Academic Half Days

GASTROENTEROLOGY & HEPATOLOGY

Volume II

Western University
London ON

Edited by

Alan B.R. Thomson

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Thank you

Alan B. R. Thomson

DEDICATIONS

To Jeannette……With Love

Forever and Ever Alan

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

Multiple Complex Esophageal Disease: Achalasia, Varices and Esophagitis

Pavithra Parthasarathy

- Achalasia

➢ Background

- ↓ LES relaxation
- Lack of smooth muscle peristalsis
  - Caused by (postganglionic denervation) loss of ganglion cells in myenteric plexus → ↓ excitatory / inhibitory nerve function

➢ Clinical

- Solid +/- liquid food dysphagia (gradual onset)
- Regurgitation (occurs once esophagus dilated and filled with food/fluid)
- Chest pain from esophageal spasm
- Aspiration pneumonia
- Weight loss
- Eckardt Score for Symptomatic Evaluation in Achalasia

Score	Weight Loss (kg)
0	None
1	< 5
2	5-10
3	> 10

0-1: stage 0
2-3: stage I
4-6: stage II
> 6: stage III

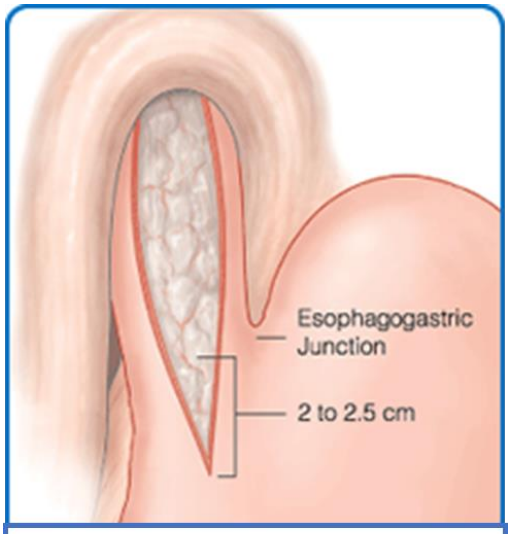
- Recurrent Achalasia

➢ Clinical

- Post-surgical (cardio myotomy) symptom recurrence in 10-25% of patients

- Proposed causes
  - Inadequate myotomy
    - Incomplete division of muscle fibers
    - Fibrosis at distal myotomy site
  - Pre-existence of sigmoid-shaped megaesophagus
  - Excessively tight fundoplication
  - Late development of esophageal carcinoma
  - Gastroesophageal reflux associated

- Treatment
  - Retrospective study in 26 patients with failed HM over 20 yr
    - Median time of recurrence 10 yr
  - Treated with
    - Endoscopic pneumatic dilation
    - Laparoscopic Heller myotomy (HM) and fundoplication
    - Esophagectomy, or
    - Stapled cardioplasty and fundoplication;
  - Follow up
    - Significant ↓ in dysphagia, regurgitation, chest pain, Eckardt score, respiratory symptoms, but
    - Absent 35% needed 3rd endoscopic/surgical procedure
  - Prospective study in 163 pts with failed HM who were amenable only to surgical reoperation
    - Reoperation (remyotomy/esophagectomy) has positive long-term symptomatic outcomes



Heller cardiomyotomy

Image courtesy of North Bristol NHS Trust webpage

Concurrent Management of Esophagogastric Varices and Achalasia

- Background
  - Complex, rare therapeutic dilemma
  - Considerations
    - Treat both with one modality or two separate modalities?
    - Variceal band vs. TIPSS vs. liver transplantation
    - Achalasia surgical revision vs. POEM vs. balloon dilation vs. botulinum
  - Combined risks of
    - Esophageal perforation
    - Variceal and non-variceal bleeding
    - Ineffective treatment
    - Aspiration

    } Even further complicated in a patient with cirrhosis
  - Leaving dysphagia/poor oral intake untreated, leading to malnutrition, can be detrimental for patients with cirrhosis (mortality and hospitalization rates); stasis and esophageal dilation can worsen esophagitis, ulcer formation, variceal bleeding

- Need to treat
  - Complications of delayed treatment (dysphagia, ↓ food intake) more frequent, severe, important in presence of hepatic cirrhosis
  - ↑ esophagitis (dilation of esophagus)
  - ↑ bleeding
    - Esophagitis
    - Ulcers
    - Varices

- Esophageal Variceal Treatment
  - Traditional management approaches (non-bleeding)
    - Band ligation
    - TIPSS
    - Non-selective beta blockers sclerotherapy
  - Concerns
    - Sclerotherapy → fibrosis / ↑ dysphagia
    - Band ligation
  - TIPSS can allow for further pneumatic dilation for achalasia

- Achalasia with Varices (Pesce M, et al. UEG Journal 2019; 7(4), 565-572)
  - International Manometry Working Group study (2019) – retrospective, multicenter case series
    - 14 patients with achalasia and varices, 7 international centers, 2008-2016
    - 20 age-matched controls with achalasia and without varices
    - Assessment with high-resolution manometry and barium swallow
    - Variceal eradication followed by achalasia treatment

➢ Treatments
  - Botulinum toxin injections (BTI)
    - Esophageal dilation
    - POEM
    - POEM then dilation
    - BTI then Heller myotomy
  - Positive short-term (6 mon)
    - Symptomatic response with similar therapeutic outcomes and complication rates (compared to controls)
      - Transient hepatic encephalopathy in two patients with TIPSS

- Botulinum Injection
  - Suggested in multiple individual case reports to treat achalasia when varices are present
    - Similar pre-treatment Eckardt scores in both groups
    - Botulinum was favoured more in the variceal group (43%) vs. in age-matched controls (5%)
    - POEM and pneumatic dilation favoured in the control group
    - Short-term study (6 mons)
  - Chosen due to patients being poor surgical candidates
    - Certain patient factors predict good response
  - Newer studies suggest use of EUS to identify large vessels to avoid injecting near/within these vessels; celiac plexus needle vs. conventional sclerotherapy needle

- Peroral Endoscopic Myotomy (POEM) with Varices

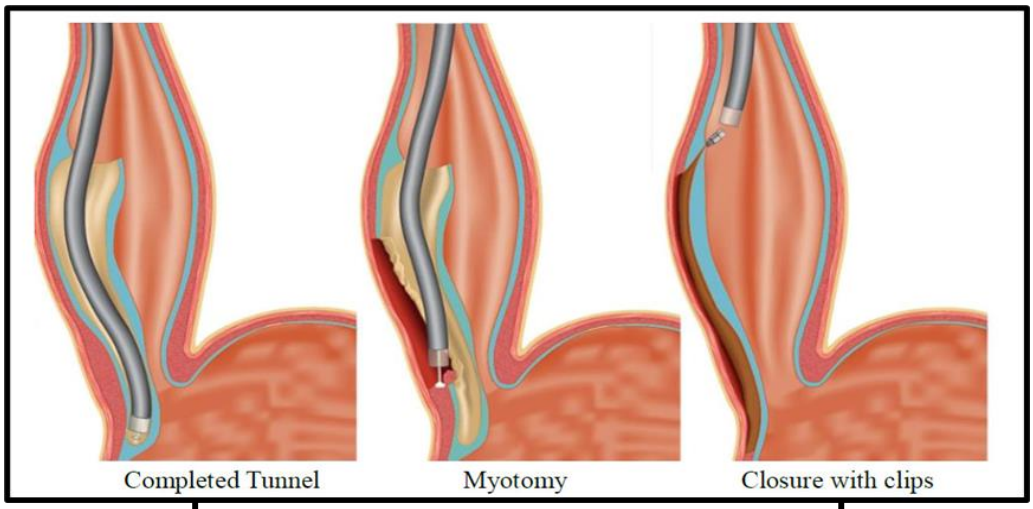


Image courtesy: Dr. R Bechara, Achalasia.ca

  - First case in 2017
  - Achalasia treatment modality
    - High remission rate
    - Low incidence of complications
    - Ability to directly visualize esophagus intraprocedurally
  - Can also provide hemostasis to varices during the procedure
  - Few case studies of POEM with varices, with extensive vessel electrocoagulation during the procedure; one case was post-TIPSS and variceal embolization

https://onlinelibrary.wiley.com/pages/journal/14431661/den13971-sup-0001-VidS1.htm

- Moderate size varices
  - No previous treatment
- Coagulation during POEM procedure
- Pneumatic Balloon Dilation
  - Done in some patients with
    - Small varices, or
    - If no other options available (e.g. failed Botox, not surgical/POEM candidate)
- Laparascopic HM: one case report only

- AXIOS Stent for Achalasia + Varices
  - Case report – July 2024
    - 65 M with decompensated liver disease, type 1 achalasia
  - Patient
    - Poor candidate for GJ tube placement
    - Not for pneumatic dilation due to perforation risks
    - Not a surgical candidate
    - POEM too high risk for patient
      - Botox - concern for hypotension
  - AXIOS stent placed at EGJ to allow passage of food
  - Esophageal varices noted during stent placement
    - Ligated
    - Stent also provides variceal tamponade
  - Patient had re-presentation with gastric ulcer, then multiorgan failure; passed away

➢ Key Points

- Achalasia with varices - rare phenomenon
- Esophagitis as a consequence of food stasis should be considered in patients with achalasia
- Treatment for both achalasia and varices needs a multidisciplinary approach, with consideration for management of both pathologies concurrently
  - Modalities include
    - Botox injection
    - POEM
    - Pneumatic dilation
    - AXIOS stenting in the right context
- Recognize that these patients are at high risk for malnutrition
- Focus on minimizing malnutrition in liver disease through enteral nutritional support/parenteral nutritional support while addressing achalasia

Suggested Reading:

Achalasia Canada. POEM procedure. https://www.achalasia.ca/poem.html.

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Diagnosis of Gastroesophageal Reflux Disease

Guideline, American College of Gastroenterology (ACG) 2022
(Katz PO, et al. Am J Gastroenterol 2022; 117: 27-56)

Pavithra Parthasarathy

- Diagnosis of GERD

➢ Definition

- Gastroesophageal reflux disease (GERD) is a condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications.
  - Objectively defined by presence of characteristic mucosal injury seen at endoscopy and/or abnormal esophageal acid exposure demonstrated on a reflux monitoring study

➢ Pathophysiology

- Poorly functioning esophagogastric junction (EGJ)
  - ↓ esophageal clearance
  - ↑ exposure of esophagus to gastric H^+ (HCl)
  - Alterations in esophageal mucosal integrity
  - Gastric juice triggers cytokine and chemokine release in esophagus → inflammatory cells migrate to this area (causing reactive changes including inflammation)
  - Esophageal hypersensitivity, ↓ salivary production

➢ Clinical

- Esophageal symptoms
  - Heartburn (substernal burning)
  - Regurgitation, +/- chest pain
  - Non-specific, can overlap with
    - Rumination
    - Achalasia
    - Eosinophilic esophagitis (EoE)
    - Reflux hypersensitivity
    - Functional disease
    - Paraesophageal hernia

- Extraesophageal symptoms
  - Hoarseness
  - Throat clearing
  - Chronic cough
  - Laryngitis
  - Pharyngitis
  - Pulmonary fibrosis

- Diagnosis
  - No gold standard for diagnosis
    - Use of PPI response as a surrogate for diagnosis has mixed evidence
  - Specific findings
    - Endoscopy
      - Erosive esophagitis
      - Barrett esophagus (BE) (> 3 cm) (LA grade B and above)
    - Reflux monitoring (to assess for acid exposure time
    - Number of reflux events
    - Correlation with “symptom index (SI)” or symptom association probability (SAP)

Key Statements

- For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms.
  - Use an 8-wk trial of empiric PPIs once daily (OD) daily before a meal (AC) (Strong recommendation, moderate level of evidence).
- In patients whose classic GERD symptoms respond to an 8-wk empiric trial of PPIs attempt to discontinue the PPIs (Conditional recommendation, low level of evidence).
- Perform diagnostic endoscopy (EGD), ideally after PPIs are stopped for 2–4 wks.
  - In patients whose classic GERD symptoms do **not** respond adequately to an 8-wk empiric trial of PPIs, or
  - Whose symptoms return when PPIs are discontinued (Strong recommendation, low level of evidence).
- If EGD off PPIs and there are no endoscopic changes of erosive esophagitis
  - Diagnose normal endoscopy (non-erosive reflux disease [NERD]) also helps in EoE investigation
- In patients who have
  - Chest pain without heartburn
  - Have had adequate evaluation to exclude heart disease, do EGD / or reflux monitoring (Conditional recommendation, low level of evidence).
- Do **not** recommend the use of a barium swallow solely as a diagnostic test for GERD (Conditional recommendation, low level of evidence).

- Do EGD as the first test of patients
  - Presenting with dysphagia or other alarm symptoms (weight loss and GI bleeding), or
  - Multiple risk factors for BE (Strong recommendation, low level of evidence).
- For LA C/D erosive esophagitis, do EGD after PPI to ensure healing and to rule out BE.
- In patients for whom the diagnosis of GERD is suspected but not clear, and endoscopy shows no objective evidence of GERD
  - Do reflux monitoring while patient is off therapy (Strong recommendation, low level of evidence). *7 days
- Do **not** perform reflux monitoring off therapy solely as a diagnostic test for GERD in patients
  - Known to have endoscopic evidence of Los Angeles (LA) grade C or D reflux esophagitis or in patients
  - With long-segment BE (Strong recommendation, low level of evidence).
- If patient is on therapy, do reflux monitoring to assess for reflux-related symptoms not responding to PPI
- Do **not** recommend high-resolution esophageal manometry (HREM) solely as a diagnostic test for GERD.
  - No HREM findings are not specific for GERD
  - May accompany severe GERD

- Special Consideration
  - Pregnancy
    - GERD occurs in ~65% of pregnant women
    - Resolves after delivery
    - Pregnancy plus weight gain are risk factors for GERD up to 1 yr post-delivery
    - Investigations rarely needed
  - NEW!
    - Catheter-based balloon with 36 channels sensors to measure mucosal impedance (pI) during endoscopy
      - May possibly help differentiate EoE vs GERD

➢ Treatment
  - Use a multifaceted approach
    - Non-pharmacologic
    - Pharmacologic, and
    - Surgical
  - Diet and lifestyle
    - Most evidence in weak or equivocal

- Nocturnal GERD symptoms
  - Elevation of head of bed (HOB) / sleeping on a wedge
  - Lie on left side while sleeping
- Some studies on foods affecting LES pressure, or having irritant effects leading to GERD – few studies to suggest avoiding these foods
- Food induced symptoms (avoid on an indicated basis)
  - ↓ intake of coffee, tea
- Stop smoking
  - 44% ↓ GERD symptoms in those who quit smoking for a year vs. 18% in those who continued to smoke
- Foods to ↓/avoid (“recommendable”)
  - Fatty meals
  - Carbonated beverages
  - Citrus
- Recommended lifestyle
  - Eat small meals
  - Lose weight
  - Avoid excessive exercise

*obesity and smoking are risk factors of cancer of distal esophagus

Key Statements

- Loose excessive body weight to ↓ symptoms of GERD (Strong recommendation, moderate level of evidence).
  - Dose-dependent improvement in GERD symptoms with weight loss in population-based Norway study
- Do **not** eat within 2–3 hrs of bedtime (Conditional recommendation, low level of evidence).
- Do **not** smoke / use tobacco products (Conditional recommendation, low level of evidence).
- Do **not** use “trigger foods” for GERD symptom control (Conditional recommendation, low level of evidence).
- Elevate head of bed for nighttime GERD symptoms (Conditional recommendation, low level of evidence).

- Pharmacologic therapy (principle: neutralize or reduce gastric acid in esophagus)
  - Antacids – for on-demand symptoms
  - Histamine 2 receptor antagonist (H2RA)
  - Proton pump inhibitor (PPI)

- Prokinetics (PKs)
  - Bind to proton pumps (Na^+/K^+ ATPase in active parietal cells)
    - Give 30-60 min before first meal of the day
    - Timing matters except for dexlansoprazole (duodenal and further small bowel absorption)
  - PPI or H2RA for
    - Faster mucosal healing (12%/wk vs 6%/wk) and
    - More complete heartburn relief (12%/wk vs 6%/wk)
  - NERD can be treated successfully with PPI, unless it is truly functional heartburn
- Overall GERD relief and healing rates not too different among 7 available PPIs except
  - Esomeprazole for 8 wk has shows ↑ healing of erosive esophagitis (NNT 25, ARR 4%)
- Beware of drug-drug interaction CYP2C19 metabolism affects PPI response by drug-drug interaction

Abbreviations: ARR, absolute risk reduction; NNT, number needed to treat, PK, prokinetic

- Use PPIs rather than histamine-2-receptor antagonists (H2RA) for
  - Healing EE (Strong recommendation, high level of evidence).
  - Maintenance of healing from EE (Strong recommendation, moderate level of evidence).
- Take PPI 30–60 minutes before a meal, not when fasting or at bedtime for GERD symptom control (Strong recommendation, moderate level of evidence).
- Stop PPIs or switch to on-demand therapy in which PPIs are taken only when symptoms occur and discontinued when they are relieved
  - For patients with GERD who do **not** have EE or Barrett's esophagus, and
  - Whose symptoms have resolved with PPI therapy (Conditional recommendation, low level of evidence).
- For patients with GERD who require maintenance therapy with PPIs
  - Give PPIs in the lowest dose of PPI that effectively controls
    - GERD symptoms and
    - Maintains healing of reflux esophagitis (Conditional recommendation, low level of evidence).
- Use maintenance PPI therapy indefinitely or anti-reflux surgery for patients with LA grade C or D esophagitis (Strong recommendation, moderate level of evidence).
  - ~100% relapse within 6 mon for LA-C, and often in as little as 1-2 wks
- Do **not** use routine addition of medical therapies in PPI non-responders (Conditional recommendation, moderate level of evidence).

- Do **not** use baclofen in the absence of objective evidence of GERD (Strong recommendation, moderate level of evidence).
- Do **not** use prokinetic agent for GERD therapy unless there is objective evidence of gastroparesis (Strong recommendation, low level of evidence).
- Do **not** use sucralfate for GERD therapy except during pregnancy (Strong recommendation, low level of evidence) (H2RAs FDA-B, PPIs FDA-B, but omeprazole FDA-C)
- Use on-demand or intermittent PPI therapy for heartburn symptom control in patients with NERD (Conditional recommendation, low level of evidence).
- There is a conceptual rationale for a trial of switching PPIs for patients who have not responded to one PPI.
  - More than one switch to another PPI cannot be supported.
- The lowest effective PPI dose, on an individual basis.
- Abrupt PPI may cause rebound acid hypersecretion, resulting in ↑ reflux symptoms (controversial: has been demonstrated to occur in healthy controls, but strong evidence for an ↑ symptoms after abrupt PPI withdrawal is lacking.
- Nocturnal acid breakthrough if PPI od fails → PPI bid if fails, add H2RA nighttime
  - Tachyphylaxis us common, consider intermitted 2 wk causes of H2RA

- Extraesophageal Reflux Syndrome (EERS)

Key Statements

- GERD may be a contributor to EERS manifestations
  - Careful evaluation for other causes should be considered for patients with
    - Laryngeal symptoms
    - Chronic cough
    - Asthma
- Diagnosis, evaluation, and management of possible EERS
  - Limited by lack of a gold-standard test, variable symptoms, and other disorders which may cause similar symptoms.
  - For example, there is difficulty in distinguishing between patient with laryngeal symptoms and normal controls
    - Do **not** do salivary pepsin for evaluation of patients with EERS.
- For patients with EERS who have not responded to a trial of twice-daily
  - Do EGD when patient has been upper endoscopy, ideally off PPIs for 2–4 wk
  - If EGD shows EE, this makes the diagnosis of GERD, but
  - Does **not** confirm that GERD is the cause of the extraesophageal symptoms
  - To determine that the EERS are due to GERD do pH/impedance testing.
- For patients with EERS
  - Do **not** routinely do oropharyngeal or pharyngeal pH monitoring.

- Proximal reflux may be associated with globus
  - Test on if pretest possible of GERD is ↑
  - Test off if pretest possible of GERD is ↓
- Surgery for extraesophageal symptoms – poor data
- Treatment of EERS
  - PPI
    - LPR, uncertain
    - Chronic cough, no
  - Surgery, uncertain
- Assess for non-GERD causes in patients with possible extraesophageal manifestations before ascribing symptoms to GERD (Strong recommendation, moderate level of evidence).
- Have patients who have extraesophageal manifestations of GERD
  - Without typical GERD symptoms (e.g., heartburn and regurgitation)
  - Test for reflux before PPI therapy (Strong recommendation, moderate level of evidence).
- With EESR plus typical GERD symptoms, use a trial of twice-daily PPI therapy for 8–12 wks before additional testing (Conditional recommendation, low level of evidence).
- Do **not** use EGD as the method to establish a diagnosis of
  - GERD-related asthma
  - Chronic cough,
  - Laryngopharyngeal reflux (LPR) (Conditional recommendation, low level of evidence).
- Do **not** make a diagnosis of LPR based on laryngoscopy findings alone
  - Do additional testing (Conditional recommendation, low level of evidence).
- In patients treated for EERS
  - Consider surgical or endoscopic anti-reflux procedures only in patients with objective evidence of reflux (Conditional recommendation, low level of evidence).

- Refractory GERD

➢ Definition

- Symptoms suspected to be due to GERD, but refractory to PPI therapy
- Heartburn more likely to respond to PPI than are regurgitation/extraesophageal symptoms

- Differential
  - Distinguish between patients with
    - Suspected of GERD who have inadequate respond to PPI, vs. objective GERD findings whose symptoms are not relieved by PPI.
  - Despite PPI therapy, abnormal reflux persists and is causing symptoms
  - Reflux hypersensitivity
    - PPIs have normalized esophageal acid exposure, but “physiologic” reflux episodes (acidic or non-acidic) associated with an evoke symptoms
  - Symptoms caused by
    - Esophageal disorders other than GERD (e.g., EoE and achalasia)
    - Non-esophageal disorders (e.g., gastroparesis, rumination, and heart disease)
  - Symptoms are functional (i.e., not because of GERD or any other identifiable histopathologic, mobility, or structural abnormality

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

Key Statements

- Stop PPI therapy in patients whose off-therapy reflux testing is negative, unless another indication for continuing PPIs is present.
- Do esophageal manometry as part of the evaluation for refractory GERD in patients with
  - Normal endoscopy and pH monitoring study
  - Being considered for surgical or endoscopic treatment.
- Do a diagnostic upper EGD endoscopy if not already performed with patient off PPIs after stopping PPI therapy (ideally for 2 to 4 wk).
  - Esophageal biopsies should be performed even if endoscopy reveals normal mucosa.
- Do high-resolution esophageal manometry (HREM) in patients with refractory GERD
  - If reflux monitoring and endoscopy are unrevealing.
- Optimize PPI therapy
  - PPI PO BID x 8 wk (Strong recommendation, moderate level of evidence).

- Do esophageal pH monitoring (Bravo, catheter-based, or combined impedance-pH monitoring) performed
  - OFF PPIs
    - If the diagnosis of GERD has not been established
    - By a previous pH monitoring study, or
    - An EGD endoscopy showing long-segment Barrett esophagus, or
    - Severe reflux esophagitis (LA grade C or D) (Conditional recommendation, low level of evidence).
  - ON PPIs if the diagnosis of GERD has been established but the symptoms have not responded adequately to twice-daily PPI therapy (Conditional recommendation, low level of evidence).
- For patients who have regurgitation as their primary PPI-refractory symptom and who have had abnormal gastroesophageal reflux documented by objective testing on PPI
  - Do anti-reflux surgery or Transoral Incisionless Fundoplication (Conditional recommendation, low level of evidence).
  - Do pH/pI to find non-acid reflux episodes (Magnetic sphincter augmentation > medical therapy in abnormal reflux)

- Surgical and Endoscopic Options for GERD

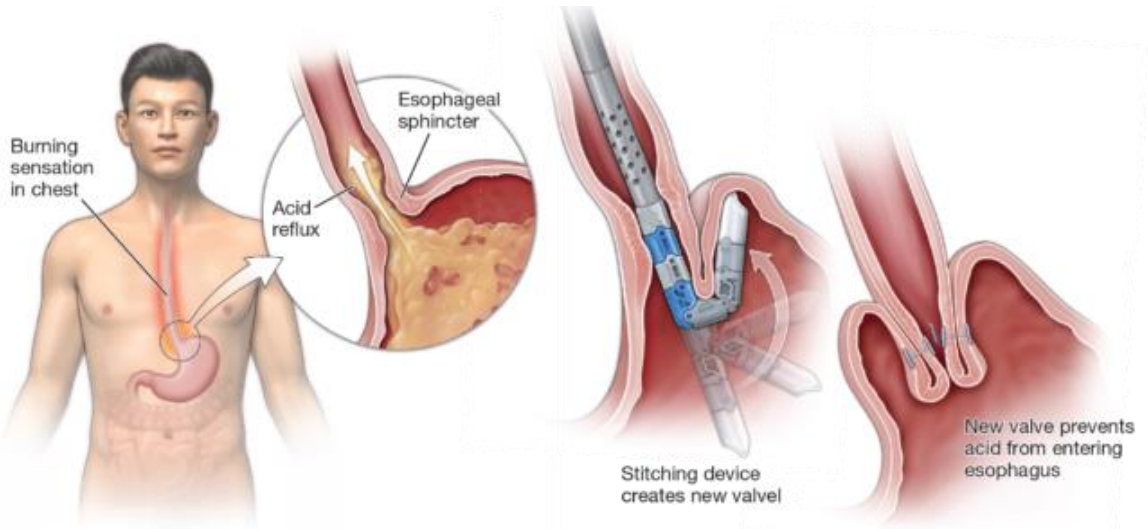
Key Statements

- Do anti-reflux surgery performed by an experienced surgeon as an option for long-term treatment of patients with objective evidence of GERD, especially those who have
  - Severe reflux esophagitis (LA grade C or D)
  - Large hiatal hernias, and/or
  - Persistent, troublesome GERD symptoms (Strong recommendation, moderate level of evidence).

  Note that partial fundoplication and LARS have a 18% symptom recurrence rate
- Consideration of Magnetic Sphincter Augmentation as an alternative to laparoscopic fundoplication
  - For patients with regurgitation who fail medical management (Strong recommendation, moderate level of evidence). Low risk of magnet erosion (unknown if superior to PPI bid)
- Consideration of Roux-en-Y gastric bypass (RYGB) as an alternative option to treat GERD in
  - Obese patients who are candidates for this procedure and
  - Who are willing to accept its risks and requirements for lifestyle alterations (Conditional recommendation, low level of evidence).

- Consider transoral incisionless fundoplication (TIF) for patients with
  - Troublesome regurgitation or heartburn who do **not** wish to undergo anti-reflux surgery, and
  - Who do **not** have severe reflux esophagitis (LA grade C or D) or hiatal hernias >2 cm (Conditional recommendation, low level of evidence).
- Because data on the efficacy of radiofrequency energy (Stretta) as an anti-reflux procedure is not recommended its use as an alternative to medical or surgical anti-reflux therapies, inconsistent and highly variable, we cannot (Conditional recommendation, low level of evidence).
- BMI > 35 is associated with 6x ↑risk of GERD
  - ↑ BMI can affect post-surgical outcomes with fundoplication
- Roux en Y
  - ↓GERD, because
    - Small gastric pouch makes less acid
    - Long alimentary loop prevents bile reflux
    - No RCTs comparing it to fundoplication; has its own complications

- Transoral Incisionless Fundoplication (TIF)



Source: https://ufhealth.org/conditions-and-treatments/tif-transoral-incisionless-fundoplication

- Effective for regurgitation; can relieve symptoms – one study, 89% were able to stop PPIs; in another study, it did not ↓ acid exposure time
  - Most patients resumed PPIs

- Before anti-reflux surgery or endoscopic therapy
  - Do HREM to rule out achalasia and absent contractility
  - For patients with ineffective esophageal motility
  - Do HREM plus provocative testing to identify contractile reserve (e.g., multiple rapid swallows).
- Do careful evaluation to ensure that GERD is present
- GERD is cause of the symptoms to be addressed by the therapy
  - To exclude achalasia (which can be associated with symptoms such as heartburn and regurgitation that can be confused with GERD)
  - To exclude conditions that might be contraindications to invasive treatment such as absent contractility.

- Long-Term PPI Issues

Key Statement

- Regarding the safety of long-term PPI usage for GERD, patients should be advised as follows: “PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions”, including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do **not** establish a cause-and-effect relationship between PPIs and the adverse conditions.
- High-quality studies have found that PPIs do **not** significantly increase the risk of any of these conditions except intestinal infections.
  - Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions.
  - For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks.” Reduced gastric secretions – pathogen effect and poor vitamin/mineral absorption; increased gastrin as a procarcinogenic effect
- Consider switching PPIs considered for patients who experience minor PPI side effects such as headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence.

- For patients with GERD on PPIs who have no other risk factors for bone disease
  - Do **not** recommend to patient
  - ↑ intake of calcium or vitamin D
  - Have routine monitoring of bone mineral density.
- For patients with GERD on PPIs who have no other risk factors for
  - Vitamin B12 deficiency
- Do **not** recommend that they
  - ↑ intake of vitamin B12
  - Have routine monitoring of serum B12 levels
- For patients with GERD on PPIs who have no other risk factors for kidney disease
- Do **not** recommend that they have routine monitoring of serum creatinine levels.
- PPIs can be used to treat GERD in patients with renal insufficiency with close monitoring of renal function or consultation with a nephrologist.
- For patients with
  - GERD on clopidogrel who have LA grade C or D esophagitis
  - Whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh their proposed but highly questionable cardiovascular risks.

- Intestinal Infections

	Hazard Ratio (HE), or Odds Ratio (OR)	95% CI
↑ risk of		
– Non-C. difficile enteric infection	1.33	1.01-1.75
– C. difficile (infection, CDI)	2.26	0.70-7.34

- The ↑ risk of enteric infection in persons on PPI in speculated to be due to
  - ↓ gastric H+ protection against organisms
- In addition, for CDI
  - ↑ survival of vegetative forms
  - ↑ expression of toxin
  - ↓ conversion of salivary nitrate to anti-C. difficile produced protective anti-reactive oxygen species

Suggested Reading:

Ganz RA, Edmundowicz SA, Taiganides PA, et al. Long-term outcomes of patients receiving a magnetic sphincter augmentation device for gastroesophageal reflux. Clinical Gastroenterology and Hepatology 2016; 14(5); 671-677.

Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Journal of American College of Gastroenterology 2022; 117(1): 27-56.

Mitchell BG and Gupta N. (2020). Roux-en-Y gastric bypass.

Patel DA, Higginbotham T, Slaughter JC, et al. (). Development and validation of a mucosal impedance contour analysis system to distinguish esophageal disorders. Gastroenterology 2019; 156(6): 1617-1626.

Qumseya B. https://ufhealth.org/conditions-and-treatments/tif-transoral-incisionless-fundoplication 2024

Emerging Evidence: Foreign Body and Food Bolus Management

Pavithra Parthasarathy

- Available Guidelines
  - 1995 AGA, ACG, SAGES, ASGE combined guideline
  - 2011 ASGE guideline
  - 2016 ESGE guideline

GI Divisional Policy, London Health Science Centre (LHSC)

- Ideally, all interactions with the patient are automatic and consistent with each presentation.
- We should try to minimize the number of endoscopies performed overall and after hours.
  - Patients will be assessed by ER tram at presentation (Psychiatry care plan will expand on this point)
    - If patient shows signs of distress, obstruction, GI bleeding, peritonitis/perforation, the appropriate services will be emergently involved
      - GI, Gen Surgery, Thoracics are required
  - If patient is stable and minimally symptomatic, they can safely wait and may not be given EGD
    - Endoscopy performed according to ASGE Guidelines (see below), IN SHORT:
      - Emergent endoscopy: ONLY if esophageal obstruction, sharp object, or button/disk battery in esophagus.
      - Urgent endoscopy: if item in esophagus not in category above, or item in stomach is large (> 6 cm long / 2.5 cm wide), sharp, or magnet. Batteries can be watched for 48 hrs.
- The vast majority of items do **not** need to be retrieved emergently.
- Do **not** immediately perform EGD if situation does **not** fall under Emergent category, as we do **not** want to promote the swallowing behaviour.
- The GI Fellow cab be contacted the following day if Emergent EGD is not required.
- ESGE provides more direction regarding use of imaging, workup for esophageal pathology, use of protective devices and extraction devices.

Timing of endoscopy for ingested foreign bodies

- Emergent endoscopy
  - Patients with esophageal obstruction (i.e., unable to manage secretions)
  - Disk batteries in the esophagus
  - Sharp-pointed objects in the esophagus
- Urgent endoscopy
  - Esophageal foreign objects that are not sharp-pointed
  - Esophageal food impaction in patients without complete obstruction
  - Sharp-pointed objects in the stomach or duodenum
  - Objects 6 cm in length at or above the proximal duodenum
  - Magnets with in endoscopic reach
- Non urgent endoscopy
  - Coins in the esophagus may be observed for 12-24 hr before endoscopic removal in an asymptomatic patient
  - Objects in the stomach with diameter 2.5 cm
  - Disk batteries and cylindrical batteries that are in the stomach of patients without signs of GI injury maybe observed for as long as 48 hrs
  - Batteries remaining in the stomach longer than 48 hrs should be removed

Adapted from: ASGE Standards of Practice Committee. Gastrointest Endosc 2011; 73(6): 1085-91.

- Approach to the Patient with Ingestion of Foreign Body

➢ Clinical

- Ingestion history
  - Suspected nature of ingestion
  - # of items
  - Time of ingestion
  - Cause of ingestion
  - Anatomic risk factors
  - Age
    - Children: accidental
    - Adults
      - Developmental delay
      - Intoxication
      - Psychiatric illness
      - Secondary gain

- Symptoms
  - Chest or abdominal pain
  - Dysphagia
  - Dyspnea
  - Hypersalivation
  - Odynophagia
  - Retrosternal pain
  - Stridor
  - Wheezing
- Physical
  - ABC!
  - Abdominal exam for obstruction/peritonitis
  - Auscultation for wheezing and aspiration
  - Check for visible FB in oral cavity
  - Subcutaneous emphysema in the chest

➢ Risk Factors for Complications

- Complications
  - Aortic/tracheal fistulas
  - Aspiration
  - Esophageal or enteric perforation
  - Hemorrhage
  - Mediastinitis and abscess formation (e.g., retropharyngeal abscess)
  - Small bowel obstruction/impaction of FB at physiologic narrowings
- Risk factors
  - Ingestion of magnets – enteroenteric fistulas, perforation, etc.
  - Lodging of batteries in the esophagus
  - Prolonged esophageal impaction (>24 hrs)
  - Altered anatomy

➢ Diagnostic Imaging

- Chest x-ray + abdominal X-ray (to assess for foreign bodies [FBs] and free air)
- 87% false negative rate in food bolus impaction
- ESGE
  - Does **not** recommend XRs if nonbony food bolus; recommends against barium swallow (aspiration risk, can worsen endoscopic view)
  - Recommends CT if perforation/other complication needing surgery is suspected

- Approach to Management
  - Upper Esophagogastroduodenoscopy (EGD)
    - Endoscopic management is ~96% successful in retrieving foreign bodies
      - No significant complications
    - Can also treat any associated complications (please see previous)
    - ESGE recommends
      - Clinical observation without EGD for blunt and small ingestions (except batteries, magnets)
      - Body packing
        - No EGD
        - Surgical referral if
          - Packet rupture
          - Failure to progress, or
          - Intestinal obstruction
  - EGD
    - Within 2-6 hrs for
      - Esophageal obstruction
      - Sharp objects in esophagus
      - Batteries; other esophageal items/incomplete obstruction: 2-24 hrs
    - For stomach
      - < 24 hrs for sharp items/batteries
      - ≥ 72 hrs for medium-sized blunt objects
    - Food bolus
      - Do **not** delay endoscopy for comorbidities
      - Attempt to gently push food into stomach 90% success over retrieval
    - When pushing, watch for significant resistance
    - Do **not** to use excessive force; consider en bloc vs piecemeal retrieval

Timing of endoscopic intervention in foreign body ingestions: emergent is preferably within 2 hr, but at latest within 6 hrs; urgent, within 24 hrs; nonurgent, within 72 hr

	Timing		
	< 6 hrs	< 24 hrs	< 72 hrs
○ Esophagus	Battery Sharp-pointed Bolus, food	Magnet Blunt < 2-2.5 cm	
○ Stomach / Small bowel		Battery Magnet Sharp FB Blunt Large > 5-6 cm	Blunt < 2-2.5 mm > 2-2.5 mm

Adapted from: Birk M, et al. Endoscopy, 48(05), 489-496 (Table 3).

V-Shape (FG-25C-1)

Rubber Tip Grasping Forceps (FG-20P-1)

Polygrab Tripod (FG-600U)

Shark Tooth (FG-32C-1)

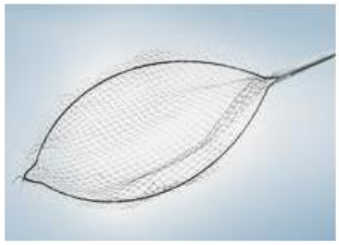
Alligator Jaw Grasping Forceps

Rat Tooth Alligator Jaw Grasping Forceps

Retrieval Basket (FG-460YR)

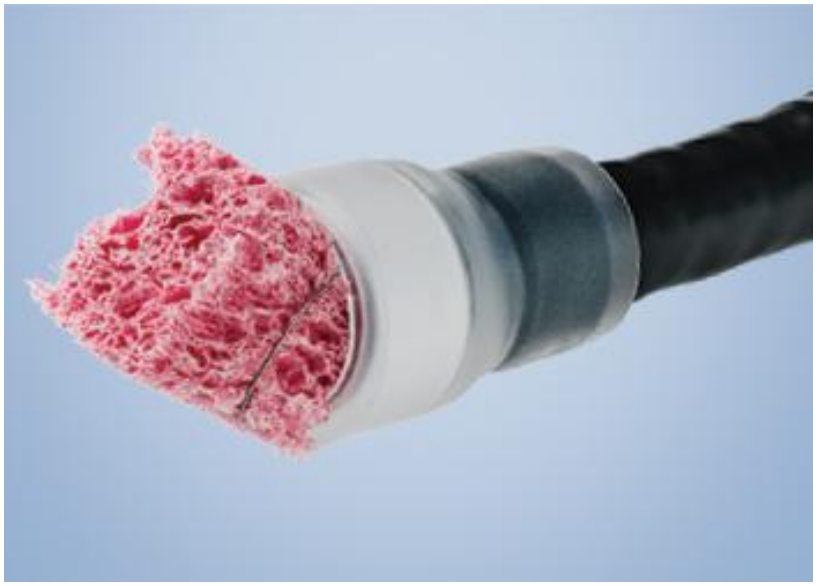
eSuction

EVIS EXERA III GIF-1TH190



SwirlNet

Images courtesy of Olympus America



Images courtesy of Olympus America

Recommendations (ESGE, 2016)

- Non-endoscopic measures
  - Do diagnostic evaluation based on the patient's history and symptoms
  - Do a physical examination focused on the patient's general condition and to assess signs of any complications (Strong recommendation, low quality evidence).
  - Do **not** do radiological evaluation for patients with non-bony food bolus impaction without complications
  - Do plain radiography to assess the presence, location, size, configuration, and number of ingested foreign bodies if ingestion of radiopaque objects is suspected or type of object is unknown (Strong recommendation, low quality evidence).
  - Do computed tomography (CT) scan in all patients with suspected perforation or other complication that may require surgery (Strong recommendation, low quality evidence)
  - Do **not** do barium swallow (risk of aspiration and worsening of the endoscopic visualization) (Strong recommendation, low quality evidence).
  - Do close observation in asymptomatic individuals who have concealed packets of drugs by swallowing (body packing)
    - Do **not** so endoscopic retrieval
    - Do surgical referral in cases of
      - Suspected packet rupture
      - Failure of packets to progress, or
      - Intestinal obstruction

      (Strong recommendation, low quality evidence)

- Endoscopic measures
  - Do emergent (preferably within 2 hrs, but at the least within 6 hrs) therapeutic esophagogastroduodenoscopy for
    - Foreign bodies inducing complete esophageal obstruction, and
    - Sharp-pointed objects or batteries in the esophagus
  - Do urgent (within 24 hrs) therapeutic esophagogastroduodenoscopy for other esophageal foreign bodies without complete obstruction (Strong recommendation, low quality evidence)
  - Treat food bolus impaction in the esophagus by gently pushing the bolus into the stomach
    - If this procedure is not successful consider retrieval (Weak recommendation, low quality evidence)

- Treat food bolus impaction in the esophagus by gently pushing the bolus into the stomach.
  - If this procedure is not successful consider retrieval (Weak recommendation, low quality evidence)
  - The effectiveness of medical treatment of esophageal food bolus impaction is debated
    - Medical treatment should not delay endoscopy (Strong recommendation, low quality evidence)
- In cases of food bolus impaction, ESGE do a diagnostic work-up for potential underlying disease, including histological evaluation, and therapeutic endoscopy (Strong recommendation, low quality evidence)
- Do urgent (within 24 hr) therapeutic esophagogastroduodenoscopy for foreign bodies in the stomach such as sharp-pointed objects magnets, batteries and large/long objects. Do non-urgent (within 72 hr) therapeutic EGD for medium-sized blunt foreign bodies in the stomach (Strong recommendation, low quality evidence).
- Use a protective device in order to avoid esophagogastric/pharyngeal damage and aspiration during endoscopic extraction of sharp-pointed foreign bodies.
  - Endotracheal intubation should be considered in the case of high risk of aspiration (Strong recommendation, low quality of evidence).
- Use suitable extraction of devices according to the type and location of the ingested foreign bodies.
  - The patient may be discharged, if foreign bodies are not or cannot be removed, a cases-by-case approach depended on the size and type of the foreign body is suggested (Weak recommendation, low quality evidence)

Suggested Reading:

Birk M, Bauerfeind P, Deprez PH, et al. Removal of foreign bodies in the upper gastrointestinal tract in adults: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016;48(5):489-496.

Demiroren K. Management of gastrointestinal foreign bodies with brief review of the guidelines. Pediatr Gastroenterol Hepatol Nutr 2023;26(1):1.

Ikenberry SO, Jue TL, Anderson MA, et al; ASGE Standards of Practice Committee. Management of ingested foreign bodies and food impactions. Gastrointest Endosc 2011;73(6):1085-1091.

Olympus Medical. Foreign body retrieval. Available at: https://medical.olympusamerica.com/procedure/foreign-body-retrieval.

Skok P, Skok K. Urgent endoscopy in patients with “true foreign bodies” in the upper gastrointestinal tract: a retrospective study of the period 1994–2018. Z Gastroenterol 2020;58(3):217-223.

ACG Clinical Guidelines: Diagnosis and Management of Achalasia

Vaezi, MF, et al. Am J Gastroenterol. 2020 Sep;115(9):1393- 1411

Zaki Alhashimalsayed

- Demography
  - Global Incidence: 0.03 to 1.63 per 10^5 persons per year
  - Global Prevalence: 1.8 to 12.6 per 10^5 persons per year
  - U.S. Prevalence: 20,000–40,000 affected patients
  - Equal incidence in men and women
  - No racial predilection
  - Peak incidence: 30 to 60 years of age

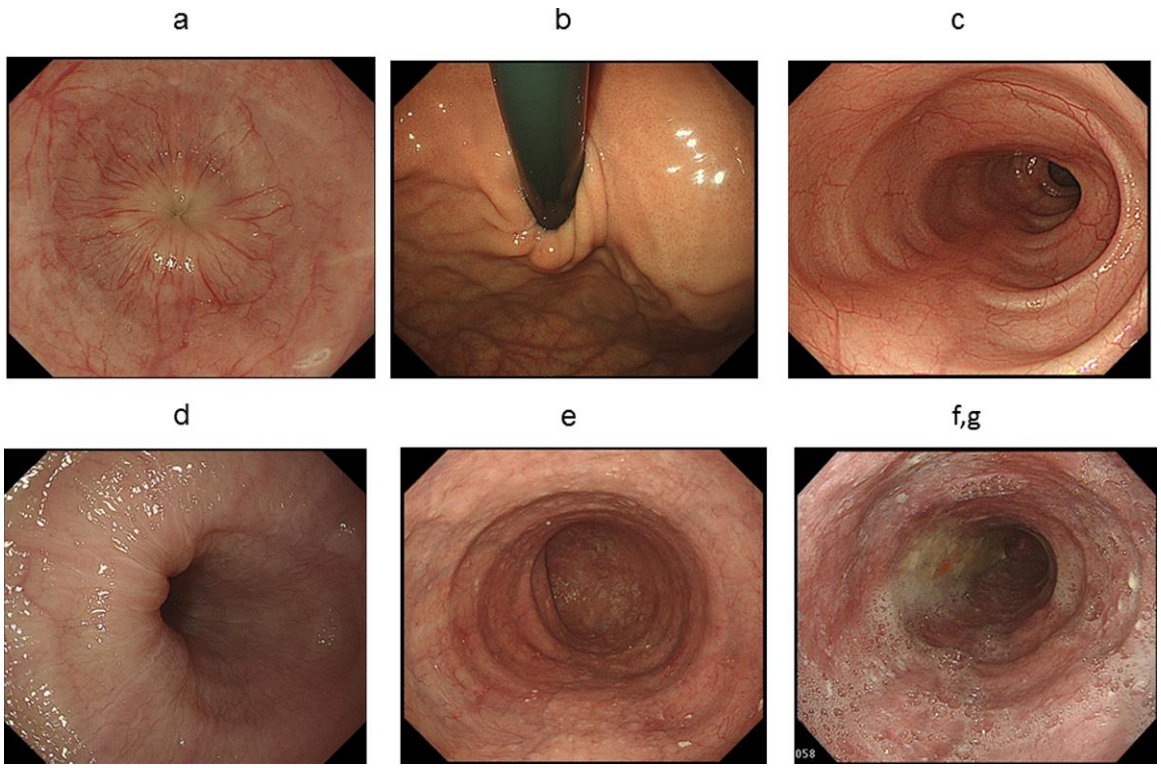
- Clinical
  - Progressive dysphagia (solids and liquids)
  - Heartburn
  - Chest pain
  - Regurgitation
  - Weight loss or nutritional deficiencies

- Pathophysiology
  - Nature: Incurable with an unknown cause.
  - Primary Cause: Loss of inhibitory neurons in the myenteric plexus of the distal esophagus and LES.
  - Mechanism:
    - Imbalance between excitatory (acetylcholine) and inhibitory (vasoactive intestinal peptide and nitric oxide) neurons.
    - Decreased inhibitory signals lead to failure of LES relaxation and disrupted esophageal peristalsis.

- Diagnostic Testing

- Endoscopy
  - Findings: Retained saliva, puckered GE junction, and a dilated esophagus.
    - Role: Identifies classic appearances, excludes pseudoachalasia or other mechanical obstructions

Endoscopic findings in esophageal achalasia.

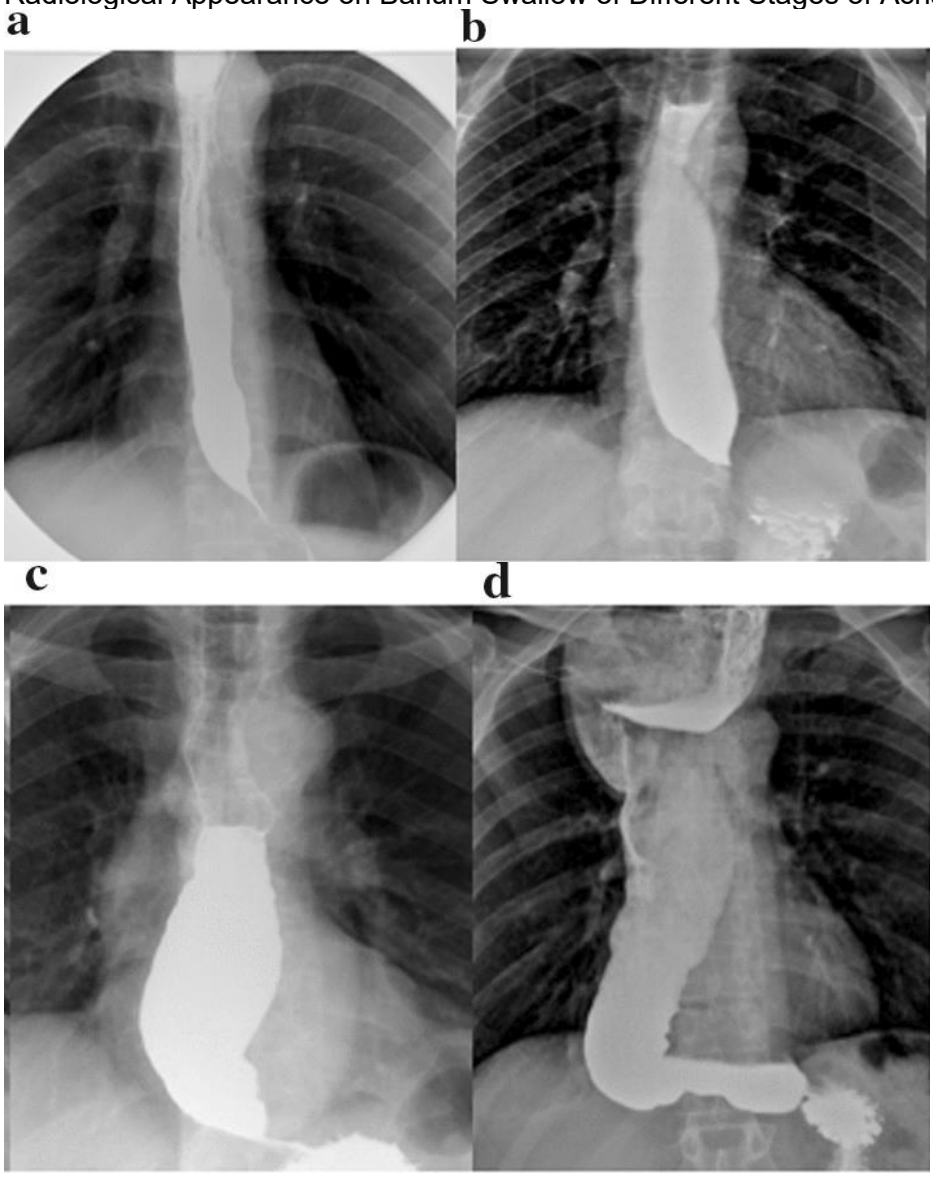


a: Functional stenosis of the esophagogastric junction. b: Wrapping around the esophagogastric junction. c: Abnormal contraction of the esophageal body. d: Mucosal thickening and whitish change. e: Dilation of the esophageal lumen. f, g: Liquid and/or food remnant.

