts
    - Sensitivity, 44%
    - Specificity, 98%
  - However, inconsistent predictability
  - Amylase < 350 U/L plus CEA < 30 ng/mL predicts SCN in 85%

- Fluid viscosity / “string sign”
  - Used to predict presence of mucinous cyst (MCN, IPMN)
  - CEA > 2000 ng/mL plus ↑ viscosity predicts MCN/IPMN with diagnostic accuracy of 89%
  - GNAS, sensitivity for IPMN, 66%
- Molecular changes
  - KRAS plus GNAS mutations, sensitivity 96%
    - Sensitivity, 12% to 50%
    - Specificity, 80% to 96%
  - “..when compared against CEA or cytology, there was no significant difference in the accuracy of comprehensive DNA analysis in detecting mucinous cysts”
  - Perhaps the role of identifying molecular changes is to improve NPV of the analysis of cyst fluid for dysplasia/cancer (MCN, IPMN)

➢ Treatment

❖ Mucinous cysts: algorithms for cyst diagnosis and treatment

- Sendai guidelines to predict malignant potential (i.e., ↑ risk factors)
  - Cyst
    - Size > 3 cm (resect all cysts > 3 cm)
    - Mural nodule
  - PD dilation
    - MD-IPMN > 5 mm
    - BD-IPMN > 6 mm
  - Symptoms
    - E.g., jaundice, pain, pancreatitis
  - FNH
    - Cytology positive

Treatment Teaser

- Give the negative issue for using the Sendai guidelines to identify high risk and need to resect a PCN.
  - The size of the cyst > 3 cm is an issue for malignancy prediction, since ~50% of PCN > 3 cm are benign
  - < 3 cm PCN, ~25% are malignant
  - PPV, 11% to 52%
  - NPV, 71% to 100%

➢ Gonda Scoring System

Cyst Size and Features	Year 1	Year 2-5	After > 5 yr of Stability
○ < 1 cm	− 12 mon	− q2 yr	− q2 yr Consider ceasing surveillance
	Measurement of CA19-9 MRI HgA1C		
○ 1-2 cm	− 6-12 mon	− q1-2 yr	− q2 yr Consider ceasing surveillance
	Measurement of CA19-9 MRI HgA1C		
○ 2-3 cm	− Alternating q6 mon	− Either in 6-12 mon	− q1 yr
	EUS		Continue surveillance
	Measurement of CA19-9 MRI HgA1C		
○ > 3 cm, or worrisome feature (when surgical resection is not pursued)	− Alternating q3 mon	− Alternation q3-6 mon	− q6-12 mon
	EUS		Continue surveillance
	Measurement of CA19-9 MRI HgA1C		

Adapted from: Gonda TA, et al. N Eng J Med 2024; 394: 832-843 (Figure 4)

➢ Differential

- In the context of a pancreatic tumour on diagnostic imaging plus the following features, give the most likely pathological diagnosis.
  - Patient – no pain or weight loss
  - Tumour – large, but no obstruction of biliary tree
  - Blood test – ↑ LDH (lactate dehydrogenase)

- Give the most likely pathological diagnosis.
  - Only 1% of pancreatic tumours are lymphomas or extranodal non-Hodgkin lymphomas, and the typical patient-, tumour- and its characteristics are given above.

- Give "pathognomonic" findings which help to differentiate between the types of pancreatic cysts.
  - ERCP-mucus dripping from ampulla of Vater → IPMN
  - CT-central, sunburst calcification → serous cystadenoma

➢ Useful Recent References

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