Source: Shiwaku H, et al. New endoscopic finding of esophageal achalasia with ST Hood short type: Corona appearance. PLOS ONE 2018; 13(7): e0199955 (Figure 1)

- Barium Esophagram
  - Findings: Dilated esophagus, bird beaking, and barium retention above the gastroesophageal junction

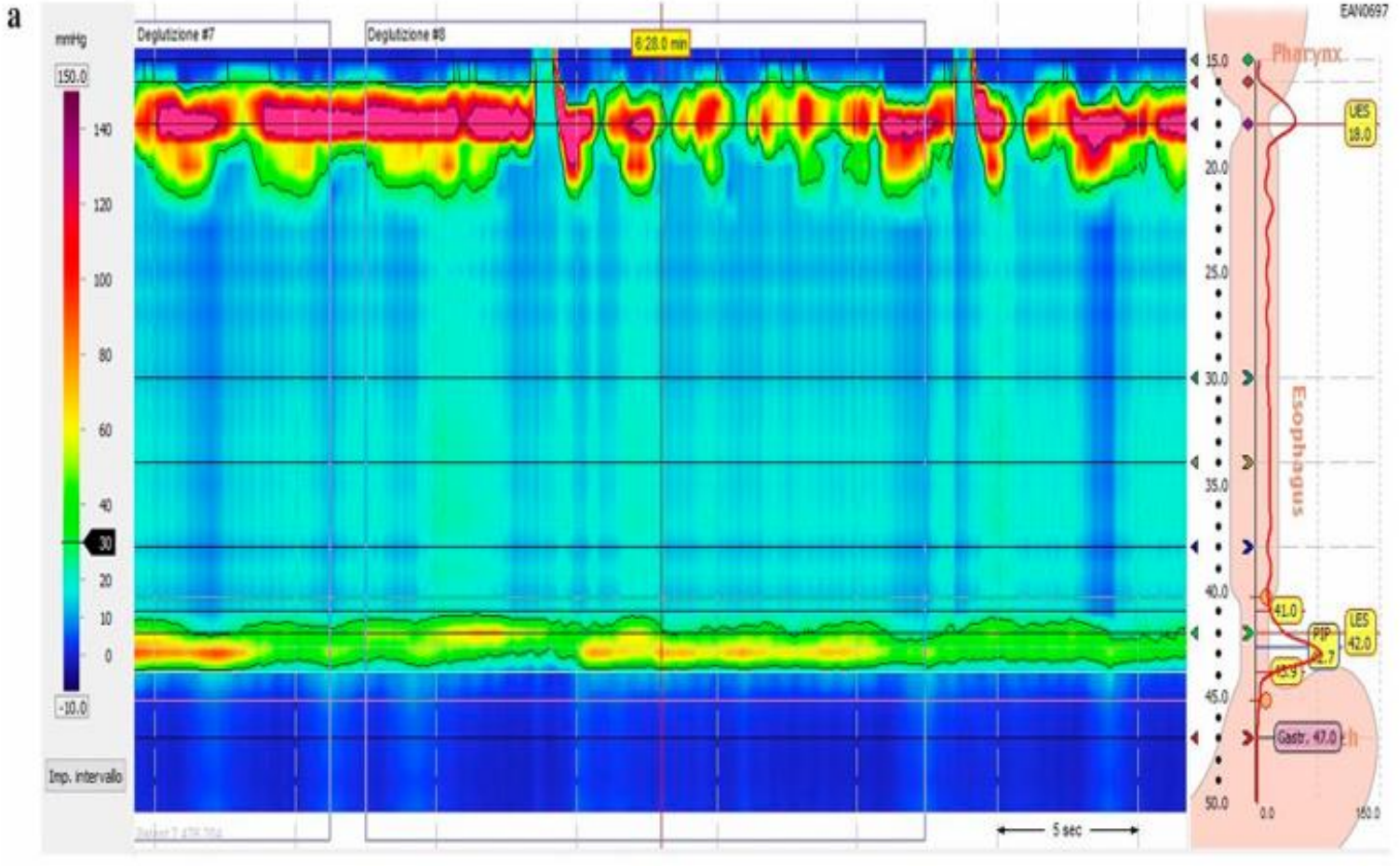
Radiological Appearance on Barium Swallow of Different Stages of Achalasia

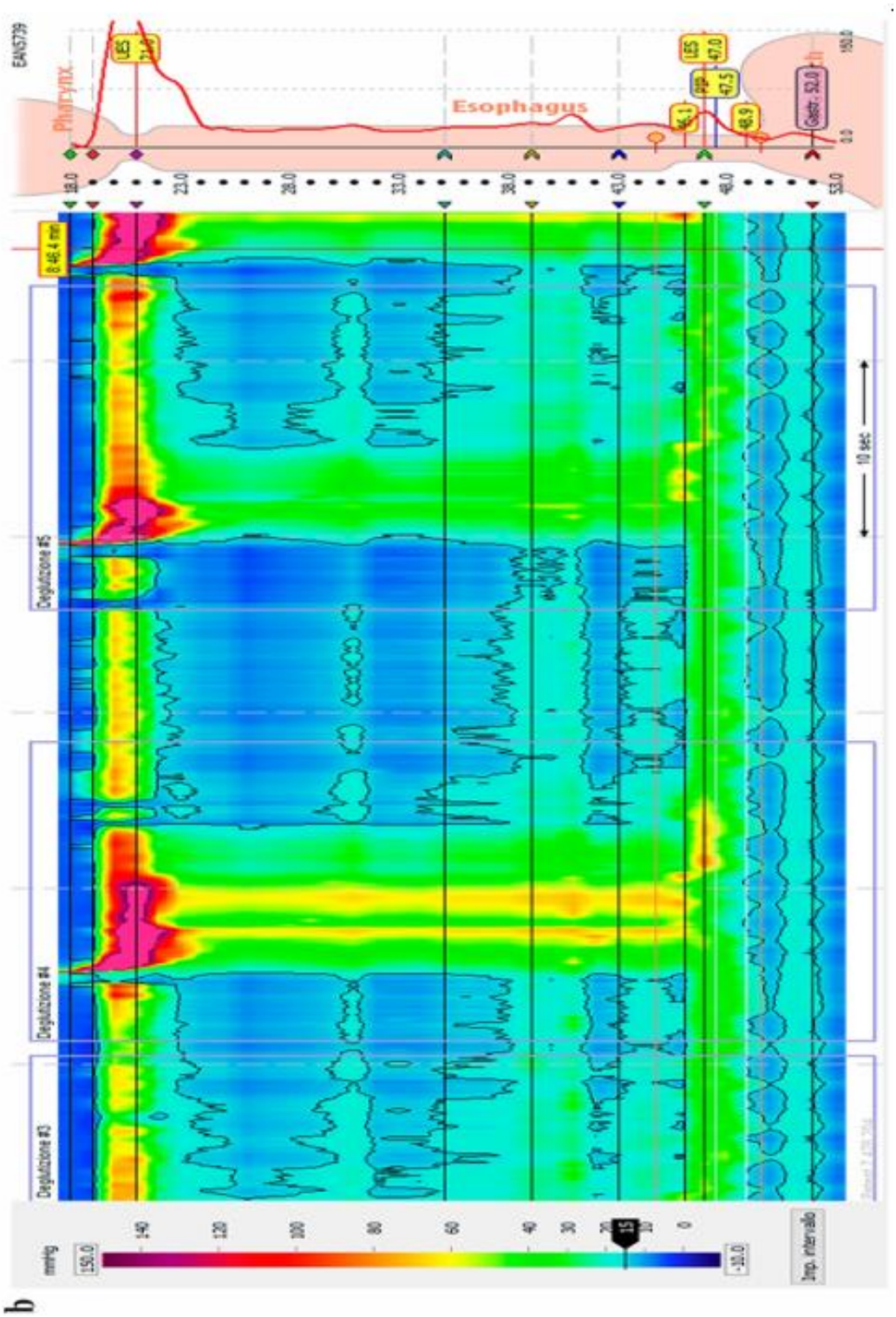


A. Stage I
B. Stage II
C. Stage III
D. Stage IV

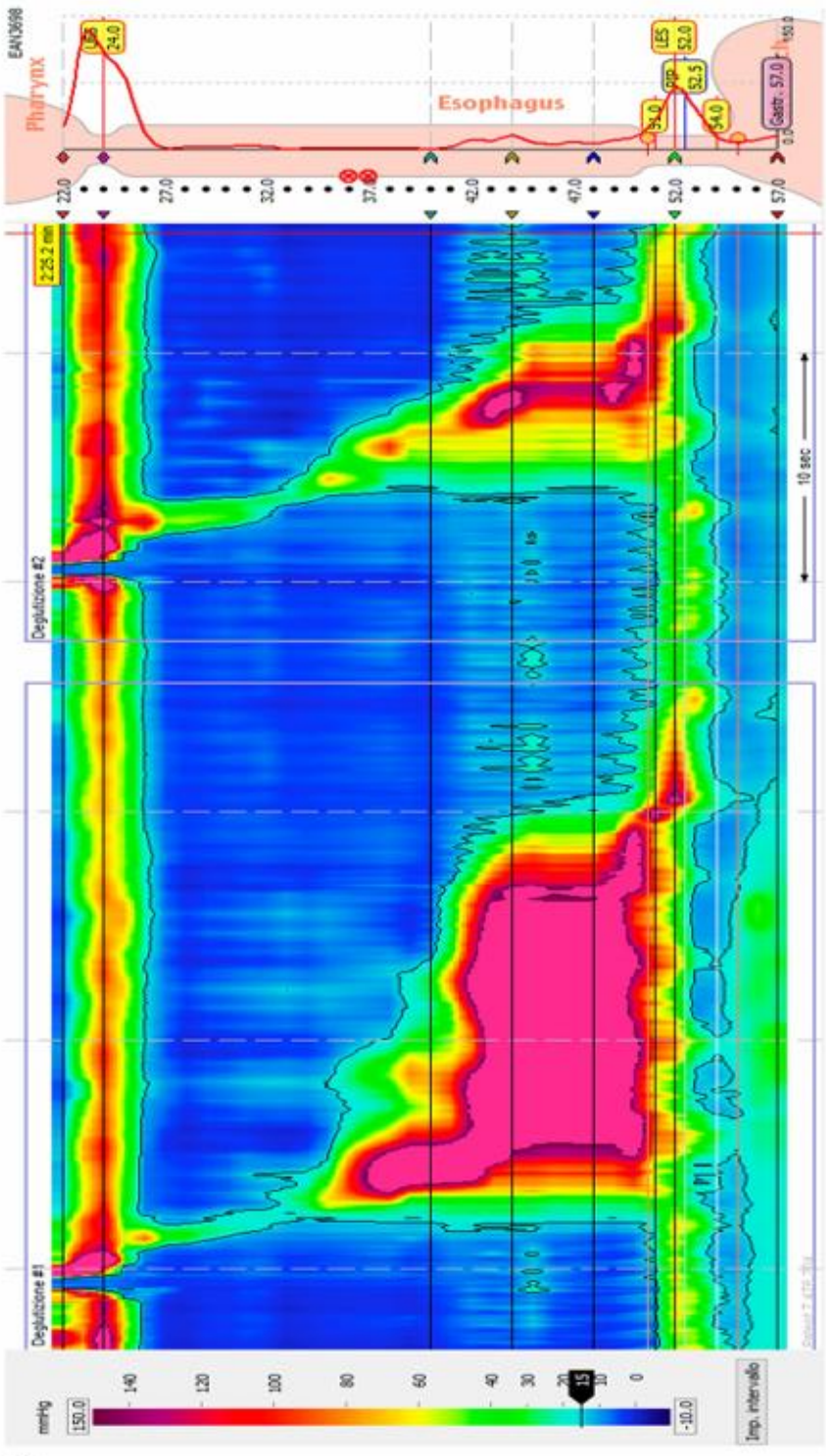
Source: Riccio F, et al. Esophageal Achalasia: Diagnostic Evaluation. *World J Surg* **46**, 1516–1521 (Figure 2)

- High-Resolution Manometry (HRM)
  - Role: Measures the pressure and coordination of esophageal muscles to confirm achalasia diagnosis.
  - Gold Standard
    - HRM is the current gold standard test for diagnosing achalasia.




Pharynx
Esophagus
Deglutizione #5
Deglutizione #4
Deglutizione #3
10 secs
mmHg

b



a Achalasia Type I. HRM picture showing an impaired EGJ relaxation (IRP > 15 mmHg) with failed peristalsis (distal contractile integral [DCI] < 100 mmHg-s-cm), and without panesophageal pressurization. **b** Achalasia Type II. HRM picture showing an elevated IRP with failed peristalsis and panesophageal pressurization. **c** Achalasia Type III. HRM picture showing an elevated IRP, and a reduced distal latency with a rapidly propagating pressurization and spastic contractions. The first swallow also had a DCI > 5000 mmHg*s*cm

Source: Riccio F, et al. Esophageal Achalasia: Diagnostic Evaluation. World J Surg 2022; 46, 1516–1521 (Figure 4)

- Comparative Studies
  - Carlson et al. Study: Superior inter-rater agreement (κ = 0.57) and diagnostic accuracy compared to conventional manometry (κ = 0.32)
  - Roman et al. Study: 26% diagnosis rate with esophageal pressure topography vs. 12% with conventional manometry
  - Additional Studies: Support high rates of inter- and intra-rater agreement for esophageal pressure topography.
- Advantages
  - Improved Resolution: Provides detailed contractile and pressure pattern descriptions
  - Refined Classification: Offers higher accuracy and reproducibility in identifying achalasia subtypes
  - Enhanced Understanding: Clarifies achalasia as a heterogeneous disease with distinct esophageal patterns

Conklin JL. J Neurogastroenterol Motil. 2013; 19(3):281-94.

Recommendations:

- Patients who are initially suspected of having GERD but do **not** respond to acid-suppressive therapy should be evaluated for achalasia.
- Esophageal Pressure Topography: Recommended over conventional line tracing for diagnosing achalasia
- Provides improved detail in esophageal pressurization and contractile patterns
- Superior accuracy and reproducibility supported by studies
- Misdiagnosis
  - 27%–42% of patients with achalasia may be initially misdiagnosed with GERD
  - Often treated with proton pump inhibitors (PPI)

➢ Historical Context and Achalasia Subtypes

- Driven from the Greek work “khalan” which means to relax “a” would mean not or without
- Before HRM and esophageal pressure topography, achalasia treatment was not tailored based on physiology or anatomy.
- Initial treatment decisions were based on physician expertise and patient preference.
- Treatment failures: 10%–20% over the first 1–5 yr.

- Chicago Classification subtypes
  - Type I: 100% failed peristalsis, no panesophageal pressurization
  - Type II: 100% failed peristalsis, panesophageal pressurization >30 mm Hg
  - Type III: Spastic contractions, with or without panesophageal pressurization
- Subtypes differ in prevalence, esophageal dilatation, and opioid use
- Type II generally shows better outcomes; Type III may require more extensive myotomy

➢ Achalasia Subtypes and Treatment Outcomes

- Subtype Outcomes
  - Type II: Best outcomes across all therapies
  - Type III: Poor response to LES-limited treatments; requires longer myotomies
- Recent Studies
  - Heller Myotomy: Similar outcomes across subtypes, with better results for Type I and III
  - POEM: Higher success, especially for Type III (98% success vs. 80% for Heller)
- Type I-absent pressurization
  - Lower esophageal sphincter relaxation is impaired
- Type II-pan pressurization
  - Lower esophageal sphincter relaxation is impaired
- Type III-spastic contractions
  - Lower esophageal sphincter relaxation is impaired

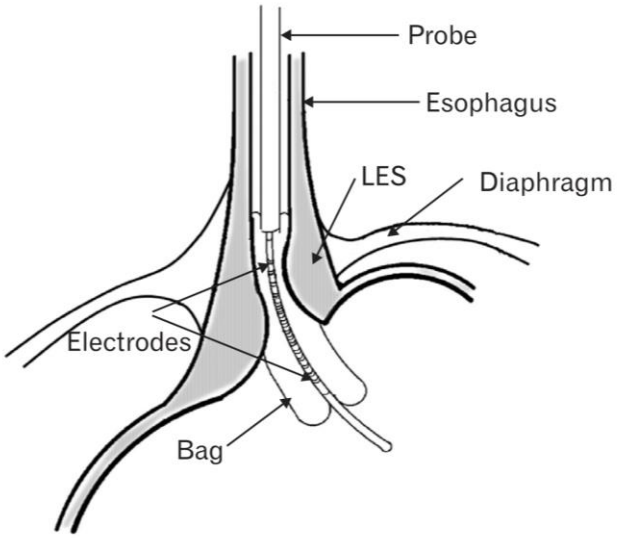
Recommendation

- Achalasia subtypes by the Chicago Classification informs prognosis and treatment choice because type II patients have very good outcomes, regardless of which therapy is selected, and type III patients require a more extensive myotomy.

➢ Diagnostic Tool

- FLIP (Functional Lumen Imaging Probe)
  - FDA-approved for assessing esophageal pressure, geometry, and motor function
  - Useful in diagnosing achalasia and post- treatment assessment
  - High concordance with manometry; valuable in equivocal cases
  - Can be performed during sedated endoscopy, offering advantages for patients unable to tolerate manometry
  - Sensitive and accurate in diagnosing achalasia
  - Potential for FLIP to reduce the need for manometry and barium esophagram
  - Cost-effective implications when performed during initial endoscopy

Schematic diagram of the esophago-gastric junction and the location of the FLIP during the test.



Source: Liao D, et al. J Neurogastroenterol and Motil 2018; 24(2): 255-267 (Figure 1)

➢ Treatment

- Goal of Treatment
  - Achalasia is chronic and incurable.
  - Treatment aims to
    - ↓ LES hypertonicity
    - ↑ esophageal emptying, and
    - ↓ further dilation
- Pharmacologic Therapy
  - Least effective, used when definitive therapies (e.g., PD, LHM, POEM) are not viable.
  - Common meds
    - Calcium channel blockers
    - Nitrates
    - Botulinum toxin
  - Short-term symptom relief (0-87% of patients)
  - Limited by side effects and short duration

➢ Non-surgical

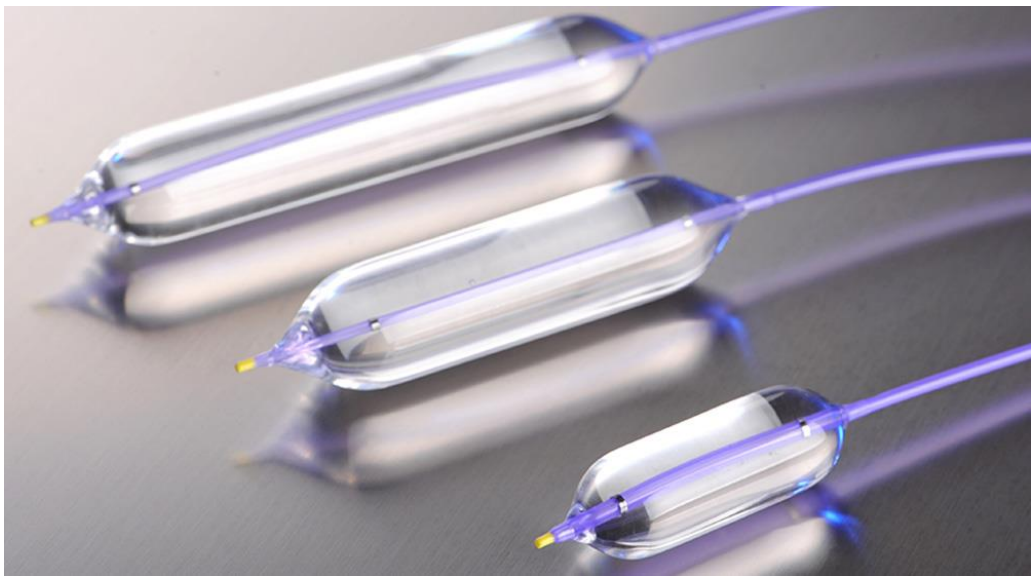
- Botulinum Toxin
  - Animal Study Insights
    - Swine esophagi treated with botulinum toxin showed mild fibrosis and severe inflammatory changes, suggesting potential tissue scarring.
  - Complications with Surgery
    - Patients treated with botulinum toxin or pneumatic dilation showed higher rates of dysphagia and perforation (10.4%) vs. surgery alone (5.4%).
    - No significant increase in complications for POEM following botulinum toxin.
  - Clinical Data
    - Prior botulinum toxin treatment may affect myotomy outcomes. (Patti et al)
    - In patients with prior botulinum toxin response, the LES becomes fibrotic, leading to less effective relief from dysphagia.
    - Limited, small observational studies with less than 2-yr follow-up make it difficult to confirm the long-term impact of botulinum toxin before definitive therapies.

Recommendation

- Botulinum toxin injection as first-line therapy for patients with achalasia that are unfit for definitive therapies compared with other less-effective pharmacological therapies.
- Treatment with botulinum toxin injection does **not** significantly affect performance and outcomes of myotomy.

- Pneumatic Dilation (PD)
  - Effectiveness
    - Achieves good to excellent symptom relief in 50%–93% of patients
    - Success rates by balloon size: 74% (3.0 cm), 86% (3.5 cm), and 90% (4.0 cm)
  - Procedure
    - Performed under sedation, often with fluoroscopy
    - Uses Rigiflex dilators (3.0, 3.5, and 4.0 cm) in a graded approach
    - Pressure of 10–15 psi held for 15–60 seconds is applied to obliterate the LES
    - Important to have surgical backup in case of perforation (1.9% rate)
  - Patient Selection
    - Predictors of favorable response: older age (>45 yrs), female sex, narrow esophagus, LES pressure <10 mm Hg after PD
    - Less favorable in younger men (<45 yrs) with thicker LES musculature
  - Complications
    - Perforation: 1.9% overall; requires conservative or surgical management
    - GERD: Occurs in 15%–35% of patients, requires PPI therapy
  - Post-Procedure Considerations
    - Routine esophagram not necessary unless clinical suspicion of perforation arises
    - No standardized protocol for balloon dilation or post-dilation recovery

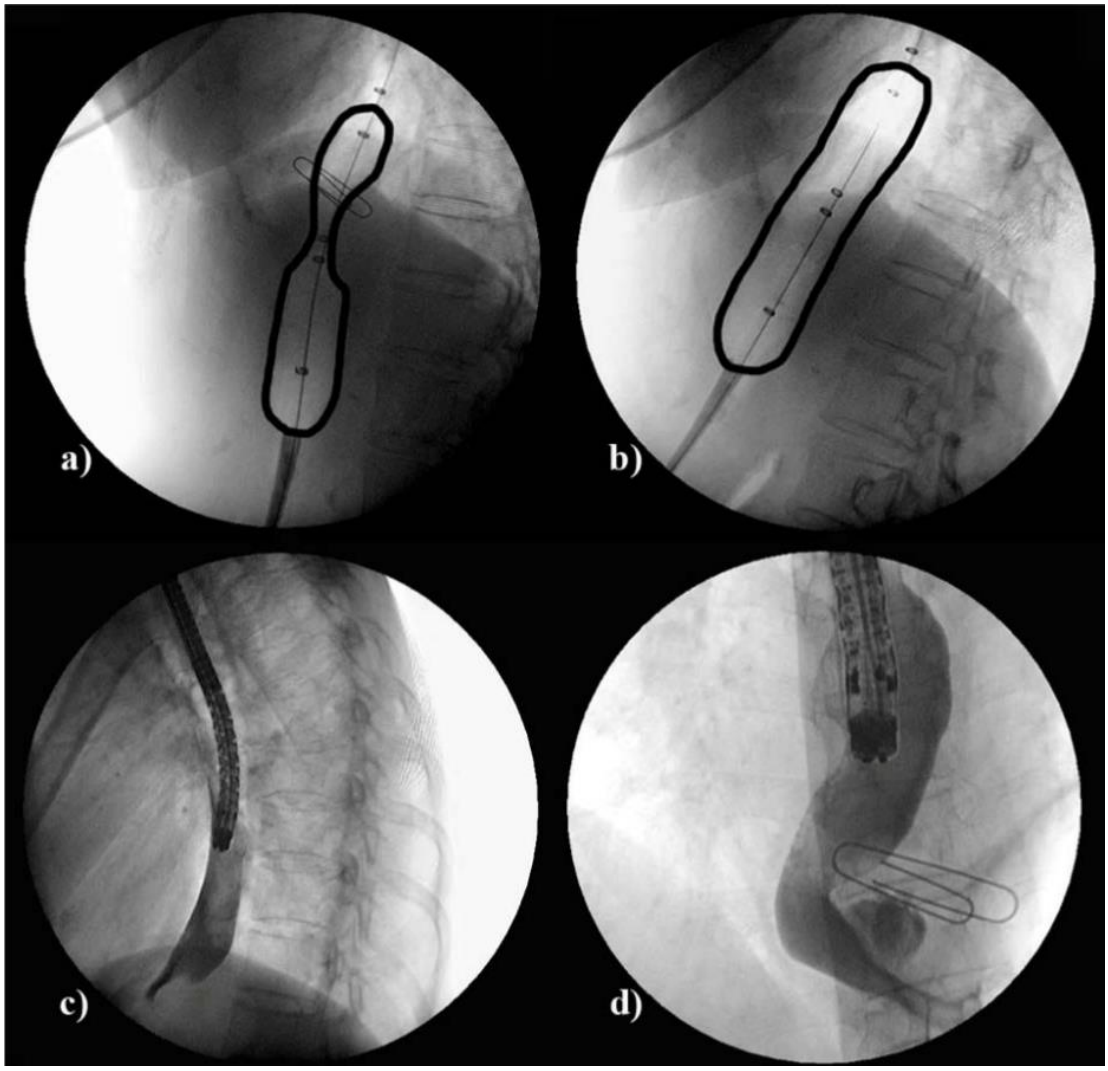
Pneumatic Dilator



Source: https://endoscopic.net/balloon-dilatation-catheter-and-pumps

- Pneumatic dilator sizes 3.0 cm (bottom), 3.5 cm (middle), and 4.0 cm (top) used in treating patients with achalasia. Graded approach of starting with the smaller 3.0-cm balloon and progressing to the larger sizes if failed therapy is recommended in all except younger male patients in whom initial approach with 3.5-cm balloon may be used.

Pneumatic dilation with immediate post-procedure esophagram



a) Balloon placement and initial inflation demonstrating waist. b) Waist obliteration with dilation. Esophagram of two different patients immediately post dilation c) Demonstrating no perforation D) Free perforation with contrast extravasation.

Source: Bechara R, et al. Gastroenterol Pancreatol Liver Disord 2016; 3(5): 1-3 (Figure 1)

Recommendation

- Do **not** suggest obtaining routine gastrografin esophagram after dilation (based on no evidence to support routine esophagram and the current shift in practice patterns to perform endoscopy after dilation to rule out and potentially treat perforation endoscopically)

➢ Surgical

- Myotomy
  - Historical Approach
    - Division of LES muscle fibers through a thoracotomy (60%-94% success over 1-36 yrs)
    - Evolved to laparoscopic myotomy due to lower morbidity and faster recovery
  - Effectiveness of Surgical Approaches:
    - Open transthoracic: 83% improvement (13 studies, 842 patients)
    - Open transabdominal: 85% improvement (10 studies, 732 patients)
    - Thoracoscopic: 78% improvement (8 studies, 211 patients)
    - Laparoscopic: 89% improvement (39 studies, 3,086 patients)
  - Efficacy Decreases Over Time
    - 89% success at 6 mons, dropping to 57% at 6 yrs
    - LHM more effective for Type I and II than Type III achalasia. Surgical view of the distal esophagus during a myotomy

- Fundoplication Post-myotomy
  - GERD Incidence After Myotomy Without Fundoplication
    - Thoracotomy (29%), laparotomy (28%), thoracoscopy (28%), laparoscopy (31%)
  - Fundoplication Reduces GERD Risk
    - Thoracotomy (14%), laparotomy (8%), laparoscopy (9%)
  - A randomized trial showed 47% abnormal pH without fundoplication vs 9% with it
  - Meta-analysis: Acid exposure higher in POEM (39%) vs myotomy with fundoplication (16.8%)

Recommendation

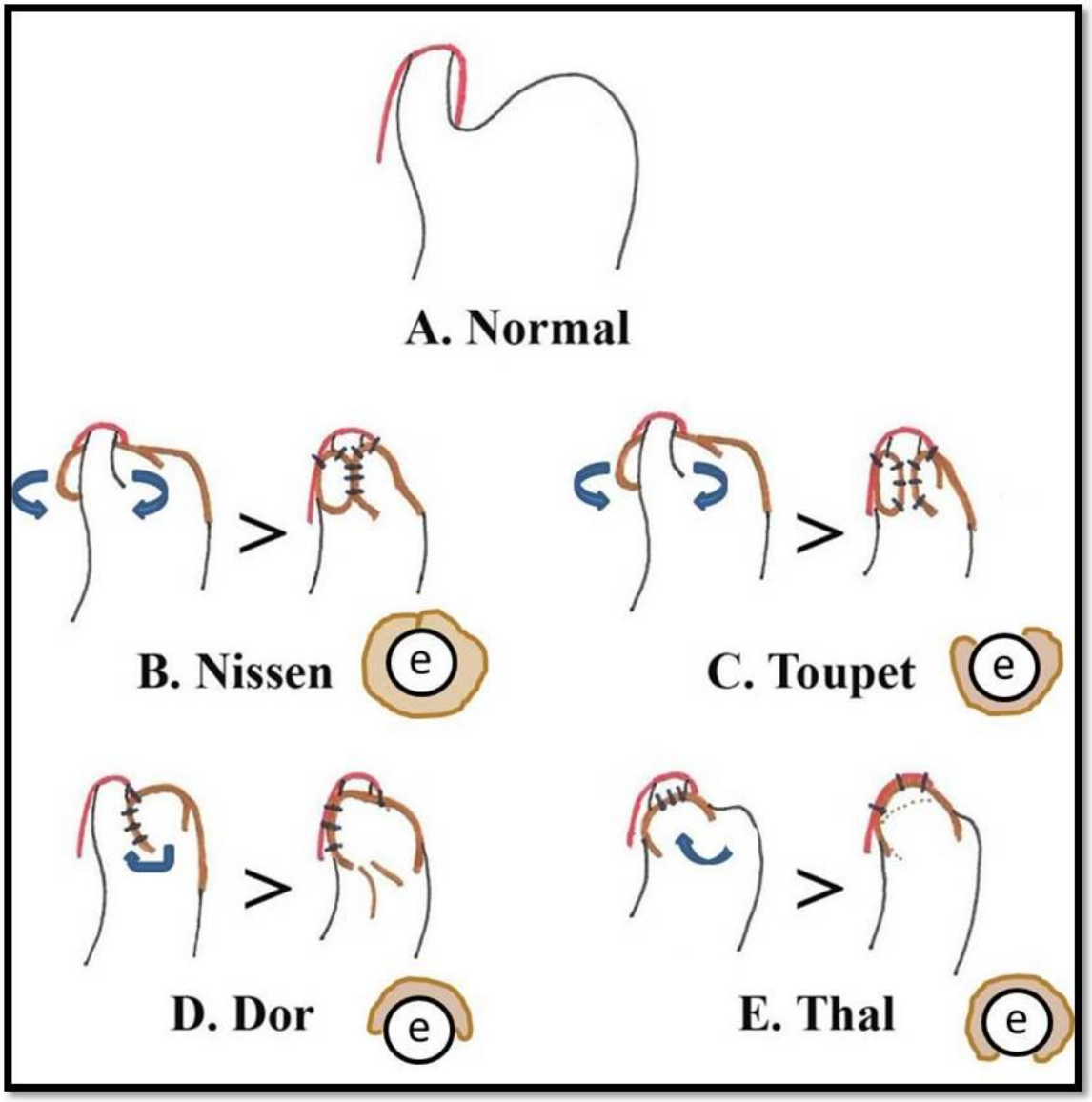
- SAGES guidelines recommend fundoplication after myotomy to prevent reflux.
- Myotomy with fundoplication is superior to myotomy without fundoplication in controlling distal esophageal acid exposure.

- Dor vs. Toupet Anti-reflux Procedures After Myotomy
  - Purpose
    - Both Dor (anterior) and Toupet (posterior) fundoplications reduce GERD after myotomy.
  - Meta-Analysis Data
    - Odds of abnormal pH test post-myotomy
      - Anterior fundoplication (Dor): 0.16 (95% CI, 0.11–0.24)
      - Posterior fundoplication (Toupet): 0.18 (95% CI, 0.13–0.25)
    - Acid exposure similar in both anterior and posterior approaches
    - Dysphagia and reintervention rates lower with Toupet fundoplication
  - Key Findings
    - A multicenter RCT found nonsignificant differences in abnormal pH results
      - Dor: 41% abnormal pH
      - Toupet: 21% abnormal pH
    - Similar symptom improvement (dysphagia, regurgitation) for both approaches
  - Recent Updates
    - Toupet superior to Dor in terms of
      - Shorter hospital stays
      - Better quality of life
    - Other factors (GERD, dysphagia, complications, treatment failure) were equivalent

Recommendation

- Either Dor or Toupet fundoplication to control esophageal acid exposure in patients with achalasia undergoing surgical myotomy

Fundoplication Types



Adapted from Campos GM., et al. Surgical Endoscopy 2009, 23(2), 347–353.

- Peroral Endoscopic Myotomy (POEM)

1. Development
    - A hybrid endoscopic technique combining natural orifice transluminal endoscopic surgery principles with myotomy
    - Developed in Japan, POEM involves endoscopic access to the circular muscle fibers and a tailored myotomy (6 cm into the esophagus, 2 cm into the cardia)

2. Effectiveness
    - Success rate > 90% in prospective cohorts
    - Alternative to laparoscopy, offering a less invasive option with promising outcomes

3. Type III Achalasia
    - Particularly effective in type III achalasia, where conventional therapies (Heller myotomy or PD) have lower success
    - Tailored myotomy length helps address long spastic segments in the esophagus

4. Key Findings
    - LHM vs POEM in type III achalasia
        - LHM success rate: 71%
        - POEM success rate: 93% (OR: 3.50, P = 0.007)
    - 2017 meta-analysis: POEM clinical success for type III achalasia: 92%
    - Complications
        - Post-POEM GERD rates: 18.8%
        - Adverse events post-POEM: 11%

5. Comparison to LHM
    - 2019 RCT: POEM superior to LHM for type III achalasia (98% vs 80.8%, P = 0.01)
    - Shorter procedure time, fewer adverse events (6% vs 27%, P < 0.01)

Recommendation
    - Tailored POEM or LHM for type III achalasia as a more efficacious disruptive therapy of the LES compared with PD

GERD Post-POEM

- GERD Concerns
  - GERD remains a significant issue after POEM, limiting its wider adoption despite its success rates for achalasia
- 2019 RCT (PD vs POEM)
  - Esophagitis at 2 yrs post-intervention
    - POEM group: 41% esophagitis (P = 0.002)
    - PD group: 7% esophagitis
  - Note: Proton pump inhibitor (PPI) use was not withheld during the endoscopy
- Nonrandomized Observational Studies
  - Post-POEM reflux seen in up to 58% of patients.
  - Post-PD reflux: 15%–35%
- 2018 Systematic Review and Meta- Analysis
- POEM vs Surgical Myotomy
  - Erosive esophagitis: OR 9.31
  - Symptomatic GERD: OR 1.69
  - Abnormal pH monitoring: OR 4.30

Recommendation

- POEM compared with LHM with fundoplication or PD is associated with a higher incidence of GERD

- Esophagectomy for End-Stage Achalasia
  - Indication
    - End-stage achalasia: Characterized by megaesophagus or sigmoid esophagus with significant dilation and tortuosity
    - Risks include aspiration, aspiration pneumonia, and malnutrition
  - Complications
    - Endoscopic myotomy in patients with sigmoid esophagus has a 2-fold increased risk of periprocedural complications
  - Limitations of Other Treatments
    - PD, surgical myotomy, or POEM may be less effective
    - Enteral feeding might be necessary for those with compromised nutrition
  - Esophagectomy Outcomes
    - Meta-Analysis Findings
      - Postoperative Respiratory Complications: 10% (95% CI: 4%–18%)
      - Mortality: 2% (95% CI: 1%–3%)

- Limitations:
  - Observational and cohort studies only
  - Lack of randomized trials
  - No direct comparisons with endoscopic or surgical myotomy
  - No accounting for disease history, age at onset, time to end-stage, or previous treatments
- Special Considerations
  - Best outcomes in highly specialized surgical centers

Recommendation

- Use esophagectomy in surgically-fit patients with megaesophagus who have failed other interventions

- Self-Expanding Stents (SEMS)
  - Overview
    - SEMS are used as a temporary measure in the treatment of achalasia
  - Evidence
    - Low-Quality Evidence: Limited data supporting effectiveness
  - Long-Term Efficacy
    - 30 mm SEMS: Superior long-term clinical efficacy compared to 20 mm and 25 mm stents
  - Symptom Remission
    - SEMS: 49.1% remission rate after 36 mon
    - Botulinum Toxin Injection: 4.2% remission rate
  - Complications
    - Chest pain
    - Regurgitation
    - Stent migration (relatively rare due to baseline esophageal aperistalsis)
  - Limitations
    - SEMS are a temporary measure and do **not** provide definitive treatment
    - Limited availability of specialized stents, like those used in the study by Dai et al., restricts their widespread use
    - The current data do **not** support routine use of SEMS for long-term symptom management

Recommendation

- Do **not** use stent placement for the management of long-term dysphagia in patients with achalasia

Comparative Effectiveness of Therapeutic Modalities: PD vs Medical Therapy

- Lack of Direct Comparisons
  - No Head-to-Head Studies: Limited direct comparison of pharmacotherapy agents with more definitive therapies like PD, LHM, or POEM
  - Study Designs
    - Mostly case series or case control studies
    - Few randomized trials comparing pharmacotherapy with placebo
- Evidence from Observational Studies
  - Dilation vs Pharmacotherapy
    - 1 Prospective Observational Study: Compared dilation with less effective Rider-Moeller dilators to sublingual nifedipine, showing similar efficacy
- General Consensus
  - Pharmacotherapy
    - Less Effective: Compared to PD, LHM, or POEM
    - Shorter Duration of Action
    - Poor Benefit: In terms of esophageal emptying and symptom relief in achalasia
- Conclusion
  - Definitive therapies (PD, LHM, POEM) are generally preferred due to their more sustained efficacy and improved symptom management.

Recommendation

- PD is superior to medical therapy in relieving symptoms and physiologic parameters of esophageal emptying.
- PD or LHM are both effective and equivalent short- and long-term procedures for patients with achalasia who are candidates to undergo definitive therapy.

Comparative Effectiveness of Therapeutic Modalities

- PD vs Botulinum Toxin Injection
  - Effectiveness
    - Study Findings
      - Randomized Trial: 42 patients; 70% success for PD vs 32% for botulinum toxin at 12 mon
      - Cochrane Review: 7 studies with 178 patients; no significant difference within 4 wks
      - 12-Mon Data: 55 of 75 PD patients in remission vs 27 of 72 botulinum toxin patients (relative risk of 1.88, 95% CI: 1.35–2.61)

- Conclusion
  - PD: Superior to botulinum toxin in long-term symptom relief and physiologic parameters for achalasia

- PD vs LHM
  - Effectiveness
    - Success Rates:
      - Observational Studies: PD and LHM both show success rates of 80%–95% (55,91–105)
      - European RCT: Similar efficacy at 2 yrs (PD 86% vs LHM 90%, P = 0.3) and 5 yrs (PD 84% vs LHM 82%, P = 0.9)
      - Quality-of-Life Outcomes: Similar between PD and LHM at 5.7 yrs and at 5 yrs in a Canadian multicenter study
  - Conclusion:
    - PD and LHM: Both are effective treatments with comparable long-term success rates and quality-of-life outcomes for achalasia

- PD vs POEM
  - Randomized Controlled Trial
    - Study: Ponds et al. - 133 adults, 6 centers
    - Follow-Up: 2 yrs
    - Results
      - POEM Success Rate: 92% (ES ≤ 3, no serious adverse event) (P < 0.001)
      - PD Success Rate: 54%
      - Adverse Events: 1 perforation after PD (1.5%); no serious adverse events with POEM.
  - Retrospective Studies
    - 2017 Study (China):
      - PD: 95% success at 3 mon, 60% at 36 mon
      - POEM: 96% success at 3 mon, 93% at 36 mon (P = 0.013)
      - Higher Success: POEM superior for all manometric subtypes, significantly for type III achalasia
      - Concerns: Longer operative time, hospitalization; 4 cases of subcutaneous emphysema
    - 2016 Cleveland Clinic Study
      - Comparison: POEM, PD, and LHM
      - Findings: No significant difference in esophagram or manometry parameters at 2 mon (P > 0.05)

- Differences in Study Design
  - Ponds Study: Limited PD to 1 or 2 dilations with 30- or 35-mm balloons; additional dilation if ES ≥ 3 or integrated relaxation pressure >10 mm Hg.
  - Previous Studies: Allowed sequential dilation up to 40-mm balloons until symptom response attained
  - Post Hoc Analysis: 76% PD success rate if patients receiving additional 40 mm dilation included
- Conclusion
  - POEM: Shows higher long-term success rates and fewer serious adverse events compared to PD, though it requires longer operative time and hospitalization
  - PD: Still a viable option with similar short-term success, but may require multiple dilations for optimal results

Recommendation

- POEM or PD result in comparable symptomatic improvement in patients with types I or II achalasia

- LHM vs Botulinum Toxin Injection:
  - Zaninnoto et al. (109) RCT compared surgical myotomy (LHM) with sequential botulinum toxin injections (8 to 100 U)
    - Participants: 80 patients (40 in each group).
    - Results (6 mon):
      - LHM: 82% symptom improvement (95% CI: 76%–89%)
      - Botulinum Toxin: 66% symptom improvement (95% CI: 57%–75%)
    - Recurrence: Symptoms recurred in 65% of botulinum toxin patients
    - 2-Yr Symptom-Free Rates
      - LHM: 87.5%
      - Botulinum Toxin: 34%
    - Economic Analysis: Initial cost lower for botulinum toxin; cost savings diminished when long-term effectiveness was considered
    - Systematic Review: Analyzed 7,855 patients from 105 studies, showing LHM with an anti-reflux procedure provided symptom relief in 90.3% of patients with a low complication rate (6.3%)

Recommendation

- LHM is preferred over botulinum toxin injection in patients fit for surgery due to better symptom relief and long-term outcomes.

- LHM vs POEM:
  - RCT Comparison: A recent trial assessed POEM versus LHM with Dor fundoplication
  - Participants: 221 patients (112 POEM, 109 LHM). Results (2 yrs): POEM: 83% clinical success. LHM: 82% clinical success. 2018 Systematic Review and Meta-Analysis
    - 12 mon: Improvement in dysphagia was 93.5% for POEM vs. 91.0% for LHM (P = 0.01). 24 mon: Improvement was 92.7% for POEM vs. 90.0% for LHM (P = 0.01) (81)
  - 2017 Systematic Review and Meta-Analysis:
    - Found a significantly higher short-term clinical treatment failure rate for surgical myotomy (OR 9.82; 95% CI: 2.06–46.80, P < 0.01)
    - Comparative Metrics
      - No significant difference in operative time, complication rate, or length of hospital stays between POEM and LHM
    - Nonrandomized Studies
      - Results are generally similar but show a potential advantage in efficacy for POEM over LHM. Variations in metrics assessed and treatment response durations exist

Recommendation:

- While both POEM and LHM have similar long-term outcomes, POEM may offer a slight advantage. Long-term, randomized studies are needed for a definitive comparison
- POEM and LHM result in comparable symptomatic improvement in patients with achalasia

Post-Therapy Assessment for Achalasia

- Treatment Failure
  - Typically determined by recurrence of symptoms
  - ES is the standard tool used to track outcomes
  - Limitations: ES developed pre-PRO criteria; newer tools question its reliability
- Causes of Recurrence
  - Incomplete LES disruption
  - GERD
  - Spastic contractions
  - Anatomical distortion

- Eckardt Score (ES)
  - Focuses on dysphagia, regurgitation, chest pain, and weight loss.
    - Each scored 0–3; total score > 3 indicates treatment failure
    - Studies suggest that dysphagia dominates the score, while chest pain and weight loss components reduce its accuracy
    - There is a need to update the tool for better outcome tracking

Diagnostic Tools for Post-Therapy Evaluation

- High-Resolution Manometry (HRM)
  - Assesses completeness of myotomy and detects spastic contractions.
  - Limited in determining GERD or bolus retention; difficult in cases of obstruction
- Timed Barium Esophagram (TBE)
  - Determines bolus retention and anatomical distortion
  - Pre-treatment: Retained barium at 1-, 2-, and 5- min intervals
  - Post-treatment: Expected esophageal emptying at 1 min
  - Reliable tool in assessing treatment success compared to HRM
- HRM vs TBE
  - No RCT comparing HRM and TBE directly
  - TBE is considered more effective for post-therapy assessment of achalasia
  - HRM has limited predictive value for treatment failure

Recommendation

- ES or HRM alone not be used to define treatment failure. TBE as the first-line test in evaluating continued or recurrent symptoms after definitive therapy for achalasia

Management of Failed Therapy or Recurrent Disease: PD after LHM/POEM

- Failure Rate
  - 5%–30% failure within 1–3 yrs for LHM/POEM; higher at 10+ yrs
  - Causes: incomplete myotomy, scarring, anatomical distortion, post-fundoplication issues (tight wrap, herniation)
- Pneumatic Dilation (PD) as Treatment
  - Less invasive, avoids another surgery
  - Addresses incomplete myotomy, scarring, tight fundoplication
  - No RCTs comparing PD with redo-LHM/redo-POEM
- Safety and Efficacy of PD
  - Success rate post-failed LHM: 89% (mean 2.5 dilations); low complication rates
  - Limited but promising data on PD after POEM

- Future Directions
  - Larger studies needed, but PD remains a robust option after failed LHM/POEM

Recommendation

- For patients with achalasia post-initial surgical myotomy or POEM in need of retreatment

LHM After PD or POEM

- Severe, Refractory Achalasia
  - Barium esophagram shows severe dilatation (>6 cm) and anatomical distortion (sink-trap)
  - Risk of aspiration, malnutrition, death without intervention
- Esophagectomy Considerations
  - High complication rate, reduced quality of life, should be last resort
  - Preferred option: more conservative treatment before considering esophagectomy
- Heller Myotomy After PD/POEM Failure
  - Reasonable before referral for esophagectomy in select patients with severe, end-stage disease
  - Success lower compared to those without previous therapies
- Workup and Decision-Making
  - Barium esophagram, endoscopy, manometry, or FLIP to evaluate LES function
  - Complete myotomy suggests esophagectomy; incomplete may allow Heller myotomy
  - Referral to high-volume centers is crucial for esophagectomy candidates

Recommendation

- Heller myotomy be considered before esophagectomy in patients who have failed PD and POEM if the anatomy is conducive and there is evidence of incomplete myotomy.

POEM After PD or LHM

- Tyberg et al. Study
  - Patients: 51 (POEM after LHM)
  - Clinical Success: 94% (Eckardt Score ≤ 3 at 12 mon)
  - Adverse Events: 7 patients, including 2 with mediastinitis (conservatively treated)

- Retrospective Cohort (2017)
  - Comparison: 90 with prior LHM vs. 90 without LHM
  - Clinical Response: 81% (post-LHM) vs. 94% (no prior LHM)
  - Adverse Events: No significant difference
- Long-term Follow-up (2018)
  - Patients: 46 (POEM after LHM)
  - Clinical Success: 95.7% (median follow-up 28 mon)
- Failed PD Studies
  - Improvements: Significant in barium height, Eckardt Score, and LES pressure
  - Study: 22 patients with failed dilations showed symptom improvement post-POEM

Recommendation

- In patients with achalasia who have previously undergone PD or LHM.

Endoscopic Surveillance for Cancer in Achalasia

- Cancer Risk
  - Esophageal Squamous Cell Carcinoma (SCC)
    - Incidence: ~1 per 300 patient years
    - Hazard Ratio: 28 for developing SCC
    - Population-based Study: 1.3% developed esophageal cancer (2000-2012)
    - Higher incidence: 312.4 cases per 100,000 patient years (SCC)
  - Esophageal Adenocarcinoma
    - Incidence: 21.23 cases per 100,000 patient years
    - Risk is lower compared to SCC
  - Mechanism
    - Poor esophageal emptying leads to stasis, inflammation, dysplasia, and carcinoma development
  - Screening Recommendations
    - Current Guidelines
      - Routine screening not recommended due to low cancer detection rates and poor survival after diagnosis
      - Estimates: 400 endoscopies required to detect one cancer
    - Surveillance Benefits
      - Potential to monitor disease progression (e.g., megaesophagus)
      - Expert recommendation: Endoscopic or radiographic surveillance every 3 yrs after 10–15 yrs of disease duration
      - Need for further studies to improve outcomes with defined intervals or new techniques

Recommendation

- Routine endoscopic surveillance for esophageal carcinoma in patients with achalasia.

Treatment Algorithm for Achalasia

- Initial Evaluation
  - Upper Endoscopy: Rule out other pathology and pseudoachalasia
  - Confirm Diagnosis:
    - High-Resolution Manometry (HRM)
    - Timed Barium Swallow (TBS)
- Treatment Options Based on Achalasia Type:
  - Types I and II Achalasia:
    - Pneumatic Dilation (PD):
      - Start with 3.0 cm balloon (or 3.5 cm for younger men)
      - Graded approach
      - If unresponsive, consider surgical myotomy
    - Surgical Myotomy (HM)
    - Peroral Endoscopic Myotomy (POEM)
  - Type III Achalasia:
    - Tailored HM or POEM
- Alternative Therapies for Patients Unfit for Definitive Therapy:
  - Botulinum Toxin
  - Smooth Muscle Relaxants
- Centers of Excellence
  - Definitive Therapies: Offered in high-volume centers with expertise
- Postintervention Follow-Up
  - Monitor for symptom recurrence and complications (e.g., GERD)
  - Assessment Tools:
    - Timed Barium Esophagram (TBE)
    - Endoscopy
  - Recurrent Disease Management:
    - Repeat PD, HM, or POEM
    - Acid-suppressive therapy for GERD
- Esophagectomy:
  - Consider for dilated esophagus (>8 cm) with poor response to initial therapy

Esophageal Disorders Caused by Medications, Trauma, or Infection

Tamoor Afzaal

- ❖ Medications (aka “Pill Esophagitis”)
  - ➢ Major Culprits
    - Antibiotics
      - Clindamycin
      - Doxycycline
      - Penicillin
      - Rifampin
      - Tetracycline
      - Cloxacillin
    - Antiviral agents
      - Nelfinavir
      - Zalcitabine
      - Zidovudine
    - Bisphosphonates
      - Alendronate
      - Etidronate
      - Pamidronate
    - Chemotherapeutic agents
      - Bleomycin
      - Cytarabine
      - Dactinomycin
      - Daunorubicin
      - 5-fFurouracil
      - Methotrexate
      - Vincristine
      - Crizotinib
    - NSAIDs
      - Aspirin
      - Ibuprofen
      - Naproxen
    - Other medication
      - Ascorbic acid
      - Ferrous sulfate
      - Lansoprazole
      - Multivitamins
      - Potassium chloride
      - Quinidine
      - Theophylline

- Pathophysiology
  - Drug-induced esophagitis
    - Patient factors
      - ↓ saliva production
      - Altered esophageal anatomy
      - Motility disorder
      - Timing and position
    - Drug factors
      - ↓ pH medication
      - Sustained-release medications
      - Gelatin capsules (hygroscopic)
      - Disruption of cytoprotective barrier

- Clinical Features
  - Acute onset chest pain
    - Could be pleuritic
  - Odynophagia
  - Retrosternal burning

- Endoscopic Diagnosis
  - Most sensitive
    - Discrete ulcers to diffuse severe esophagitis with pseudo membranes
    - Fistula
    - Hemorrhage
    - Perforation (less likely)

- Pathology
  - Dilated intercellular spaces
  - Infiltrated with mainly T lymphocytes and eosinophils

- Treatment
  - Removal of offending agent
  - Symptom control
    - Viscous lidocaine +/- systemic pain medications
  - Ensure adequate hydration
  - Prevent acid reflux
    - No evidence behind this but can consider PPI therapy
  - Usually, clinical resolution in 2-3 wks

- Prevention
  - Proper administration of medications
    - At least 8 oz of water (236 mL) with intake
    - Remaining upright at least 30 mins after administration of pills plus water (avoid recumbent position)
  - Avoid administration prior to bedtime

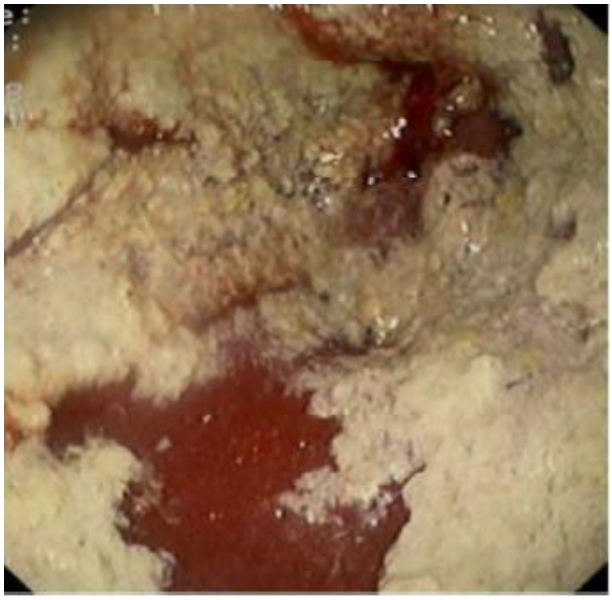
Esophageal Infection

Candida Albicans Infection

- Multiple species of Candida have been implicated (tropicalis, guilliermondii)
  - C. albicans account for the majority
  - Risk factors
    - Immunodeficiency
    - Eosinophilic esophagitis

- Clinical
  - Dysphagia
  - Thrush
    - In 50% of patients with esophageal “thrush”, there are also changes in the mouth
    - Black esophagitis (acute esophageal necrosis) associated with
      - CMV infection
      - Malnutrition
      - Renal failure
      - Diabetes mellitus
      - Heart failure
      - Trauma
      - Hypercoagulation
  - Odynophagia
    - Rarely upper GI bleeding, perforation

- Endoscopy
  - White pseudomembranous / plaque like lesions (confirmed via brushings)

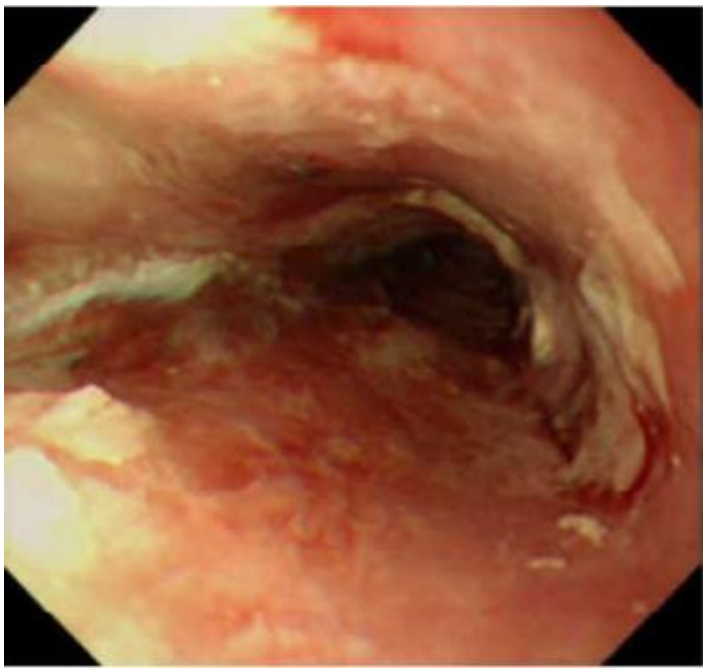


Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Histopathology
  - Inflammation
  - Budding yeast
  - Hyphae
- Treatment
  - Topical nystatin, 200,00-400,000 U qid 14 d
  - Systemic fluconazole, 100-200 mg/d

- Herpes Simplex (HSV) Infection
  - Primary infection or reactivation of latent virus in the distribution of the laryngeal, superior cervical, and vagus nerves
    - Reactivation more common
  - Affects all ages, will see oropharyngeal lesions in 1 in 5 cases

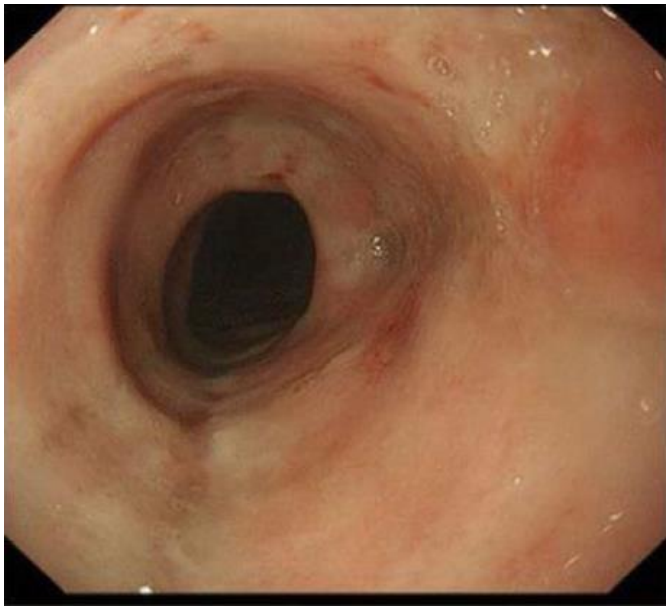
- Clinical
  - Severe odynophagia
  - Heartburn
  - Fever
  - Nausea/Vomiting
  - Chest pain
- Endoscopy
  - Mostly seen in the distal esophagus
  - Earliest manifestation is vesicles (rarely seen), they then coalesce to form ulcers (usually < 2 cm) with normal appearing intervening mucosa → exudates, plaques, diffuse erosive esophagitis
  - Ulcers are well circumscribed and have a volcano like appearance



Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Histopathology
  - Biopsy edge of ulcer (HSV affects the periphery of epithelial cells)
  - Histology: 3-Ms
    - Multinucleated giant cells
    - Nuclear moulding
    - Margination of nuclear chromatin
- Treatment
  - Can treat with 7-10 d course of acyclovir or valacyclovir
  - If severe odynophagia, IV acyclovir

- Cytomegalovirus (CMV) Infection
  - A member of the herpes family
    - Mostly associated with esophageal infection in immunocompromised hosts
  - Was a recent case series (retrospective 1500 bed tertiary care center)1
    - For apparently immunocompetent hosts found only 4 cases of positive CMV PCR and endoscopic findings for CMV esophagitis
    - Median age was 81
- Endoscopy
  - A few long, deep, serpiginous, discrete, clean-based ulcers
  - Giant esophageal ulcers
  - Large, single, discrete ulcers
  - Mucosal irregularity – esophagitis
  - May not be distinguishable from HSV or HIV esophagitis



Source: Umemoto K, et al. J Med Case Rep 2016; 10: 259.

- Histopathology
  - Large cells
  - Vasculitis, thrombosis of arterioles and
  - Intranuclear inclusion bodies (owl's eye appearance)
  - Surface injury, eosinophils
  - Endothelial and/or stromal cell inclusions
  - Cytoplasmic inclusions
    - Scattered, multiple, irregular, basophilic (blue/purple)
    - Nuclear inclusions are large, solitary, eosinophilic and often surrounded by a halo.
    - Cytomegalovirus inclusion
    - May be surrounded by inflammation and granulation tissue
- Treatment
  - Ganciclovir / foscarnet IV
  - ↓ associated immunosuppression, if possible
  - Anti-retroviral therapy if associated HIV infection

- Trypanosoma Cruzi Infection
  - Culprit for chagas disease
  - Pathogenesis consists of destruction of the enteric neurons and development of antimuscarinic receptor antibodies in response to the infection
  - Esophageal manifestations may appear 10-30 yrs after the acute infection

➢ Clinical
  - Dysphagia
  - Chest pain
  - Cough
  - Regurgitation
  - Nocturnal aspiration
  - Similar manometric and clinical presentation as achalasia

➢ Diagnosis
  - Characteristic motor abnormalities of the esophagus + positive laboratory diagnosis of chronic Chagas disease (IgG T. Cruzi ELISA test)

➢ Treatment
  - Similar to achalasia, lower the pressure of the LES
    - Initially nitrates, balloon dilation, or myotomy
    - Intractable symptoms or pulmonary complications secondary to megaesophagus may be candidates for esophagectomy

- Mycobacterium Tuberculosis Infection
  - Mainly due to direct extension from adjacent mediastinal structures
    - Rare cases of primary esophageal TB

➢ Clinical
  - Secondary TB
    - Chest pain
    - Cough
    - Dysphagia
    - Fever
    - Weight loss

- More severe disease
  - Bleeding
  - Perforation
  - Fistula (esophagus to respiratory tract)
- Mimic cancer
  - Ulcerating mass lesion
  - Paratracheal adenopathy on CT imaging

➢ Endoscopy

- Send esophageal mucosal biopsies / brushings for acid-fast stain, mycobacterial culture, and PCR
- Shallow ulcers, heaped-up lesions, and extrinsic compression of the esophagus

➢ Treatment

- Best practice, guideline-based treatment of TB infection
- Manage esophageal complications (fistula, bleeding, perforation)

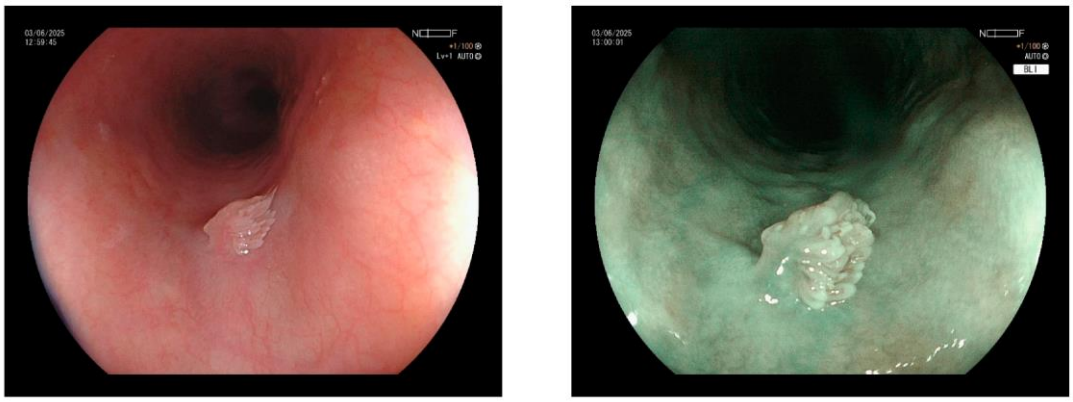
- Human Papilloma Virus (HPV) Infection
  - Small double stranded DNA virus that infects squamous epithelium
  - Produces warts, condylomas that can be sexually transmitted

➢ Clinical

- Often asymptomatic

➢ Endoscopy

- Found in the mid to distal esophagus
- Erythematous macules
  - White plaques
  - Nodules



(A) (B)

(**A**): White light endoscopy (WLE) showing a small, solitary, whitish-pink lesion with well-demarcated margins. (**B**): Virtual chromoendoscopy using blue light imaging (BLI), highlighting the characteristic triad of exophytic growth, wart-like surface projections, and crossing vessels, features associated with high diagnostic accuracy.

Source: Mercurio M, et al. Cancers 2025; 17(14):2404 (Figure 1)

- Histopathology
  - Koilocytosis (atypical nucleus surrounded by a ring), giant cells or by immunohistochemical staining
- Treatment
  - Often not needed
  - Variable response to interferon α, bleomycin, etoposide
  - Larger lesions can be considered for endoscopic removal

- Treponema pallidum Infection
  - Syphilis can rarely cause esophageal disease in immunocompetent individuals
- Endoscopy
  - Submucosal granuloma's (Gummas), diffuse ulceration, and strictures in tertiary syphilis
  - Consider syphilis for inflammatory stricture of esophagus with no other explanation

- Histopathology
  - Perivascular lymphocytic infiltration
  - Need immunostaining to confirm diagnosis

Esophageal Trauma

Penetrating trauma

- Types
  - Cervical esophageal
  - Lower esophagus
- Causes
  - Gunshot / knife wounds
  - Cervical spine surgery → esophageal perforation
- Diagnosis
  - Extraluminal air on chest X Ray or CT scan
    - Endoscopy would be a relative contraindication

Blunt Trauma

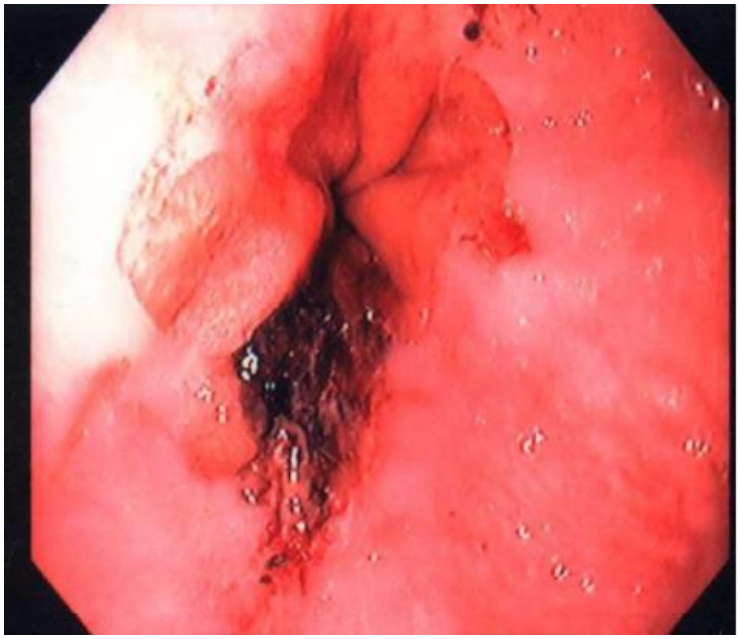
- Esophageal perforation (very rare)
  - Would be seen with cervical esophagus rupture after MVC
- Motor vehicle accident → shearing forces cervical esophageal rupture / transection

Esophageal Tears

Mallory-Weiss

- Definition
  - Non-transmural tear of portion of wall of esophagus within 2 cm gastroesophageal junction / proximal stomach due to ↑ intra-abdominal pressure
  - Laceration as a result of shearing forces on the GE junction and proximal stomach

- Causes
  - Cough
  - Hiccup
  - Vomit
  - Straining
  - Retching
  - Hiatus hernia
  - Risk factors
    - Alcohol
    - Aspirin use
- Clinical
  - Upper GI bleeding (UGIB)
    - Massive bleeding in 10%



Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

➢ Treatment

- Guideline-based practice for UGIB
  - Endoscopic hemostatic therapy, ↓ bleeding (26% → 6%)
  - ↓ length if hospital stay (5.5 d → 3.7 d)
  - Trend to ↓ transfusion requirements

- Boerhaave

➢ Definition

- Transmural tear of lower esophagus with perforation at the contact between clasp and oblique (sling) esophageal muscle fibers

➢ Causes

- Similar to Mallory-Weiss
  - Sudden ↑ intraabdominal pressure
  - Previous abnormal esophageal mucosa (e.g., esophagitis including EoE, infections)

➢ Clinical

- Chest pain
- Shock/Sepsis
- Subcutaneous edema
- Pneumomediastinum
- Left pleural effusion / frank empyema

➢ Treatment

- Surgical repair and drainage
  - If diagnosed early, consider non-operative with self-expandable metallic stent and clip

❖ Esophageal Hematomas (Spontaneous Esophageal Hematoma)

➢ Definition

- Sudden bleeding occurs between mucosa and muscularis propria of the entire esophageal wall

- Causes
  - Not completely spontaneous (multiple associated factors)
    - Aspirin use
    - Coagulopathy
    - Pre-eclampsia
    - ↑ pressure gradient between the intra-abdominal and intra thoracic area

- Clinical
  - Triad of
    - Chest pain
    - Dysphagia
    - Hematemesis
  - 50% of these patients have ≥ 2 of these symptoms

- Diagnostic imaging
  - CT Chest
    - “Double barrel” sign

- Endoscopy
  - Obliteration of the esophageal lumen with long, deep, friable, blue submucosal mass +/- visible tear

- Treatment
  - Conservative management
    - No oral intake
    - Monitor hemodynamic status
    - Monitor progress with CT or endoscopy (at 1-wk intervals)

STOMACH

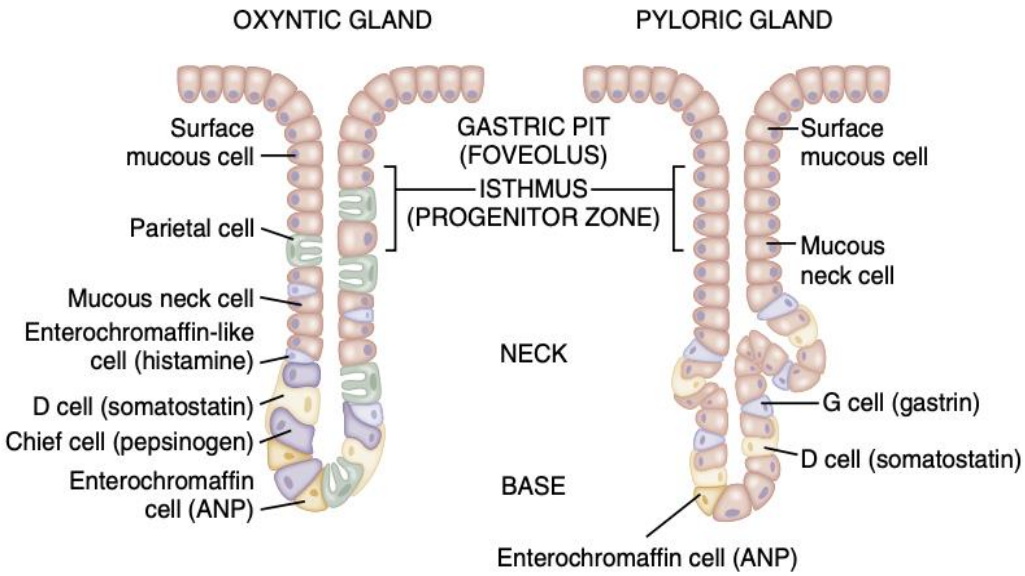
Gastritis and Gastropathy

AGA Clinical Practice Update (2021) and Expert Review

Navneet Natt

Gastric Gland Anatomy

- Oxyntic glands (body and fundus)
  - Parietal cells (80%)
    - Secrete HCl acid / intrinsic factor
    - Also produces other neurohormonal factors (e.g. hepcidin, leptin, TGFα)
  - D cells
    - Secrete somatostatin → inhibit HCl release from parietal cells
  - Enterochromaffin-like cells
    - Secrete Histamine → activates HCl release from parietal cells via histamine subtype 2 receptors (H2R)
- Pyloric glands (antrum)
  - G-cells (20%)
    - Secrete gastrin → activate CCK-2 receptors on parietal cell which stimulate HCl release



Source: https://abdominalkey.com/gastric-secretion/

- Functional Anatomy of the Stomach
  - Fundus and corpus
    - Characterized by presence of oxyntic glands of which the hallmark is the HCl-secreting parietal cells
  - Antrum
    - Characterized by presence of pyloric glands which have predominant gastrin-secreting G-cells

Acute Gastritis

- Demography
  - Acute gastritis is rare
- Histopathology
  - Dense infiltration of neutrophils +/- necrosis
- Clinical
  - Patients appear septic
    - Fever
    - Hypotension
    - Peritonitis
  - Mortality rate, 70%!
- Diagnostic/Endoscopic Imaging
  - Abdominal x-ray
  - Gastroscopy biopsy
    - Thick edematous gastric wall
    - +/- granular green-black exudate

- **Acute phlegmonous gastritis**
  - Infection of the submucosa and muscularis propria; spares the mucosa
  - May spread to liver and spleen
  - Associated with severe sepsis
  - Implicated organisms
    - Group A Streptococcus
    - Gram negative bacilli
    - Anaerobes
    - Fungi (e.g. mucormycosis)

- Other risk factors
  - Alcohol
  - Immunocompromised states
    - Post-transplant
    - Cancer
    - AIDS

- **Acute Emphysematous Gastritis**
  - Severe form of phlegmonous gastritis
    - Caused by gas-producing organisms
      - Clostridium perfringens
      - S. aureus
    - Radiographic findings: gas in wall of stomach
    - Risk factors
      - Recent upper GI surgery
      - Ischemic injury to GI tract
  - Treatment
    - Broad spectrum antibiotics
    - Definitive drainage
    - Gastric resection

Chronic Gastritis

- **Helicobacter Pylori (HP) Gastritis**
  - Acute → chronic gastritis
  - Gram negative helical flagellated bacteria
  - Affects superficial layers of the gastric mucosa causing a
    - Diffuse antral gastritis
    - Only colonizes gastric mucosa
      - Not seen in gastric mucosa with intestinal metaplastic changes

➢ Demography
  - Usually acquired in childhood with persistent chronic infection and re-infection; new de novo adult infection is rare (<0.5% cases/yr)

➢ Risk factors
  - Socioeconomic status during childhood
  - Crowding

- Microbiology
  - Transmission
    - Gastro-oral
    - Fecal-oral
    - Exposure to an infected family member with acute GI illness (vomiting or diarrhea) is risk factor for infection
  - Humans are the main reservoir for infection, but also isolated in
    - Domestic cats
    - Sheep
    - Primates
  - HP can remain viable in water for several days
    - Consumption of infected water can also lead to infection

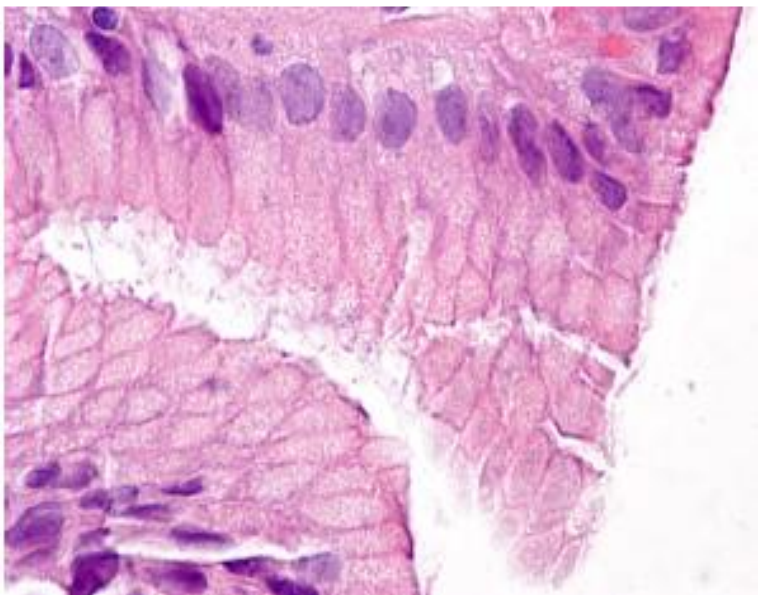
- Diagnosis

	Advantages	Disadvantages
• Non-endoscopic tests		
○ Serology (qualitative or quantitative IgG)	− Indicates present or past infection ▪ Widely available ▪ Inexpensive ▪ Good NPV	− Poor PPV if Hp prevalence is low − Not useful after treatment
○ Urea breath (^{13}C or ^{14}C)	− Perform tests when patient > 2 wk off antibiotics, PPIs or recent upper GI bleeding ▪ Identifies active infection ▪ Accuracy (PPV, NPV) not affected by Hp prevalence ▪ Useful both before and after treatment	− Available and reimbursement inconsistent − Accuracy affected by PPI and antibiotic use − Small radiation dose with ^{14}C test
○ Stool antigen	− Perform tests when patient > 2 wk off antibiotics, PPIs or recent upper GI bleeding Identifies active infection ▪ Accuracy (PPV, NPV) not affected by Hp prevalence ▪ Useful both before and after treatment	− Fewer data available Accuracy affected by PPI and antibiotics use

	Advantages	Disadvantages
• Endoscopic tests		
○ Biopsy urease	−Rapid results −Accurate for patients not using PPIs or antibiotics −No added pathology cost	− Requires endoscopy − Less accurate after treatment or in patients using PPIs
○ Histology	−Excellent sensitivity and specificity, especially with special immunostaining −Provides additional information about gastric mucosa	− Expensive (endoscopy and pathology costs) − Some interobserver variability − Accuracy affected by PPI and antibiotic use
○ Culture	−Specificity 100% −Allows antibiotic sensitivity testing	− Difficult culture protocol − Not widely available − Expensive

➢ Histopathology

- ○ Chronic active gastritis with diffuse lymphoplasmacytic infiltrate and neutrophils in the lamina propria / gastric pits
- ○ Shrunken vanished glands in the antrum
- ○ Foci of intestinal metaplasia surrounded by fibromuscular tissue



Courtesy of Dr. Aducio Thiesen, University of Alberta

- **Other Infectious Gastritides: Viral**
  - CMV
    - More common in immunocompromised hosts (stem cell or solid organ transplant, cancer, AIDS, chemo, or chronic steroids) but can occur in immunocompetent individuals as well
    - Clinical features
      - Fever +/- abdominal pain +/- atypical lymphocytosis
    - Endoscopy
      - Thickened edematous antral mucosa
      - Multiple ulcers
      - Hemorrhagic folds (may resemble malignancy)
    - Histology
      - Enlarged cells with CMV “owl-eye” intranuclear inclusions on H&E
  - HSV-1
    - Rare
      - Occurs in immunocompromised patients who develop re-activation of dormant virus
    - Clinical Features
      - Nausea/vomiting
      - Abdominal pain
      - Fevers
      - Weight loss
    - Endoscopy
      - Multiple ulcerated plaques
      - Superficial erosions that confer a cobblestoning appearance
      - Brush cytology recommended to make diagnosis +/- viral culture and PCR of biopsy samples
  - Rubeola virus (measles)
    - Rarely causes gastritis
    - Characteristic histology
      - Multinucleated giant cells (Warthin Finkeldey cells)

- **Other Infectious Gastritides: Bacterial**
  - Actinomycosis (rare)
    - Gram positive anaerobic bacteria → normally colonizes the mouth
    - Multiple abdominal/gastric wall abscesses and fistulas
    - Mimics a gastric tumour
      - Circumscribed ulcerated mass
    - Treatment
      - High dose penicillin or amoxicillin-clavulanate for 6-12 mon

- Mycobacterium Tuberculosis (rare)
  - Gastric TB associated with
    - GI bleeding secondary to ulcers
    - Gastric outlet obstruction secondary to granulomatous inflammation, hypertrophy,
  - Histology
    - Foamy histiocytes
    - Acid-fast bacilli
  - Treatment
    - As per Canadian Tuberculosis Standards

- Syphilis
  - Endoscopy
    - Thickened gastric folds with
      - Nodularity
      - Shallow serpiginous ulcers with white exudate
  - Histology
    - Dense plasma cell infiltrate in the lamina propria
    - Gland destruction
    - Vasculitis
    - Granulomas
    - Spirochetes seen with Warthin-Starry silver stain
  - Treatment
    - Penicillin

- **Other Infectious Gastritides: Fungal Infections**
  - Aspergillosis
  - Candidiasis
    - Candidal colonization of stomach is not uncommon
    - Present as superficial erosions; can progress to deep linear ulcers
    - Yeast/pseudohyphae visible on H&E or periodic acid-Schiff-diastase (PAS-D) stain
  - Cryptococcosis
  - Histoplasmosis
  - Mucormycosis

- **Other Infectious Gastritides: Parasitic Infections**
  - Anisakidosis
  - Ascariasis
  - Capillariasis
  - Cryptospiridiosis
  - Giardiasis
  - Granulomatous Gastritides
  - Necatoriasis
  - Strongyloides

Granulomatous Gastritides

- **Collagenous gastritis**
  - Co-exists with celiac disease and/or collagenous colitis
  - Patchy chronic superficial gastritis
  - Unclear
    - Etiology
    - Natural history
    - Treatment

- **Crohn Disease**
  - Gastric Crohn disease is uncommon
    - Usually occurs in conjunction with intestinal disease
  - Clinical features
    - Nausea/vomiting
    - Anorexia
    - Abdominal pain
    - Weight loss
  - Endoscopy
    - Serpiginous
    - Longitudinal ulcers concentrated in the antrum

- **Gastric Lymphoma**
- **Granulomatosis with Polyangiitis**
- **Langerhans Cell Histiocytosis**
- **Lymphocytic gastritis**
  - Lymphocytic infiltration of gastric pits
  - May occur in patients with
    - H. pylori, and
    - Improve with H. pylori eradication
  - May also occur in patients with celiac disease and improve after initiating gluten-free diet
- **Sarcoidosis**
  - Gastric antrum is the most common part of the GI tract involved by sarcoidosis followed by liver/spleen
  - Presents between age 30-50
  - Clinical features
    - Epigastric pain
    - Gastric outlet obstruction
    - Pernicious anemia
    - Massive GI hemorrhage
  - Endoscopy
    - Thick gastric folds with cobblestoning, prepyloric ulcers/erosions
  - Histology
    - Non-caseating granulomas
  - Treatment
    - Prednisone
- **Xanthogranulomatous gastritis** – extremely rare

Chronic Atrophic Gastritis

- Definition
  - Pre-malignant condition
  - Loss of gastric glands (parietal cells / chief cells) and
    - Replacement with connective tissue +/- metaplasia
      - Metaplasia commonly involves intestinal cells but can also include pseudopyloric, pancreatic, ciliated, or squamous cells
    - Histopathologic diagnosis*
    - Etiology
      - H Pylori (most common)
      - Autoimmune

- Pathophysiology
  - Cell loss from the gastric mucosa > the capacity of progenitor stem cells to replace lost cells → thinning of the gastric mucosa

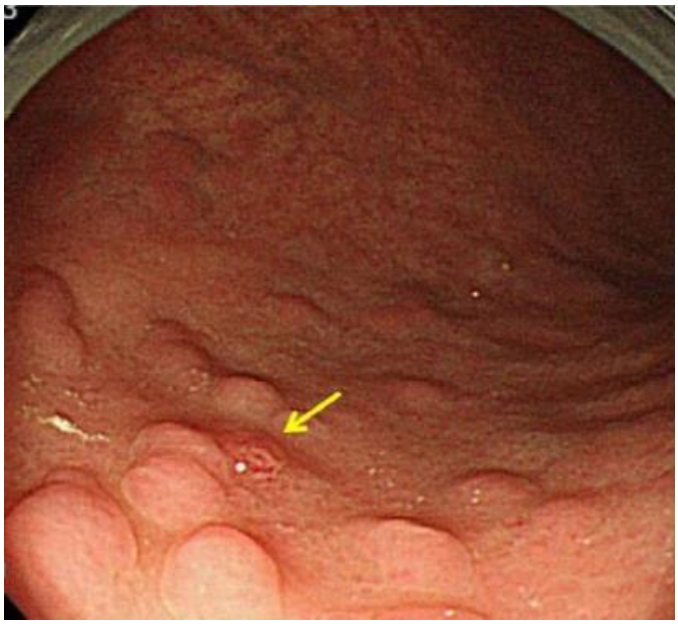
- Subtypes

- **Multifocal Atrophic Gastritis** (EMAG)
  - H pylori associated gastric atrophy that involves both antrum and body
    - Atrophic changes start in antrum and extend proximally to involve the body; can involve entire stomach in severe cases
  - Endoscopic findings
    - Pale shiny mucosa
    - Prominent submucosal vessels
  - Take biopsies as per Sydney Protocol
    - 2 from the antrum along the lesser and greater curvature within 2-3cm of pylorus
    - 2 from the gastric corpus
      - 1 from the lesser curvature at 4 cm proximal to the incisura angularis
      - 1 from the middle portion of the greater curvature of the gastric body at 8 cm from the cardia
      - 1 from the incisura angularis
  - Risk of gastric neoplasia (dysplasia or cancer) is 1%/yr
  - Treatment = test and treat for H pylori

- **Diffuse Corporal Atrophic Gastritis** (AMAG)
  - Autoimmune T-cell mediated destruction of glands in gastric body and fundus; precursor to pernicious anemia
    - Associated with anti-parietal cell Ab (PCA) and anti-intrinsic factor (IFA)
    - Reduced or absent gastric acid production leads to gastrin and antral G-cell hyperplasia
  - Associated with AI thyroid disease (Graves and Hashimotos), T1DM, celiac, AI pancreatitis
    - Consider screening patients with T1DM w/ EGD and mucosal biopsy; also supported by ACG 2024 H Pylori guidelines
  - Antral sparing is characteristic of AMAG – if antral changes seen on endoscopy, test for H. pylori
  - More common in Northern European, Scandinavian, and African American populations
  - Clinical Manifestations
    - Asymptomatic; incidental finding
    - Dyspepsia
    - B12 and Fe deficiency anemia
  - Associated with Type 1 Gastric NET

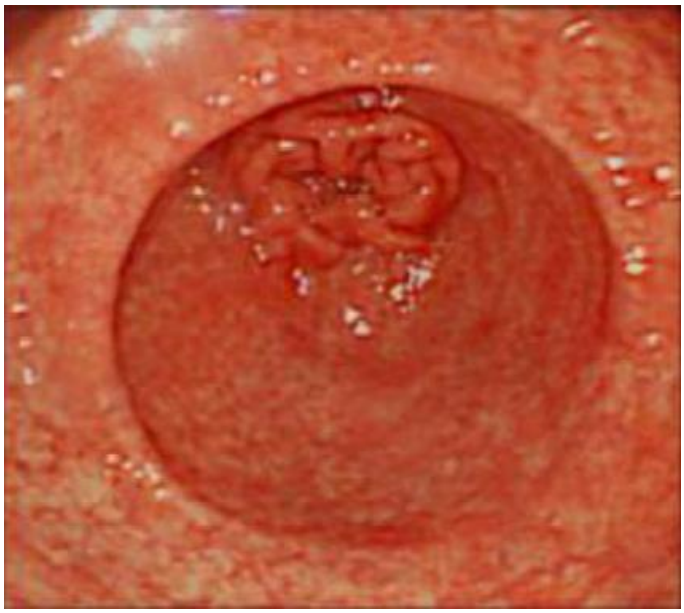
➢ Endoscopy
  - Ensure adequate air insufflation and mucosal cleaning to optimize visualization
  - Examine
    - Entire gastric lumen for characteristic changes
    - Use photographic documentation of cardia, fundus, lesser and greater curvature of antrum and corpus, angularis
    - Use narrow-band imaging (NBI) to detect intestinal metaplasia (IM) – sensitivity of 87%, specificity of 97%

Atrophic Gastritis



Source: Yagi K, et al. Case Reports in Medicine, vol. 2012, Article ID 368160, 4 pages, 2012.

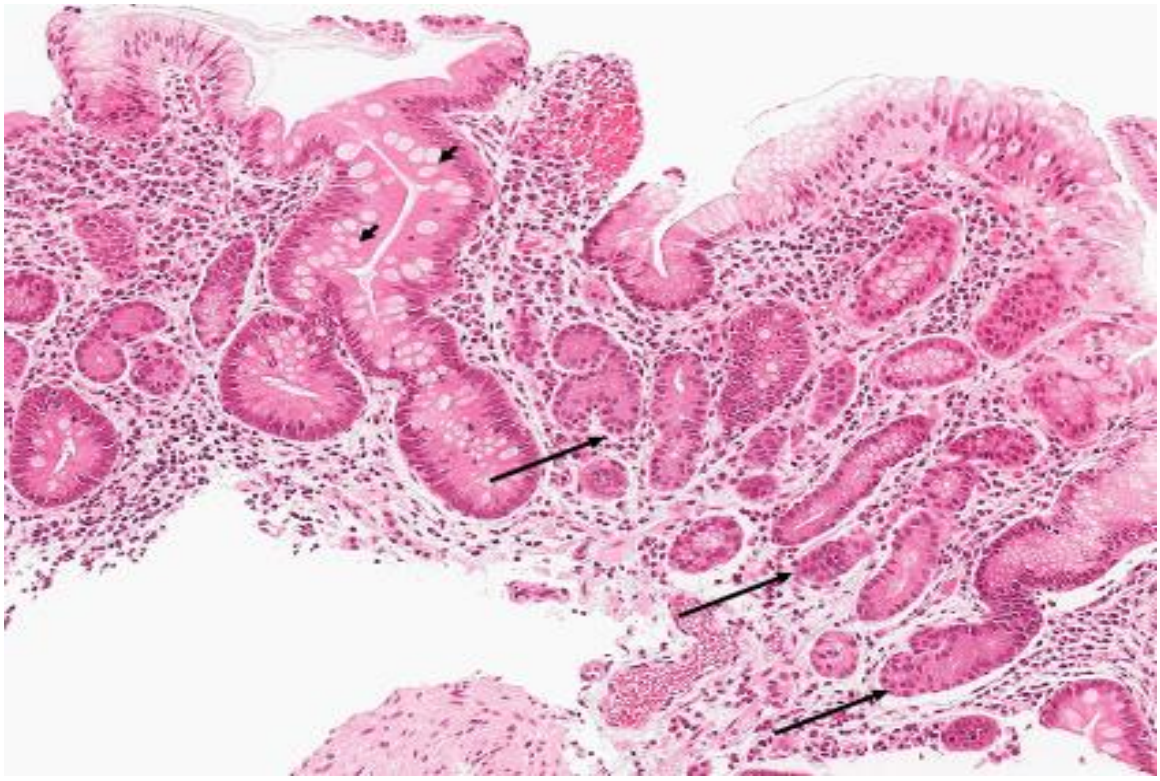
Atrophic Gastritis



Source: Park YH and Kim N. J Cancer Prev 2015; 20(1): 25-40.

- Serology
  - Anti-parietal cell antibody (PCA)
    - Most sensitive biomarker for autoimmune gastritis (AIG)
  - Anti-intrinsic factor antibody (IFA)
    - Poor sensitivity but highly specific for AIG
- Histology
  - ↓ size / ↓ number of gastric glands
  - Lymphoplasmacytic infiltrate
  - Intestinal metaplasia
  - Absence of parietal and chief cells
  - Background of inflammatory cells

Autoimmune Atrophic Gastritis

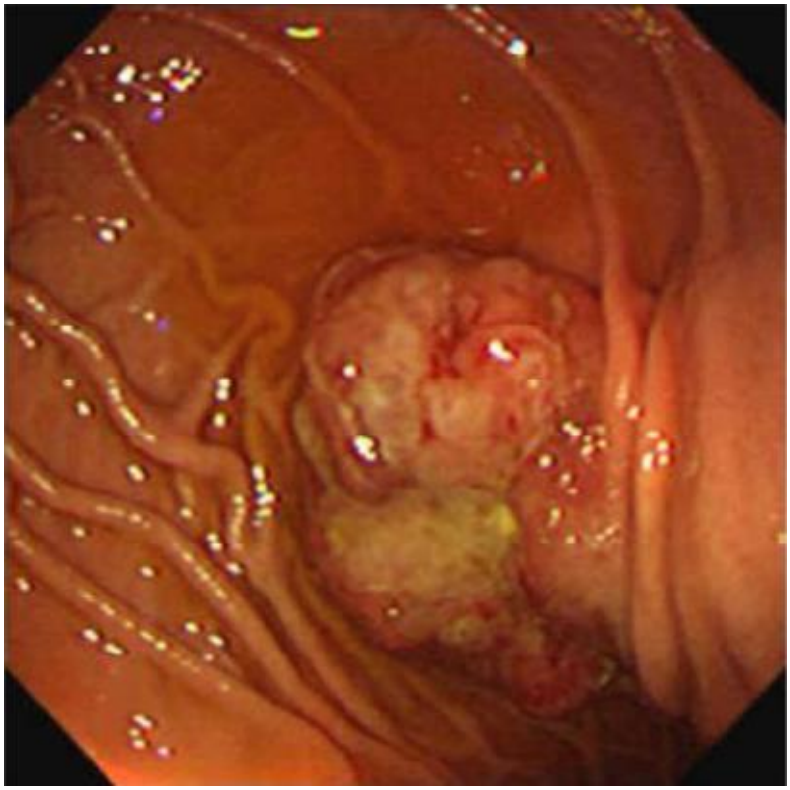


Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

Atrophic Gastritis: AGA 2021 Clinical Practice Guideline Statements

- Providers should recognize typical endoscopic features of AG including:
  - Pallor of gastric mucosa
  - Thinning of gastric wall
  - Loss of gastric folds
  - ↑ visibility of vasculature
- Endoscopic biopsies should be obtained from antrum/incisura and body (in separate jars) with targeted biopsies from the suspected atrophic area
- AG diagnosis should be confirmed by histopathology.
  - If H. pylori confirmed, evaluate for:
    - H pylori – most common cause of AG
    - Anti-parietal cell Ab, intrinsic factor Ab – for autoimmune (AI) etiology
    - CBC, Vitamin B12, ferritin, transferrin saturation – for anemia as a consequence
- If AI AG confirmed:
  - Screen for AI thyroid disease with TSH
  - Screen for Type 1 NET with upper endoscopy and remove tumour endoscopically if small
- Optimal endoscopic surveillance interval is unclear and should be based on anatomic extent and histologic grade of IM
  - Consider screening q3y for advanced AG.
  - Consider screening q1-2y if removing small type 1 gastric NET

- Atrophic Gastritis and Gastric NETs
  - Type 1 Gastric Neuroendocrine Tumours
  - Most common gastric NET
  - Associated with AI atrophic gastritis
  - Polypoid lesions with yellow/reddish colour
  - Usually asymptomatic and discovered incidentally
  - Management of small lesions < 1 cm
    - Endoscopic resection
    - Surveillance q1-2y
  - Management of lesions >1-2 cm
    - Use EUS to evaluate depth of invasion
    - Consider surgical resection



Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

Endoscopy Algorithm for clinical management of AG

- Obtain topographical biopsies to determine anatomic extent and histologic severity for risk stratification
- Surveillance endoscopy should be considered in patients with*
  - Advanced AG q3y
  - 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
- Evaluate for active NETs and manage accordingly
- Test for H. pylori infection
  - Treat if positive and
  - Confirm eradication

- Evaluate for anemia
- Evaluate for micronutrient deficiencies, such as iron and vitamin B12 (irrespective of anemia)
- In patients with AIG
  - Screen for autoimmune thyroid disease
  - Low threshold to evaluate other autoimmune disease based on clinical presentation (e.g., type I diabetes)
- Check PCA and IFA in patients with endoscopic/histologic findings consistent with AIG*

Abbreviations: AG, atrophic gastritis; AIG, autoimmune gastritis; IFA, intrinsic factor antibodies; NET, neuroendocrine tumour; PA, pernicious anemia; PCA, parietal cell antibodies

*Advanced AG is defined based on 1. anatomic extent and 2. histologic grading

Adapted from: Shah SC. et al. Gastroenterology 2021; 161(4): 1325 - 1332.e7 (Figure 3)

Gastropathy

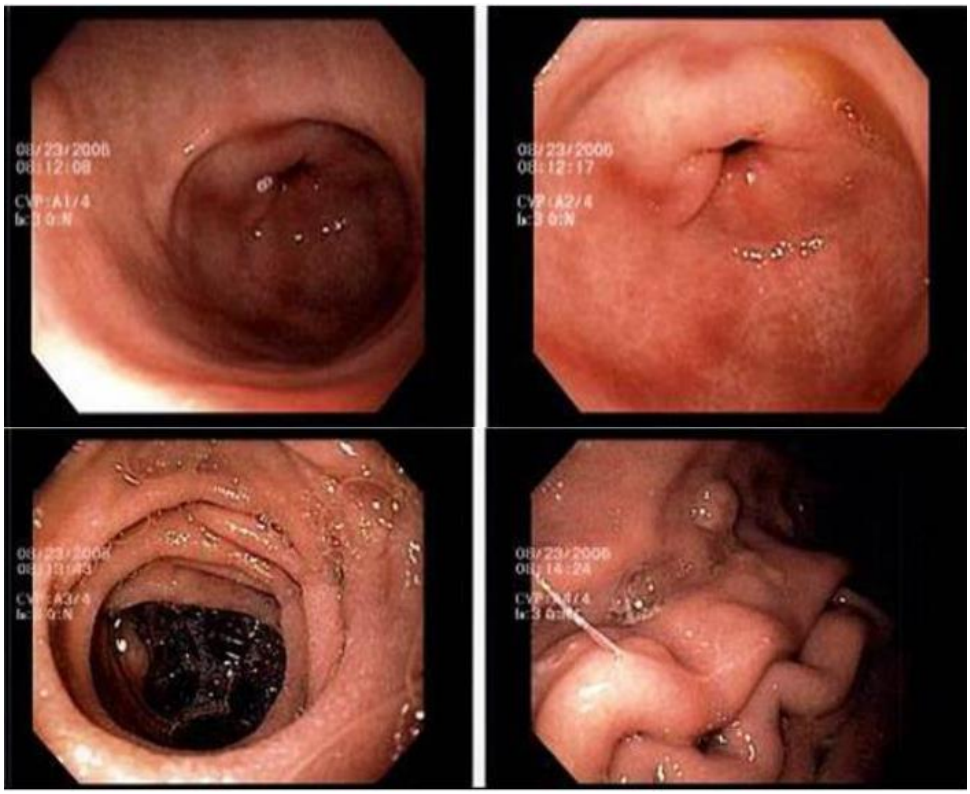
- **Reactive Gastropathy (Acute erosive gastritis)**
  - Damage to epithelial cells of gastric mucosa but no the inflammatory infiltrate characteristic of gastritis
    - Cellular injury → rapid cell turnover → foveolar hyperplasia (sign of epithelial regeneration)
  - Endoscopy
    - Red streaks
    - Subepithelial hemorrhage
    - Mucosal erosions
    - Less commonly ulcers
  - Causes
    - Bile Reflux
    - Drugs/toxins (e.g. NSAIDs, Fe supplement, alcohol, crack cocaine)
    - Ischemia
    - Radiation

Ménétrier Disease

- Definition
  - Hyperplastic gastropathy characterized by
    - Giant gastric folds with epithelial hyperplasia predominantly affecting the corpus
    - Premalignant associated with gastric adenocarcinoma (GAC)

- Causes/Associations
  - Reduced/absent HCl secretion (achlorhydria)
    - Due to replacement of parietal / chief cells with mucous cells
  - Protein loss
  - Hypoalbuminemia
  - Anemia
  - CMV infection in childhood

- Endoscopy

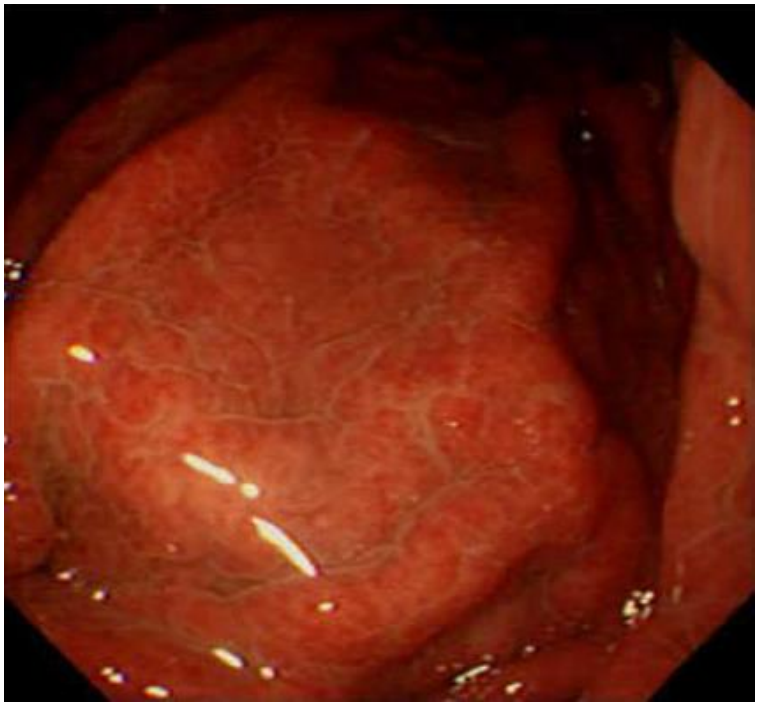


Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Differential
  - Zollinger-Ellison syndrome
    - Gastric malignancy
    - Granulomatous gastritis
    - H. pylori infection
- Treatment
  - In children
    - May be self-limiting and resolve spontaneously by 10 years of age
  - In adults
    - Test and treat for concomitant H. pylori
    - Cetuximab
    - Octreotide
    - Gastric resection for refractory symptoms

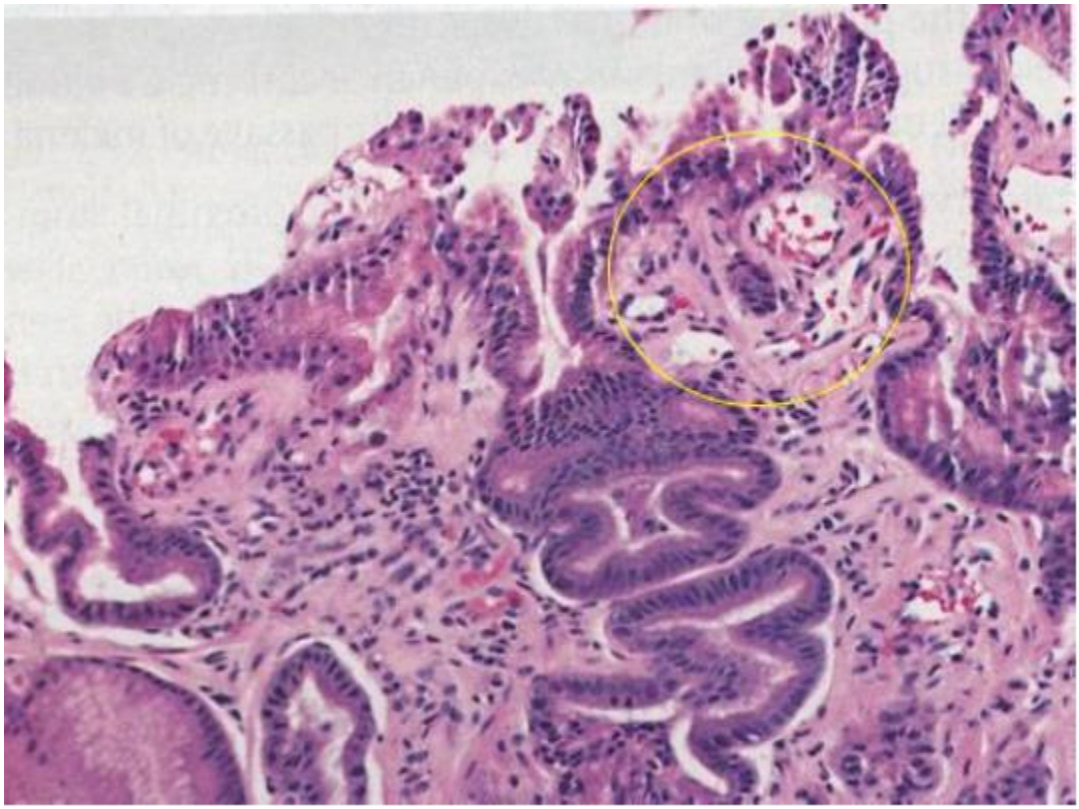
- **Portal Hypertensive Gastropathy (PHG)**

- Definition
  - Endoscopic/histological changes in the stomach associated with cirrhosis and portal hypertension.
  - Often co-exists with gastric antral vascular hyperplasia (GAVE) and hyperplastic polyps in the antrum/duodenum
  - Patients may also have concomitant portal hypertensive enteropathy +/- portal hypertensive colopathy
- Clinical
  - In patients with cirrhosis and portal hypertension
  - Common cause of GI blood loss, Fe deficiency anemia, and chronic transfusions in patients with cirrhosis
- Pathophysiology
  - ↑ portal pressure → submucosal vascular hyperemia → venous and capillary ectasia
- Endoscopy
  - “Snakeskin” mucosal pattern with variable degrees of intraepithelial hemorrhage (presents with red-brown spots)



Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Histopathology
  - Venous/capillary ectasia and congestion



- Ectatic capillaries in the lamina propria (circled)
- Foveolar hyperplasia

Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Treatment:
  - Non-selective beta-blockers (NSBB) to prevent GI bleeding from esophageal/gastric varices
  - TIPS for refractory transfusion-dependent bleeding

Baveno III Classification of Portal Hypertensive Severity

Feature	Score
○ Mucosal mosaic pattern	
− Mild	1
− Severe	2
○ Red markings	
− Isolated	1
− Confluent	2
○ Gastric antral vascular ectasia (GAVE)	
− Absent	1
− Present	2

Note: Mild PHG ≤ 3; Severe PHG ≥ 4

Adapted from: Kaplan DE, et al. Hepatology. 2024;79(5):1180-1211.

Treatment AASLD Guidance Statement (2024): Risk Stratification and Management of Portal Hypertension and Varices in Cirrhosis

- Patients with moderate/severe PHG should be presumed to have CSPH
  - Consider for prophylactic NSBB to prevent decompensation
  - This intervention may also prevent hemorrhagic complications or iron-deficiency anemia from severe PHG.
- In acute bleeding from severe PHG, use vasoactive therapy (e.g., somatostatin, somatostatin analogs such as octreotide, or terlipressin if available for 2-5 d at doses used for variceal bleeding.
- Use NSBB to ↓ risk of rebleeding from PHG and PH-related polyps.
- If bleeding from PHG becomes transfusion-dependent despite HSBB, consider TIPS placement.

Suggested Reading:

Chey WD, Howden CW, Moss SF, et al. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2024;119(9):1730–1753.

Fallone CA, Chiba N, van Zanten SV, et al. The Toronto consensus for the treatment of Helicobacter pylori infection in adults. Gastroenterology 2016;151(1):51–69.e14.

Feldman M, Friedman LS, Brandt LJ. Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 11th ed. Philadelphia, PA: Saunders; 2021.

Gupta S, Li D, El Serag HB, et al. AGA clinical practice guidelines on management of gastric intestinal metaplasia. Gastroenterology 2020;158(3):693–702.

Kaplan DE, Ripoll C, Thiele M, et al. AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024;79(5):1180–1211.

Shah SC, Piazuelo MB, Kuipers EJ, et al. AGA clinical practice update on the diagnosis and management of atrophic gastritis: expert review. Gastroenterology 2021;161(4):1325–1332.e7.

SMALL BOWEL

Celiac Disease

Melanie Beaton

- Definition
  - Chronic, autoimmune disease affecting the small bowel (SB)
    - Precipitated by ingestion of gluten in genetically predisposed individuals PLUS
  - Villous atrophy of SB mucosa with
    - Histological improvement following strict adherence to gluten-free diet (GFD)
    - Relapse (histologic and clinical) when gluten reintroduced

- Terminology – Symptomatic Disease
  - Classic CD
    - Symptoms of Malabsorption
    - Villous Atrophy and Autoantibody +
    - Resolution of atrophy and symptoms on GFD
  - Atypical CD
    - Minor GI complaints
    - May have
      - Anemia/iron deficiency
      - Aphthous ulcers
      - Arthritis
      - Associated autoimmune diseases
      - Infertility
      - Osteoporosis
      - ↑ transaminases
    - Villous Atrophy and Autoantibody +
  - Potential CD
    - Serology positive plus ↑IEL but otherwise normal small bowel biopsy
  - Latent CD
    - Serology positive plus normal biopsy
    - Have had previous villous atrophy that responded to GFD, i.e.:
      - Treated in childhood and now tolerates regular diet later in life
      - 10-20% of children with CD will become gluten tolerant in teens (clinical and histologic)
  - Asymptomatic CD
    - Serology positive but villous atrophy
    - 7x more common than CD
    - No symptoms
    - Does **not** respond to GFD
    - Found via population/risk group screening

- Refractory CD (RCD)
  - Symptomatic plus villous atrophy which is unresponsive to 12 mon strict GFD
  - Diagnosis of exclusion
  - Types I and II (RCD1, RCD2)
  - Usually tTG negative (if tTG positive - think gluten ingestion)

	Symptoms	Genetic susceptibility HLA DQ2/DQ8 TTG	Mucosal Lesion
Symptomatic CD	+	+	+
Silent CD	-	+	+
Latent CD	-	+	-

➢ Demography

- < 5-10% of current cases in Canada have been diagnosed
- Prevalence 1% in susceptible populations
  - Female: Male - 1.5:1
  - Average age of diagnosis - 50s and 25% > 60 yr
- 4.5 times more prevalent than 50y ago
  - Cause for this
    - ↑ awareness – screening high risk groups
    - Better Testing
    - Diet (↑ gluten/wheat ingestion worldwide)
    - Environment changes, unknown
    - Lactation practices
    - Microflora
    - ↑ prevalence unknown: speculation

➢ Pathology

• Gross/Endoscopic (EGD)

- Folds
  - Scalloping
  - Atrophy
- Differential diagnosis of scalloping on EGD

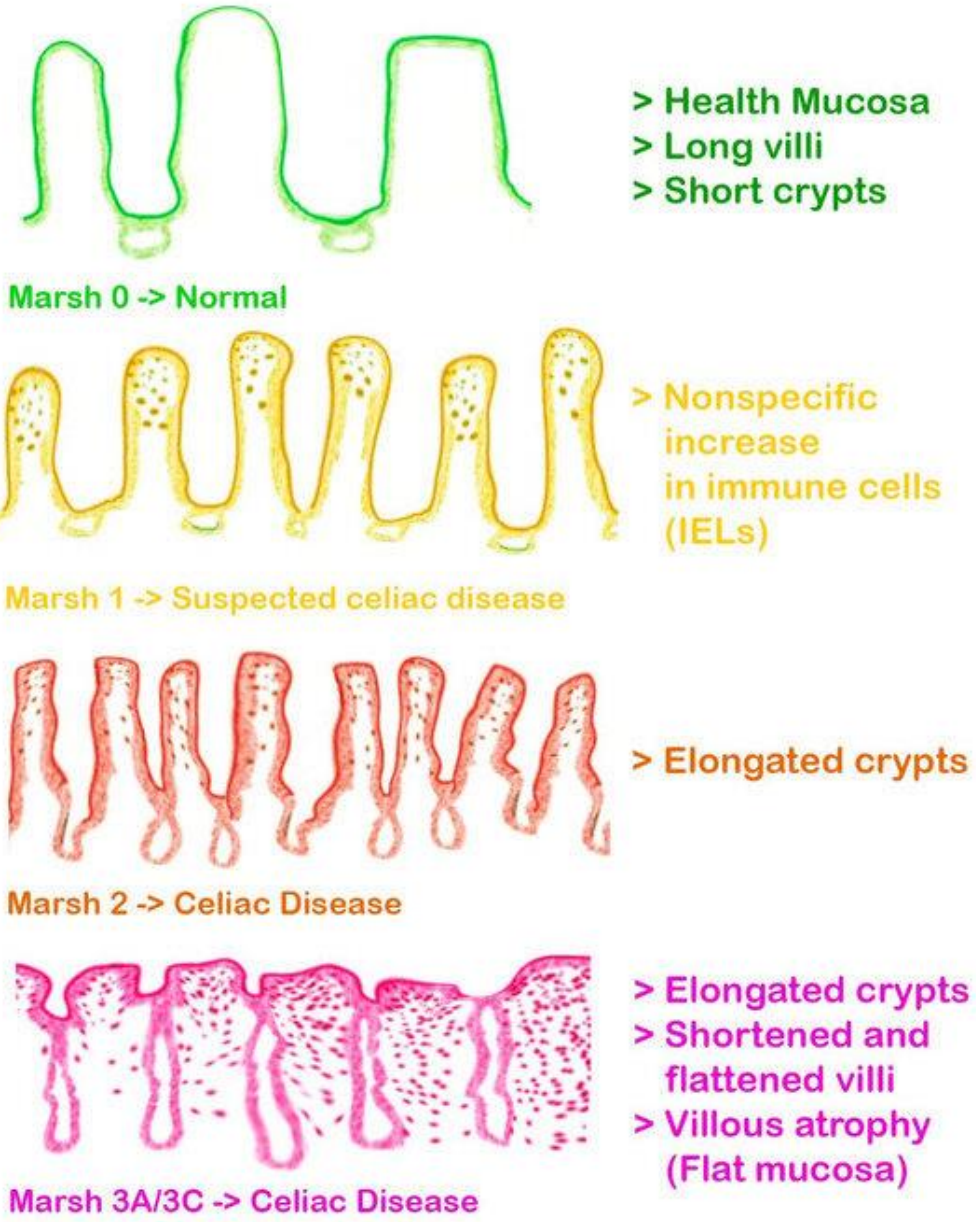
- Histopathology
  - Mucosal disease
    - Significant variability in severity and extent
    - Loss of normal villous structure → ↓ digestion (↓ digestive enzymes) / ↓ absorptive epithelial surface area (↓ mature enterocytes)
  - Lamina propria increased cellularity
    - Plasma cells and lymphocytes
    - # IELs increased
      - Normal <20/100 epithelial cells, >40 Pathological
      - $CD8^{2+}$ vs. mainly CD^{4+} in healthy
  - Villous cells become immature
    - Gliadin-associated toxic effect on maturing enterocytes → ↓ mature / ↑ immature enterocytes along villous
    - ↓ BBM (brush border membrane)
    - Cuboidal shape rather than column
    - Loss of basal nuclear polarity
  - Crypt Cells
    - ↑ rate of formation of immature enterocytes stem cells in crypts
    - ↑ size of crypts to ↑ quantity of enterocytes needed to replace rapid loss from the villous tips

➢ Classification

- The Marsh-Oberhuber Classification

<table>
<tr><th>Marsh Type</th><th>Intraepithelial Lymphocytes (IEL) per 100 Enterocytes</th><th>Crypts</th><th>Villi</th></tr>
<tr><td>0</td><td>< 40</td><td rowspan="2">Normal</td><td rowspan="2">Normal</td></tr>
<tr><td>1, infiltrative</td><td rowspan="5">> 40</td></tr>
<tr><td>2, hyperplasia</td><td rowspan="4">↑</td><td rowspan="3">Atrophy</td></tr>
<tr><td>3A, destructive</td></tr>
<tr><td>3B, subtotal villous atrophy</td></tr>
<tr><td>3C, total villous atrophy</td></tr>
<tr><td>4, hyperplastic, uncommon</td><td>Complete loss</td></tr>
</table>

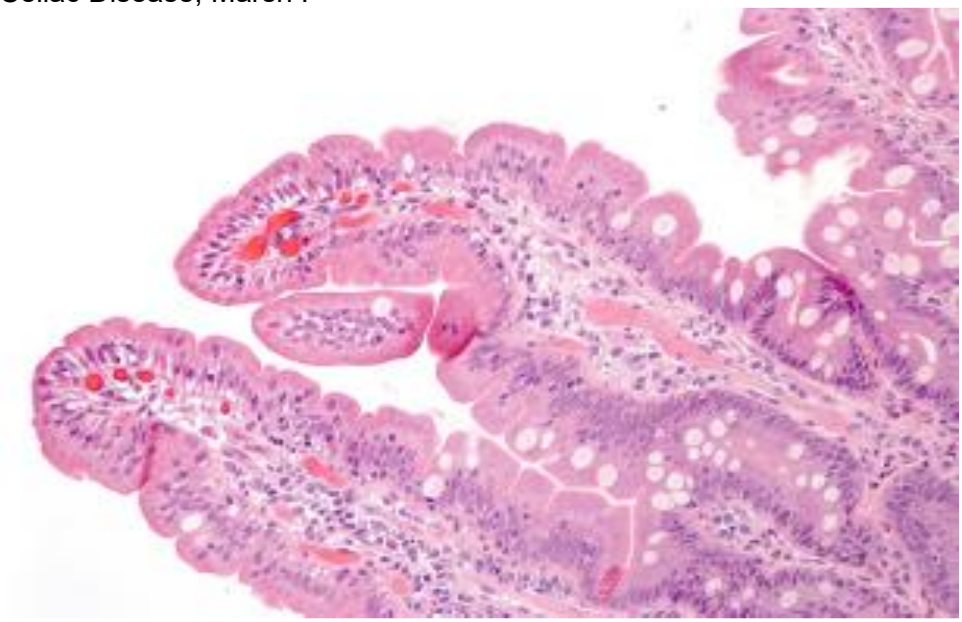
- Marsh Classification



(0) Normal mucosa; (1) Increased number of intraepithelial lymphocytes, usually exceeding 20 per 100 enterocytes; (2) Proliferation of the Crypts of Lieberkühn; (3) Variable villous atrophy, subdivided from A to C depending on the severity of the atrophy.

Source: Inchingolo AD, et al. J Clin Med 2024; 13(5):1382 (Figure 8)

Celiac Disease, Marsh I



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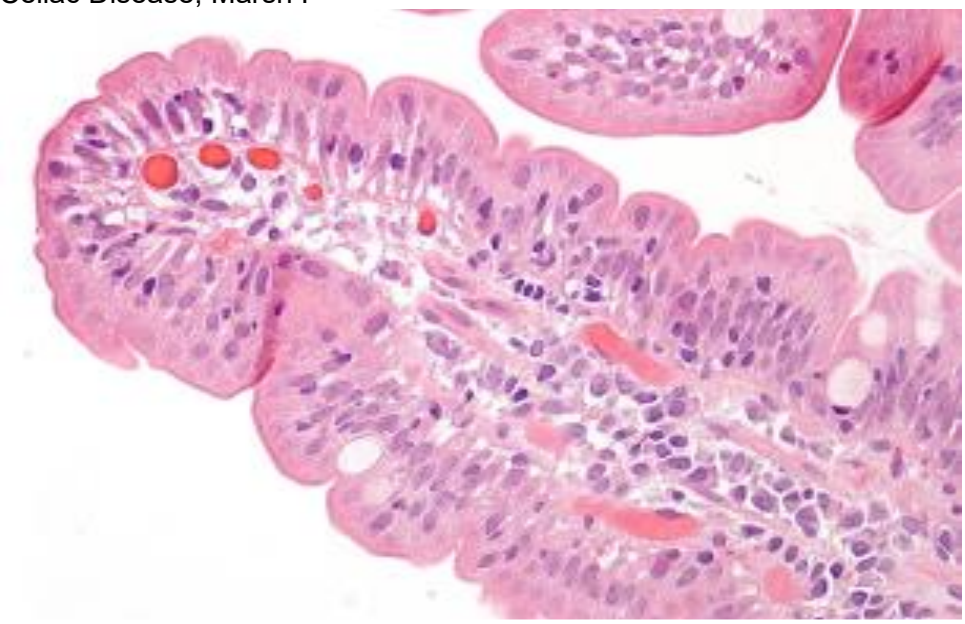
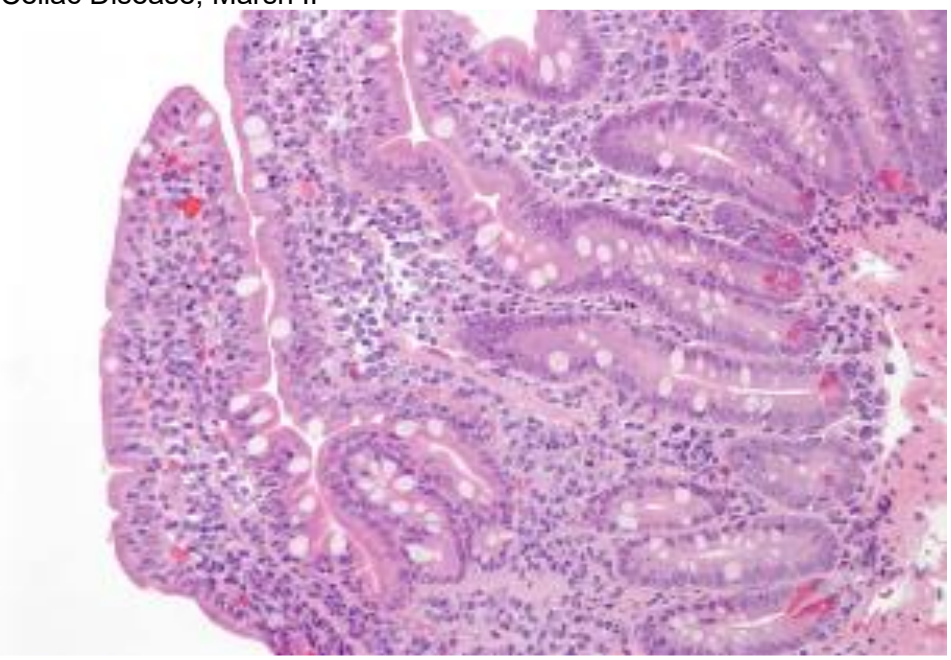
Celiac Disease, Marsh I



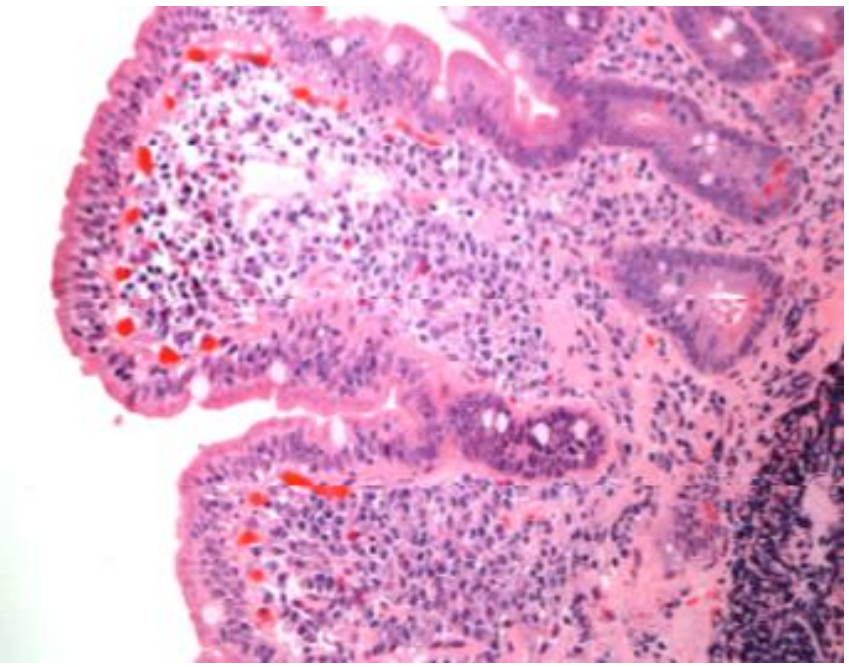
Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

Celiac Disease, Marsh II



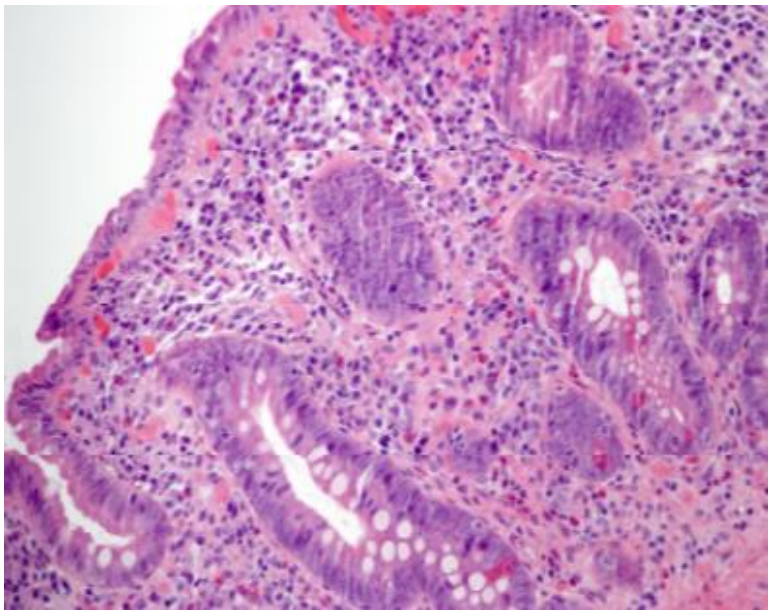
Courtesy of Dr. Aducio Thiesen, University of Alberta

Celiac Disease, Marh IIIB



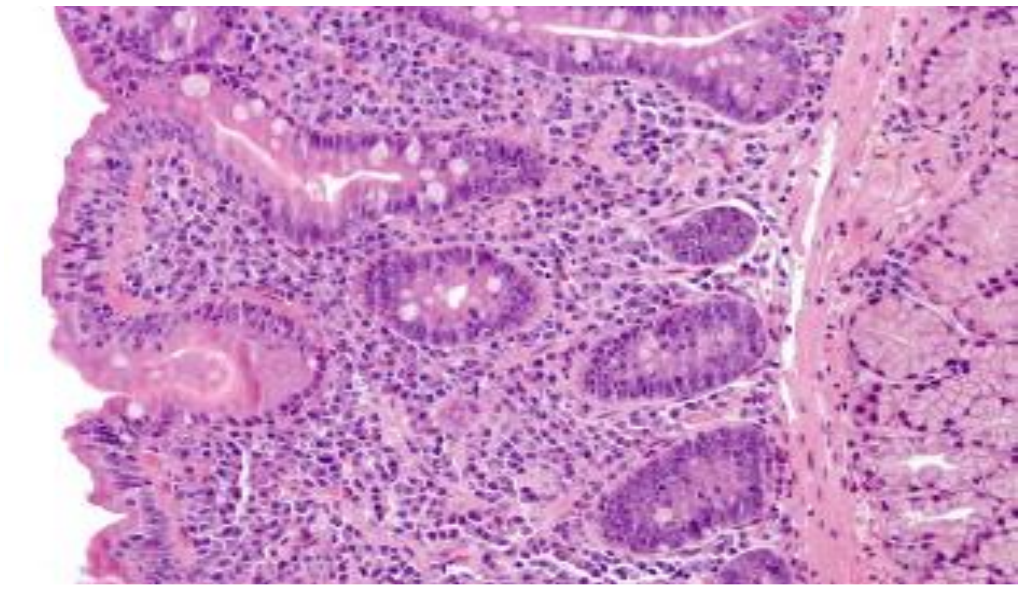
Courtesy of Dr. Aducio Thiesen, University of Alberta

Celiac Disease, Marh IIIC



Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

Celiac Disease, Marsh IIIC



Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Differential of Villous Atrophy
  - Infectious
    - H pylori
    - SIBO
    - AIDS Enteropathy
    - Viral enteritis
    - Whipple Disease
    - Mycobacterium avium complex
    - Giardiasis
    - Strongyloidiasis, Coccidiosis, Hookworm
    - Post-viral gastroenteritis
    - Intestinal TB
  - Celiac
    - Refractory Sprue
    - Tropical Sprue
    - Collagenous Sprue
    - Tropical Sprue
    - Autoimmune Enteropathy
    - Eosinophilic Enteritis
    - Lymphocytic/Collagenous Enteritis
    - Connective Tissue Disease
      - SLE, RA, Autoimmune enteropathy
    - AIDS Enteropathy
    - Immune Deficiency
      - CVID, IgA Deficiency
  - Condition
    - Amyloidosis
    - Zollinger-Ellison Syndrome
    - Crohn
    - Neoplastic
      - Intestinal Lymphoma
      - Graft vs. Host Disease
  - Medications
    - NSAIDS
    - PPIs
    - Olmesartan and Losartan
    - CTLA-4 Antibody (checkpoint inhibitor)
    - MMF
    - Colchicine
  - Malnutrition
    - Cow's milk or soy protein intolerance

- Histologic Response to Treatment
  - BBM
  - IELs
  - Villi

  } Return towards normal

  - Distal small bowel mucosa improves more rapidly than proximal
  - May take months to years to completely normalize

- Gluten toxicity
  - Gluten in typical Western Diet 10-20 g/d
    - 1 Slice bread = 3.5 g
  - Enough to cause damage in CD, 100 mg
  - Gluten free (GF), < 10 mg

- Pathogenesis
  - Interplay of numerous components, but requires
    - HLA DQ2/DQ8 genotype
    - Gluten intake

- Environmental Factors
  - Gluten exposure essential for developing CD
  - ↓ gluten tolerance (development of CD) can occur at any time in life
    - Implies additional triggers play role
  - Breast feeding / time of gluten introduction have no impact on risk of CD

- Genetic Factors
  - HLA-DQ2.5
    - >90% of celiac vs. 35% non-CD Caucasians
    - Only a minority develop CD
      - Heterozygous 3%
      - Homozygous 30%
  - HLA-DQ8 or HLA-DQ2.2
    - Positive in almost all remaining CD patients, vs. 10% general population

Clinical Tip

- HLA-DQ2.2/8 Negative rules out CD
  - But Positive is NOT of diagnostic value!
  - This is because NPV > 99% (PPV only 12%)

- Immune Factors
  - Tissue Transglutaminase (tTG) Enzyme
    - The target autoantigen within the endomysium
    - Gliadin – preferred substrate for tTG
    - tTG deamidates neutral glutamine residues in gliadin and converts them into negatively charged glutamic acid, facilitating antigen presentation

gluten → gliadin → glutamine $\xrightarrow{tTG}$ glutamic acid residues, negatively charged

Steps

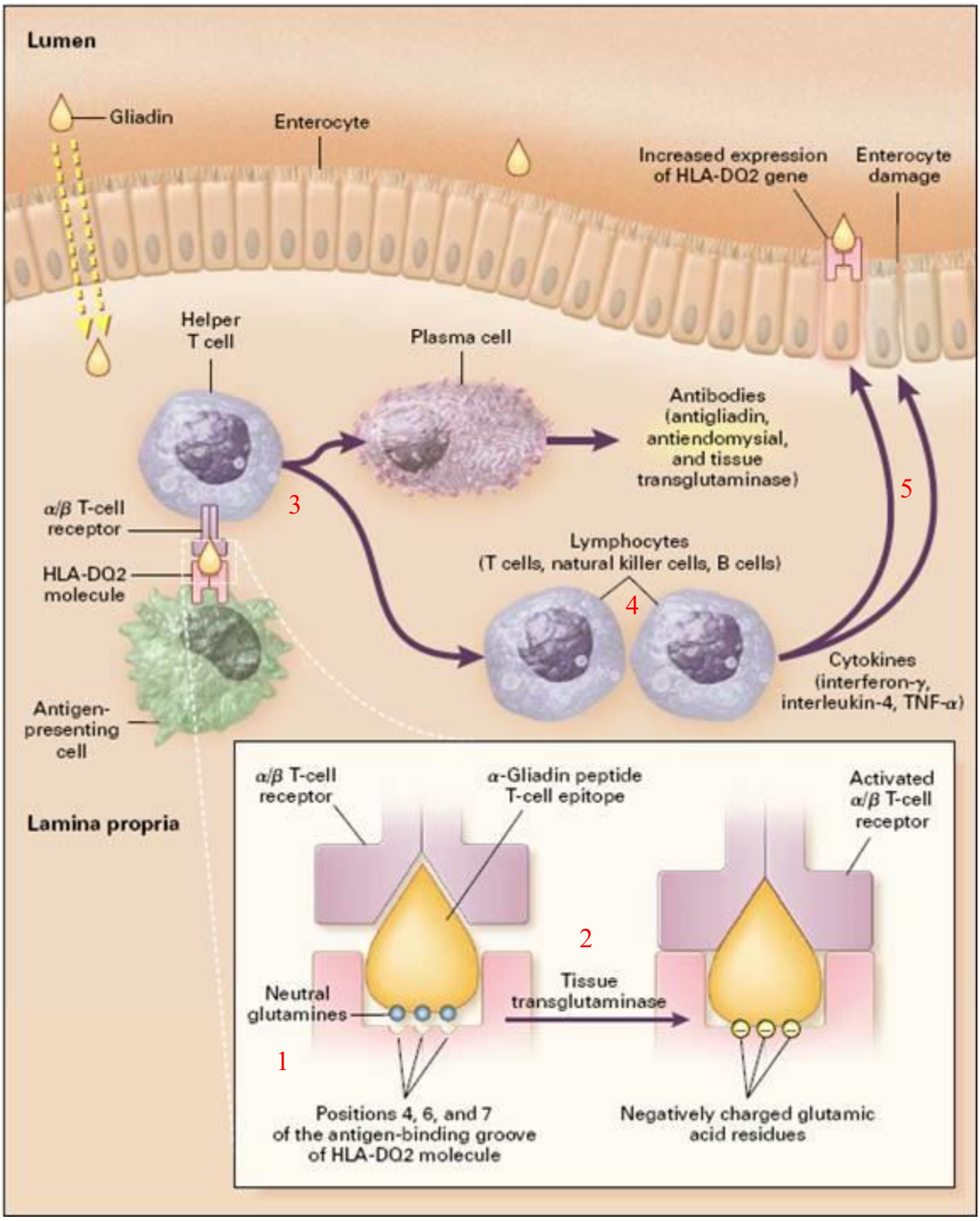
(1) Gliaden (component of gluten) interacts with HLA receptor on antigen presenting cell (APC)

(2) TTG converts glutamine residues to glutamic acid residues making a more potent antigen

(3) T helper-cells activated and in turn activate B and killer T cells

(4) Plasma cell Abs bind to gliadin bound to enterocytes, TTG and reticular fibers surrounding gut smooth muscle (endomysial Abs)

(5) T cells release inflammatory cytokines and inflict tissue damage



Source: https://bio.davidson.edu/movies/Immunology/Students/spring2006/Mohr/celiac.html

➢ Clinical

- GI
  - Altered bowel habit (diarrhea/constipation)
    - Episodic > continuous
    - Osmotic, secretory and/or inflammatory
  - Bloating, dyspepsia, flatulence

  These symptoms may mimic those of the patient with irritable bowel syndrome (IBS)

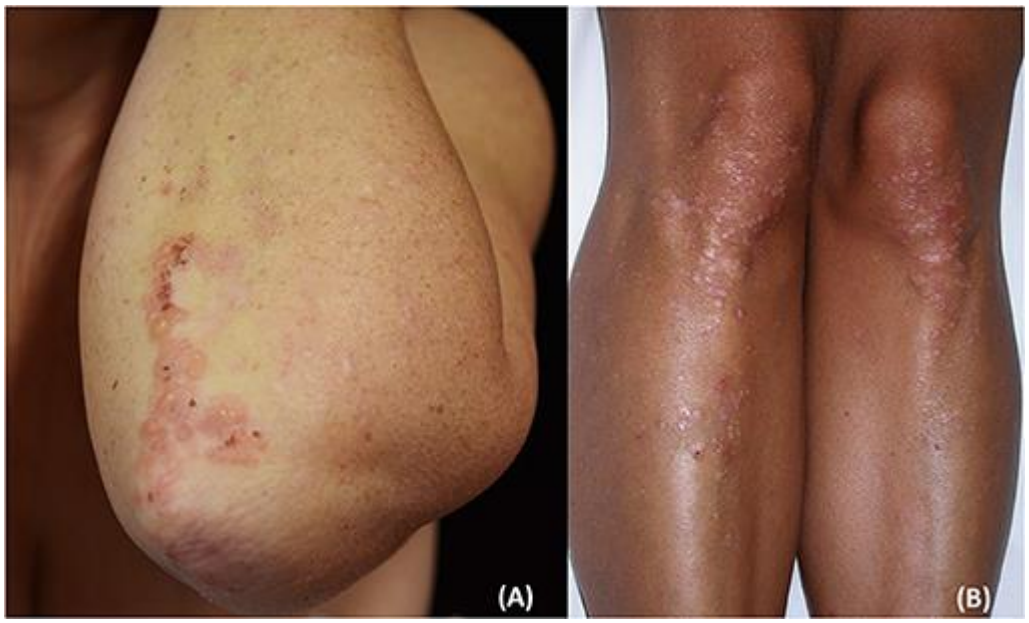
  - Body Weight
    - Body Weight loss or gain
  - Other GI parts
    - Mouth
      - Aphthous stomatitis
    - Esophagus
      - Eosinophilic esophagitis
    - Small bowel
      - Jejunoileitis
      - Adenocarcinoma
      - Lymphoma
    - Colon
      - ↑ MC (microscopic colitis)
    - Pancreas
      - ↑ chronic pancreatitis (secondary)
    - Liver
      - ↑ ALT/ ↑ AST
      - ↑ AIH, PBC, PSC
    - Skin
      - Alopecia
      - Areata
        - Bruising
        - Dermatitis
        - Dermatitis Herpetiformis
        - Edema
        - Follicular hyperkeratosis
        - Psoriasis
    - Endocrine
      - Secondary Hyperparathyroidism (if prolonged Ca^{2+} malabsorption, begin to mobilize from bone)
      - Hashimoto thyroiditis
      - DMT1
      - Addison disease
      - Impotence
      - Autoimmune myocarditis

- Hematology
  - Anemia (iron, folate, B12)
  - Hemorrhage (Vit K)
  - Thrombocytosis and Howell-Jolly bodies (hyposplenism)
- Muscular
  - Atrophy
  - Tetany
  - Weakness
  - Short stature
  - Osteopenia (#1 complication, 70% of untreated celiac, due to ↓ Ca^{2+} and Vit D absorption)
  - Osteoporosis (25%)
- Neurologic
  - Depression
  - Schizophrenia
  - Peripheral neuropathy
  - Gluten Ataxia (immunological damage to cerebellum, epilepsy, spinal cord and peripheral nerves)
  - Demyelinating Disease
  - Seizures
  - Night blindness (Vit A deficiency)
  - Peripheral Neuropathy / Ataxia (usually do **not** respond to gluten withdrawal)
  - Chronic fatigue syndrome
- Autoimmune
  - Sjogren syndrome
  - Rheumatoid arthritis (RA)
  - Systemic lupus erythematosus (SLE)
- Miscellaneous
  - Down / Turner syndrome
  - IgA Deficiency
  - Nephropathy
  - Chronic Fatigue
  - Aphthous Stomatitis
  - Dermatitis Herpetiformis (DH)
  - Amenorrhea
  - Delayed Menarche
  - Early Menopause
  - Recurrent spontaneous abortions
  - Infertility
  - Libido

- Dermatitis Herpetiformis (DH)

➢ Demography
  - DH in patients with celiac disease (CD), 80%
  - CD in patients with DH, ~10%
  - M > F, 2:1

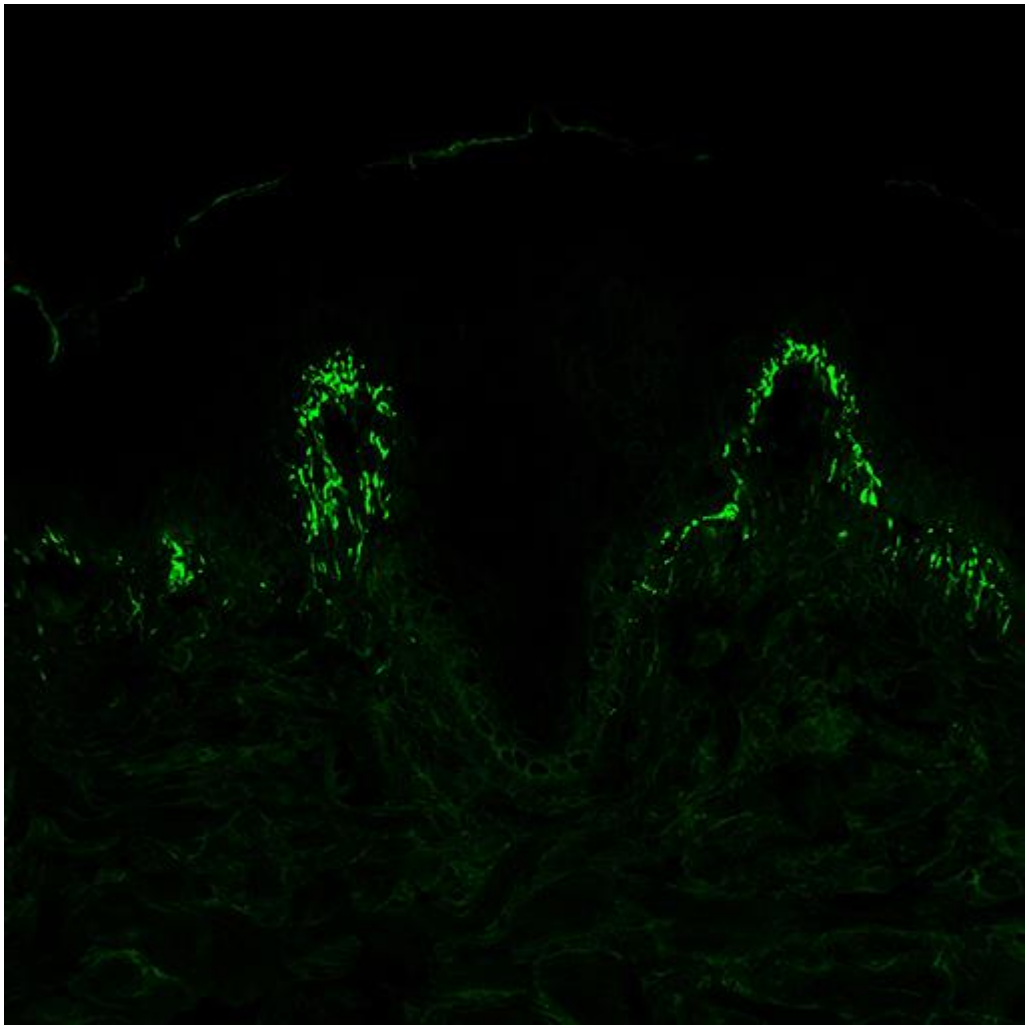
➢ Clinical
  - Multiple grouped (herpetiform) papules / vesicles
  - On elbows, dorsal forearms, knees, scalp, back / buttocks
  - Intensely Pruritic



Clinical presentation of dermatitis herpetiformis: grouped papules and vesicles associated with excoriations and crusts at the elbows **(A)** and lower limbs **(B)**. Post-inflammatory pigmentary changes such as hypo-pigmentation could be also appreciated **(B)**.

Source: Antiga E, et al. Front. Immunol 2019; 10:1290 (Figure 2)

➢ Histopathology
  - Granular IgA basement membrane deposits along dermal papillae
  - Subepidermal bullae with numerous neutrophilic abscesses



Direct immunofluorescence of perilesional skin specimens from patients with dermatitis herpetiformis (DH). Granular IgA deposits at the dermal papillary tips are considered a pathognomonic finding of DH (magnification 400×).

Source: Antiga E, et al. Front. Immunol 2019; 10:1290 (Figure 4)

- Laboratory
  - Serology (Test for Celiac ACG 2023 Guidelines: 2023)
  - Symptoms, signs, family history (1st degree relative) suggestive of malabsorption
  - Unexplained ↑ ALT / ↑ AST
  - GI symptoms in DM1, other autoimmune diseases (Down syndrome, Turner disease)
  - Basis of IgA tTG/ EMA
    - tTG as target antigen
    - AGA / DGP
    - Gliadin is target
  - DGP – Deamidated Gliadin Peptide
    - IgG, useful if IgA deficient or if patient < 2 yr old
    - Isolated +DGP in low risk patients often false positive

- Performance characteristics of serology

Serologic Test		**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
IgA	tTG	95-100	97-100	80-95	100
	EMA	85-98	97-100	98-100	80-95
IgG	DGP	92	100	98-100	87-97
	AGA	69-85	73-90	20-95	41-88
	tTG	40% (higher in IgA deficiency)	98%		

  - To monitor adherence to GFD
    - Often normalize within 3-12 mon
    - tTG half-life approximately 6-8 wk
  - To screen asymptomatic reasons (Not routinely recommended)
  - Poor idea
    - Challenging diet
    - Possible psychological effect of diagnosis
    - Natural history of undetected celiac unknown

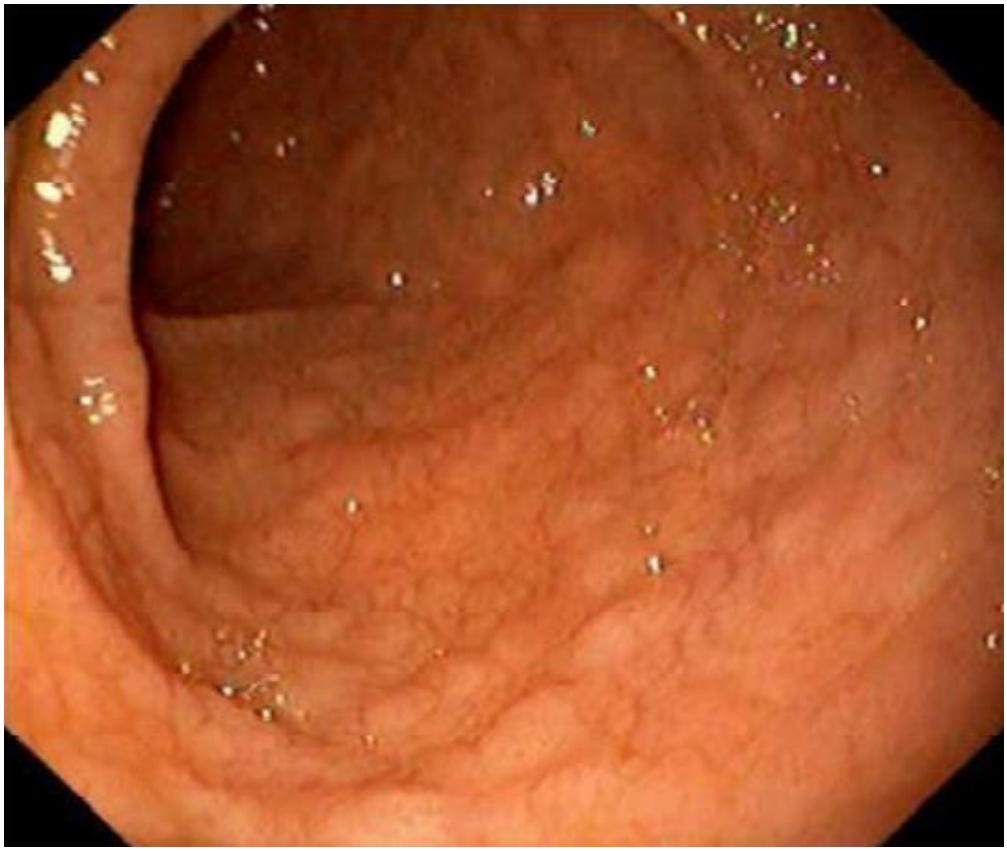
- Possible good idea
  - ↓ risk
    - Malignancy
    - Other autoimmune disorders
  - Improve
    - Mild/ignored GI symptoms
  - Treat unrecognized nutritional deficiencies

False Negative tTG

- Very young (< 2 yr of age)
- Mild celiac
- Low gluten/gluten free diet
- IgA deficiency
  - 1% of people being tested, 2-3% of CD patients
  - If IgA deficient measure
    - tTG IgG and/or DGP IgG
    - Perform EGD duodenal biopsies
  - IgA deficient patients more likely to have other causes of villous atrophy
    - Giardia
    - SBBO
    - CVID
- Patient taking corticosteroids, immunosuppressants, biologics

➢ Endoscopy

- Take 5-6 duodenal (D) mucosal biopsies (1-2 for D1, ≥ 4 from D2)
- D1 may have architectural distortion due to other disease causes
- Diagnosis of CD, number of biopsies
  - < 4%, 0.7%
  - > 4%, 1.8%
- Features
  - 1/3 look Normal
  - Folds
    - Scalloping
    - Loss/ ↓ number
    - Fissures/Mosaic-appearance



Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Gluten Challenge (GC)
  - Consider GC if already on a GFD without previous testing
    - Measure HLA-DQ2/8 prior
      - If negative, excludes CD
      - If positive, consider GC
  - Start 3 g gluten per day (1-1.5 bread slice)
    - Double intake of bread q2-3d until equivalent of ≥4 slices/d for 6-12 wk
  - Repeat serology / EGD plus biopsy after 6-12 wk of GC
    - If GC still negative, repeat EGD again 2-6 wk after end of GC challenge
  - If biopsy / tTG negative
    - Monitor symptoms on regular (gluten-containing) diet; consider repeat GC test (serology, EGD plus biopsy) at 6 mon

- Treatment
  - Lifelong Adherence to GFD
    - Pure oats safely tolerated by majority, but introduce slowly because of possible contamination from sources of gluten such as wheat from the milling process. I
  - Registered dietician for nutritional assessment / education
  - At diagnosis, test/treat for micronutrient deficiencies
    - Iron
    - Vitamin ADEK
    - Vitamin B12
    - Folate
  - Follow-up with dietician/physician
  - Follow-up with specialist improved adherence to GFD: 97% vs. 40%

- Gluten-free diet (GFD)
  - < 10 mg of gluten in a screening
    - Look for label on food, or go to the gluten-free section of your store
  - Reassess for being on GFD
    - ↓ risk of prevent nutrient deficiency leading to complications such as anemia, osteoporosis, scurvy
      - Malignant development
      - Other anemia-mediated conditions
      - Infertility, low birth weight body, protein deficiency
  - Possible impairment in symptoms not recognized as being from gluten intake, e.g.,
    - Depression
    - Fatigue
    - Dyspepsia
  - Do **not** use a therapeutic trail of a GFD in patient with non-diagnosed CD, because
    - They may have rare celiac gluten sensitivity (NCGS)
    - Other causes of Cd-like symptoms used to be diagnosed and treated
  - Gluten-free diet is used for many reasons
    - They may have none celiac gluten sensitivity (NSGS)
    - Other causes of CD-like symptoms used to be diagnosed and treated
  - Gluten-free diet is used for many reasons
    - Only about 5% used of GFD is for CD

    - Other uses
        - Psychoneurological to
            - ↑ mental function, 13%
            - ↓ stress, 12%
            - ↓ depression, 9%
        - Bowel cleansing program, 10%
        - To ↓ pain from joints, 18%
        - To ↑ skin health, 20%

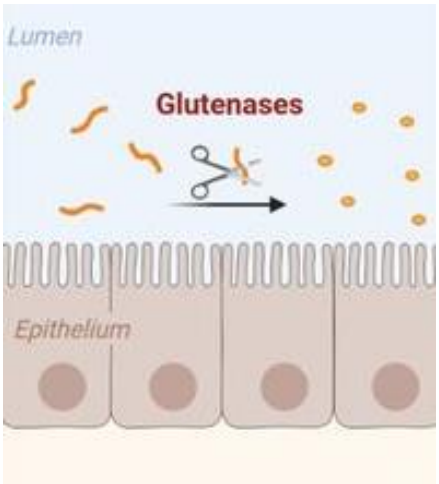
- Challenges to following GFD
    - In despite presence of gluten
    - Potential non-food sources of gluten
        - High risk
            - Airborne flour (e.g., bakeries)
            - Play putty
            - Communion wafers
            - Dietary supplements
            - Gastric emptying test meals
            - Some alcoholic beverages (e.g., beer, rye whisky)
            - Food condiments
        - Low risk
            - Prescription medications
            - Over-the counter medications
            - Lipstick
            - Toothpaste or dental fixative
            - Barium suspension
        - No risk
            - Shampoo
            - Skin cream
            - Cosmetics
            - Stamps
            - Envelops
    - Cutaneous sensitivity to wheat proteins can cause dermatitis
        - Is it probably an allergic (IgE-mediated) phenomenon (not CD).

- Complications
    - Osteoporosis
        - Consume minimum 1000 mg calcium per day
        - Monitor blood level of Ca^{2+}, vitamin D, PTH, TSH, Alkaline Phosphatase
        - Assess bone mineral density (DEXA scan) at the diagnosis, or 1 yr after starting of GFD if RF or > 55 yr
            - Repeat after ≥ 2 yr if low initially or treatment started

- Hyposplenism
  - Does **not** correlate with duration of CD
  - Pneumococcal vaccination recommended at diagnosis of CD
  - Unknown whether Haemophilus, Meningococcus and Influenza also should be recommended
  - May have weaker response to HBV vaccine

Ludvigsson JF, et al. Gut. 2014; 63(8): 1210-28.

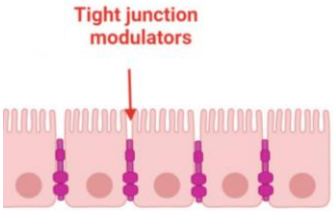
- Investigational Therapeutic Targets
  - Gluten
    - Develop gluten proteins without CD-toxic motifs
    - Maintain properties that help viscoelastic properties of breads
  - Oral Glutenases
    - Degrades gluten in bowel lumen



Source: Levescot A, et al. Gut 2022; 71: 2337-2349.

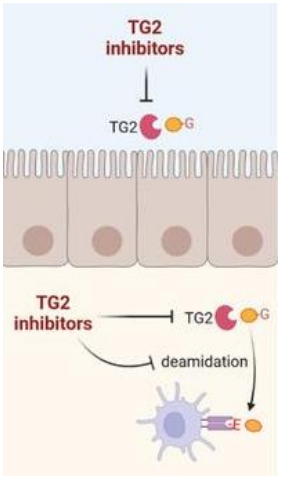
  - Bind gluten in intestinal lumen
    - Prevent peptide translocation cross BBM and into lamina propria

- Brush border membrane
  - Develop drugs to block passage of gluten into the enterocyte



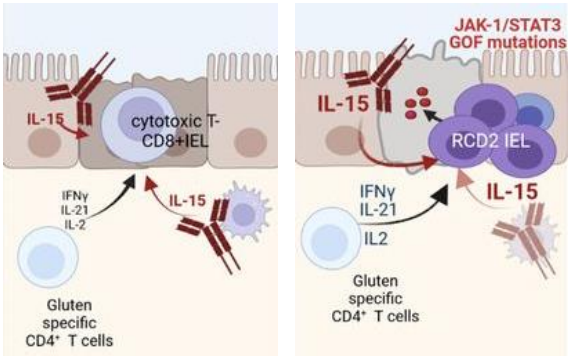
Source: Crepaldi M, et al. Pharmaceuticals 2024; 17(1): 4

- Immune mediated
  - Inhibiting tTG (↓ deamidation of gliadin)



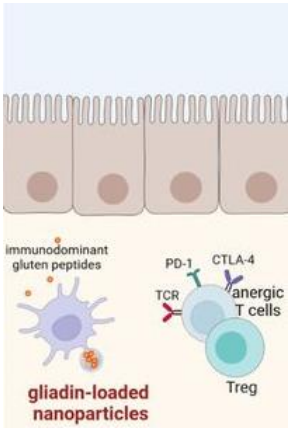
Source: Levescot A, et al. Gut 2022; 71: 2337-2349.

- T Cell activation (Block formation of APC – T Cell complex)
- Monoclonal Antibody Small Molecules target IL-15 / IL-15 receptor



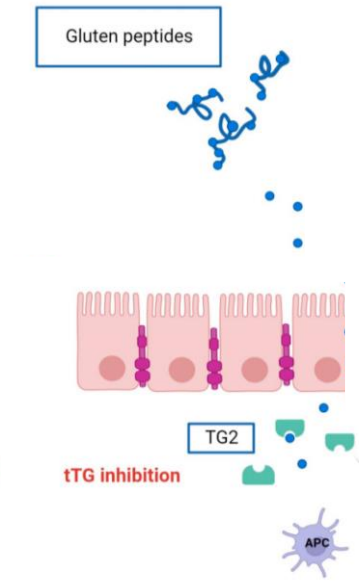
Source: Levescot A, et al. Gut 2022; 71: 2337-2349.

- Immunodominant gluten peptides / gliadin-loaded nanoparticles (TAK-101) (development of tolerance to gluten specific T cell)



Source: Levescot A, et al. Gut 2022; 71: 2337-2349.

- Tissue Transglutaminase (tTG2) Inhibitors
  - Oral Small Molecule
  - Selectively binds active tTG2
  - Proof of concept, 6 wk randomized clinical trial of po tTG-Inhibitor
  - Symptoms similar in both groups
  - ↓ mucosal damage in CD patients



Source: Crepaldi M, et al. Pharmaceuticals 2024; 17(1): 4

- Nonresponsive/Refractory Celiac Disease
  - Celiac disease
    - Chronic enteropathy caused by gluten
    - Association with HLA-DQ2 and HLA-D8 phenotypes
    - Typical diagnostic features include
      - Villous atrophy
      - Crypt hyperplasia
      - Intraepithelial lymphocytosis
      - Presence of anti-tTG2 antibodies
      - Mainstay of treatment is a gluten-free diet
  - RCD I
    - Predominantly individuals > 50 yr
    - Recurrence or persistent villous atrophy
    - No abnormal IELs
    - Most common symptoms
      - General malaise
      - Anemia
      - Diarrhea
      - Abdominal pain
    - Treatment is based on nutritional support and, if necessary, immunosuppressive drugs
    - Generally, has a benign course
  - RCD II
    - Predominantly individuals > 50 yr
    - Accumulation of abnormal IELs (sCD3-, ICD3+, CD8+)
    - Considered a low-grade, no-mass lymphoma
    - Treatment focuses on preventing development of lymphoma
    - Treatment includes cladribine or fludarabine, and auSCT if necessary
    - Untreated RCD II has a poor prognosis
  - Slow responders
    - Recovery of mucosa delayed
    - Full recovery of villous atrophy can take 2-5 yr
    - Other clinical improvements
    - Fatigue is a persisting problem
    - Substitution of vitamins remains mandatory
  - EATL
    - Very aggressive disease
    - Poor prognosis
    - Treatment includes surgery: chemotherapy and auSCT

Abbreviations: auSCT, autologous stem cell transplantation; EATL, enteropathy-associated T-cell lymphoma; iCD3, intraepithelial lymphocyte; RCD, refractory celiac disease; sCD3, surface CD3; TG2, transglutaminase 2

Source: van Gils T, et al. Nat Rev Gastroenterol Hepatol 2015: 12; 572–579.

- Nonresponsive Celiac Disease

➢ Definite

- Persistence of symptoms, signs or laboratory abnormalities typical of celiac disease despite adherence to a GFD for 6-12 mon

➢ Prevalence

- 5-30% of Celiac patients
  - #1 Cause is gluten ingestion (35-50%)
  - Persistent ↑tTG
  - Lactose/fructose intolerance also common

➢ Differential Diagnosis

- Small intestinal bacterial overgrowth (SIBO)
- Irritable bacterial syndrome (IBS)
- Microscopic Colitis
- Refractory CD

- Refractory Celiac Disease (RCD)

➢ Definition

- Celiac disease with persistent symptoms of malabsorption and villous atrophy despite at least 12 mon of strict adherence to a GFD

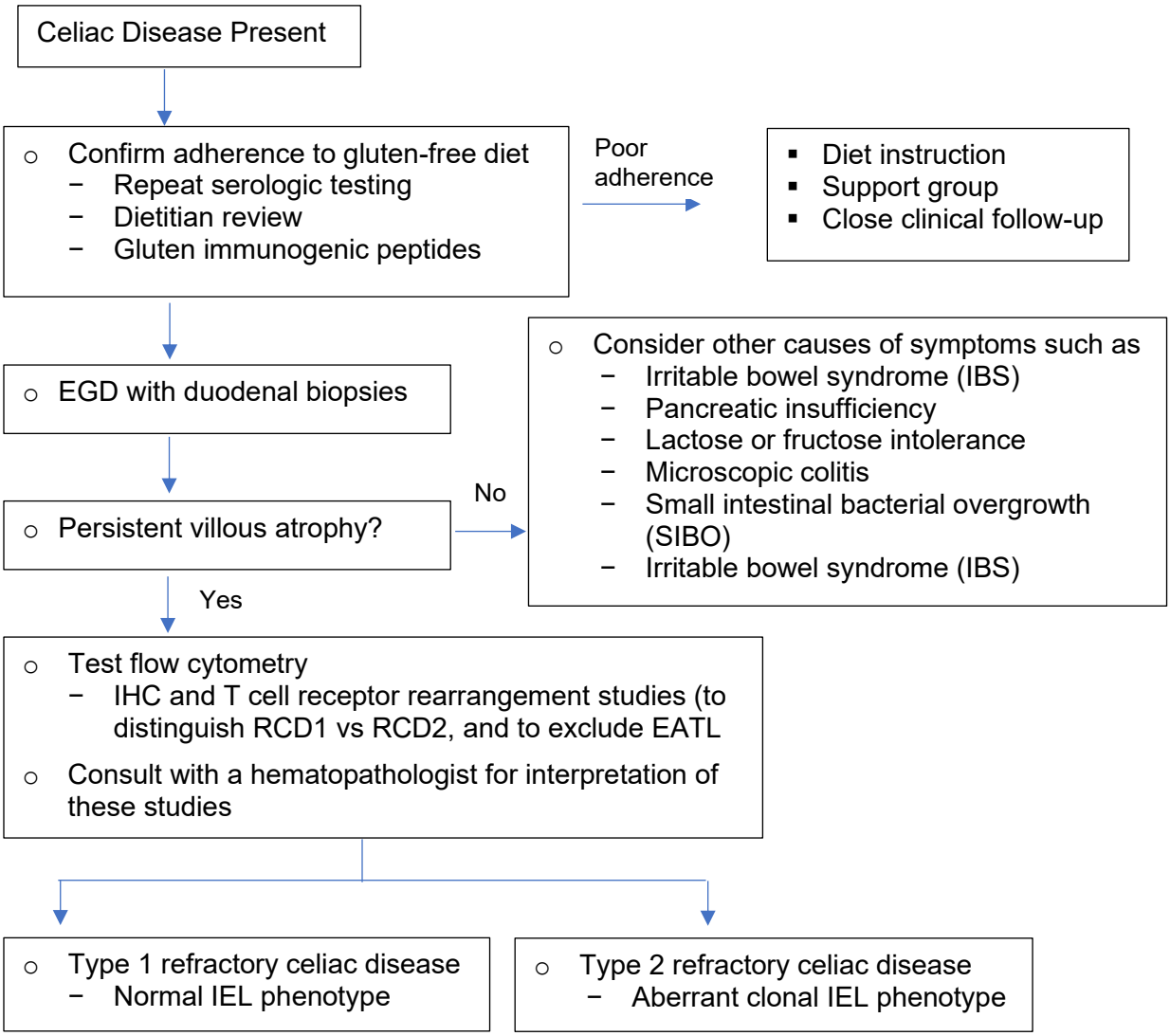
➢ Demography

- Effects < 1% Celiac patients

➢ Subtypes

- RCD1
  - Villous atrophy but no cellular atypia
- RCD2
  - Aberrant clonal T cell expansion
  - ↑ risk of development ulcerative jejunitis or enteropathy associated T-cell lymphoma (EATL)

Algorithm for Investigation of Patients with Suspected RCD



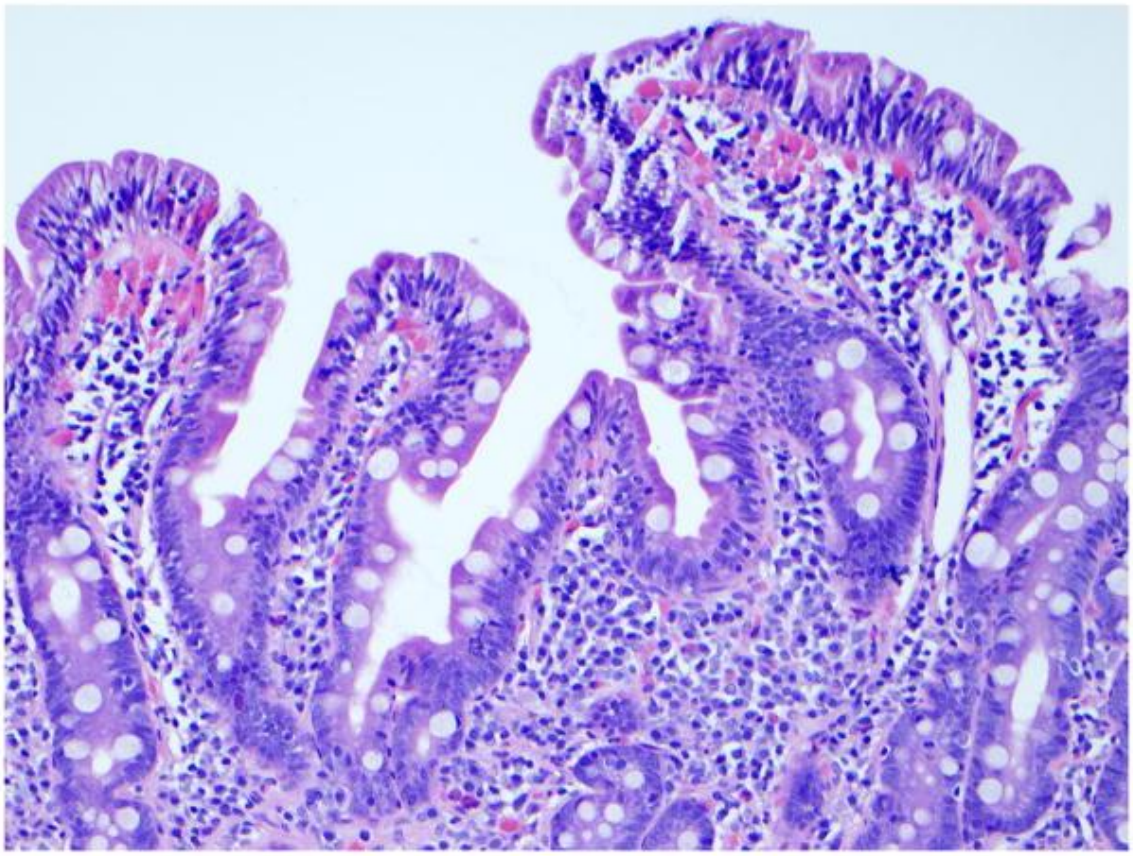
Adapted from: Rubio-Tapia, A; et al. Am J Gastroenterol 2023; 118(1): 59-76.

- Steroids mainstay for >40y
- Retrospective Cohort (N=20) Type I RCD[1]
  - 25% mucosal recovery with 1y Budesonide
  - 86% Recurrence among responders
  - Suggests need for longer/maintenance therapy

- Cohort (N=19) 1 yr Prednisone + AZA
  - 8 Responded, 4 Complete (all RCD1)
  - 6 Developed EATL (all RCD2)

Immunophenotype of intraepithelial lymphocytes in RCD by CD3 and CD8 immunostaining

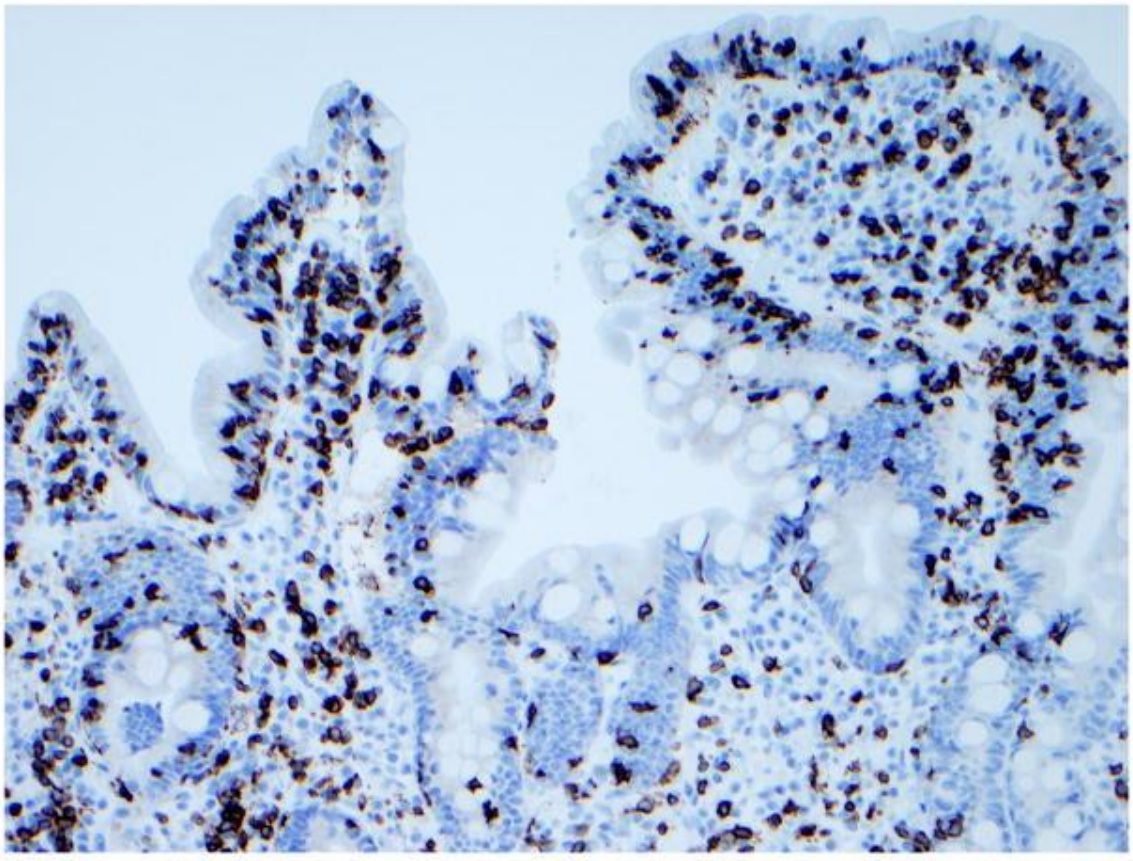
RCD Type 1



Duodenal biopsy specimen from a patient with RCD type 1 (hematoxylin and eosin, 20x original magnification) showing partial villous atrophy and an increased number of intraepithelial lymphocytes with normal immunophenotype characterized by expression of CD3 and CD8.

Printed with permission: Rubio-Tapia A, Murray JA. Gut 2010; 59:547-557 (Figure 3)

RCD Type 2



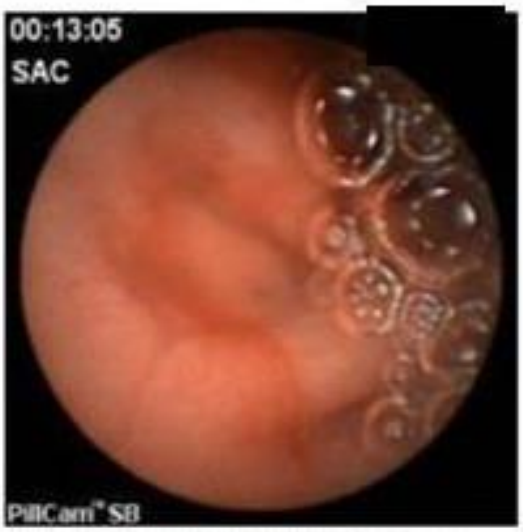
Duodenal biopsy specimen from a patient with type 2 RCD (hematoxylin and eosin, 20x original magnification) showing villous atrophy and abnormal intraepithelial lymphocytes characterized by expression of CD3 (Panel B2) but mostly CD8. Brown color denotes positive immunostaining (20x original magnification).

Printed with permission: Rubio-Tapia A, Murray JA. Gut 2010; 59:547-557 (Figure 3)

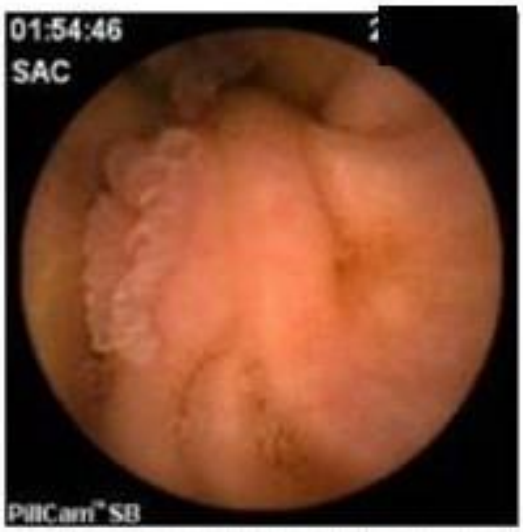
- Ulcerative Jejunitis (formally called Ileojejunitis)
  - Rare, serious complication
  - Ulcer and strictures of small bowel
    – Often cause obstruction and hemorrhage
  - Many ultimately diagnosed with lymphoma
  - Suspect if, patient has systems not responding to GFD
    – Weight loss, abdominal pain and diarrhea not responsive to GFD

➢ Diagnosis
  - Video fluoroscopy (VCE)
  - CT enteroscopy (CTE)
  - MR enteroscopy (MRE)
  - Enteroscopy plus biopsies
  - Surgery

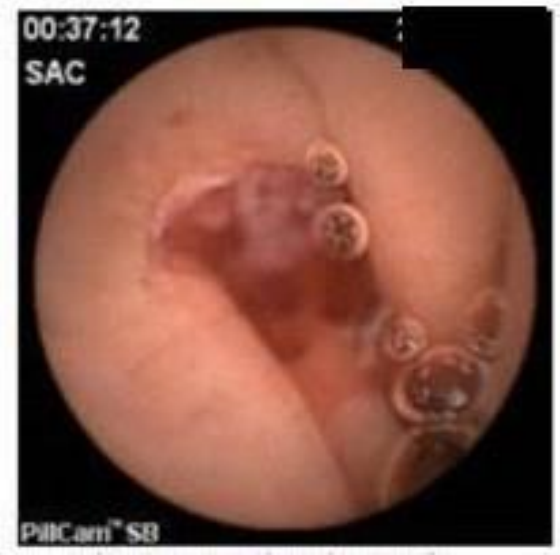
Enterography, CT, Capsule, Surgery



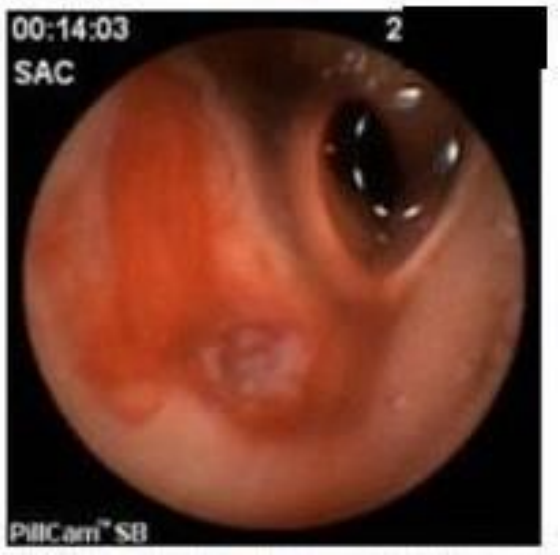
Scalloping of distal duodenal folds



Elevated mucosal lesion with broad villi mid jejunum



Fibrin covered and actively bleeding mucosal ulceration, jejunum



Fibrin covered, actively bleeding mucosal ulceration in proximal jejunum; Villous atrophy

Wireless Capsule Endoscopy Initial Exam (Normal Diet). Findings highly suggestive of celiac disease complicated by ulcerative jejunitis.

Source: Sigman T, et al. BMC Gastroenterol 2014; 14(1), 29 (Figure 1)

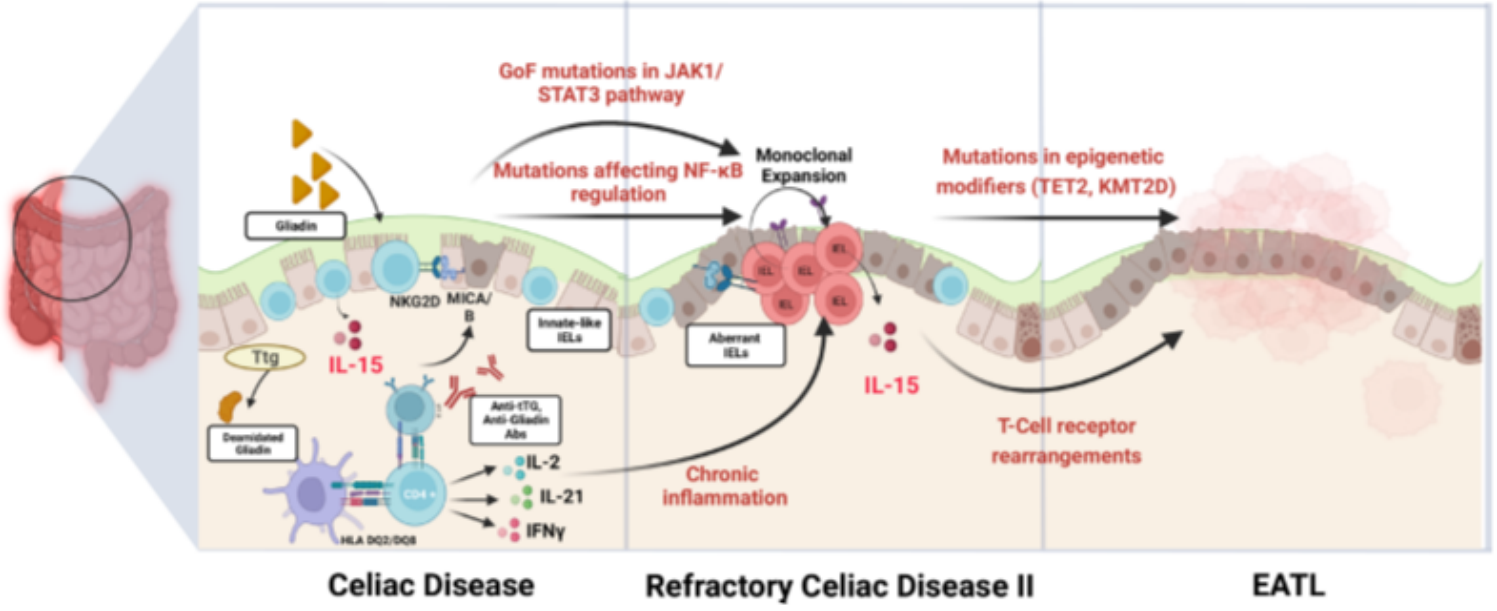
- Enteropathy-Associated T-cell Lymphoma (EATL)

➢ Definition
  - Transformation from Type 2 RCD to EATL

➢ Clinical
  - Usually > 50 yr
  - Insiders symptoms, no response to GFD
  - Complications
    - Ulcers → bleeding, perforation
    - Lymphadenopathy

➢ Diagnosis
  - Requires full thickness surgical biopsy to diagnose

➢ Pathogenesis



Schematic representation of key findings in the pathogenesis of celiac disease (CD) to refractory CD (RCD) type II and EATL. Dietary gluten consists of gliadin peptides which are deamidated by tissue transglutaminase enabling their presentation to T cells by dendritic cells in conjunction with HLA-DQ2 or HLA-DQ8 molecule. This triggers cytotoxic responses and proinflammatory cytokine release, causing enterocyte death and inflammation. Progression to RCD II and consequently EATL is driven by somatic gain-of- function mutations in the JAK1-STAT3 pathway. Recurrent mutations in negative regulators of the NF-κB pathway (TNFAIP3 and TNIP3) and oncogenic mutations in TET2, KMT2D and DDX3X have also been implicated. Interleukin 15 (IL-15), along with other mediators, promotes activation of cytotoxic CD-8+ T-lymphocytes and inhibits apoptosis. T cell receptor (TCR) rearrangement also plays important roles in the clonal proliferation of malignant intraepithelial lymphocytes in the landscape of chronic inflammation

Printed with permission: Rajagopal A, et al. BMJ Case Reports CP 2023;16: e258265 (Figure 3)

- Prognosis
  - 5 yr survival rate ~10%

- Non-celiac Gluten Sensitivity (NCGS)

- Definition
  - Symptomatic response to gluten ingestion but with
    - No serologic or histologic evidence of CD
    - HLA DQ2/8 negative
    - Not associated with complications of CD
    - Consider diagnosis of NCGS only after CD has been excluded with appropriate testing

Marsh Classification

Nisha Howarth

- Definition
  - Celiac disease (CD) "… is an immune-mediated inflammatory disease of the small intestine due to sensitivity to dietary gluten in genetically predisposed individuals"

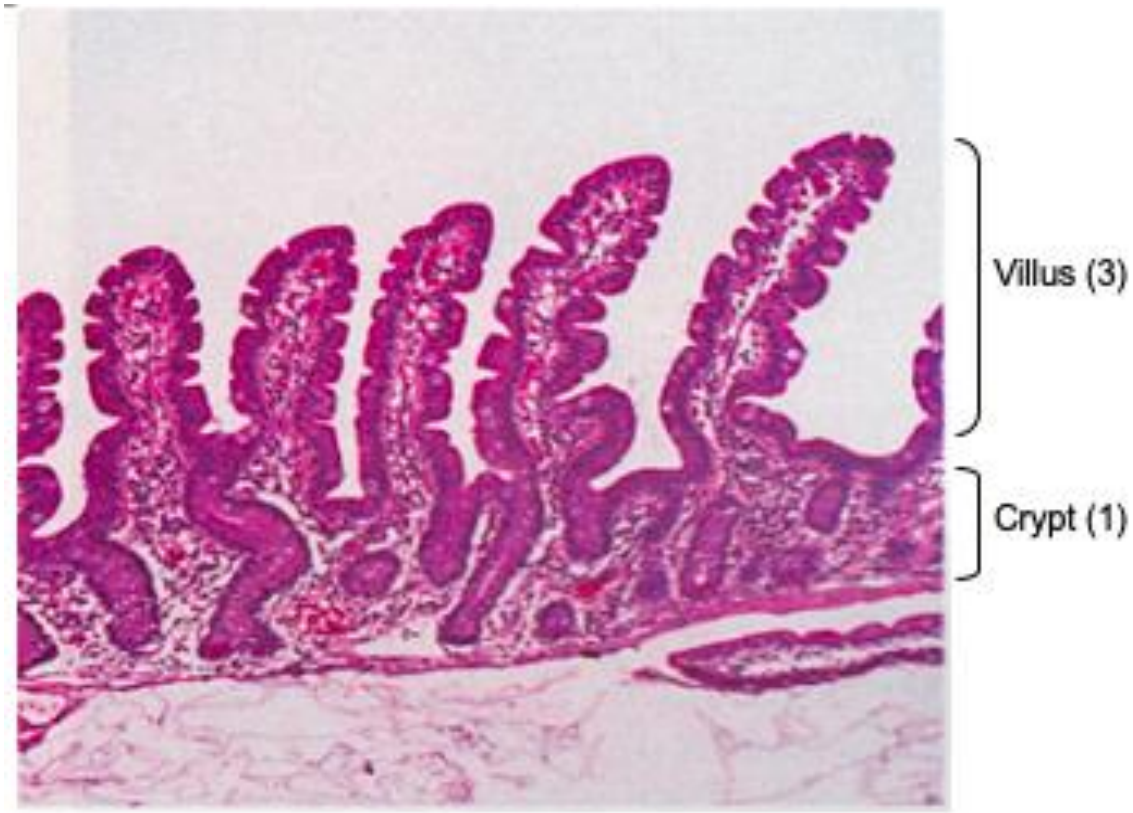
- Introduction
  - Duodenal biopsy is the gold standard for diagnosis of CD
  - Should perform duodenal biopsy in:
    - Patients with
      - Positive celiac serology
      - Risk factors for CD
    - High probability patients with clinical symptoms
  - Marsh Classification was developed in 1992 to describe the histopathological changes seen in the small intestine in patients with CD
  - Modified scheme published in 1999 (Marsh-Oberhuber (M-O) Modified Classification)
    - Widely used by pathologists today
    - Subcategorized Marsh type 3/4 into M-O type
      - 3a: mild villous atrophy
      - 3b: marked villous atrophy
      - 3c: total villous atrophy (flat mucosa)
    - Added numerical cutoffs for the number of IELs (< or > 40 IELs/100 enterocytes)
  - Early subtle pathological changes of celiac disease.
    - Villus enterocytes
      - Reduced BBM
      - Cuboidal/squamoid shape
      - Cytoplasm more basophilic
      - Basal polarity of nucleic lost
      - Lysosomes large
      - Endoplasmic reticulum decreased
      - Vacuoles in cytoplasm and mitochondria
    - Crypt cells
      - ↑ mitosis
    - Tight junctions
      - Abnormal
    - Immunocytes
      - ↑ IEL
      - ↑ CD8+ T cells
      - ↑ lymphocytes (> 40 / hpf)
        - IgA, IgM, IgG producing
        - ↑ CD4+ T cells in lamina propria
      - ↑ PMNs and eosinophils

- Severe celiac disease on duodenal biopsy
  - May look like colon, but if you see Brunner's glands-must be duodenum
- Note – in celiac disease the small bowel mucosal biopsy is compatible with the diagnosis, but is **not** pathognomonic.

➢ Normal small intestine histology

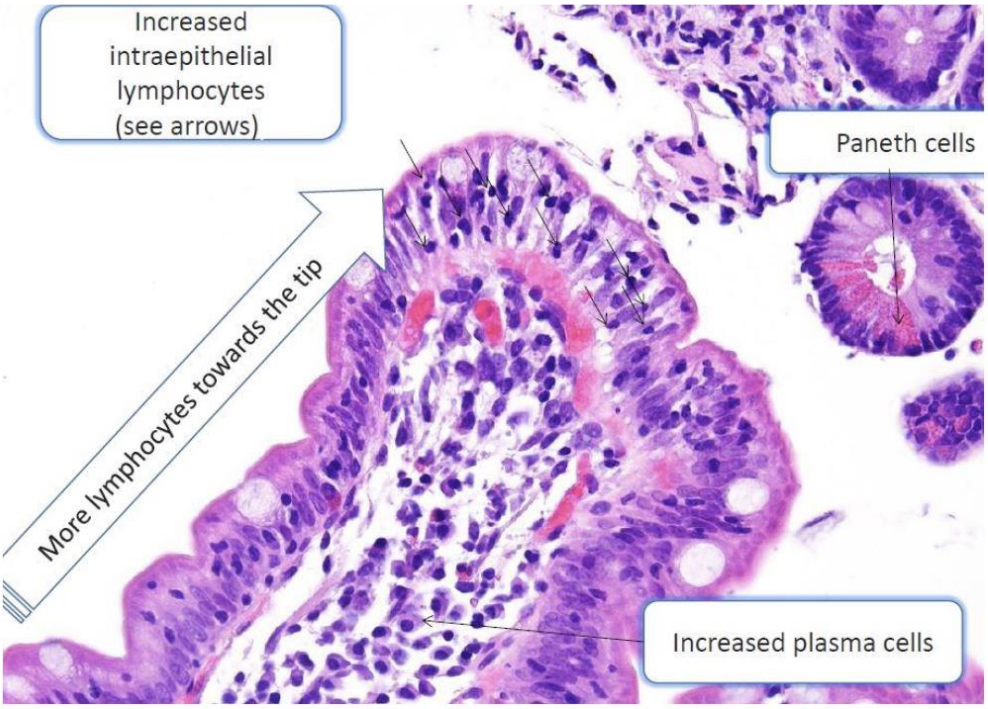
- Slender finger-like villi lined with
  - Epithelial cells, and
  - Crypts in between villi
- Villous length: crypt is typically 3-5:1
- No increase in intraepithelial lymphocytes (IELs)
- ↑ lymphocytes at the base of the villi compared to the tip

Normal Duodenum



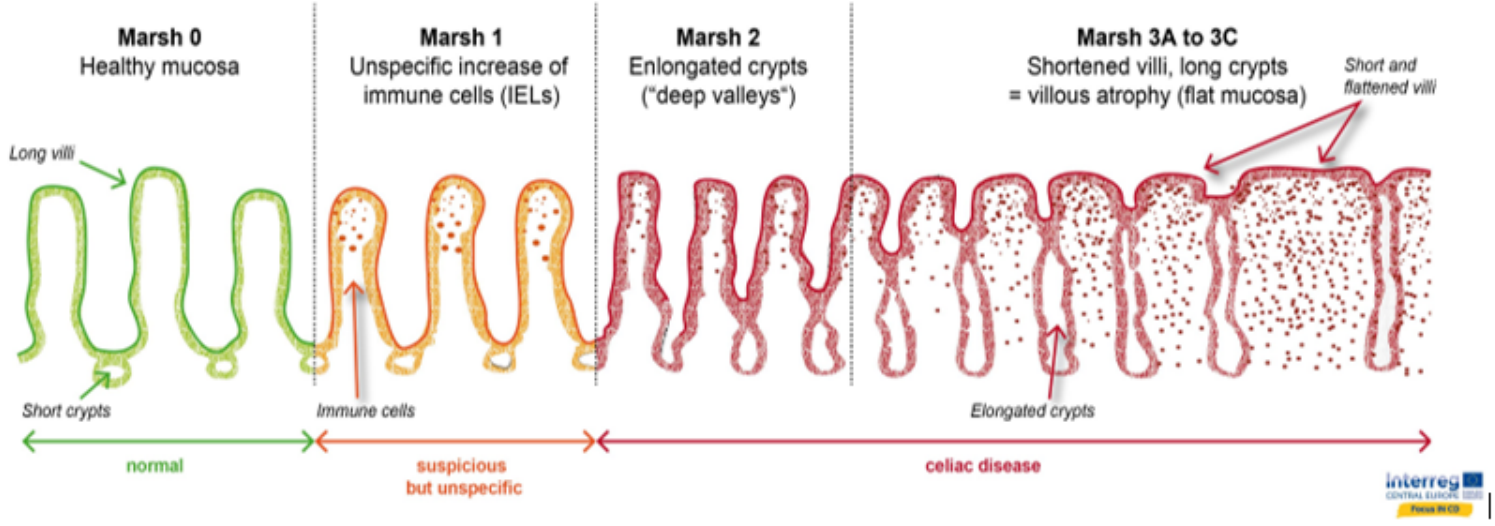
Source: Thomson ABR, Walsh JC. Images in gastroenterology and hepatology: Part 1. CAPstone Publishers; 2021. ISBN: 979-8719829074.

- Intraepithelial lymphocytes
  - CD3/CD8+ T lymphocytes within the gut mucosa
  - Measured in the context of 100 enterocytes
  - IELs follow local or systemic immune activation
  - Normal jejunal IELs <40/100; normal duodenal IELs <25/100



- Initial Marsh Classification
  - Type 0 (pre-infiltrative): normal mucosa
    - Normal, CD highly unlikely
  - Type 1 (infiltrative): ↑ IELs
    - Not specific for CD but can be seen in patients on GF diet, patients with dermatitis herpetiformis, or in family members of patients with CD
  - Type 2 (hyperplastic)
    - Crypt hyperplasia plus ↑ IELs
    - Very rare, seen occasionally in patients with dermatitis herpetiformis
  - Type 3 (destructive): villous atrophy plus ↑ IELs
    - Spectrum of changes seen in CD
  - Type 4 (hypoplastic): hypoplasia of villous architecture
    - Extreme end of gluten sensitivity; uncommon
    - Very rare, seen in patients with refractory CD or EATL

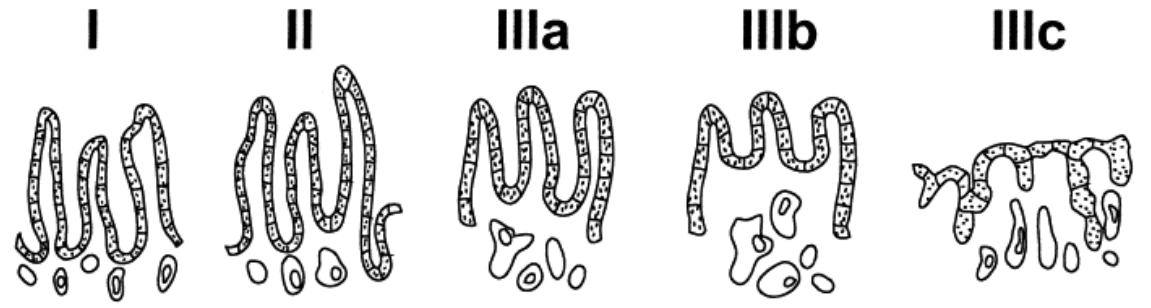
- Marsh-Oberhuber Classification (Marsh Modified Classification)

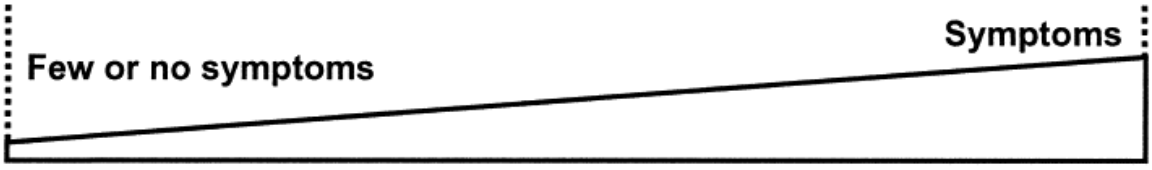


Modified Marsh Classification of Histologic Findings in Celiac Disease				
Marsh Type	IEL/100 Enterocytes (Jejunum)	IEL/100 Enterocytes (Duodenum)	Crypt Hyperplasia	Villi
0	< 40	< 30	Normal	Normal
1	> 40	> 30		
2			Increased	
3a				Mild/moderate
3b				Marked
3c				Complete

Modified from Celiac Disease Foundation, 2022

Histopathological architecture



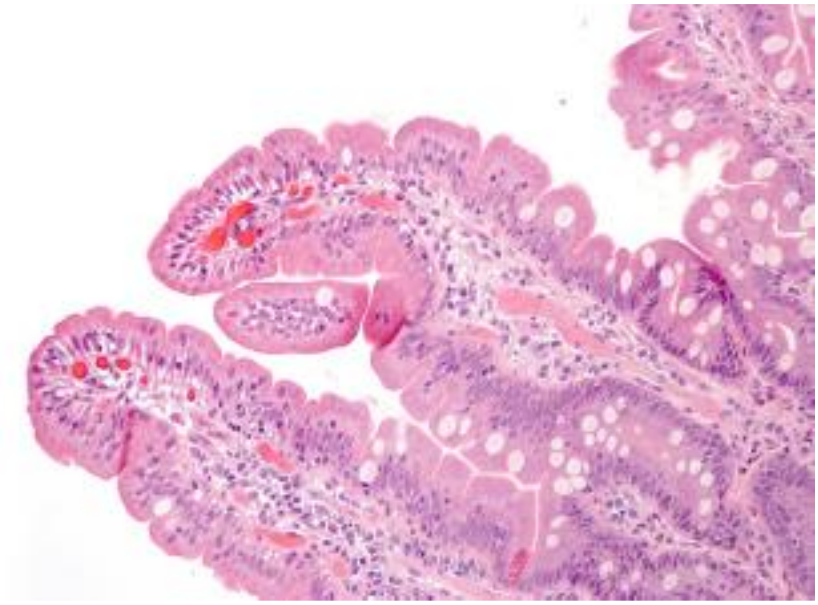


- Little malabsorption
- No villous atrophy
- Little crypt hyperplasia
- increased IELs

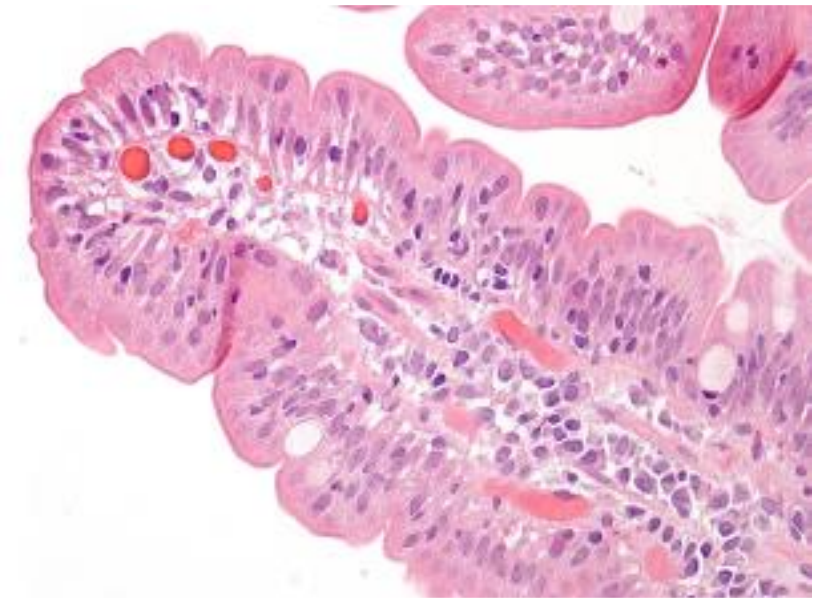
- Minimal malabsorption
- Partial villous atrophy
- Some crypt hyperplasia
- Increased IELs

- Extensive malabsorption
- Complete villous atrophy
- Marked crypt hyperplasia
- Increased IELs

- Histopathology (Marsh Classification)
  - ↑ IEL (intraepithelial lymphocytes)
    - Starts in tips of villi → all if mucosa
    - CD3 immunostain-positive for T cells
  - Mucosal architecture
    - ↓ height of villi
    - ↑ depth of crypts
  - Chronic inflammation
    - Patchy, or
    - Diffuse
  - Complications
    - Intestinal
      - T cell or B cell lymphoma
      - Adenocarcinoma
      - Ulcerative ileojejunitis
  - Lamina propria has small lymphoid cells but no plasma cells.
  - Total villous atrophy
  - Crypt hyperplasia
  - Active chronic inflammation
  - Intraepithelial lymphocytosis characterizes the well-developed malabsorption pattern
  - Avillous mucosa - cuboidal degenerating epithelial layer
  - Crypt hyperplasia
  - Lympho-plasmocytic infiltration of lamina propria
  - Flat mucosa extending over variable length of small bowel up to terminal ileum
  - Paneth cell deficiency
  - Gastric surface mucus cell metaplasia
  - Ulceration and fibrosis (ulcerative jejunoileitis)
  - Brown pigmentation of muscle cells due to vitamin E deficiency
  - Subepithelial collagen deposition

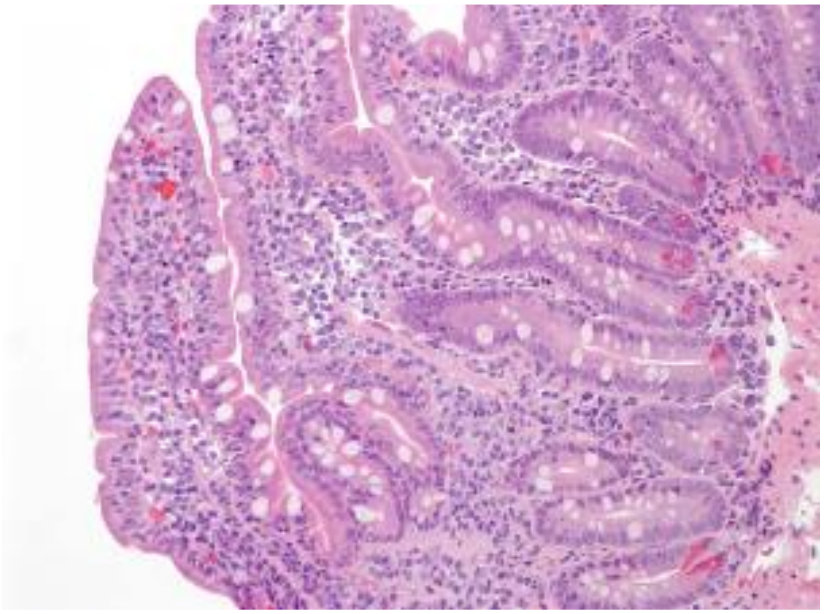


Marsh I



Marsh I

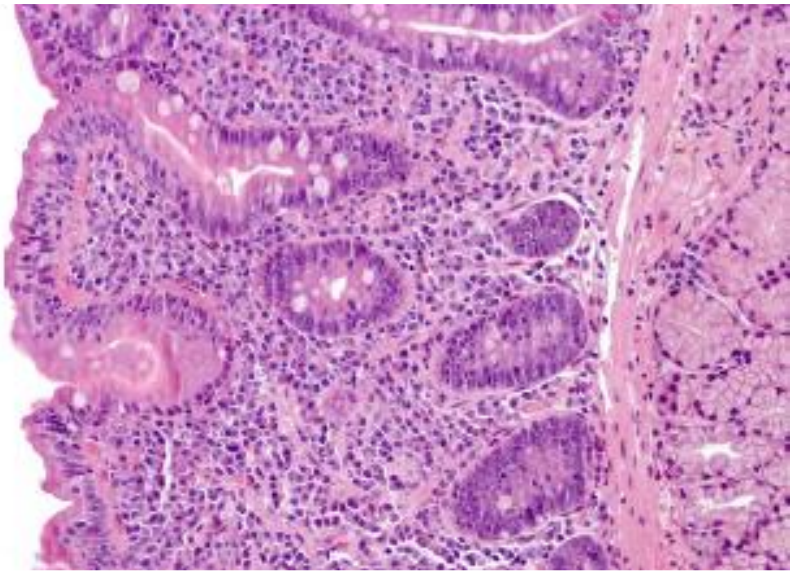
- Crypt hyperplasia; Marsh II



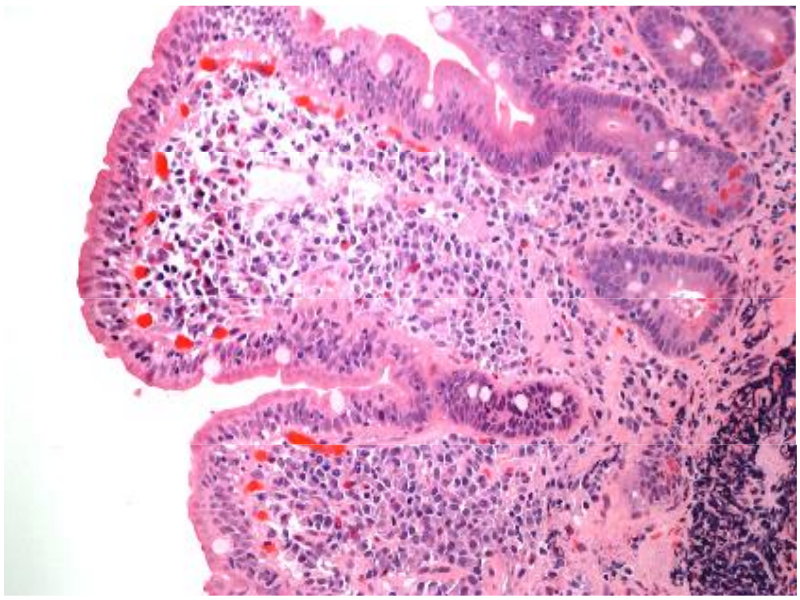
Marsh II

Kindly provided by Dr. Aducio Thiesen, University of Alberta

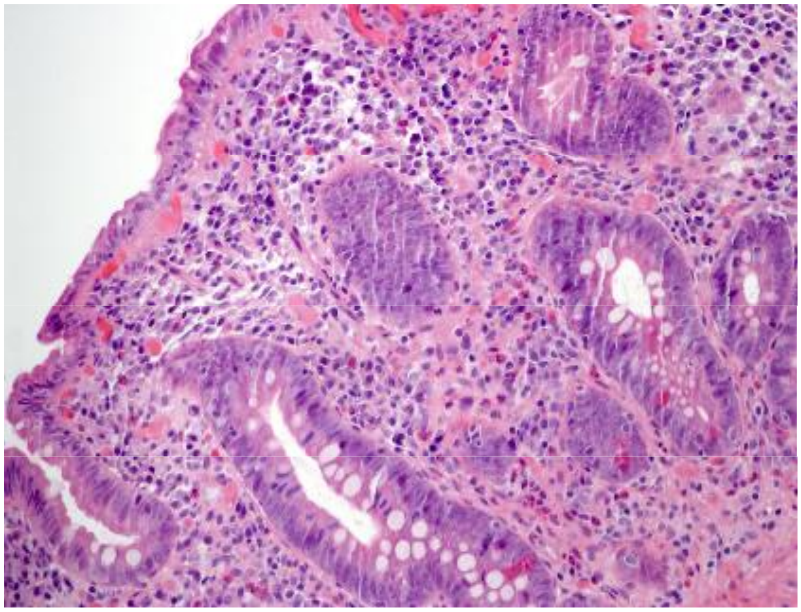
- Increased intraepithelial lymphocytes
  - Increased intraepithelial lymphocytes; Marsh III
  - Total villous atrophy
  - Chronic inflammation
  - Intraepithelial lymphocytosis (see ↓)
- Collagenous Sprue
  - Thick subepithelial collagen band (∗), villous atrophy, and intraepithelial lymphocytes (↓).



Marsh IIIA



Marsh IIIB



Marsh IIIC

Kindly provided by Dr. Aducio Thiesen, University of Alberta

Causes of ↑ IELs (normal villous structure)

- Infection
  - Viral enteritis
  - Giardia
  - Cryptosporidia
  - Helicobacter pylori
- Small Intestinal Bacterial Overgrowth (SIBO)
- Drugs (e.g., NSAIDs)
- Hashimoto thyroiditis
- Rheumatoid arthritis
- SLE
- Autoimmune enteropathy

- Corazza-Villanacci classification
  - Grade A / Type 1
    - ↑ IELs but no villous atrophy
    - Seen in
      - Patients on gluten-free diet (suggesting minimal amount of gluten or gliadin are being ingested)
      - Patients with dermatitis herpetiformis
      - Family members of celiac disease patients
      - Not specific, may be seen in infections
  - Grade B1 / Type 2
    - Villi still present but shortened, ↑ IELs
    - Seen in symptomatic celiac disease
  - Grade B2 / Type 3
    - Complete villous atrophy, ↑ IELs
    - Seen in symptomatic celiac disease
  - IELs cutoff lower (25/100 cells) given that is represents the ULN for duodenal cells

➢ Collecting biopsies

- Histological abnormalities associated with CD can be patchy
- Take multiple biopsies of the duodenum (↑ probability of diagnosis) (4 at D2, and 1-2 at duodenal bulb)
- Additional biopsies of the duodenal bulb at the 9- or 12-o'clock region increases the diagnostic yield because in early CD you can get villous atrophy exclusively in proximal duodenum

Suggested Reading:

Celiac Disease Foundation. 2022. Diagnosis of Celiac Disease | Celiac Disease Foundation. [online] Available at: https://celiac.org/about-celiac-disease/screening-and-diagnosis/diagnosis/

CorazzaGR, VillanacciV, ZambelliC, et al. Comparison of the interobserverreproducibility with different histologiccriteria used in celiac disease. Clin Gastroenterol Hepatol 2007; 5: 838-43

Cureceliacdisease.Org, 2022, https://www.cureceliacdisease.org/wp-content/uploads/0909CeliacCtr_News_v3final.pdf.

Marsh MN. Gluten, major histocompatibilitycomplex and the small intestine. A molecular and immunobiologicapproach to the spectrum of gluten sensitivity ("celiac sprue"). Gastroenterology 1992; 102: 330-54

Approach to Obscure Gastrointestinal Bleeding

Michael Sey

- Types
  - Acute
    - UGIB
      - Esophagitis
      - PUD
      - Variceal
    - LGIB
      - Colitis
      - Diverticular
      - Hemorrhoids
  - Chronic
    - UGIB
      - Angioectasias
      - Gastric antral vascular ectasia (GAVE
    - LGIB
      - Angioectasias
      - Hemorrhoids
      - Radiation proctopathy
    - Small bowel bleed
      - Dieulafoy
      - Ectopic varices
      - Meckel diverticulum

- Comparison of acute vs. chronic GI Bleeding

	Acute	Chronic
Natural history	- Single event	▪ Long term
Recurrence	- Rare	▪ Common
Presenting symptoms	- Hematemesis - Melena - Hematochezia	▪ Iron deficiency anemia (2/3) ▪ Melena (1/3) ▪ Hematochezia (< 1%)
Common etiologies	- Esophagitis - PUD - Varices - Diverticular - Hemorrhoids	▪ Angioectasia
Response to endoscopic hemostasis	- Usually successful	▪ Often less successful

	Acute	Chronic
○ Difficulty of endoscopic hemostasis	− Usually successful	▪ Often less successful
○ 1st line treatment	− PPI − Endoscopic hemostatic therapy (EHT)	▪ Iron replacement
○ 2nd line treatment	− IR, surgery	▪ Endoscopic hemostasis

Adapted from Sey M. Best Pract Res Clin Gastroenterol 2019; 42-43: 101611; Sey M, Dig Dis Sciences 2018; 63: 1280-85.

- **Obscure GI Bleeding (OGIB)**
  - OGIB ≈ small bowel bleeding
    - ~10-15% of OGIB are due to missed lesions in the UGI or LGI tract
  - "Obscure" b/c it is beyond reach of conventional upper and lower endoscopies
  - Formal definition Not undifferentiated anemia)
    - GIB after negative EGD and colonoscopy
    - Overt OGIB if melena or hematochezia (rare)
    - Occult OGIB if iron deficiency anemia only

Gerson LB, et al. Am J Gastroenterol. 2015;110(9):1265-87

➢ Diagnosis

Overt Bleeding
↓
EGD-negative Colonoscopy-negative
↓
Overt OGIB

Occult Bleeding (iron deficiency anemia)
↓
EGD-negative Colonoscopy-negative
↓
Consider
- ↓ intake (vegetarian, dietary misadventure)
- ↓ absorption (celiac, atrophic gastritis, RYGB)
- ↑ non-GI losses (epistaxis, menorrhea)

↓
Occult OGIB

- Tools to Assess the Severity of OGIB
  - Hemoglobin concentration
  - IV iron requirement (# infusions/yr)
  - Blood transfusion requirement (# transfusion/ 6 mon)
  - Failure of IV iron →requiring chronic blood transfusions
- Limitations of the Hemoglobin Nadir
  - A hemoglobin nadir is a function of both the rate of bleeding and duration of bleeding
  - A very slow bleed over long periods of time can result in a very low hemoglobin nadir
  - A very fast bleed can result in profound hemodynamic instability with a relatively high hemoglobin nadir
  - Unstable UGIB in the CCTC on multiple pressors and rapid transfusion protocol x 6 units with a hemoglobin nadir of 103
- Clues to Indicate Chronicity
  - Prior hemoglobin levels in PowerChart, etc.
  - Downward graph of hemoglobin trends
  - Presence of microcytosis
    - ↓ ferritin concentration
    - ↓ % transferrin saturation
- Investigations
  - Endoscopy
    - Esophagogastroduodenoscopy
    - Colonoscopy
    - Video capsule endoscopy (VCE)
  - Enteroscopy
    - Push
    - Deep
    - Intraoperative
  - Diagnostic imaging
    - Barium studies
    - Enterography (CTE)
    - Angiography (CTA)
    - RBC scan

- The patient with risk of enlarged, severe OGIB has risk of small bowel bleeding and will require endoscopy / diagnostic imaging for diagnosis/treatment
- Small bowel bleeding source such as angioectasia may be missed on diagnostic imaging, and enteroscopy will be needed

➢ Risk factors for Small Bowel Angioectasias
- Elderly
- Aortic stenosis
- CHF
- Pulmonary hypertension
- Scleroderma
- CKD
- Cirrhosis

- **Deep Enteroscopy**
  - Careful selection of OGIB patients most likely to benefit from deep enteroscopy safely is required.
  - Benefit
    - Possible hemostasis double balloon enteroscopy (DBE)
  - Risks
    - Procedural
      - Pancreatitis
      - Perforation
      - Deep sedation
    - Patient factors
      - Pulmonary hypertension
      - Advanced age

- **Push Enteroscopy**

  - Passage of a pediatric colonoscope (1.6 m) into the small bowel
    - ~1 m of scope is used to reach the 2nd part of the duodenum
      - This leaves ~ 60 cm to reach most the proximal jejunum (average small bowel length ~6 m)
  - Excellent choice if the abnormality is within reach (e.g. distal duodenum, proximal jejunum)
  - Severely limited by lack of reach deep into the small bowel, which results in a diagnostic rate for OGIB ~25%
  - Length of enteroscope is limited by looping of the small bowel/intussusception resulting from force applied by endoscopist causing movement of enteroscope

- **Double Balloon Enteroscopy**

Source: Yamamoto H, et al. Gastrointest Endosc. 2001; 53(2):216-20.

- Depth of insertion
- Complete enteroscopy: 18-86%
- Mean depth antegrade: 220-253 cm
- Retrograde: 107-140 cm
- Time for procedure: 1-4 hr

➢ Limitations of DBE Therapeutics

- Invasive nature / procedure risks
  - Pancreatitis: 1% risk
  - Length of procedure, 2 hr
  - Anesthesia requirement
  - General anesthesia / propofol

- No guarantees of success
  - Reaching the location / identifying/treating the angioectasia
  - If the angioectasia is ablated it
    - It might grow back
    - A new one might grow elsewhere

- **Video Capsule Endoscopy (VCE)**

3.0 gr ~$1000/pill

  - Given imaging SB3
    - Camera
      - Resolution: 0.07 mm
      - Field of view: 156°
      - Adaptive frame rate: 2-6 fps
    - Flash
      - 4 LED
    - Battery (silver oxide)
      - Duration: 12+ hrs
  - Day before
    - Clear fluids
    - 2L PEGLYTE
    - NPO @ midnight
  - > 50,000 images
  - Limitations
    - Only diagnostic (no therapeutic potential)
    - Total # of patients worldwide who achieved hemostasis from the capsule itself = 0
  - Diagnostic Rate of VCE for obscure overt GI bleeding, 49% to 76%

- Diagnostic Performance of DBE in OGIB
  - Endoscopy therapy is effective initial therapy, but the rebleeding risk is 36% (for small bowel angioectasia, rebleeding rate is 46% over ~2 yr
    - The pooled odds ratio for bleeding cessation with octreotide was 14.5 (95% CI, 5.9-36)
    - In patients with Heyde syndrome (angiodysplasia plus aortic stenosis), replacement of the aortic valve was associated with a over 4 yr post-operatively.

Jackson CS, et al. Am J Gastroenterol 2014; 109; 474-483

  - Performance characteristics
    - Diagnostic yield (p = 0.16)
      - VCE, 65%
      - DBE, 58%

Teshima CW, et al. J Gastroenterol Hepatol 2011; 26: 796-801.

  - VCE superior to barium studies of small bowel: VCE, 67%; barium, 8% (P = 0.00001) (Triester SL, et al. Am J Gastroenterol 2005; 100: 2407-18)
    - Barium studies do **not** detect flat, small lesions, such as angioectasias
    - CTA/RBC scan do **not** detect slow bleeding from angioectasias

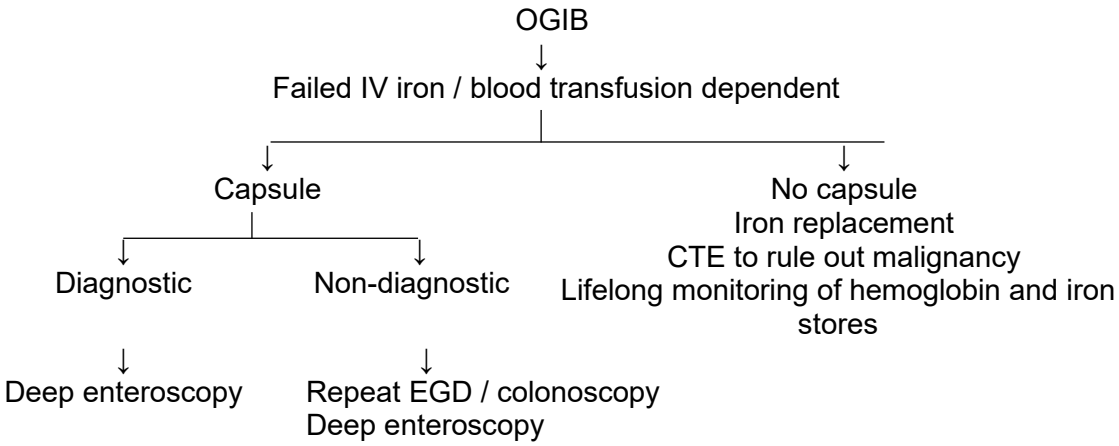
- **Intraoperative Enteroscopy (IOE)**
  - Operating room, stent protocol, patient under general anesthesia
    - Endoscopist controls dial while surgeon advances tip of scope
    - Access via oral route or enterotomy via jejunum or ileum and use of sterile bag
  - Highly invasive
  - Diagnostic rates similar to capsule endoscopy (VCE, 75%; IOE, 72%; p-value not significant)
  - Primarily used only for
    - Cases that can't be reached by deep enteroscopy
    - Malignant causes of bleeding
    - Massive bleeding with failure of other means of control

Hartmann D, et al. Gastrointest Endosc 2005; 61: 826-32.

- Challenges of IOE
  - Complete enteroscopy not usually possible (2 m scope for ~5 m of small bowel)
    - Often requires bidirectional approach via enterotomy via ileum
  - Poor scope control and some scope trauma due to endoscopist handling dials and surgeon manipulating tip
  - Transillumination due to laparotomy makes visualization difficult
  - Overdistension of bowel loops may affect ability to close the abdomen
  - 30-day mortality following IOE is up to 6%

Schulz H-J and Schmidt H. Gastrointest Endosc Clin N Am 2009;19: 371-9.

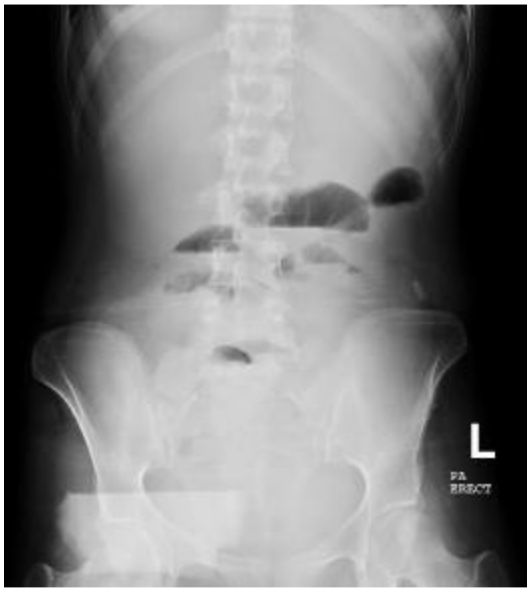
- Suggest Management



Intestinal Ultrasound for Assessment of Inflammatory Bowel Disease Severity

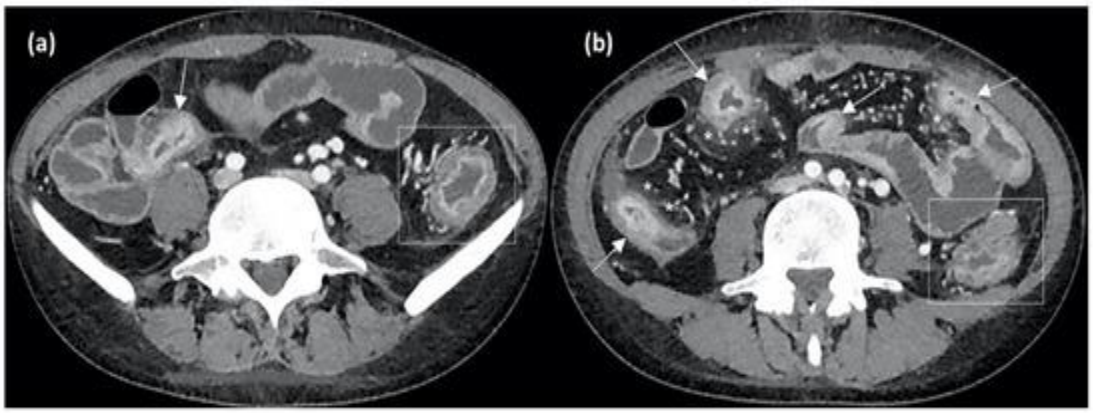
Vadim Iablokov

- **Abdominal X-ray**



Small bowel obstruction upright PA film, air fluid lesion

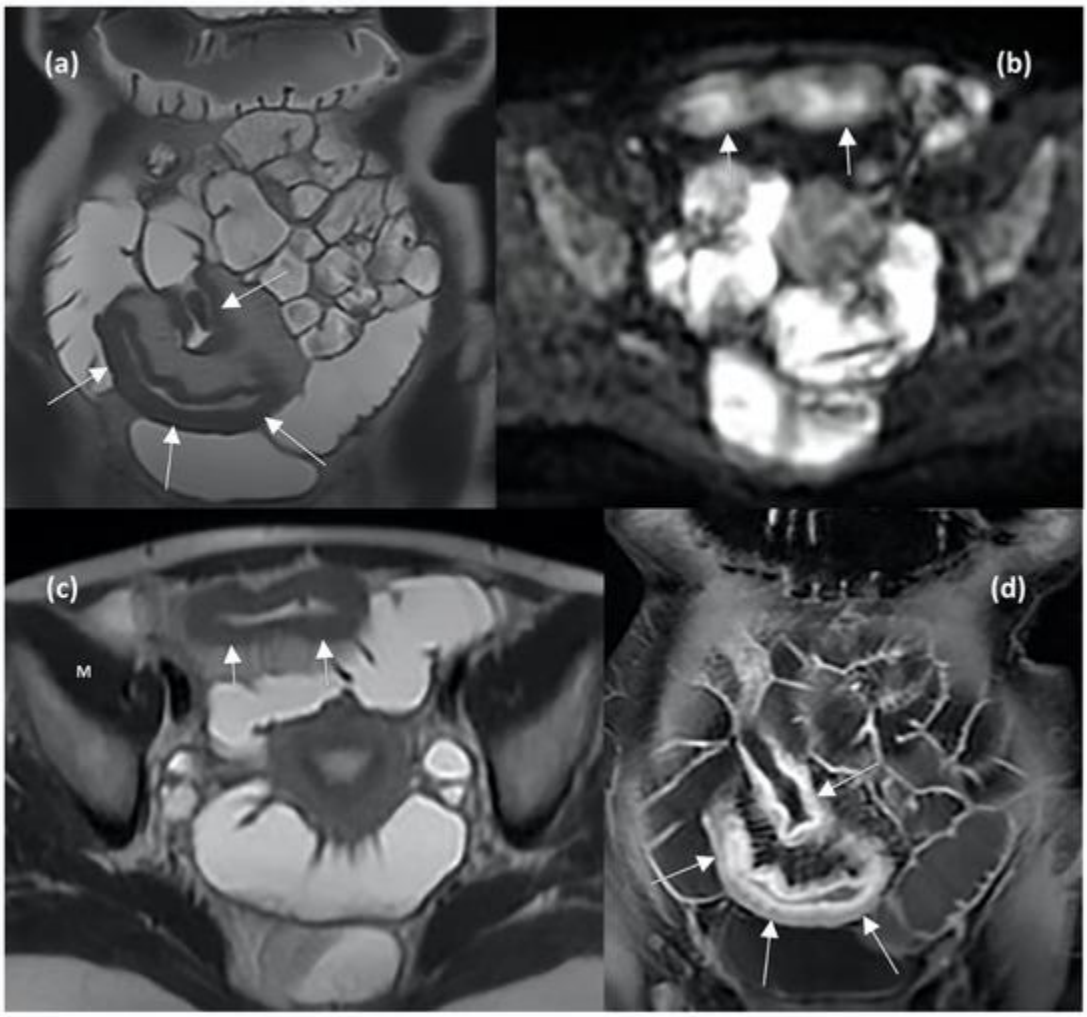
- **CT Enterography (CTE)**
  - CTE sensitive for the detection of small bowel disease in CD, and
    - Comparable to MRE
  - Uses narrow slices through the abdomen
    - Mucosal enhancement, mesenteric hypervascularity and mesenteric fat stranding
  - Delivers approximately 1.5 to 2 times the dose of radiation compared to conventional abdominal / pelvic CT
  - Advantages
    - Sensitivity, 90%
  - Disadvantages
    - Patients with CD receive 2.46 times higher dose of radiation than UC
    - Upper quartile of patients receive 2-11 times the average background radiation
    - Potentially ↑ risk of cancer



Axial CT enterography (CTE) images after contrast medium injection show wall thickening of the terminal ileum (arrow in (**a**)) and of other small bowel loops (arrows in (**b**)), with stratified contrast enhancement due to hyperdense aspects of the mucosal layer and hypodensity of the submucosal layer, indicating active inflammation. Perienteric fat stranding and local hypervascularization (asterisks in (**b**)) and left colonic wall thickening (rectangles in (**a**, **b**)) are also evident.

Source: Mignini I, et al. J Clin Med 2023; 12: 5933 (Figure 5)

- **MRE**
  - Assessment of the small bowel without radiation exposure
  - Wall enhancement, mucosal lesions, T2 hypersensitivity
  - Similar sensitivity as CTE
  - MRE is preferable to CT due to absence of radiation for <35 yr
  - High cost
  - Lengthy acquisition times
  - Patient dissatisfaction
  - Limited access



MRE enterography (MRE) images in axial and coronal planes show wall thickening of the distal ileum (arrows in (a,b)), characterized by hyperintense signal compared to muscle (indicating the presence of oedema, letter M in (b)), restricted diffusion in DWI sequence (arrows in (c)), and stratified contrast enhancement after gadolinium injection (arrows in (d)), indicating active inflammation.

Source: Mignini I, et al. J Clin Med 2023; 12: 5933 (Figure 4)

- **Capsule Endoscopy**
  - Direct visualization of small intestine mucosa
  - Superior to small bowel barium studies, CTE and ileocolonoscopy with suspected CD (incremental diagnostic yield of 32%, 47% and 22%)
  - Villous appearance, ulcers and strictures
    - Risk of capsule retention up to 5.4%
    - May require cross sectional imaging prior
    - Limited access
    - High cost

- **Endoscopy**
  - Advantages
    - Gold standard to assess for disease activity
    - Important to assess because endoscopic healing is long term target of therapy (STRIDE II)
    - Invasive procedure (risks)
  - Disadvantages
    - Endoscopy complications
    - Sedation
    - Bowel preparation
    - Long use of endoscopy time
    - Not always practical during severe flare due to risk of perforation

Peyrin-Biroulet L, et al. Am J Gastroenterol 2015; 110: 1324–1338
Turner D, et al. Gastroenterology 2021; 160: 1570–1583

- **Transabdominal intestinal US (TA-IUS)**
  - Advantage
    - Non-invasive
    - Radiation-free
    - Tolerated by patients
    - No preparation
    - Low cost
    - Safe
  - Disadvantage
    - Rectum and proximal jejunum not well visualized
    - Well studied role in monitoring response to therapy
    - Role in Crohn disease more established than UC

Maaser C, et al. J Crohn Colitis. 2019;13(2):144-164.

- **Intestinal ultrasonography (IUS)/small intestinal contrast ultrasound (SICUS)**
  - Procedure
    - Patient fasted (8 hrs)
    - Ingestion of 375 mL PEG contrast solution
      - Anechoic fluid enabling are intestinal loop to be dissociated from the others
    - Mid to high frequency probe (>5 MHz) gives high resolution
      - Convex transducer (1-8 MHz)
      - Linear-array transducer (3-11 MHz)
    - Abdominal probe does **not** have enough resolution for mural inflammation
    - Consistent settings need to be used
    - Median exam time 40 minutes in studies

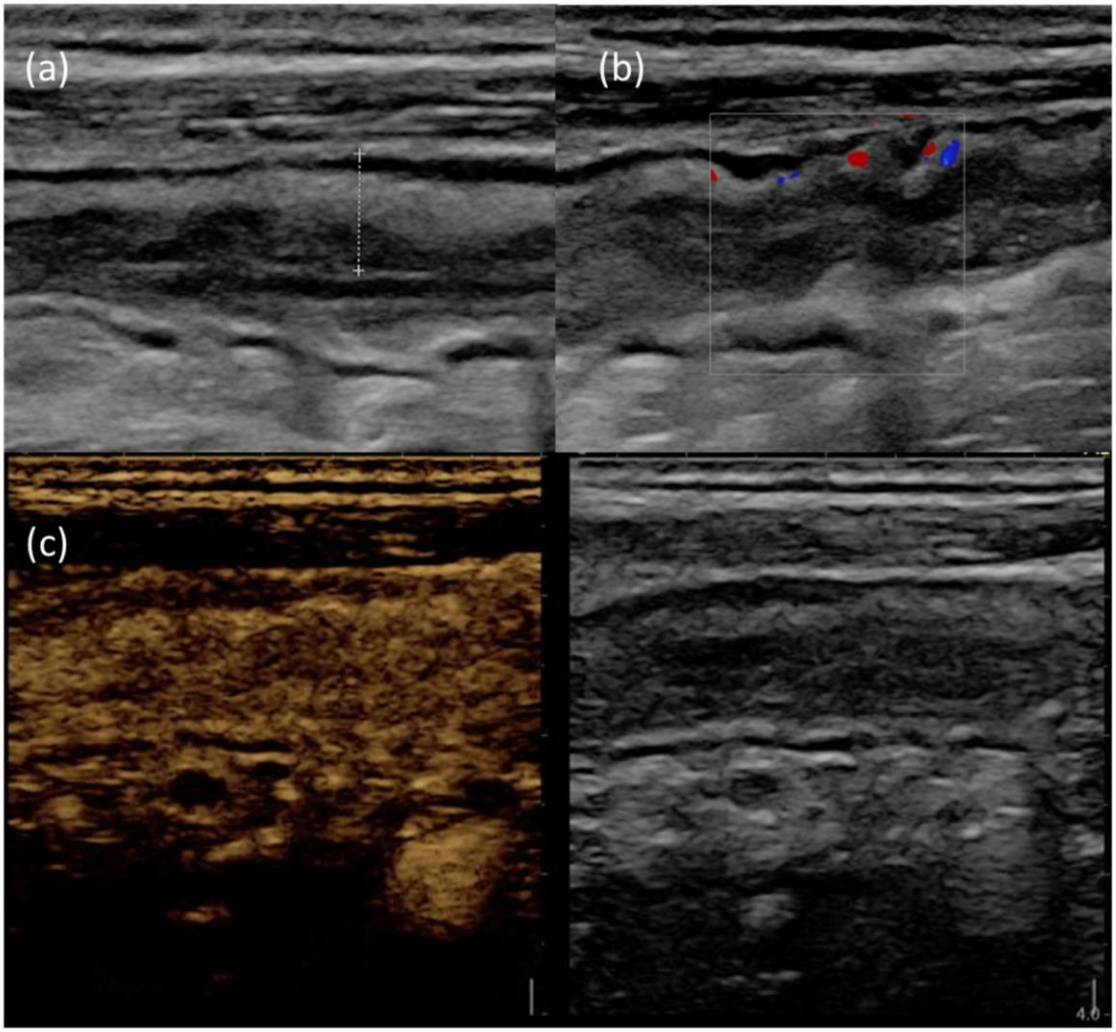
Calabrese E, et al. Inflamm Bowel Dis 2005; 11: 139–145.
Ilvemark JFK, et al. J Crohns Colitis 2021; 16: 554–580.

  - Key measurements
    - Bowel wall thickness in
      - Small intestine (SI), >3 mm
      - Sigmoid colon, >4 mm
    - Assess absolute mm and relative % change from baseline
    - Assessment of response to treatment depends on
      - Baseline thickness
      - Class of drug
      - Disease duration
      - Segment characteristic (active inflammation/fibrotic/both)
    - Treatment response time shorter in
      - UC vs CD
      - Colonic disease vs SI
  - Assessment of length of disease
    - Involved segments of colon
    - For TI disease
      - Distance in cm
      - Distance for IC valve
    - Correlates well with results of MRE
  - Bowel dilation = >2.5cm
  - Bowel stricture (lumen diameter <1 cm)
  - Abnormal motor activity
  - Presence of fistulas
    - Hypoechoic tract +/- hyperechoic content seen
    - Outside the bowel loop
    - Between loops of bowel
    - Between the loop and the urinary bladder
  - Mesenteric enlargement or masses

- Abscesses
  - Roundish anechoic lesions with irregular walls
  - Internal echoes and posterior echo enhancement
- Vascularization of bowel assessed by Doppler

Ilvemark JFK, et al. J Crohns Colitis 2021; 16: 554–580.

IUS images of the terminal ileum in a patient with active CD.



(a) B-mode IUS showing increased BWT (dotted line) with preserved wall stratification. (b) The use of color doppler highlights increased intramural vascularization. (c) After Sonovue® injection, the affected bowel wall shows increased contrast enhancement.

Source: Mignini I, et al. J Clin Med 2023; 12: 5933 (Figure 3)

Crohn Disease: Comparison of SICUS vs. Other Diagnostic Imaging

- SICUS significant correlation with endoscopy for detecting CD recurrence after surgical resection
  - BWT correlated with Rutgeert Score
  - SICUS recurrence detection:
    - Sensitivity, 92.5%
    - Specificity, 20%

Calabrese E, et al. Inflamm Bowel Dis 2009; 15(11), 1635–1642.

- SICUS detection of small bowel complications of CD

Complication	Sensitivity	Specificity
Abscesses (intraabdominal)	100%	95%
Fistulas	96%	91%
Strictures		
> 1	98%	100%
≥ 2	75%	100%

Pallotta N, et al. Inflamm Bowel Dis. 2012; 18(1):74-84.

- SICUS is comparable to CTE at detecting small bowel lesions

Complication	SICUS		CTE	
	Sensitivity	Specificity	Sensitivity	Specificity
Strictures	92%	0%	100%	0%
Dilation	100%	50%	78%	0%
Fistulas	60%	88%	60%	88%
Abscess	100%	80%	67%	100%

Onali S, et al. World J Gastroenterol 2012: 18; 6088–6095.

- CTE for small and large bowel involvement
  - SICUS for colonic lesions compared to colonoscopy or to CTE
    - Sensitivity, 71%
    - Specificity, 100%
  - SICUS not sensitive at detecting colonic stenosis

Calabrese E, et al. Clin Gastroenterol Hepatol 2013; 11(8), 950–955.

- MRE at detecting complications of CD
  - 67 Patients with CD investigated with either SICUS and/or MRE
    - 25 underwent US, 17 MRE and 25 both
  - Required surgery within 6 mons
  - Surgical pathology gold standard
  - High correlation of SICUS between
    - UD
    - Surgery in localizing strictures
    - Fistulas, and
    - Abscesses
  - US comparable to MRE for
    - Strictures
    - Abscesses
  - US superior to MRE
    - Fistulas
    - Bowel dilatation/thickening

Complication	US		MRE	
	Sensitivity	Specificity	Sensitivity	Specificity
Strictures	88%	88%	100%	91%
Fistulas	86%	94%	67%	100%
Abscess	100%	95%	100%	93%
Bowel Dilation	100%	75%	67%	73%
Bowel Wall Thickening	95%	50%	82%	100%

Kumar S, et al. J Gastroenterol Hepatol 2015; 30(1): 86-91.

- Clinical scores with anti-TNF therapy in CD
  - Multicenter study of 234 patients with ileocolonic CD over 12 mon
  - US assessment at baseline, 3, 6, and 12 mon
  - Flare defined as HBI >7 triggered treatment intensification usually with Anti-TNF
  - US can accurately monitor clinical response after treatment initiation
    - Not compared to endoscopy or MRE

Kucharzik T, et al. Clin Gastroenterol Hepatol 2017; 15: 535-542.e2.

- US useful in monitoring biologic-induced bowel activity
  - Prospective multicenter study of 188 CD patients
    - Started on biologic therapy
      - 55% ADA, 16% INF, 13% VED, 20% UST

- US used at 3, 6 and 12 mon to assess
  - Transmural healing (TH): normalization of BWT, lesion length, echo pattern, blood flow
  - Improved lesions: 2 improved parameters
- At 12 mon 28% achieved TH (37% with INF)

Calabrese E, et al. Clin Gastroenterol Hepatol 2022; 20(4): e711-e722.

- US useful in monitoring biologic-induced bowel activity
  - Transmural healing in terms of
    - BWT
    - Lesion extent
    - Penetrating complications, and
    - Vascular signals in distal ileum of CD

Ulcerative Colitis (UC)

- IUS is accurate at assessing for disease activity in UC
  - IUS vs. Mayo (endoscopic) score for active UC
  - IUS
    - BWT
    - Vascularity
    - Colonic wall pattern
    - Mesenteric lymph nodes
  - CWT>3 mm + FC > 101 ug/g predicted Mayo 2/3 disease
    - Sensitivity, 84%
    - Specificity, 93%

Abbreviations: CWT, colonic wall thickness; FC, fecal calprotectin

Allocca M, et al. J Crohns Colitis 2018; 12(12): 1385-1391.

- IUS can detect decreased disease activity in UC after treatment
  - Proctosigmoid, left-sided or pancolitis
  - In clinical relapse and with ↑ BWT (↑ in 89%)
    - SCCAI > 5 activity score
  - Received standard of care therapy
    - 89% with clinical relapse had ↑ BWT
  - Patients had
    - Normalization of ↑ BWT
    - ↓ vascularity

- IUS correlates well with fecal calprotectin (FC) after treatment in UC
  - 89% of patients at baseline with ↑ BWT had FC>250
  - At 12 wks (T2)
    - 84% with increased BWT had FC>250
    - 44% with normal BWT had FC>250
  - BWT normalization (edema) occurs faster than resolution of musical inflammation
    - Not compared to endoscopy

Maaser C, et al. Gut 2020; 69(9): 1629-1636.

➢ Guideline recommendations for the use of US in patients with IBD

- ECCO-ESGAR Guidelines Diagnostic GL 2018
  - CD
    - All newly diagnosed CD patients should undergo small bowel assessment (IUS, MRE and/or capsule endoscopy)
    - Extramural complications should be assessed by
      - IUS
      - MRE
    - Symptomatic small bowel disease can be investigated with MRE, IUS, and/or capsule endoscopy
    - Detect postop recurrence with IUS, MRE, FC
    - MRE or IUS should be used to detect small bowel stricture
    - IUS, MRI and CT detect penetrating disease or abscesses with IUS, MRI, CT
    - None

Maaser C, et al. J Crohns Colitis. 2019;13(2):144-164.

- ACG Crohn's Disease 2018 and ACG Ulcerative Colitis 2019
  - None

Lichtenstein GR, et al. Am J Gastroenterol. 2018; 113(7): 1101.
Rubin DT, et al. Am J Gastroenterol. 2019; 114(3): 384-413.

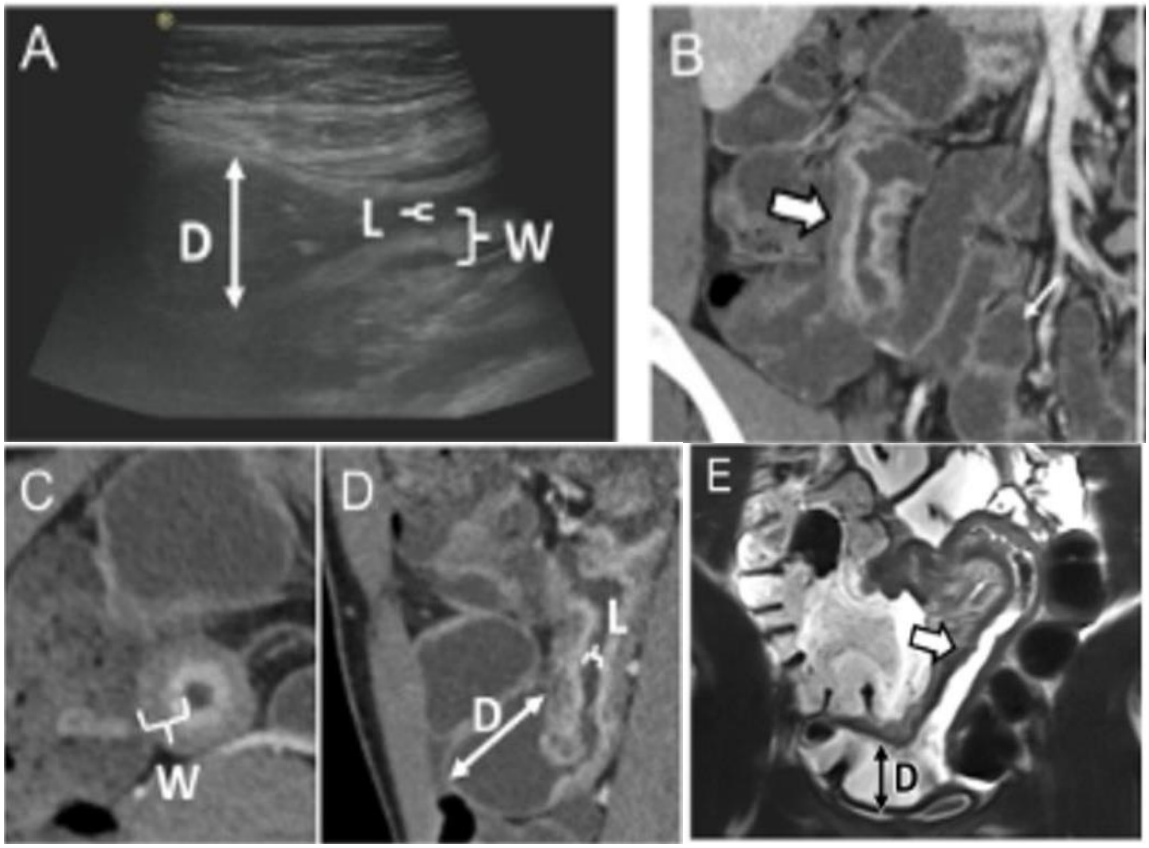
➢ Conclusion

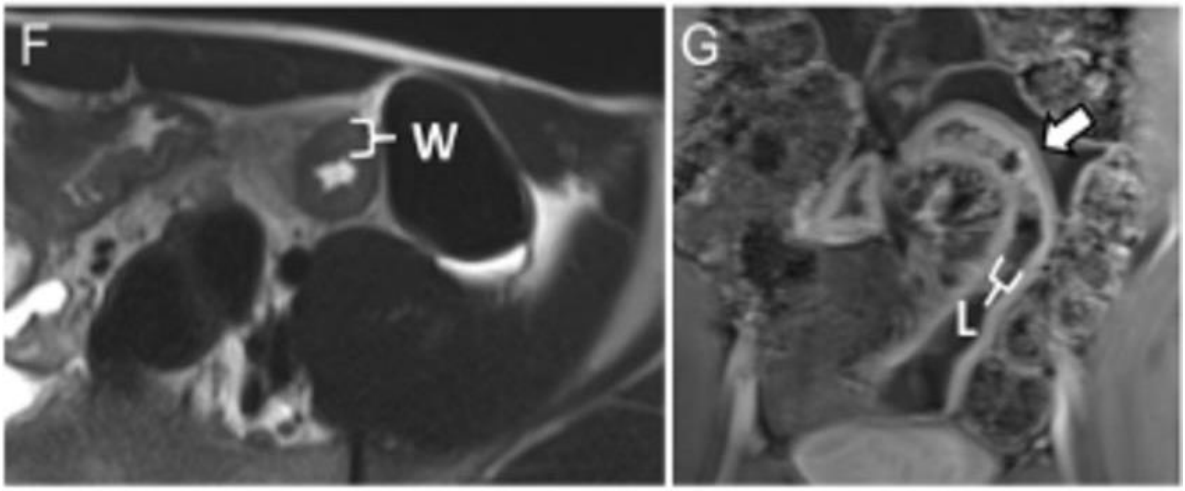
- Crohn disease
  - US performs similarly to CTE at detecting CD extent
  - US can be used to track response to treatment or recurrence in CD
    - Can examine bowel segments unreachable by endoscopy/capsule due to strictures

- US performs as well or better than CTE/MRE for detecting complications of CD
  - Training in point of care assessment for fellows
  - Potentially decrease time to treatment and length of stay
  - Decrease number of CT used on our CD population
- Limits radiation exposure for those diagnosed at a young age
- Eliminates endoscopy risks for older patients and/or with comorbidities

- Ulcerative Colitis
  - Role for US in UC becoming better validated
    - Can detect Mayo 2/3 disease with high sensitivity, especially when paired with FC
    - Use to assess response to treatment
    - US not sensitive for disease in rectum
  - Clinical scores are not adequate to be only method to detect IBD disease activity

Transabdominal ultrasonography, CT and MR enterography demonstrating a distal ileal stricture.





(A) Ultrasound image depicting the three core items for stricture diagnosis wall thickness (W, *bracket*), luminal narrowing (L, *bracket*) and prestenotic dilation (D, *double arrow*). (B–D) CT enterography demonstrating a distal ileal stricture with imaging findings of active inflammation and partial small bowel obstruction. (B) Coronal image demonstrating a distal ileal stricture with wall thickening, luminal narrowing and mural stratification and hyperenhancement (*large white arrow*). Active inflammatory Crohn's disease is also present in the terminal ileum (arrowhead), as is a short segment jejunal stricture (*small white arrow*). (C) Enlarged axial image through distal ileal stricture better demonstrates luminal narrowing and increased wall thickness (W, *bracket*). (D) Sagittal image through distal ileal stricture shows prestenotic bowel dilation (D, *arrows*) and luminal narrowing within the stricture (L, *bracket*). (E–G) MR enterography demonstrating a distal ileal stricture with imaging findings of active inflammation. (E) Coronal half-Fourier single-shot fast spin echo (HASTE) shows ileal stricture with wall thickening and luminal narrowing (large white *arrow*) with upstream dilation (D, *arrows*). (F) Axial HASTE shows cross section through the stricture demonstrating increased wall thickness and how wall thickening is measured (W, *white bracket*). (G) Postcontrast axial 3D volumetric interpolated breath hold examination (VIBE) shows wall thickening and mural stratification and hyperenhancement, indicating inflammation with luminal narrowing (L, *bracket*). The three core items for stricture diagnosis are increased wall thickness, luminal narrowing and prestenotic dilation. CTE, CT enterography; MRE, MR enterography.

Printed with permission: Bettenworth D, et al. Gut 2019; 68: 1115-1126 (Figure 1)

- STRIDE I
  - Clinical scores which are no longer acceptable as sole indicator of disease activity or a therapeutic target.

- Crohn disease (CD)
  - Absence of ulceration on endoscopy is most appropriate therapeutic target
  - CDAI <150 somewhat sensitive for mucosal healing (MH), but is not specific (sensitivity, 80%; specificity, 35%)
  - CDAI cannot predict remission in CD patients on AZA or infliximab
  - Cross sectional imaging assessment of resolution is target when endoscopy is unable to evaluate
    - CT/MR/US have similar accuracy (80%)
  - Biomarkers are not suitable targets
    - CRP < 0.8 mg/dL (sensitivity, 86%; specificity, 37%)

- Ulcerative colitis (UC)
  - Endoscopic Mayo score ≤1, 0 is optimal target
  - Not suitable targets in UC
    - Cross sectional imaging (CRE, MRE, US)
    - Biomarkers prediction of endoscopic remission

Peyrin-Biroulet L, et al. Am J Gastroenterol 2015; 110(9):1324-38.

- Predictive of remission
  - PRO2 more strict definition of remission in CD
    - Stool frequency ≤1.5 and abdominal pain <1 (optimal cut points for CDAI < 150)

Khanna R, et al. Aliment Pharmacol Ther 2015; 41(1):77-86.

  - UC patients with rectal bleeding likely not in remission
    - Mayo score 0 or 1
      - No blood seen = sensitivity, 77%; specificity, 81%
      - Normalization of stool frequency (SF) = sensitivity, 62%; specificity, 95%
      - SF+ Rectal bleeding (RB) = sensitivity,54%; specificity, 95%
    - Endoscopic remission associated with
      - Absence of RB, but
      - Not with complete normalization of SF

Stool frequency
0 = Normal no. of stools for this patient
1 = 1 to 2 stools more than normal
2= 3 to 4 stools more than normal
3 = 5 or more stools more than normal

Rectal bleeding
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2= Obvious blood with stool most of the time 3 = Blood alone passes

Colombel JF, et al. Gut. 2017; 66(12): 2063-2068.

- STRIDE II
  - Clinical response or remission is insufficient to be used as long-term treatment targets
    - CD PRO2: weighted total stool frequency and abdominal pain
    - UC PRO2: rectal bleeding and stool frequency
  - Transmural healing by CTE, MRE or bowel ultrasound not a treatment target
  - Normalization of CRP and fecal calprotectin (to 100-250 ug/g) intermediate target

COLON

Microscopic Colitis, Ischemic Colitis and Segmental Colitis Associated with Diverticulitis

Pavithra Parthasarathy and Melanie Beaton

❖ **Microscopic Colitis**

- Inflammatory disease of colon associated with chronic watery diarrhea, and diagnosed on mucosal biopsies of the colon
- Often mislabeled as irritable bowel syndrome, diarrhea predominant (IBS-D)

➢ Demography

- In persons with chronic diarrhea and with a normal appearing mucosa on endoscopy, > 10%
- Typical middle age females

➢ Clinical

- Insidious or Sudden onset
- Urgency, incontinence, nocturnal stooling
- Abdominal pain and bloating
- Weight loss – reduced intake +/- fluid loss
- Chronic, intermittent course in most

➢ Pathophysiology (theories)

- Genetic susceptibility
- Collagen metabolism abnormalities
- Abnormal epithelial barrier function
  ↓
- Diarrhea
  - Mucosal inflammation
    - Severity correlates with inflammation in lamina propria but not collagen thickness
    - Imbalance
    - Secretory
      - ↓ NaCl absorption
      - ↑ Cl secretion

      Concurrent bile acid malabsorption in some patients

➢ Risk Factors

- Females
  - Age > 60
- Smoking (current/previous)

- Autoimmune disease
  - Celiac disease
  - Thyroid
  - Diabetes mellitus type 1
  - Rheumatoid Arthritis (RA)
  - Inflammatory bowel disease (IBD)
  - Sjögren disease
- Medications (NSAID/Aspirin, SSRIs, PPIs, H2RAs, Acarbose, Ticlopidine)
  - Consider withdrawing drug with chronological relationship to diarrhea onset
  - Association does **not** flare causation
- Solid organ transplantation

➢ Diagnosis

- Exclude other causes of chronic diarrhea
  - Infection (C difficile, Culture and sensitivity, Ova and parasites)
  - Celiac serology
    - Seen in 15% of patients with lymphocytic colitis
    - Refractory celiac disease

➢ Laboratory

- Non-specific
  - 50% have mild anemia, ↑ CRP, and/or autoantibodies

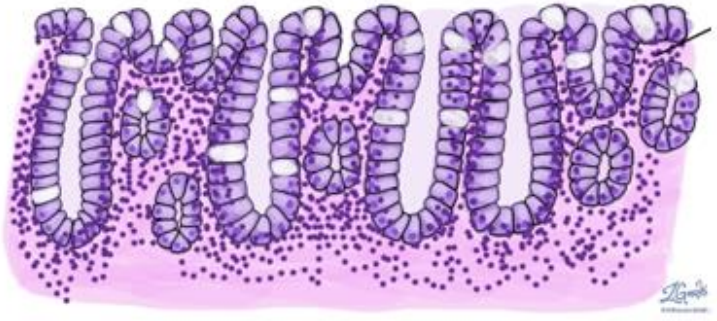
➢ Colonoscopy

- Usually, normal mucosa
- Sometimes
  - Isolated linear ulcerations/lacerations
  - Irregular vascular patterns
  - Take 2 mucosal biopsies from right and 2 from left colon, and placenta in same jar

➢ Histopathology

Lymphocytic

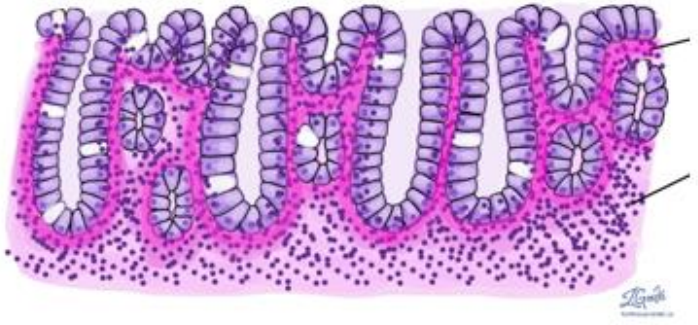
- Normal crypt architecture



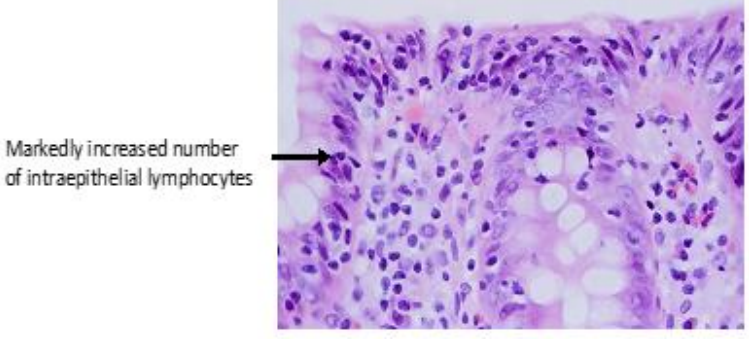
- ↑ intraepithelial lymphocytes (≥ 20/100 epithelial cells
- Higher rates of resolution or significant improvement than collagenous
- 3x more common than collagenous

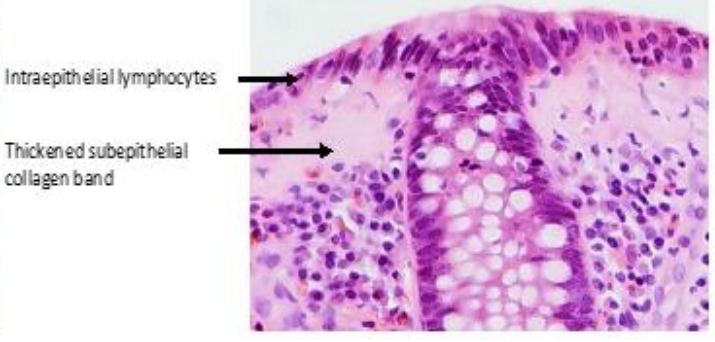
Collagenous

- Thickened subepithelial collagen band > 10 µm



- ↑ intraepithelial lymphocytes
- Tends to occur later in life





- Treatment
  - May spontaneously remit with or without therapy
  - Lower relapse rated with antidiarrheal or steroid therapy
  - Long term resolution or significant improvement more likely in lymphocytic colitis
  - Correct risk factors
    - Avoid culprit medications
    - Stop smoking
  - Treat associated conditions
  - Pharmaceutical
    - First-line
      - Budesonide given as long taper: 9 mg po od x8 wk, then 6 mg po od x2 wks, then 3 mg po od x2 wk
      - Induces clinical remission; 50-75% relapse in 1st year
      - Low dose budesonide to maintain remission if relapse
        - No evidence for serious adverse events, but can lower BMD
        - Slow taper: 9 mg po od x8 wk, then 6 mg po od x 6 mon or alternating 3 mg and 6 mg po od x12 mon
      - Adjunctive therapies if mild symptoms persist
        - Loperamide, Cholestyramine, Bismuth
    - Second-line
      - Mesalamine not superior to placebo in LC
      - UEGJ 2021 guidelines recommend against mesalamine for induction
      - Lack of evidence to recommend bismuth, antibiotics
      - Recommend against prednisone/other corticosteroids.
      - Advise loperamide in mild cases; cholestyramine in bile acid diarrhea
      - Immunomodulators/biologics (not methotrexate): to be used where budesonide not effective

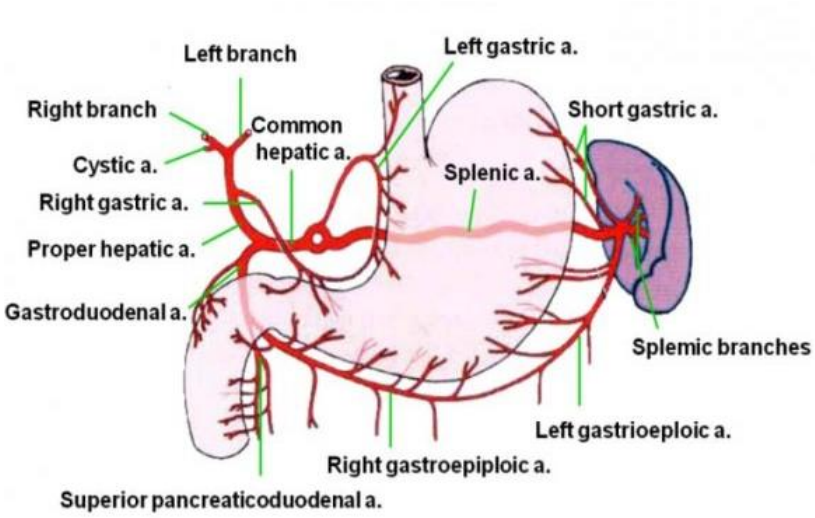
Note: No role for monitoring response by endoscopy or measurement of fecal calprotectin to monitor response

Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 11th ed. Philadelphia, PA: Elsevier; 2020.
Miehlke S, et al. United European Gastroenterol J 2022; 9(1): 13–37.
Qayed E. Gastroenterology Clinical Focus: High Yield GI and Hepatology Review for Boards and Practice. Atlanta, GA: Emad Qayed; 2024.

❖ Intestinal Ischemia

Celiac Artery

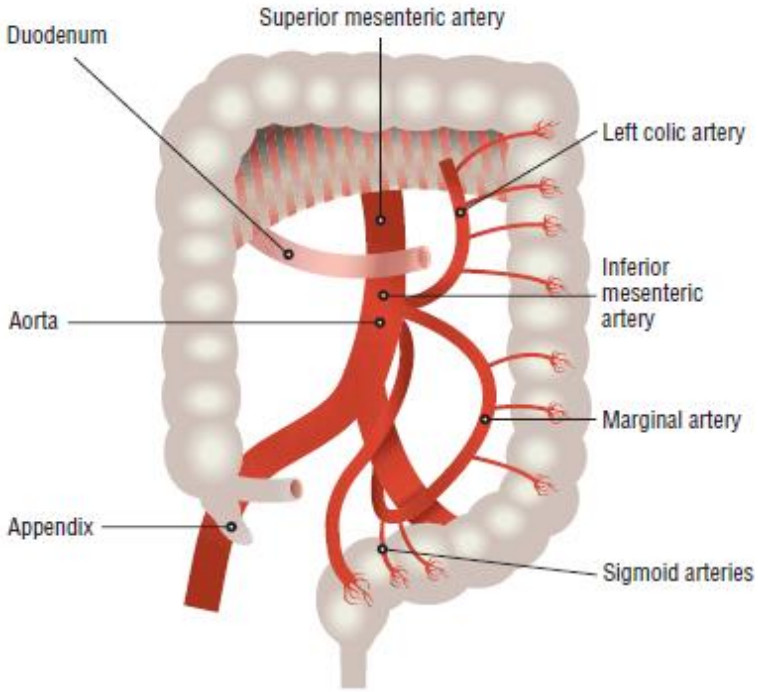
Supplies stomach, duodenum, pancreas, liver



Source: https://medicalresearchjournal.org/index.php/GJMR/article/download/533/8-Surgical-Anatomy-of-Coeliac-Trunk_html?inline=1

Inferior Mesenteric Artery (IMA)

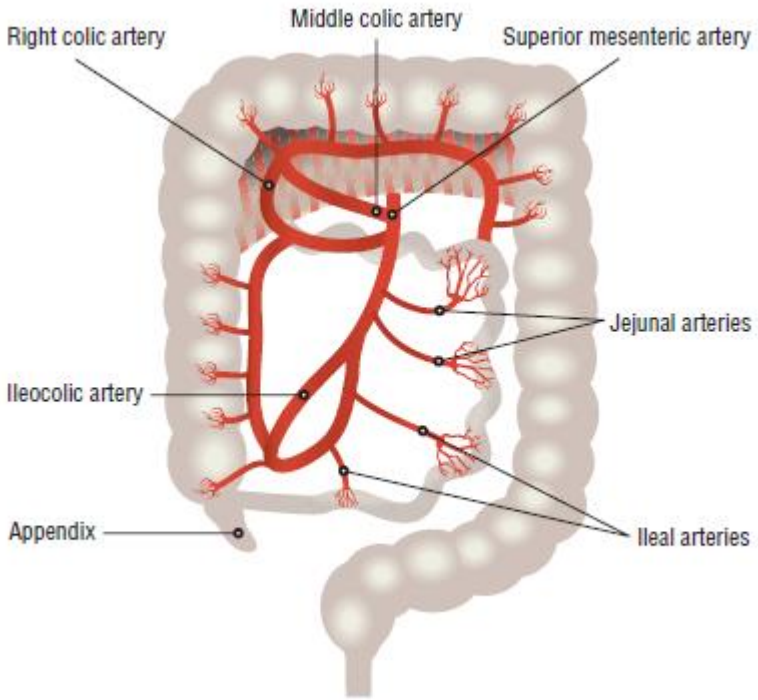
Distribution of blood flow to the colon originating from the inferior mesenteric artery, branches of which include the left colic, marginal, and sigmoid arteries and supply the left colon and superior portion of the rectum



Printed with permission: Sreenarasimhaiah J. Diagnosis and management of intestinal ischaemic disorders BMJ 2003; 326 :1372 (Figure 2).

Superior Mesenteric Artery (SMA

Distribution of blood supply to the small intestine and colon from the superior mesenteric artery, branches of which include the middle, right, and ileocolic arteries as well as jejunal and ileal arteries and arterioles



Printed with permission: Sreenarasimhaiah J. Diagnosis and management of intestinal ischaemic disorders BMJ 2003; 326 :1372 (Figure 1).

Types and Approximate Frequency of Intestinal

Types of Intestinal Ischemia	Frequency (%)
○ Colonic*	75
○ Acute mesenteric*	25
○ Focal segmental*	<5
○ Chronic mesenteric ischemia	<5

*Include mesenteric venous thrombosis. Mesenteric venous thrombosis can manifest as colonic ischemia, acute mesenteric ischemia, or focal segmental ischemia

Qayed E. Gastroenterology Clinical Focus: High Yield GI and Hepatology Review for Boards and Practice. Atlanta, GA: Emad Qayed; 2024.

- Types
  - Acute/chronic
  - Mesenteric/colonic
  - Focal, segmental
  - Arterial, venous, hypoperfusion
  - Area, length of bowel affected

➢ Collaterals

- Several collaterals to stomach, duodenum, rectum
- Splenic flexure and sigmoid – limited anastomosis, ischemic damage more common (watershed areas)
- Celiac superior pancreaticoduodenal branch + SMA inferior pancreaticoduodenal branch (pancreaticoduodenal arcade)
- SMA + IMA
  - Marginal artery of Drummond – closest to colon
  - Central anastomotic artery – larger, central
  - Arc of Riolan – base of mesentery
  - Meandering artery – in SMA/IMA occlusion

➢ Pathophysiology (common for ischemic injury)

- Major vessel occlusion → collaterals open immediately, distal to the obstruction
  - Several hours of ischemia → vasoconstriction in obstructed bed → ↓ collateral flow
  - Prolonged vasoconstriction becomes irreversible
- Hypoxic injury and nutrient deprivation → loss of cellular integrity
- Bowel can manage with only 25% of mesenteric blood flow and oxygen consumption for up to 12 hr due to compensatory mechanisms
- Reperfusion injury also a contributor: reactive oxygen- and nitrogen-derived free radicals → damage cellular structures → cell lysis/necrosis

❖ Ischemic Colitis

Brandt LJ, et al. Am J Gastroenterol 2015; 110: 18-44

➢ Demography

- Most common form of intestinal ischemia
- F>M
- ~7/10^5
- ↑ incidence in persons with irritable bowel syndrome (IBS)

- Rising incidence
  - Better recognition
  - Aging population
  - More surgical interventions
  - Polypharmacy
- Often misdiagnosed; late presentations
- Initial presentation does **not** predict course of disease
  - Exception is ascending colon injury, often occurs with small bowel injury

➢ Pathophysiology

- Local hypoperfusion and reperfusion injury caused by:
  - Changes to systemic circulation
  - Anatomic and functional changes in mesenteric vasculature
- Often, no cause found – likely detected localized nonocclusive ischemia
- Relative to small bowel, colon is particularly at risk for ischemic injury because of
  - ↓ low blood flow
  - Lack of collaterals
  - ↓ blood flow during functional activity
  - Sensitivity to autonomic stimulation

➢ Histopathology

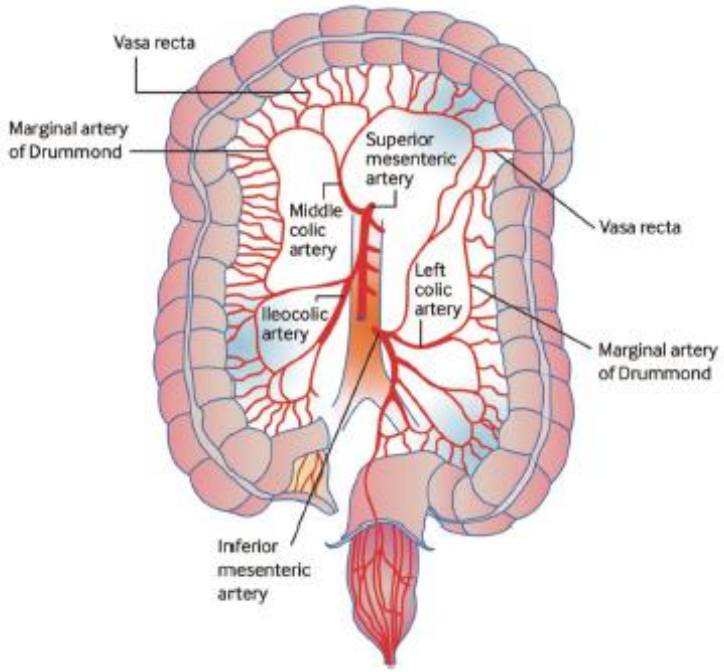
- Mucosal / submucosal hemorrhage / edema
- Necrosis / ulceration
- Chronic ulcers, crypt abscesses
- Pseudopolyps (mimics IBD!); pseudomembranes
- Ghost cells pathognomonic for ischemic colitis (cell outlines without cytoplasm/nucleus)
- Strictures – fibrosis in muscularis propria
- Transmural infarction – most severe form of ischemic damage

➢ Types

Types and Approximate Frequencies of Colonic Ischemia in Patients Seen at a Tertiary Referral Hospital

Type	Frequency (%)*
Reversible Colopathy and transient colitis	>50
Chronic colitis	5-10
Stricture	10
Gangrene	15
Fulminant universal colitis	<5

*Because of the approximate nature of the frequencies, the total of the frequencies of all types of colonic ischemia is not 100%



Arterial supply of the colon and the most common sites for ischemic colitis. The colon receives blood from both the superior and inferior mesenteric arteries. However, there are weak points, or ‘watershed’ areas, at the borders of the territory supplied by each of these arteries, such as the splenic flexure and the transverse colon. These watershed areas are most vulnerable to ischemia when blood flow decreases as they have the fewest vascular collaterals.

Printed with permission: Trotter JM, et al. Ischaemic colitis BMJ 2016; 355: i6600 (Figure 1)

- Risk Factors for Colonic Ischemia
  - Most associated comorbidities
    - Heart
      - Atrial fibrillation
      - Heart failure
      - Hypertension
      - Peripheral vascular disease
      - Vasculitis
    - Lung
      - COPD
    - Endocrine
      - Diabetes
    - MSK
      - Rheumatologic disease
    - GI
      - Constipation
      - Diarrhea
    - Blood
      - Coagulopathy
      - Thrombophilia
    - Iatrogenic
      - Drugs
        - Cocaine
        - Estrogens
        - Serotoninergic agents
      - Surgery

- Causes
  - Always consider drug as possible contributor
  - Antibiotics
    - CI-mediated antibiotic-associated hemorrhagic colitis
      - 2-7 days post-antibiotic initiation
  - Appetite suppressants
  - Anti-inflammatory NSAIDs, ASA
  - Chemotherapeutic medications
    - Either direct injury to epithelium or due to anti-angiogenic activity
  - Constipation-inducing medications
    - Possibly through pathway that colonic slow transit is associated with
      - ↓ baseline mucosal blood flow
      - ↓ cholinergic innervation
      - ↑ sympathetic stimulation
      - ↑ intracolonic luminal pressure → ↓ epithelial blood flow
  - Constipation-treating medication
    - Osmotic mucosal injury
    - Non-occlusive mesenteric ischemia by fluid shifts
    - Vasoconstriction

- Decongestants
- Diuretics
- Hormones
- Immunomodulators / interferon
- Serotonin affecting drugs
- Statins
- Vasopressors

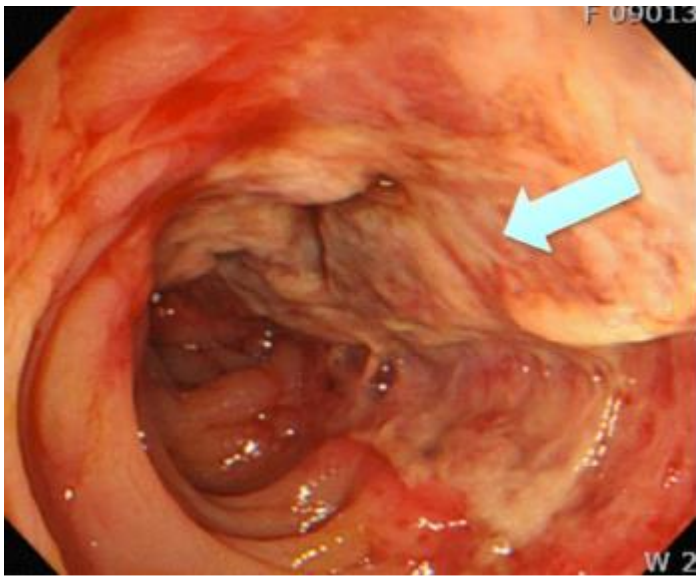
➢ Clinical Presentation

- Ischemic injury usually confined to one territory; pancolonic and rectal involvement infrequent
- Sudden abdominal pain, cramping, in the areas involved
- Urgent desire to defecate; hematochezia, bloody diarrhea
- Bleeding not usually hemodynamically significant
- Small proportion (10-16%) at risk for recurrence; some are seropositive for IBD immune markers

➢ Laboratory

- Blood tests
  - Albumin
  - Amylase
  - Complete blood count
  - Creatinine kinase (CK)
  - Electrolyte panel
  - Lactate
  - Lactate dehydrogenase (LDH)
- Stool tests
  - Clostridium difficile toxin assay
  - Culture and sensitivity
  - Ova and parasite
  -

- Colonoscopy with biopsy
  - Gold standard
    - Perform within 48 hrs of symptoms
    - Avoid overdistension – ↑ intraluminal pressure reduces blood flow
  - Findings
    - Hemorrhagic nodules represent
      - Bleeding into subepithelium (radiologic thumbprinting)
    - Segmental distribution, with or without ulceration
    - Mucosal gangrene
    - Colon single-stripe sign
      - Single line of erythema or ulceration, longitudinally placed – associated with milder course
    - Rectal sparing
    - Rapid spontaneous evolution → resolution



Endoscopic findings of inflamed mucosa and single-stripe sign (a single longitudinal strip of ulcerated or inflamed colon (arrow)) in the segment of ischemic colitis

Printed with permission: Trotter JM, et al. Ischaemic colitis BMJ 2016; 355: i6600 (Figure 4)

❖ Segmental Colitis Associated with Diverticulosis (SCAD)

- Definition
  - Chronic inflammation of the colon around diverticula
- Demography
  - ~1% of patients with diverticulosis
- Clinical
  - Often seen in left colon, with rectal sparing; rare
  - Diarrhea
  - Cramping
  - Rectal bleeding
- Colonoscopy
  - Patchy erythema around diverticula
  - Aphthous ulcers (mimics Crohn) or continuous inflammation and mucosal friability (mimics UC)
- Histopathology
  - Mild
  - Chronic
  - Range of active inflammation to severe, acute inflammation
  - Crypt abscesses
  - Crypt architectural distortion (mimics IBD)
- Differential
  - Diverticulitis
  - IBD
  - Radiation colitis (consider if persistent disease)
- Treatment
  - Usually self-limiting (incidental finding)
  - If symptomatic, use with
    - Antibiotics (ciprofloxacin/metronidazole), or
    - 5-ASA
    - Prednisone for severe disease

Suggested Reading:

Brandt LJ, Feuerstadt P, Longstreth GF, et al. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am College of Gastroenterology| 2015; 110(1): 18-44.

Feldman M, Friedman LS, and Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 2020Elsevier Health Sciences.

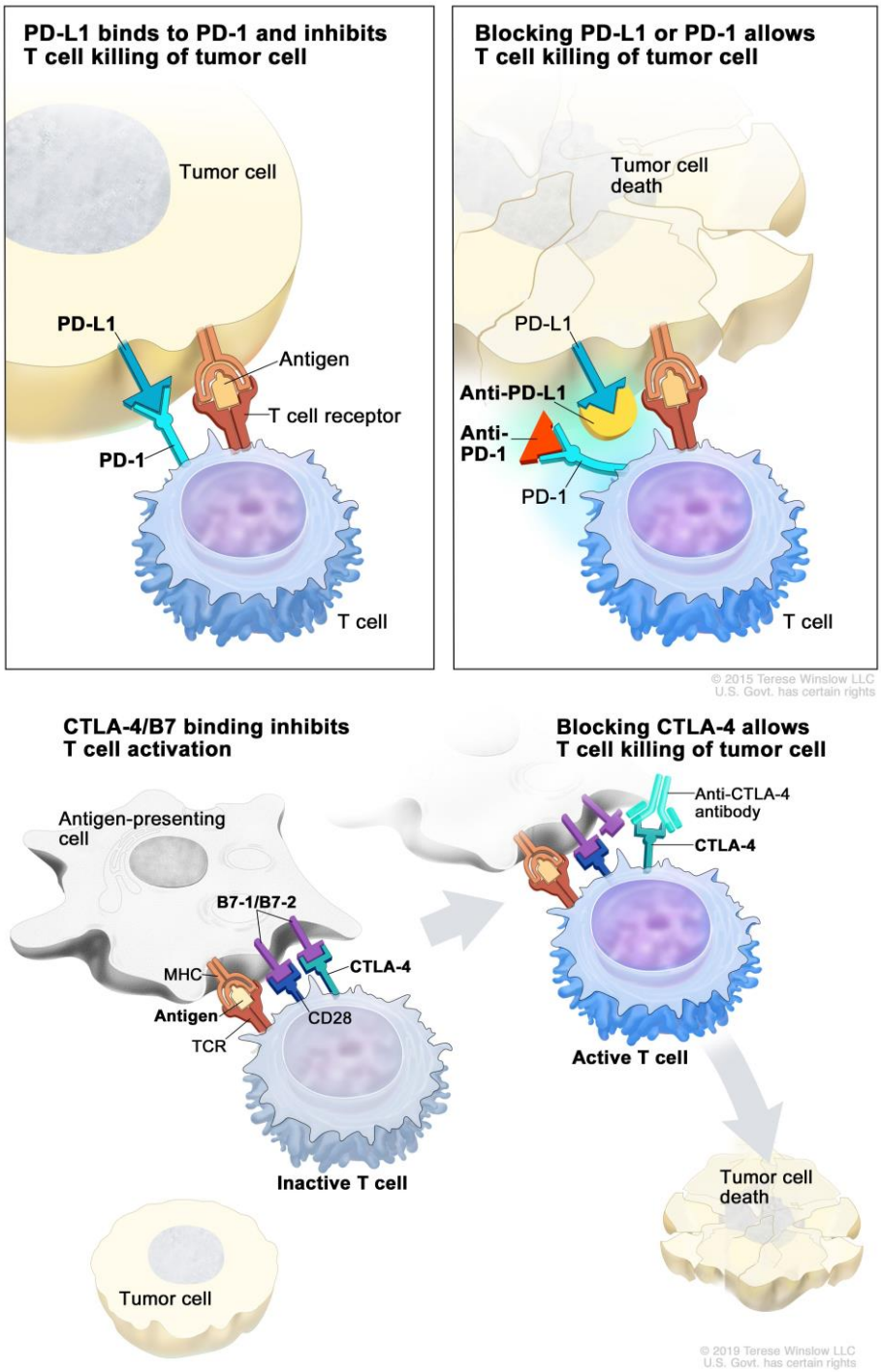
Miehlke S, Guagnozzi D, Zabana Y, et al. European guidelines on microscopic colitis: United European Gastroenterology and European Microscopic Colitis Group statements and recommendations. UEG Journal 2021; 9(1), 13-37.

Qayed, E. Gastroenterology clinical focus: high yield GI and hepatology review for boards and practice 2024. Emad Qayed.

Immune Checkpoint Inhibitors Enterocolitis: Management

Abdulaziz Alajmi

- Pharmacology



Source: www.cancer.gov

- Targets
  - Programmed cell death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1)
    - PD-1: Nivolumab, Pembrolizumab, Cemiplimab, and Dostarlimab
    - PD-L1: Atezolizumab, Avelumab, and Durvalumab
  - Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)
    - Ipilimumab and Tremelimumab

- Immune-related adverse events (irAEs)
  - ICI have become the standard of care for several cancers.
  - As the use ICI have increased, several ICI-related adverse events have been recognized.
  - Adverse events could affect multiple body system.
  - Organs Affected by Immune Checkpoint Blockade

Organ/System	Immune-Related Adverse Events
– Brain	▪ Aseptic meningitis ▪ Encephalitis
– Pituitary gland	▪ Hypophysitis
– Eyes	▪ Uveitis
– Thyroid gland	▪ Thyroiditis ▪ Hypothyroidism ▪ Hyperthyroidism
– Mouth	▪ Dry mouth ▪ Mucositis
– Skin	▪ Rash, vitiligo
– Lungs	▪ Pneumonitis
– Heart	▪ Myocarditis
– Blood	▪ Anemia ▪ Thrombocytopenia
– Liver	▪ Hepatitis
– Adrenal glands	▪ Adrenal insufficiency
– Kidneys	▪ Nephritis
– Pancreas	▪ Autoimmune diabetes ▪ Pancreatitis

Organ/System	Immune-Related Adverse Events
– Intestines	▪ Colitis, enteritis
– Joints	▪ Arthralgia
– Blood vessels	▪ Vasculitis
– Peripheral nerves	▪ Neuropathy

- Possible Mechanisms Underlying Immune-Related Adverse Events
  - Activated T cells may target antigens shared by tumours and healthy tissues, leading to immune-related damage in normal organs.
  - Preexisting autoantibodies (e.g., anti-thyroid antibodies) can predispose patients to autoimmune complications during immunotherapy.
  - Inflammatory cytokines released by activated T cells amplify systemic immune responses and contribute to collateral tissue effects.
  - Anti-CTLA-4 antibodies may bind directly to CTLA-4 expressed on normal tissues (e.g., pituitary gland), triggering complement-mediated inflammation and immune-related adverse events.

Immune-related adverse events (irAEs)

	CTLA-4	PD-1	PD-L1	P	PD-1 + CTLA-4	PD-L1 + CTLA-4	P (all columns)
N	4284	4074	2448		495	99	
irAEs any grade	54.1%	26.9%	18.7%	<0.001	Not Reported	Not Reported	<0.001
Diarrhea	28.3%	12.3%	3.1%	<0.001	36.4%	30.2%	<0.001
Colitis	8.3%	1.6%	0.7%	<0.001	13.3%	10.1%	<0.001
Rash	27.3%	16.3%	11.7%	<0.001	47.8%	28.6%	<0.001
Hypophysitis	3.2%	0.4%	0.1%	<0.001	8.7%	2.0%	<0.001
Hypothyroidism	1.3%	9.5%	8.6%	<0.001	8.3%	8.1%	<0.001
Adrenal insufficiency	1.6%	0.9%	0.4%	<0.001	4.2%	2.0%	<0.001
Pneumonitis	0.5%	3.9%	2.1%	<0.001	6.5%	4.0%	<0.001
Infusion-related reaction	0.2%	2.7%	4.4%	<0.001	1.2%	2.0%	<0.001
Increased ALT	2.7%	2.4%	2.5%	0.71	4.2%	2.0%	<0.001
ORR	10.6%	27.5%	10.7%	<0.001	47.8%	28.6%	<0.001

Source: El Osta B, et al. Annals of Oncology 2016; 27, vi369.

- Clinical
  - Defined according to the definition of ASCO.
  - Severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events.
  - irAEs can affect any portion of the GI tract
    - The lower GI tract is most involved (diarrhea and enterocolitis)

CTCAE Version 5

Adverse Effect	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	−↑ < 4 stools per day over baseline −Mild increase in ostomy output compared to baseline	−↑ < 4-6 stools per day over baseline −Moderate increase in ostomy output compared to baseline	−↑ 7 or more stools per day over baseline −Incontinence −Hospitalization indicated −Severe ostomy output compared to baseline −Limiting self-care ADL	−Life-threatening consequences −Urgent intervention indicated	Death
Colitis	−Asymptomatic −Clinical or diagnostic observations only −Intervention not indicated	−Abdominal pain −Mucus or blood in stool	−Severe abdominal pain −Change in bowel habits −Medical intervention indicated −Peritoneal signs	−Life-threatening consequences −Urgent intervention indicated	Death

Adapted from: US Department of Health and Human Services. Common Terminology Criteria for Adverse Events. National Institute of Health, National Cancer institute, 2017 Version 5.

➢ Risk factors

- Gut microbiome
  - In a prospective study.
    - Analysis of the gut microbiota
      - ↓ Bacteroidetes species patients developed colitis

Dubin K, et al. Nat Commun 2016; 7: 10391

- Immune checkpoint inhibitor therapy in patients with pre-existing inflammatory bowel disease
  - In a multicenter retrospective study of patients with documented IBD who received ICI (49 patients with Crohn disease, 49 with ulcerative colitis, and 4 with unclassified IBD)
    - 40% had GI irAEs (40%), ~35% patients had colitis.

Abu-Sbeih H, et al. J Clin Oncol 2020, 38(6), 576–583.

➢ Treatment

- Symptomatic treatment of diarrhea.
- Grade 1 diarrhea, less than 4 stools/day.
  - Continue ICI therapy

- Glucocorticoids
  - Retrospective study total of 687 patients with grade 1 symptoms beyond 5 days to be managed symptomatically Diarrhea/Colitis identified with use of ipilimumab
  - Patients with grade 1 diarrhea, 18% were managed with steroids, and 67% diarrhea resolved with fluids and symptomatic therapy
  - Patients with grade 2 diarrhea, 46% were managed with corticosteroids, and the majority improved.
  - Resolution/downgrading of symptoms occurred in 90% of grade 3-4 with corticosteroids.

O'Day S, et al. J Clin Oncol 2011;29: abstract 8554.

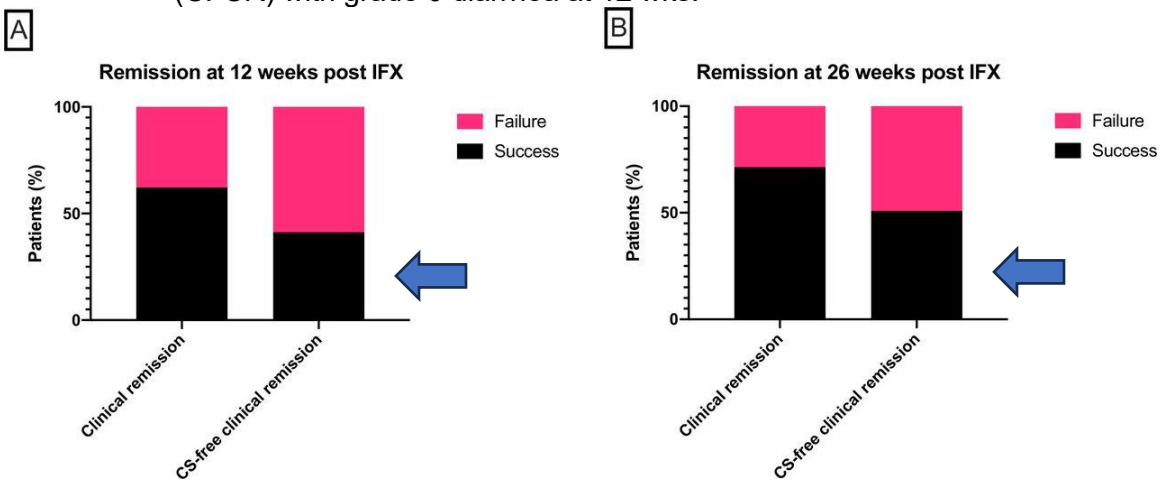
  - Recommended as first-line therapy.
    - Given in doses of 0.5-2 mg/kg prednisone equivalent daily.
    - Taper of 4-6 wks.
  - In patients with grade 2 symptoms or higher, ICI should be withheld.

Food and Drug Administration. 2011. Highlights of prescribing information; p. 1–20.

- Infliximab
  - Associated with faster symptom resolution compared with corticosteroids alone for management of immune-related enterocolitis

Johnson DH, et al. J ImmunoTher Cancer 2018, 6(1): 103.

- Superior endoscopic improvement
- Corticosteroids-free remission, clinically and histopathological
  - Retrospective cohort study
    - 127 patients, primary outcome was corticosteroid free clinical remission (CFCR) with grade 0 diarrhea at 12 wks.



(A) The proportion of patients achieving clinical remission (left bar; n=74; 62.2%) and corticosteroids (CS)-free clinical remission (right bar; n=49; n=49, 41.2%) at 12 wk after starting infliximab (IFX). (B) The proportion of patients achieving clinical remission (left bar; n=75; 71.4% and CS-free clinical remission (right bar; n=54; 50.9%) at 26 wk after starting IFX.

Source: Alexander JL, et al. J ImmunoTher Cancer. 2021; 9: e002742 (Figure 2)

Baseline Features at IFX initiation and association with corticosteroids-free clinical remission after 12 wks of IFX in multivariable logistic regression

Feature	ORs	95% CI	P value
Male gender	0.69	0.29 to 1.63	0.40
Age	1.00	0.97 to 1.04	0.83
Rectal bleeding	0.19	0.04 to 0.80	0.03*
CTCAE grade for diarrhea	1.88	0.99 to 3.71	0.06
Ulcers on lower GI endoscopy	0.66	0.25 to 1.70	0.40
Combination CPI therapy	1.10	0.46 to 2.66	0.83
Lymphocytic infiltrate	0.83	0.31 to 2.16	0.70
Crypt abscesses	2.93	1.13 to 8.05	0.03*
Apoptosis	0.83	0.28 to 2.35	0.72
Chronic active inflammation	0.82	0.35 to 1.95	0.66

Significant factors with OR<1 or >1 predicted IFX resistance or IFX responsiveness, respectively.
*Statistical significance is indicated by <0.05.
CPI, checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; IFX, infliximab.

Source: Alexander JL, et al. J ImmunoTher Cancer. 2021; 9: e002742 (Table 3)

- Vedolizumab (VEDO)
    - VEDO vs. IFX
        - Multicenter, retrospective cohort study with a total of 184 patients (62 Vedolizumab, 94 Infliximab, 28 both).
            - Achieving remission was similar (89% vs 88%, P=0.79).
            - Vedolizumab group had:
                - Shorter steroid exposure (35 vs 50 days, P<0.001)
                - Less hospitalization (16% vs 28%, P=0.005)
                - Shorter hospital stay (median 10.5 vs 13.5 days, P=0.043)
                - Longer time to clinical response (17.5 vs 13 days, P=0.012)
        - Clinical remission achieved in 95% of patient who didn't receive IFX. (18/19)
        - Clinical remission achieved in 67% of patients who failed IFX. (6/9)

Source: Abu-Sbeih H, et al. J ImmunoTher Cancer; 2018: 6(1).

    - IFX Failures
        - Identified 7 patients with steroid refractory/dependent ICI colitis.
        - One patient received IFX and failed.
        - Steroid-free clinical remission with calprotectin normalization in 85% of patients. (6/7)

Source: Bergqvist V, et al. Cancer Immunol ImmunoTher 2017; 66(5): 581-592.

- Fecal Microbiota Transplantation
  - Patients with ICI induced colitis, refractory to immunosuppressants
  - Patients with symptom improvement after FMT – no (~73%)
    - Median days from FMT to symptom improvements (IQR) – 10 (7-14)
  - Mortality – no (~27%)

Source: Wang Y, et al. Am J Gastroenterol 2020; 115: S68.

- Calcineurin inhibitors

Parameters	Numbers
Median time to	
− Colon in weeks (SD)	4.43 (± 19.53)
− Checkpoint inhibitors to colitis (SD	2 (± 2.07)
− Symptom onset to infliximab in days (SD)	22 (± 55.07)
− First infliximab infusion to calcineurin inhibitor or third-line therapy in days (SD)	33 (± 28.01)
− Colitis to calcineurin inhibitor or third-line therapy in days (SD)	70 (± 66.06)
Bactrim prophylaxis (%)	11 (100%)
Median duration of follow up in days (range)	126 (± 161.23)
− Response of colitis with calcineurin inhibitor	9 (81.8%)
− Duration of calcineurin inhibitor in those who achieved remission in days (SD)	54 (± 28.96)

Abbreviation: SD, standard deviation

Source: Zhang E, et al. JGH Open 2021; 5(5): 558-562.

- Tofacitinib
  - Case series of 4 patients.
    - Three of four patients received IFX with no improvement.
    - One patient received steroids, IFX, Vedolizumab, and Ustekinumab before receiving Tofacitinib.
    - All patients had clinical remission on tofacitinib

Source: Bishu S, et al. Gastroenterology 2021; 160(3): 932-934.e3.

- Summary
  - Immune checkpoint inhibitors have become the standard of care for many cancers, and their uses and indications are growing fast.
  - GI toxicities from ICI are of the most common toxicities and cause of morbidity and interruption of cancer therapy.
  - Diagnosis of ICI enterocolitis needs careful history and examination and investigations to rule out other causes of diarrhea or abdominal pain.
  - Following a management algorithm that follow CTCAE severity grade have shown good results.
  - Corticosteroids therapy has been the first-line therapy for almost all irAEs with ICI and have shown good results with GI toxicities.
  - Infliximab have been used the most as a second-line therapy. More studies are needed for the doses and numbers.
  - Vedolizumab have shown good initial results as a second-line therapy.
  - Calcineurin inhibitors, Tofacitinib, and Fecal Microbiota Transplantation have low quality data with good results.
    - More studies need to be done.

Pathophysiology of Crohn Disease

Vadim Iablokov

- Etiology
  - Unknown
- Background Characteristics
  - Higher incidence of CD than ulcerative colitis (UC)
  - Affects intestinal tract from mouth to rectum
    - Skip lesions
    - Chronic, relapsing transmural inflammation
    - Abdominal pain, diarrhea
  - Half-develop strictures or fistulas within 10 yr
    - Require surgery within 20 yrs
- Pathophysiology
- Genetics
  - Family history
    - With a first-degree relative ↑ IBD RR 8-10x
    - Eastern European (Ashkenazi) Jews 2-4x ↑risk of developing IBD
    - Monozygotic twins' concordance rate
      - ↑ 30% for CD
      - ↑ 15% for UC
  - Multiple genes involved
    - No one gene confers risk
    - Each increases risk very modestly (OR 1.1-1.2)
    - Does **not** explain entire variation in risk

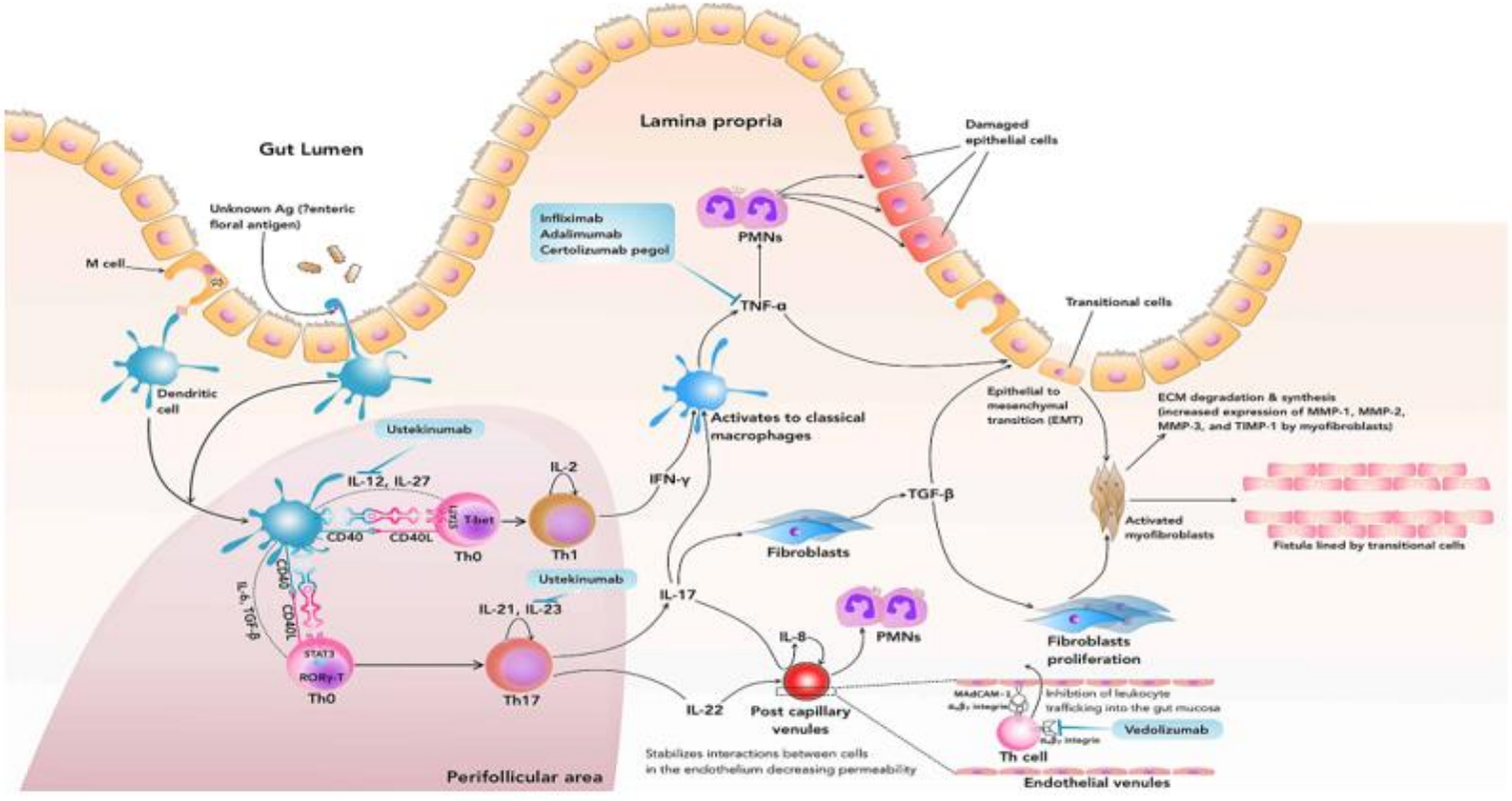
Roda G, et al. Nat Rev Dis Primers 2020; 6(1): 22.

  - 70% risk loci shared with other immune-mediated disorders, e.g.
    - Diabetes mellitus type 1 (DM1), celiac, rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis
  - Important pathways
    - Autophagy
    - Epithelial barrier
    - T-cell signaling/responses

Liu JZ, et al. Nat Genet 2015; 47(9): 979-986.

  - Overly aggressive T-cell mediated immune responses
    - Most drugs work here
  - Innate immunity
    - Epithelial cells
    - Macrophages/monocytes
    - Neutrophils
    - Dendritic cell
  - Adaptive immunity
    - CD4+ helper T cells
    - CD8+ Killer T cells
    - B-cells

Immunopathogenesis of Crohn Disease and Fistula Formation and the Development of Novel Target Immune Therapies (Biologicals) Affecting the Pathway



Abbreviations: Ag, antigen; CD, cluster of differentiation; IFN, Interferon; IL, interleukin; MAdCAM, mucosal addressin cell adhesion molecule; MMPs, matrix metalloproteinases; PMNs, polymorphonuclear leukocytes; RORγ, RAR-related orphan receptor gamma (a member of the nuclear receptor family of transcription factors); STAT, signal transducer and activator of transcription (a transcription factor); T-bet, (T-box expressed in T cells, a T-box transcription factor); TGF, transforming growth factor; Th, T helper cells; TIMPs, tissue inhibitors of matrix metalloproteinases; TNF, tumour necrosis factor

Source: Feroz S, et al. Cureus 2020; 12(12): e11882 (Figure 1)

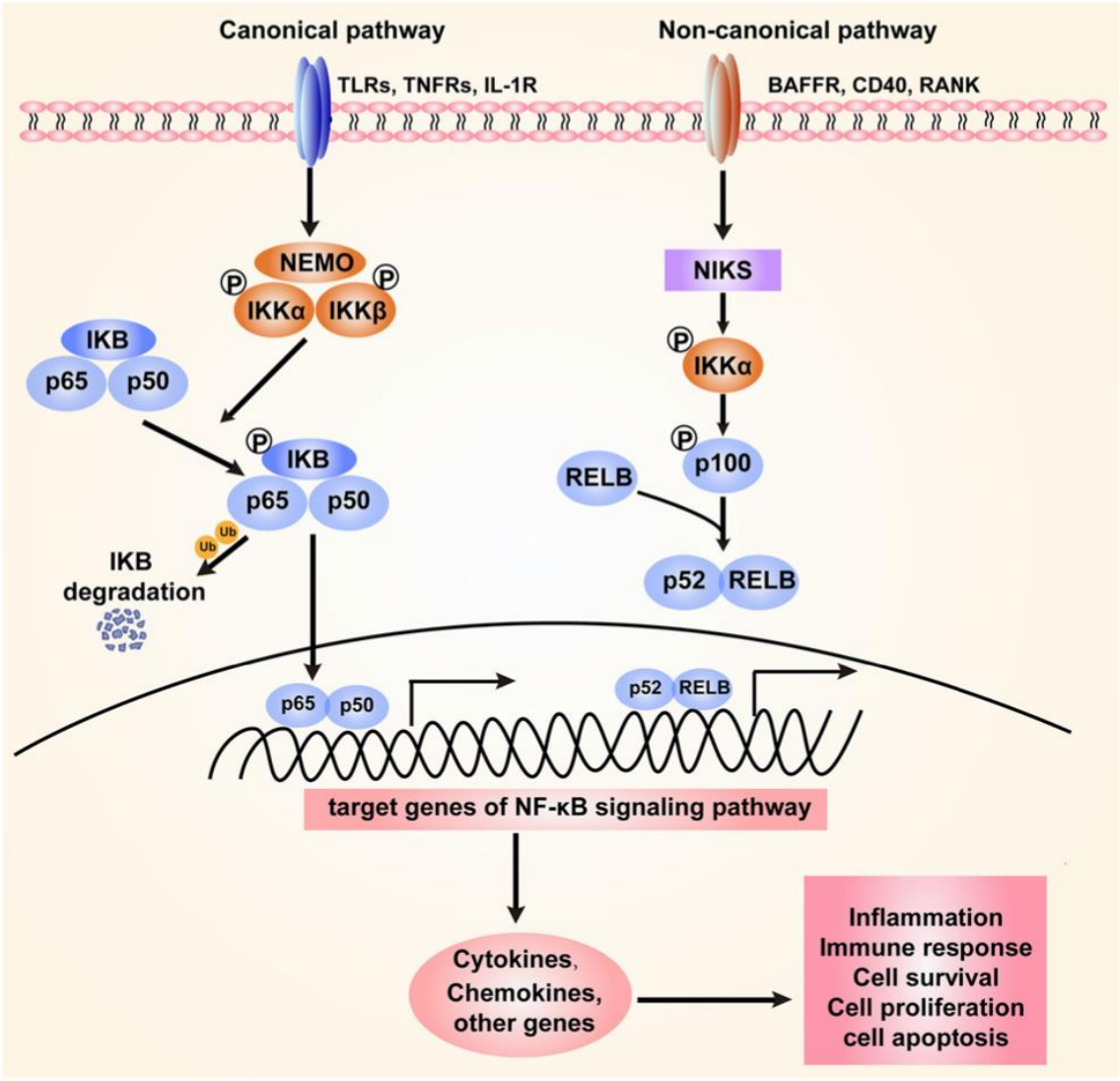
- Genome-wide association studies (2012)
  - Meta-analysis of 15 studies
    - 75,000 cases of CD, UC and controls of European decent
  - Compare SNP frequency in IBD vs controls and see if they're different
  - 163 common genetic variants/loci found
    - 110 contribute to both IBD subtypes (IL23R, MUC19, JAK2)
    - 30 specific to CD (NOD2 and ATG16L1)
  - Loci explain only ~14% of variance in disease risk
    - Rarer loci may exist conferring more risk

Jostins L, et al. Nature. 2012; 491(7422): 119-24.

- Genome-wide association studies (2015)
  - Meta-analysis of genetic studies in 2015 added to previous work
    - 86,640 Europeans
    - 9,846 East Asian, Indian and Iranian decent
  - Added 38 new loci that contributed to IBD risk
    - 7 specific to CD
    - Asian NOD mutations different, ATG16L1 not associated with CD
  - Now 201 loci are known
    - 37 total for CD
    - 13% in disease risk of CD

Liu JZ, et al. Nat Genet 2015; 47(9): 979-986.

- NOD2
  - Nucleotide-binding oligomerization domain containing 2 gene (NOD2)
  - Homozygous disease-associated mutations = RR 38 for CD
  - Cytosolic protein that senses bacteria
    - Binds muramyl dipeptide (MDP) component of peptidoglycan cell wall
    - Activates NF-kB → TNF
    - ↑ NF-kB signaling in CD



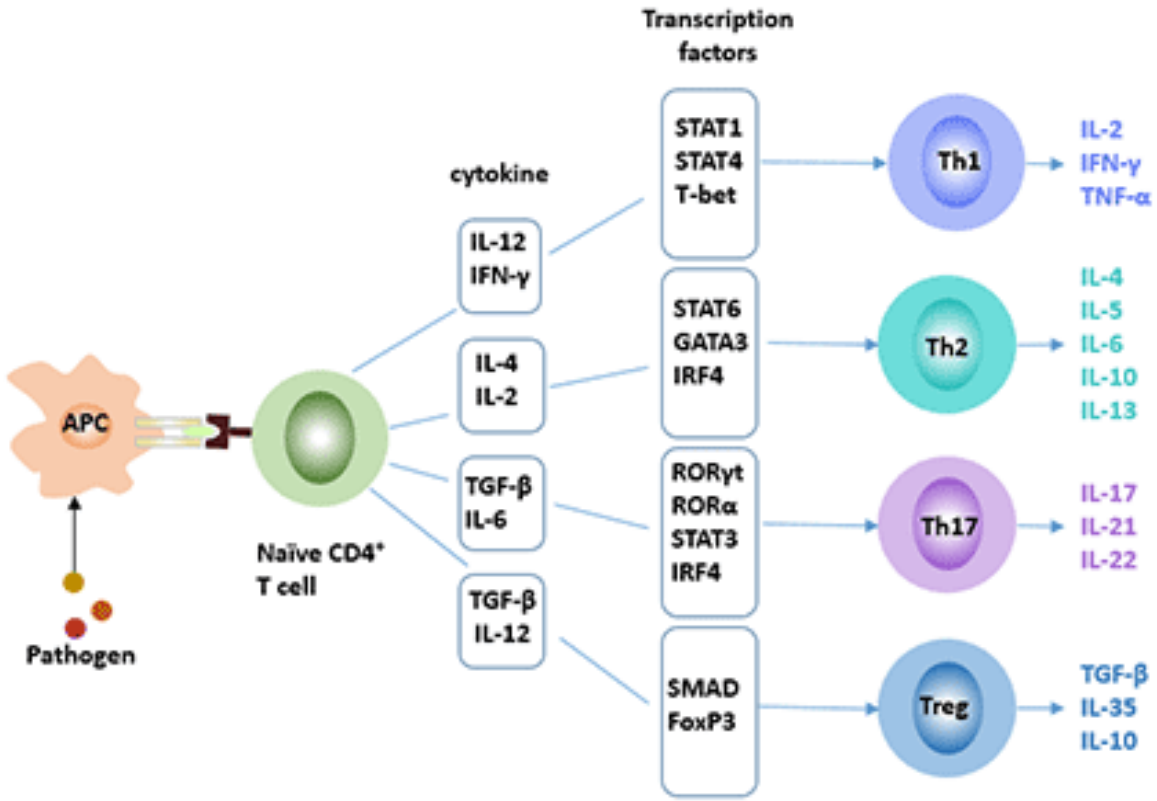
Source: Peng C, et al. Front Immunol. 2020; 11:1387 (Figure1)

- Autophagy
  - Highly conserved mechanism to clear cytoplasmic proteins
    - Long lived
    - Misfolded
    - Aggregated
    - Apoptotic bodies
  - Cytoplasm is isolated within a membrane and delivered to lysosomes
    - Directly kills pathogens (macrophages, epithelial cells)
    - Activates Toll-like and NOD-like receptor pathways → ↑ NFκB
    - ↑ inflammatory cytokines (IFN-y, IL-1b) in macrophages
    - Delivers antigens to HLA class II molecules in APCs

Kuballa P, et al. Annu Rev Immunol. 2012; 30: 611-46.

  - Autophagy Loci
    - ATG16L1 (Autophagy-related 16-like 1 gene)
      - Required for formation of autophagosome
      - Mutation → to ↓ autophagy
      - ↓ Paneth cells
    - IRGM (immunity-related GTPase family member M)
      - CD mutations alter expression
      - Important in resistance to intracellular pathogens (mycobacteria, Listeria, monocytogenes, toxoplasma gondii)

- IL-23R
  - IL-23 composed of p19 and p40 subunits
    - p40 shared with IL-12 (ustekinumab)
    - Produced by dendritic cells and macrophages in response to bacteria
  - Naive CD4 helper T-cells upregulate IL-23R in response to IL-6 and TGF-B
    - Become Th17 cells that clear extracellular bacteria and fungi
    - IL23 promotes stabilization and proliferation of Th17 cells
    - Signaling through JAK/STAT pathway (tofacitinib)
  - Overexpression of IL23R in CD
  - Rare mutations in IL23R predictive for CD



Source: Cusabio technical resource, http://www.cusabio.com/c-20858.html

- Environmental factors
  - Incidence of IBD mirrors urbanization
    - Agricultural -> manufacturing
    - ↑ population density
    - Changed diet and lifestyle
  - Incidence exploded from 1950's in wealthy westernized countries
    - Now incidence stabilizing in west
  - Cases of IBD began to emerge in Asia at the turn of the 21st century
    - Mirrors "westernization" of culture
    - Incidence rates like those of Western countries in 1970s
  - Increasing cases in Middle East, Africa and South America
  - Migration from low-prevalence to high prevalence = increased risk of CD

- Cigarette smoking
  - 2x↑ risk in Western CD
  - Not European or Asian
  - Associated with worse disease phenotype
- Antibiotic use in childhood
  - ↑ risk in Western countries
  - ↓ risk in Eastern Asian countries
- Breastfeeding
  - Protective against IBD in dose-dependent manner
- ↑ vitamin D levels → ↓ CD risk
- Tea/coffee ↓ risk of IBD among Asians
- ASA and NSAIDs ↑ risk of CD
- Oral contraceptives ↑risk for CD

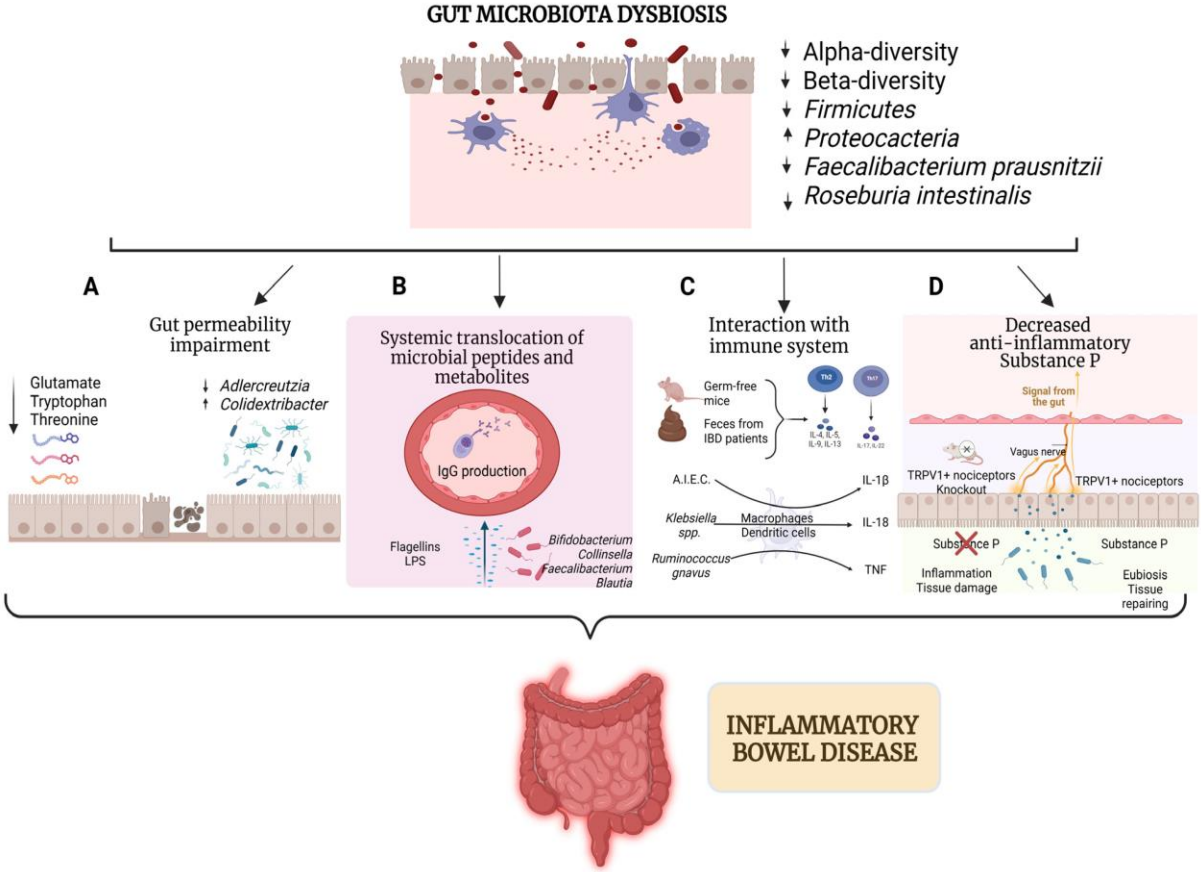
Kaplan GG and Ng SC. Gastroenterology. 2017; 152(2): 313-321.e2.
Wills-Karp M, et al. Nat Rev Immunol. 2001; 1(1): 69-75.

- Diet
  - Transition from rural to urban
    - ↑ food abundance
    - Packaged fast food
    - ↑ consumption of fat, refined sugar and processed food
    - Use of antibiotics in people and livestock
  - Dietary fiber ↓ risk of CD
    - 170,776 US female nurses followed up over 26 yr, self-administered questionnaire
    - 24 g/day of fiber ↓ risk of CD by 40%
    - Mainly fruit but not whole grain or legume fiber
  - Animal protein ↑ risk of CD
    - 67,581 women in France age 40-65, self-administered questionnaire
    - 2.1 g/kg protein associated with a 3X↑ risk of CD over 10 yr
    - Meat and fish, not eggs or dairy

Ananthakrishnan AN, et al. Gastroenterology. 2013; 145(5): 970-7.
Kaplan GG and Ng SC. Gastroenterology. 2017; 152(2): 313-321.e2.
Jantchou P, et al. Am J Gastroenterol. 2010; 105(10): 2195-201.

- Microbiome
  - Early microbe exposure primes immune system
  - Having pets in childhood, larger family, drinking unpasteurized milk all lower CD risk
  - Antibiotic use alters microbiome
  - IBD is a state of sustained immune response
    - Appropriate response to unrecognized pathogen?
      - Inappropriate response to innocuous stimuli?
  - IBD occurs preferentially in portions of the bowel that have the highest bacterial concentration
  - Three CD patients underwent resection of terminal ileum with ileocolonic anastomosis
    - Temporary diverting loop ileostomy proximal to anastomosis
    - 3-6 mon diversion
    - Infused ileal effluent into distal limb QID for 8 days
    - Neo TI biopsies then displayed ↑ inflammation
      - Mononuclear cells, neutrophils, edema, villi blunting
  - Germ free mice or rats do **not** have intestinal inflammation
    - Rapidly develop inflammation after bacterial colonization
  - Patients with IBD have broad changes in microbiota
    - ↓ aggressive groups/ ↑ protective groups
  - ↓ microbiota diversity
    - Snacking,
    - Sugar sweetened soda
    - High-fat milk
    - Wine, coffee, tea associated with increased diversity
    - Antibiotics and filtered tap water
  - ↓ butyrate / ↓ SCFA producing species
    - Main energy source for colonocytes
    - ↑ small intestinal IEC proliferation
    - Promote epithelial barrier function
  - ↑ invasive E. coli

The impact of gut microbiota dysregulation on IBD pathogenesis.

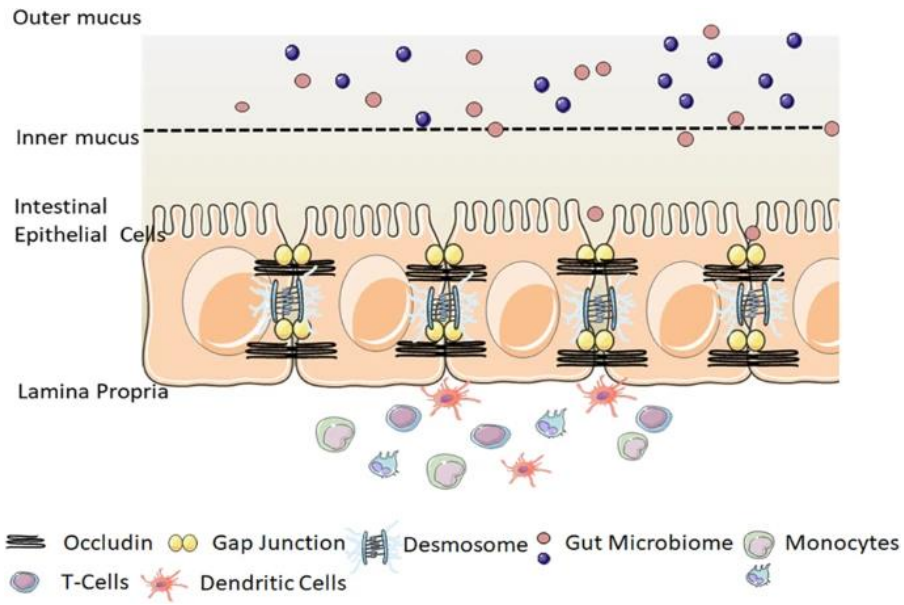


Reduced microbial diversity, depletion of beneficial taxa such as Faecalibacterium prausnitzii and Roseburia intestinalis, and enrichment of pathogenic taxa like Proteobacteria are the core features of gut dysbioisis. This disruption impairs gut permeability by reducing key amino acids and altering microbial composition, allowing microbial components to penetrate the intestinal barrier (**A**). Translocated microbial peptides and metabolites, such as flagellins and LPS, enter systemic circulation, triggering IgG production and amplifying inflammation (**B**). Immune system activation involves increased inflammatory cytokine production following exposure to microbial products, as observed in germ-free mice receiving fecal transplants from IBD patients. Pathogenic bacteria, including Klebsiella spp. and Ruminococcus gnavus, further stimulate macrophages and dendritic cells to release pro-inflammatory cytokines like IL-1β, IL-18, and TNF (**C**). Additionally, dysbiosis disrupts TRPV1$^+$ nociceptor signaling, reducing levels of the anti-inflammatory mediator Substance P. This impairment compromises vagus nerve-mediated tissue repair, enhances inflammation, and deranges pain perception (**D**).

Source: Calvez V, et al. Biomedicines 2025; 13(2):305 (Figure 2)

- Epithelial Barrier
  - First line of defense of mucosal immune system
  - Physical barrier with
    - Adhesion proteins and mucin
    - Tight junctions, adherens junctions, desmosomes
    - Disruption of AJ in mice leads to inflammation resembling CD
    - Mouse models of IBD work by disrupting the epithelial barrier (DSS, acetic acid)
    - Interepithelial cells (IECs) express class II MHC antigens → act as antigen-presenting cells (APCs)
  - Small intestinal Paneth cells produce defensins
    - Antimicrobial activity
    - CD patients with ileal disease express less α-defensin

Wehkamp J, et al. Proc Natl Acad Sci U S A. 2005; 102(50):18129-34.
Hermiston ML and Gordon JI. Science 1995; 270(5239):1203-7.

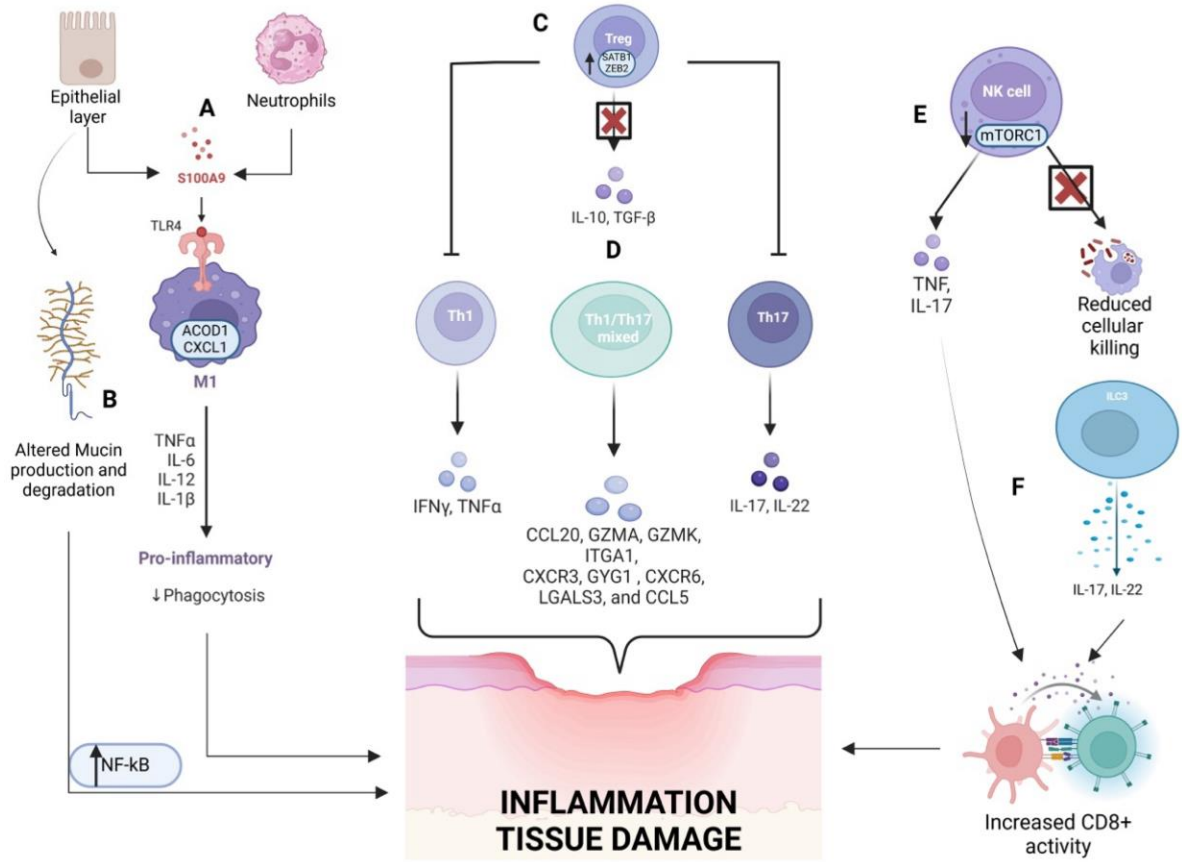


Epithelial cells form a layer that functions as a physical barrier facilitated by tight connections between each cell. A number of tight junction protein components seal the paracellular pathway and conduct gate and fence functions. The mucosal layer is a chemical barrier that is critical to limit the contact between the microbiome and epithelial cells. Immune cells are also a major participant in the immune response and the tolerance of the host against external substances. The graphical illustration was drawn by using the images from Servier Medical Art by Servier, with slight modifications

Source: Chelakkot C, et al. Exp Mol Med. 2018; 50(8):1-9 (Figure 1)

❖ Immune dysregulation

Dysregulated immune responses contributing to inflammation and tissue damage in IBD pathogenesis.



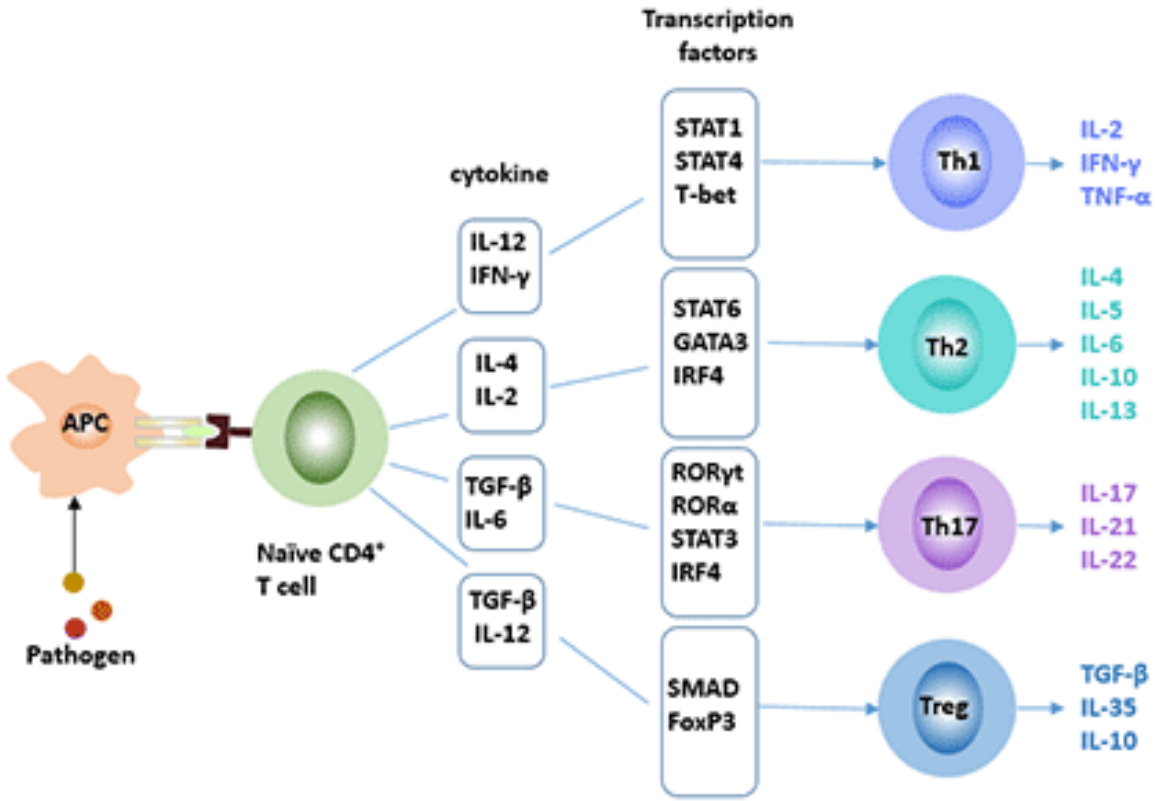
Epithelial barrier disruption and neutrophil recruitment trigger the release of S100A9, which activates Toll-like receptor 4 (TLR4) signaling in M1 macrophages. These macrophages produce pro-inflammatory cytokines (TNFα, IL-6, IL-12, IL-1β), promoting inflammation and reducing phagocytosis (**A**). Altered production and glycosylation of mucin molecules contribute to amplify inflammation via NFkB (**B**). Dysregulated T-cell responses include reduced regulatory T cell (Treg) activity (**C**) and increased Th1, Th17, and mixed Th1/Th17 responses, producing IFNγ, TNFα, IL-17, and IL-22. These cytokines induce recruitment of inflammatory cells and expression of chemokines (CCL20, GZMA, ITGA1, etc.), amplifying tissue damage (**D**). NK cells with impaired mTORC1 signaling show reduced cytotoxicity, further aggravating inflammation (**E**). Innate lymphoid cells (ILC3) produce IL-17 and IL-22, enhancing $CD8^+$ T cell activation and exacerbating tissue injury (**F**).

Source: Calvez V, et al. Biomedicines 2025; 13(2):305 (Figure 2)

- Immune tolerance is a normal state of the intestine
  - IECs produce TGFB stimulating dendritic cells, which produce IL-10
  - Anti-inflammatory / TGF-β Treg cells
- Antigen
  - Dendritic cells express TLR2 and TLR4
    - Extracellular bacterial products stimulate cytokine production
  - Intracellular bacterial products stimulate NOD2 pathway → ↑ cytokine production
- APC process antigens within autophagosome
  - Epithelial cells, dendritic cells, macrophages
  - Display antigen on MHC class II
  - Activates NFκB pathway
    - ↑ transcription of IL-1, IL-6, IL-8, TNF
    - ↑ immune cell
      - Proliferation
      - Activation
      - T-cell homing

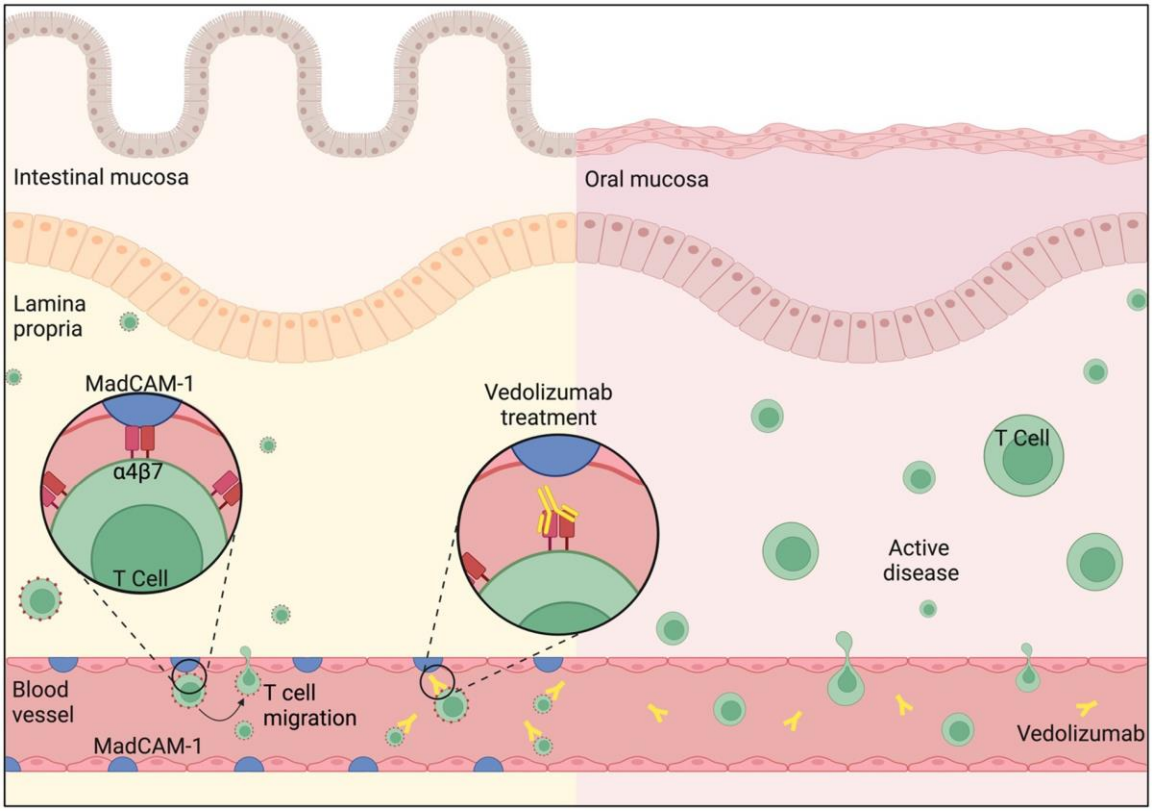
Abraham C and Medzhitov R. Gastroenterology. 2011; 140(6): 1729-37.

- Antigen presented to T-helper (Th) cells to induce differentiation
  - Co-stimulatory signal needed
  - Differentiation into Th1 (IL-12 + IFN-y) and Th17 cells (IL-6 + TGF-β)
  - Clear pathogens
- Crohn Disease
  - Unrestrained inflammation
  - ↓ bacterial clearance



Source: Cusabio technical resource, http://www.cusabio.com/c-20858.html

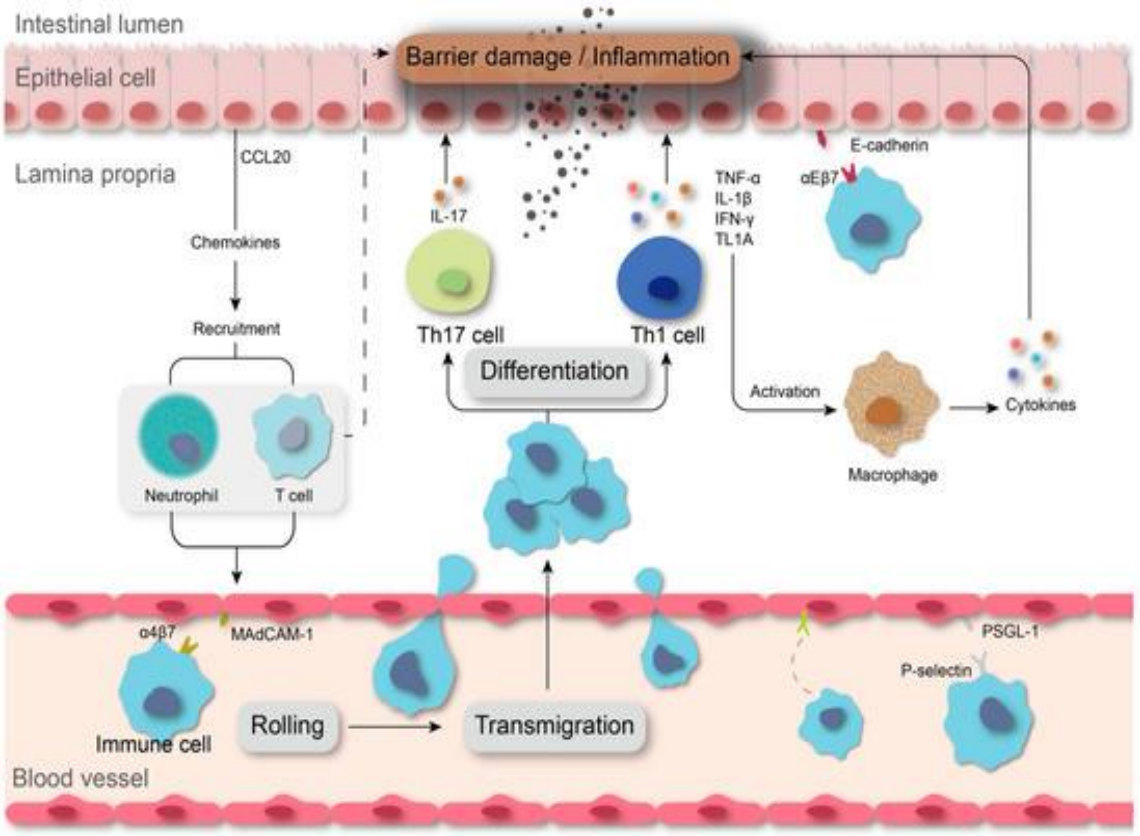
- Immune cell homing
  - T-cells become activated in gut-associated lymphoid tissue → recruited to sites of inflammation
  - Integrins on leukocytes →adhesion molecules on endothelial surface
    - A4B7 integrin gut specific
    - Blocked by vedolizumab
    - Also thought to block monocyte and dendritic cell homing to gut



Intestinal mucosa: MAdCAM-1 (Mucosal Addressin Cell Adhesion Molecule-1) is primarily expressed on the endothelial cells of blood vessels in the intestinal mucosal tissue and is upregulated in CD. It binds to 'Gut-homing T cells', a specialized subset of T cells found in the gastrointestinal tract, via integrin α4β7 on the T cell surface. This binding mediates the adhesion and migration of T cells to sites of inflammation in the gut, triggering the Inflammatory cascade. Vedolizumab binds selectively to the α4β7 integrin, blocking its interaction with MAdCAM-1, and thereby preventing T cell translocation from the blood into inflamed intestinal mucosa. Oral Mucosa: MAdCAM-1 is not expressed in the oral mucosa. T cell trafficking and retention primarily relies on alternative adhesion molecules and chemokine receptors which drives disease activity in CD. Therefore, Vedolizumab does not prohibit T cell migration in the oral mucosal tissue.

Source: Harte M, et al. Front Med (Lausanne). 2024; 11: 1485394 (Figure2)

Immune cell homing and cytokine storming drive IBD progression.

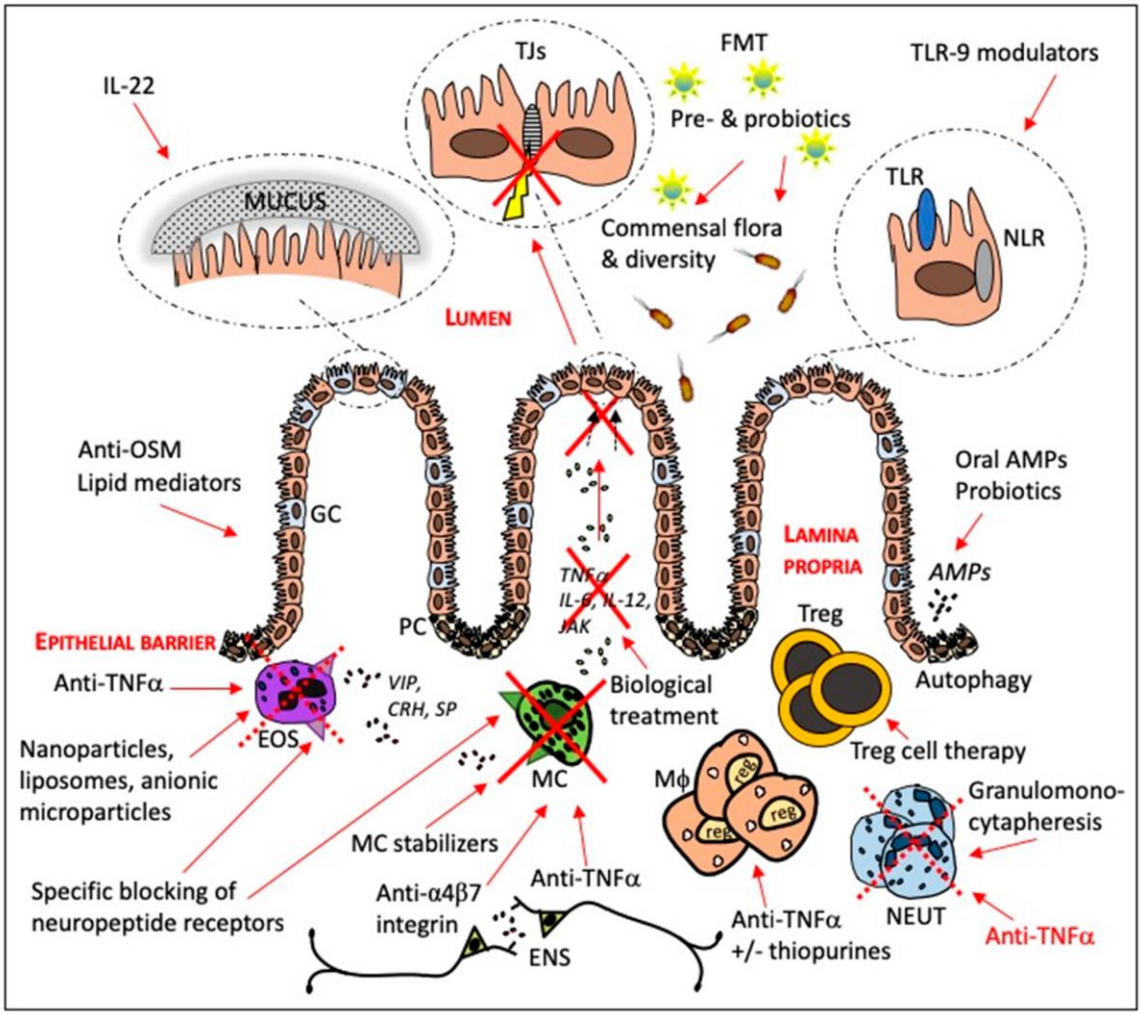


Lymphocytes roll, adhere, and transmigrate at the site of the lesion through the combined action of integrins, selections, and chemokines, with residence in the lamina propria. Excessive immune responses and external stimulus synergistically lead to a proinflammatory cytokine storm hindering disease recovery.

Source: Song Y, et al. Pharmaceuticals 2022; 15(9):1080 (Figure 1)

➢ Treatment

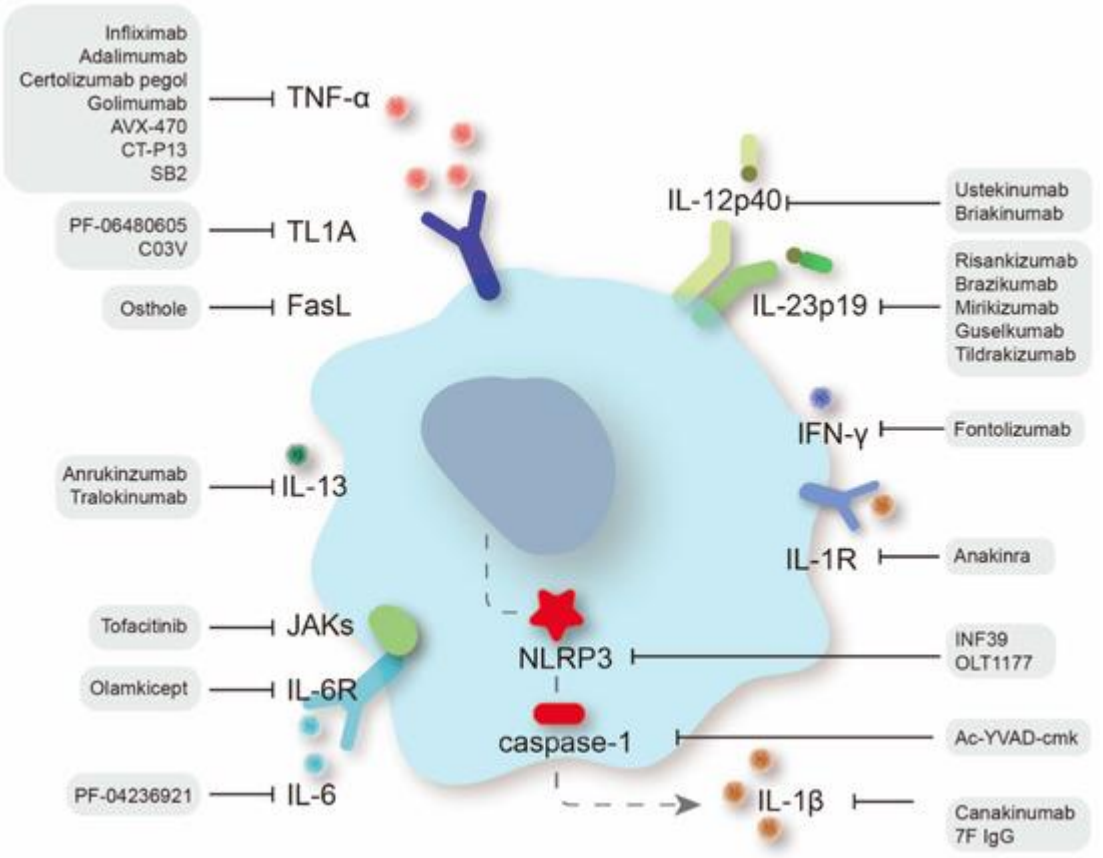
Current and potential therapies directed against targets to reduce inflammation and improve intestinal barrier function in patients with inflammatory bowel disease.



Abbreviations: AMPs, antimicrobial peptides; CRH, corticotrophin releasing hormone; ENS, enteric nervous system, EOS, eosinophil; FMT, fecal microbiota transplantation; GC, goblet cell; JAK, Janus kinases; Mϕ, macrophage; MC, mast cell; NEUT, neutrophil; NLR, nod-like receptor; OSM, oncostatin M; PC, Paneth cell; SP, substance P; TJs, tight junctions; TLR, toll-like receptor; Treg, regulatory T cell; VIP, vasoactive intestinal polypeptide

Source: Schoultz I and Keita ÅV. *Cells* 2019; 8(2): 193 (Figure 2)

Therapeutic targets of proinflammatory cytokines in IBD treatment and specific therapeutic agents



Source: Song Y, et al. Pharmaceuticals 2022; 15(9):1080 (Figure 2)

➢ Prognostic Factors

High risk factors for aggressive Crohn disease

- Patient features
  - < 40 yr at diagnosis
  - Polymorphisms in NDO2, ATG16L1
  - Smoking
- Disease features
  - Perianal disease
  - Stricturing disease
  - Upper gastrointestinal tract (esophagus, stomach, duodenum, and jejunum)
- Disease burden
  - Location
  - Duration
- Treatment
  - Need for corticosteroids on the first flare-up
  - Lack of mucosal healing after induction of clinical remission
- Endoscopy
  - Appears for example the presence of deep ulcers
  - Epithelioid granulomas
- Laboratory markers
  - ↑ serum
    - C-reactive protein
    - Anti-Saccharomyces cerevisiae antibodies
  - ↑ fecal
    - Calprotectin
  - ↓ serum
    - Albumin
    - Hemoglobin

Roda G, et al. Nat Rev Dis Primers 2020; 6(1): 22.

Irritable Bowel Syndrome

Ziad Hindi

- Definition
  - Abdominal pain associated with disturbed defecation
    - Not defined by a single symptom alone
      - It should not be diagnosed in the absence of abdominal pain
  - The abdominal pain may be poorly localized, intermittent, may be aggravated by eating or stressful life events
  - If the abdominal pain not likely to be related to IBS if related to physical activity, continuous
    - Menstruation
    - Urination
    - Unrelated to defecation
  - Chronic condition
    - Symptoms should be present ≥ 6 mon
  - Up to 33% of patients with celiac disease (on gluten-free diet) and up to 40% of patients with IBD may have IBS
  - Be wary of transient bowel symptoms that are acute or subacute due to
    - Pregnancy
    - Dietary indiscretion
    - Food poisoning
    - Travelers' diarrhea
    - Bed rest
    - Weight loss, and
    - Acute stress (nervous diarrhea)

- Rome IV Criteria
  - Recurrent abdominal pain ≥ 1 day/wk in the last 3 mon associated with ≥ 2 of the following:
    - Related to defecation
    - Associated with a change in frequency of stool
    - Associated with a change in form (appearance) of stool
  - Performance characteristics
    - Sensitivity, 63%
    - Specificity, 97%

- Subtypes (3 subtypes, a patient's subtype may change along their disease course)
  - Constipation Predominant (IBS-C)
  - Diarrhea Predominant (IBS-D)
  - Mixed (IBS-M/CD)

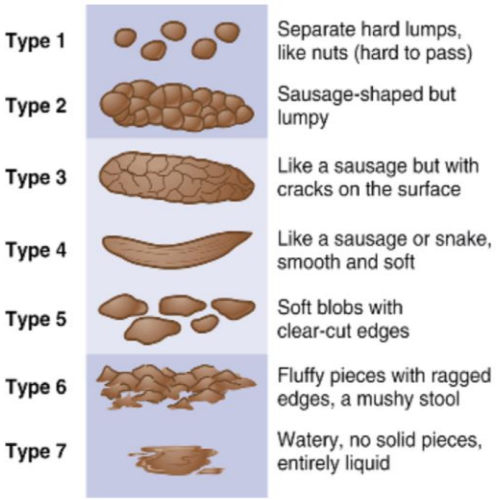
- Care should be taken on the patient's definition of constipation or diarrhea as these have different meanings to different people

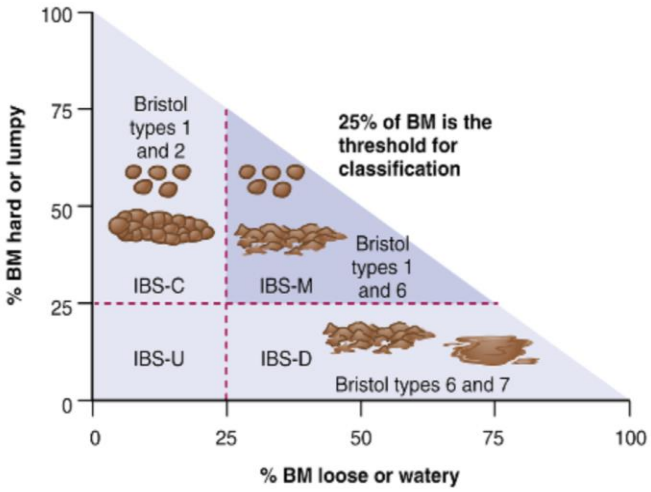
➢ Demography

- Prevalence – 1-45% worldwide
- Highly dependent on criteria used
- ↑ prevalence in older population
  - Can be present at any age
- Females>Males (OR 1.67 - 2012 Meta-analysis)
  - Men are more likely to report diarrhea, whereas women more likely to report constipation
  - Women vs men have
    - ↑ rectal sensitivity
    - ↓ colonic transit, and
    - ↓ stool outputs than men

➢ Clinical

Bristol Stool Chart





- Bloating, 60%
- Abdominal Distension
  - Characteristic, but less common than bloating
- Non-colonic Symptoms
- GERD, ↑ 4x
- Epigastric Discomfort, ↑ 8x

- Extraintestinal Symptoms
  - CNS
    - Headache
    - Impaired sleep
    - Chronic fatigue
    - Dizziness
  - CVS
    - Palpitations
  - MSK
    - Backache
    - Joint pains
  - GU
    - Dyspareunia
- ↓ quality of life
  - Does IBS cause reduction in QoL
  - Does ↓ QoL result in IBS? Maybe both?
- IBS can result in substantial costs
  - ↓ work
  - ↓ productivity
  - ↑ time for physician visits and cost to healthcare system/cost of testing
    - Medication use and cost

➢ Risk Factors

- Infectious gastroenteritis
  - 10% or more may develop IBS after an acute episode
  - Risk: Protozoan > bacterial > viral
- Female gender (RR 3.0)
- Pre-existing psychologic issues (anxiety, depression (RR 3.2), hypochondriasis (RR 2.0))
  - Adverse life events (RR 2.0)
  - Smoking (RR 4.8)
- Others
  - Affluent childhood environment
  - Previous antibiotic use
  - Food intolerance

➢ Pathophysiology

- Altered Motility
  - Diarrhea
    - Colonic / small bowel transit time are accelerated
    - ↑ high-amplitude propagated contractions
    - ↑ gastrocolic reflex
    - ↑ rectal hypersensitivity
  - Constipation
    - Colonic / small bowel transit time are delayed
    - ↑ segmental contractions (non-propulsive)
    - ↓ high amplitude propagated contractions
    - ↓ rectal sensation.
    - ↑ small intestinal motor stimulation than controls after
      - CCK infusion
      - A fatty meal, or
      - Ileal distention

- Visceral Hypersensitivity
  - Balloon distention of rectum → pain at lower volumes in those with IBS
  - Present in up to 60% of those with IBS

- Abnormal Gas Handling and Abdominal Accommodation
  - Intestinal gas → ↑ pain than controls
  - A paradoxical diaphragmatic contraction with gaseous distension (suggesting abnormal accommodation in distension)

- Low-Grade Mucosal Inflammation
  - Low-grade inflammation in the intestine
  - ↑ cytokines, ↑ mast cells potential effect on enteric nerve system (ENS)
  - Cytokines → active the intestinal immune system → ↑ gut permeability to luminal toxins

- Abnormal 5-hydroxytryptamine Metabolism
  - Normal
    - Pressure from meal → 5-HT secretion from enterochromaffin cells → activates intrinsic and extrinsic neurons → communicating with the CNS
    - Postulation → IBS-C → ↓ secretion of 5-HT
    - IBS-C / IBC-D → ↓ re-uptake of 5-HT

- Food Intolerance
  - Lactose-intolerance may mimic IBS
  - Gluten
    - Non-celiac gluten sensitivity
    - Celiac disease may be associated with IBS
    - Non-celiac gluten-sensitivity
  - Insoluble fiber
    - May ↑ symptoms of IBS
  - Fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) diet of benefit

- Abnormal Intestinal Microbiota
  - Modified intestinal microbiota in
    - Post-infection IBS
    - Non-infectious IBS
  - Study showed that 80% of patients with IBS have SIBO (lactulose hydrogen breath test)
    - Another study using intestinal-aspirates found no difference in prevalence of SIBO

- Abnormal Bile Acid Metabolism
  - ↑ total fecal bile acid levels with IBS-D
  - ↓ with IBS-C (compared with health controls)
  - A cause or an effect of rapid transit?

- Genetic Factors
  - Relatives of patients with IBS
    - ↑ 3x more likely to report symptoms congruent with IBS
  - Twin studies demonstrate a greater concordance of IBS in monozygotic than in dizygotic twins
  - No definitive genes identified

- Diagnosis
  - Alarm features non-IBS (organic cause of symptoms)
  - Colonoscopy not required to diagnose IBS
    - Both CAG and ACG recommend AGAINST colonoscopy in those without alarm features < 50 years old
    - If the patient is above 50, or with alarm features, very reasonable to undergo colonoscopy (Sleisenger)
      - CAG disagrees with this when described as ROUTINELY*
      - CAG notes to undergo colonoscopy with new IBS symptoms when aged 50 or older
  - If diarrhea is persistent, colonoscopy should be considered to assess for microscopic colitis (MC)
    - Predictors for UC
      - Recent new medication starts
        - Age > 50, and
        - Co-existent autoimmune disease
  - Serology, stool analysis, flexible sigmoidoscopy
    - RCT analyzed use of these costly tests in IBS patients and found no difference in QoL, symptoms, or patient satisfaction between those who were investigated and those who weren't
    - Serology for Celiac
      - Sleisenger - Not recommended; mixed evidence for testing for celiac disease
      - CAG and ACG – Recommend Serology
  - C Reactive Protein (CRP)?
    - <1% chance of IBS in individuals with symptoms suggestive of IBS with a CRP <0.5 mg/dL - same for fecal calprotectin < 40 ug/g.
      - CAG recommends against
      - ACG recommends for CRP and Fecal Calprotectin
  - Hydrogen Breath Test (lactose intolerance or SIBO), capsule endoscopy, small bowel imaging (not recommended – Sleisenger and CAG)
    - Not testing for Food allergies or sensitivities (CAG and ACG agree)

- Treatment

- Education and Support
  - Establish a strong physician-patient relationship
    - Associated with ↓ use of medical services

- Investigate the reason for referral
  - Stressors
  - Factors in diet
  - Changes in medications
  - Fear of serious disease
  - Impact on life
- Educate patients on the disease and reassure
  - Why is my pain occurring?
  - Why am I going to the bathroom so much / so little?

- Diet and Lifestyle
  - Fiber
    - Use soluble fiber (psyllium hydrophilic mucilloid)
      - CAG and ACG agree
    - Global benefit with NNT of 7
  - Insoluble fiber
    - No better than placebo for
      - Pain
      - Can benefit constipation
  - Fiber may induce bloating/gas and pain
    - Start at low dose
    - Titrate up slowly start at 6 g fiber (1 tablespoon) and up-titrate by 3 g/1-2 wks (1/2 tablespoon) to a goal of 10-15 g fiber per day (1.5-2.5 tablespoons of fiber/day).
  - Soluble fiber (NNT 7)
    - 74% (any individual AE)
    - No serious/life-threatening AEs have been reported
  - FODMAP Diet
    - Improves abdominal pain
    - Bloating
    - Stool frequency/consistency
    - Urgency (compared with a diet based on the NIH Excellence Guidelines)
    - Recommended eventual reintroduction of some foods
    - May have deleterious effects on microbiome, however (reversible)
    - Low FODMAP diet (NNT 4-5)
      - No AEs reported
      - Small trials only, some cross-over design; benefit over standard dietary advice is unclear
      - CAG and ACG both recommend a trial of low FODMAPs

Abbreviation: FODMAP, fermentable oligo-, di-, and monosaccharides and polyols;

- Gluten-Free Diet (in IBS patients without associated celiac disease)
  - 68% vs 40% control of symptoms compared to control arm in patients with IBS
  - ↑ intestinal permeability in patients with IBS when exposed to gluten
    - CAG does **not** recommend a Gluten free Diet
    - ACG does **not** comment

- Medication
  - Anticholinergics/Antispasmodics
    - Poor quality of data, but overall improved abdominal pain and global scale
      - CAG recommends for, while ACG recommends against
  - Promotility drugs
    - Prucalopride – 5-HT4 agonist
    - CAG recommends against in IBS-C
  - Laxatives
    - PEG (osmotic laxative) – improves stool frequency, with no difference on abdominal pain
      - CAG / ACG both recommend against (uncertain benefit)
  - Secretagogues
    - Lubiprostone (intestinal chloride channels), linaclotide/plecanatide (guanylate cyclase receptor agonist) → intestinal fluid secretion
    - Constella/Linaclotide – approved for IBS-C – at 290 µg once daily (can try lower dosing 145/72 µg)
      - CAG / ACG recommend
    - Tenapanor/Ibsrela – Na/H exchanger 3 inhibitor
      - ↓ sodium absorption / ↑ luminal water secretion and motility
      - 50 mg bid
  - Opioid Receptor agonists
    - Loperamide mu-opioid receptor agonist efficacious in RCTs in IBS-D
      - No improvement in abdominal pain or bloating
      - Dose 2-16 mg/day, best taken prophylactically rather than in response to symptoms
        - CAG recommends against *continuous* use, ACG no comment
    - Eluxadoline/Viberzi – agonist of delta, kappa and u opioid receptors
      - Approved for 75 or 100 mg BID for IBS-D, but no benefit for abdominal pain
      - A/E – Pancreatitis, Sphincter of Oddi dysfunction
        - Do **not** use in those with alcohol misuse or pancreaticobiliary disease
          - CAG and ACG recommend offering this

- 5-HT Receptor Antagonists
  - Alosetron/Tegaserod – IBS-D
    - A/E – ischemic colitis, severe constipation
      - ACG recommends, CAG no comment
  - Ondansetron/Ramosetron
- Antidepressants
  - Tri-cyclic antidepressants (TCAs) – efficacious in IBS for global symptoms and pain
    - Start at low dose and titrate
      - Desipramine/nortriptyline – 10-25 mg, and increase by 10-25 mg per week
      - Most benefit noted in IBS-D, as they can be constipating
      - A/E – dry mouth, drowsiness (take at night)
        - CAG and ACG recommend
  - SSRIs
    - Mixed report of benefit
      - CAG recommends against, ACG no comment
  - SNRIs
    - More studies needed
      - No comment by CAG or ACG
- Antibiotic
  - Rifaximin
    - Improved global symptoms and bloating in those with IBS-D
      - 550 mg TID x 2 wks/14 days
        - Expensive! No LU code, and still difficult to get through private insurance still.
    - Symptoms often recur 10 wks after therapy, but repeat courses are recommended.
      - CAG no comment, ACG recommends a trial
- Probiotics (NNT 7)
  - AE rate similar to placebo
    - Magnitude of the benefit and the most clinically appropriate strains are difficult to determine

Efficacy of Selected Pharmacologic Treatments for IBS

Pharmacological Treatment	Number Needed to Treat	Approximate Number Needed to Harm or AEs	Comments
IBS-C			
○ Chloride channel activators (lubiprostone)	13	NA	Up to 25% were reported to suffer nausea, no serious AEs Long-term data report less nausea than previously
○ Guanylate cyclase agonists (linaclotide and plecanatide)	7-14	20	Diarrhoea is the most common adverse event (~15% incidence).
○ Selective serotonin reuptake inhibitors	4	NA	None
IBS-D			
○ Rifaximin	11	8971	None
○ 5-HT3 receptor antagonists (alosetron, ondansetron)	8	19	Rare ischemic colitis with alosetron; use is currently restricted to women under a risk evaluation and mitigation strategy
○ Opioid receptor drugs (eluxadoline, loperamide)	7-15	NA	Rare reports of sphincter of Oddi dysfunction and pancreatitis with eluxadoline; not to be used in patients without gallbladder or those with alcohol dependence
○ Tricyclics Antidepressants	4	9	Most common AEs are dry mouth and drowsiness
○ Antispasmodics	5	17-18	Most common AEs are dry mouth, dizziness, and blurred vision Efficacy of anticholinergics is not established
○ Peppermint*	3	NA	AE rate is comparable to placebo

*CAG and ACG both recommend against

Adapted from Halland M, Talley NJ, Nat Rev Gastroenterol Hepatol 2012; 10:13–23)

Selected Emerging Pharmacologic Treatments for IBS

Drug Class	Example of Drug	Comments
○ Drugs Acting on Pain Receptors		
− Calcium channel inhibitors	Pregabalin and gabapentin	▪ ↑ pain scores ▪ ↑ rectal compliance ▪ ↑ thresholds for pain, discomfort, and bloating
○ Drugs Targeting Visceral Hypersensitivity		
− Serotonin synthesis inhibitors	LX1031	▪ Positive phase II trial data, including a favorable adverse event profile ▪ The effect is attenuated with time
− CCK-1 antagonists	Dexloxiglumide	▪ Satisfactory relief of symptoms is higher than with placebo in women with IBS-C
○ Drugs Targeting Motility		
− Neurokinin-2 receptor antagonists	Ibodutant	▪ Satisfactory relief of symptoms is higher than with placebo in women with IBS-C
− 5-HT4 agonists	Velusetrag, prucalopride, naronapride	▪ Prucalopride is effective in chronic constipation; data from trials in IBS patients are awaited
○ Drugs Targeting Inflammation		
− Mast cell stabilizers	Ketotifen and ebastine	▪ Promising data from 2 small RCTs
− 5-aminosalicylic acid	Mesalamine	▪ Well-designed trials in IBS patients showed no benefit
○ Drugs Acting on ion Channels		
− Sodium/hydrogen ion exchanger inhibitors	Tenapanor	▪ Higher responder rates in terms of an increase in stool frequency and an improvement in abdominal pain, relief of pain, bloating, and cramping ▪ Response rates are also significantly higher than with placebo in IBS-C

Drug Class	Example of Drug	Comments
○ Bile Acid Modulators		
− Bile acid sequestrants*	Colesevelam and colestipol	▪ Case reports of efficacy and limited trial data
− Bile acid transporter inhibito	Elobixibat	▪ Promising data from patients with chronic constipation
− Bile acid	Chenodeoxycholate	▪ Healthy volunteer data have demonstrated accelerated colonic transit

*CAG and ACG both recommend against

Adapted from Hutton and Talley, NJ. New treatment for IBS. Nat Rev Gastroenterol Hepatol 2012; 10: 13-23

- Psychologic Therapy
  - Psychotherapy, hypnotherapy, and cognitive behavioral therapy (CBT) are useful in the treatment of IBS
    - CAG and ACG recommend CBT and hypnotherapy
  - Unclear benefit of
    - Mindfulness meditation
    - Yoga
    - Stress management
  - Long-term benefit of these may outweigh costs
  - Hypnotherapy (NNT 4)
    - No reports of AEs in published RCTs
    - Several controlled trials in different settings and populations support long-term effectiveness

- Alternative Treatments
  - Benefit over placebo
    - STW-5/Iberogast - a combination of various plant extracts, including bitter candytuft, chamomile, peppermint, caraway fruit, licorice root, lemon balm leaves, celandine, angelica root, and milk thistle
      - CAG recommends against, ACG no comment
    - Chinese herbal medicines (7 or 20 herbs)
      - CAG recommends against, ACG no comment
    - Melatonin
    - Peppermint Oil
      - CAG and ACG recommend offering this

- Fecal Microbiota Transplant
  - RCT: 65.5 % response vs. 42.9 % (placebo) at 3 mon (p = 0.049), however this was not sustained at 12 mon
  - RCT (2019): Dose-dependent effect – 23.6 % response (control), 76.9 % response (30 g), and 89.1 % response (60 g) at 3 mon
    - ACG recommends against, CAG no comment

- No benefit
  - St. John's Wort
  - Exercise (NNT 6-7)
    - No AEs reported | Single RCT only; results are not statistically significant

➢ Prognosis

- No effect on mortality
- Over 10-13 yrs follow-up in one trial
  - 92% - symptoms did not resolve
  - 47% - undergone a repeat structural colonic evaluation to no avail
- Patients may have improvement of symptoms over time, but it can be a relapsing condition
- Poorer prognosis is indicated by the presence of
  - Excessive psychologic stress
  - Anxiety
  - Long duration of complaints

Suggested Reading:

Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 11th ed. Elsevier; 2020.

Lacy BE, Pimentel M, Brenner DM, et al. ACG clinical guideline: management of irritable bowel syndrome. Am J Gastroenterol. 2021;116(1):17-44.

Moayyedi P, Andrews CN, MacQueen G, et al. Canadian Association of Gastroenterology clinical practice guideline for the management of irritable bowel syndrome (IBS). J Can Assoc Gastroenterol. 2019;2(1):6-29.

HEPATOBILIARY

Classification of Focal Liver Lesions

Navneet Natt

- Classification
  - Solid
  - Cystic

  } – Benign / – Malignant

    - Benign
      - Solid
      - Cystic
    - Malignant
      - Solid
      - Cystic

- General cause of a
  - The clinical history may help to suggest the FLL< e.g.,
    - No liver disease, but use of OCAs
      - Hepatocellular adenoma (HCA)
    - Chronic liver disease with advanced fibrosis/cirrhosis
      - Hepatocellular cancer (HCC)
  - "Rule of thumb"
    - In the patient with advanced fibrosis/cirrhosis plus an ultrasound demonstrated FLL, always exclude possibility of HCC, always to CT or MRI with contract triple phase study
      - Late arterial
      - Portal venous
      - Delayed venous

      } Characteristic pattern highly suggests an HCC

❖ Benign Hepatic Tumour

• **Hepatocellular Adenoma** (HA)

- Demography
  - Incidence in women
    - On OCA, $34/10^6$
    - Not on OCA, $1/10^6$
  - ↑ incidence > 25 yr in patient with glycogen storage disease (GSD)

- Risk factors
  - GSD
    - IA, 22-75%
    - III, 25%

- Treatment
  - Continuous nocturnal feeding may
    - ↓ GSD tumour size
    - Surgical resection / liver transplantation
  - Exogenous estrogen (e.g. oral contraceptive pill [OCP])
    - Incidence $30/10^6$ OCP users vs. $1/10^6$ non-OCP users
    - Regression of adenomas seen with cessation of estrogen use
  - Anabolic steroids
- Obesity / metabolic syndrome
  - May ↑ progression of HA
  - Combination

➢ Clinical

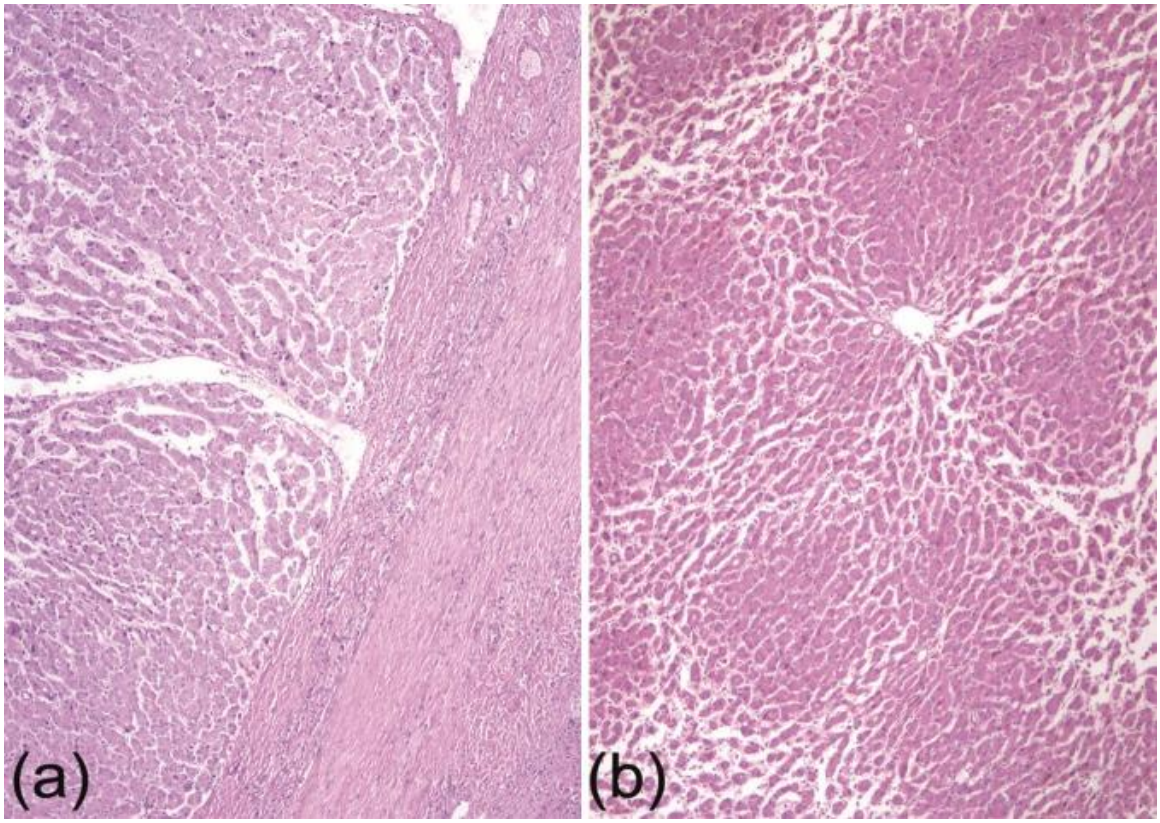
- Incidental
  - Asymptomatic / RUQ Discomfort
- Rare presentations
  - Malignant transformation to hepatocellular cancer (HCC)
    - Associated with Beta-catenin mutation / activation in
      - Men with adenomas and glycogen storage disease
  - Tumour rupture (11-29% risk)
    - Acute pain, shock, and hemoperitoneum
    - Seen when HA > 5 cm

➢ Diagnosis

- CT Liver
  - Well demarcated homogenous lesion, with
  - Peripheral enhancement
- MRI (enhanced with gadobenate dimeglumine)
  - Very effective to distinguish HA from other benign liver lesions (e.g. focal nodular hyperplasia [FNH])
  - Differentiates between subtypes of HA
    - Hepatic adenomatosis
    - Telangiectatic hepatocellular adenoma

➢ Histopathology (Liver biopsy)

- Indication inconclusive imaging due to risk of bleeding
- Solitary well-demarcated, light brown to yellow tumour
- No true capsule may form pseudocapsule from surrounding liver tissue



Source: Martinez-Mier G, et al. BMJ Case Rep 2013; bcr2013202111.

- Cords of normal looking hepatocytes
  - Bile ducts or portal tracts absent
  - Positive IHC staining with glutamine synthetase → diagnosis of Beta-Catenin-activated subtype

➢ Treatment

- < 5 cm
  - Discontinue OCP or anabolic steroids
  - CT surveillance q6mon x 2 yr, then annually if stable
- 5 cm
  - Surgical resection
  - If poor surgical candidate → Embolization

Acute HA

- ABCs
- Massive transfusion protocol
- Vasopressor support
- Achieve hemostasis through:
  - Packing of liver
  - Emergent hepatectomy
  - Hepatic artery embolization
  - Liver transplant (rare)
- Pregnancy
  - ↑ HA size during pregnancy
  - If tumour size
    - < 5 cm, pregnancy is not contraindicated
    - ≥ 5 cm, avoid pregnancy until lesion is resected

Recommendations

- Avoid oral contraceptives, hormone-containing intrauterine devices, and anabolic steroids in patients with HA (Strong recommendation, moderate quality of evidence).
- Indication for biopsy for cases in which imaging is inconclusive, and biopsy is deemed necessary to make treatment decisions (Strong recommendation, low quality of evidence).
- If HA < 5 cm in pregnant patient, take an individualized approach (Conditional recommendation, low quality of evidence).
- In hepatocellular adenomas ≥5 cm, treat surgically or non-surgically to ↓ risk of rupture and malignancy (Conditional recommendation, low quality of evidence).
- If no therapeutic intervention is pursued for lesions suspected of being HA, CT or MRI q6-12 mon.
  - The duration of monitoring is based on
    - The growth patterns and
    - Stability of the lesions over time

    (Conditional recommendation, low quality of evidence).

- **Cavernous Hemangioma** (CA)

➢ Definition
  - Vascular lesions that arise from congenital hamartomas

➢ Demography
  - Most common benign liver lesion (prevalence, 0.4-20%)
    - No malignant transformation
  - Present in ages 30-50 yr
  - F>>M

➢ Pathology
  - Most CA are small (<3cm) and asymptomatic
  - May ↑ size during pregnancy and OCP

➢ Clinical
  - When >5 cm
    - Abdominal pain
    - Palpable mass in epigastrium
    - Early satiety
    - Vomiting
    - Rare presentations
      - Kasabach-Merritt Syndrome: thrombocytopenia
      - Disseminated intravascular coagulopathy (DIC)
      - Spontaneous bleeding

Do **not** biopsy due to risk of severe bleeding!

➢ Diagnostic Imaging
  - Ultrasound
    - Echogenic mass, with
    - Uniform echodensity
  - Contrast-Enhanced CT
    - Hypodense centre
    - Peripheral enhancement with centripetal fill-in
  - MRI with contrast
    - Contrast takes on ring / C-shaped configuration of contrast → avascular centre (highly specific for diagnosis)

- Treatment
  - Conversative management
    - No need for surveillance imaging
  - Estrogen-containing medications and pregnancy are safe
  - For large symptomatic hemangiomas:
    - Surgical resection
    - Radiation
    - IR embolization

Recommendations

- Perform MRI or CT scan to confirm a diagnosis of hemangioma (Strong recommendation, moderate quality of evidence).
- If the radiologic features of a hemangioma are present do **not** do liver biopsy (Strong recommendation, low quality of evidence).
- Safe for pregnancy and the use of oral contraceptives or anabolic steroids (Conditional recommendation, low quality of evidence).
- If symptoms plus ↓ quality of life (QoL) refer for surgical or non-surgical therapeutic modalities by an experienced team (Conditional recommendation, low quality of evidence).

- **Focal Nodular Hyperplasia** (FNH)

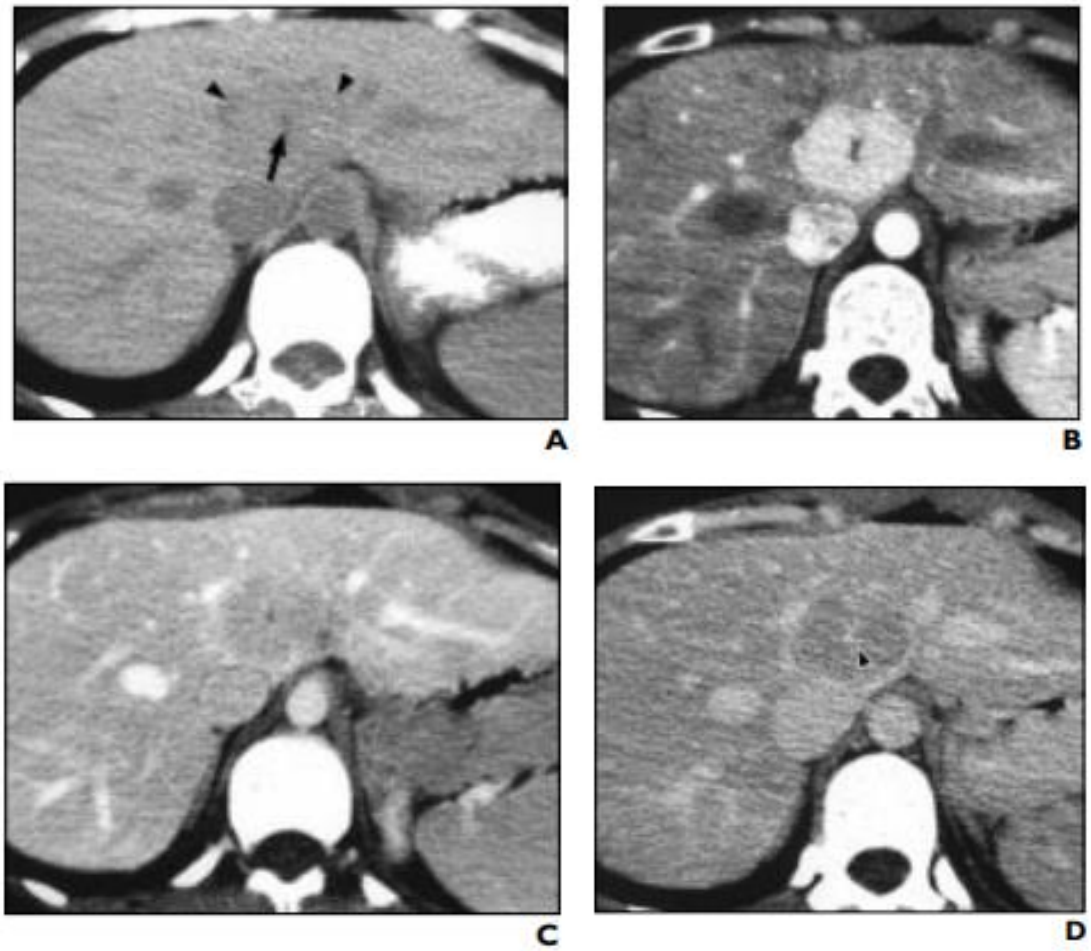
- Demography
  - Second most common liver lesion
    - Prevalence, 0.3-3%
  - Presents at ages 30-40s
  - F>M

- Pathology
  - Portal tract injury → AV shunts →↑ oxidative stress → stellate scar in solitary lesion

- Clinical
  - Usually asymptomatic
  - Rarely: pain from bleeding or necrosis of lesion, rupture, HCC

- Associations
  - Cavernous
    - Hemangioma
    - Transformation of the portal vein
  - Congenital absence of the portal vein
  - Epithelioid hemangioendothelioma
  - Hereditary hemorrhage telangiectasia (HHT, aka Osler-Weber-Rendu Syndrome)
  - Liver transplant (LT) (detection in graft)
  - Neonatal hepatic hemangioma
  - Spinal and pulmonary arteriovenous malformations
- Complications
  - Budd-Chiari syndrome (BCS)
  - Compression of the inferior vena cava (IVC)
- Laboratory
  - Alpha-fetoprotein (AFP) concentration normal
- Diagnostic Imaging
  - Diagnosed by US/CT if pathognomonic findings visualized
    - Contrast enhanced lesion with
      - Central spoke-wheel scar plus lack of enhancement
      - Feeding artery may be visualized
  - MRI with contrast
    - Most sensitive and specific imaging modality
    - Isointense lesion, relative to liver parenchyma
    - Early enhancement with central scar enhancement of delayed phase

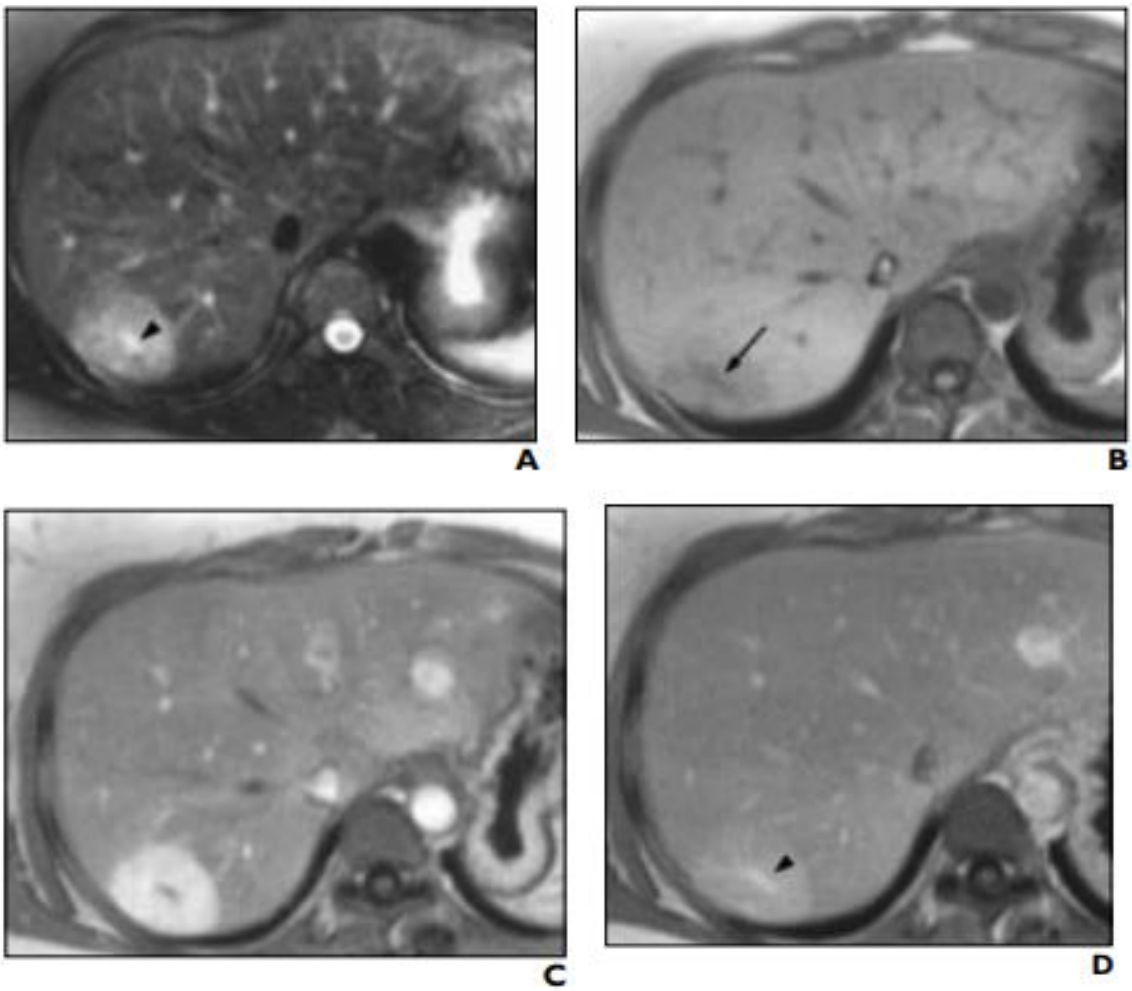
Typical CT Finding of Focal Nodular Hyperplasia in a 30-yr-old woman



A: Unenhanced CT scan shows a lesion in the left lobe of the liver (arrowheads), which is slightly hypodense to the remainder of the liver. Note three hypodense central scar (arrows).
B: Arterial contrast-enhanced CT scan shows strong homogeneous enhancement of the lesion, caused by arterial vascular supply. Note focal central area of low attenuation, representing central scar.
C: Contrast-enhanced CT scan during the portal venous phase shows persistent lesion slightly hypointense compared with surrounding liver because of reduced contrast material washout.
D: Delayed phase contrast-enhanced CT scan shows persistent enhancement of central scar (arrowheads).

Source: Mortelé KJ, et al. AJR Am J Roentgenol. 2000; 175(3):687-92 (Figure 2)

Typical MR Findings of Focal Nodular Hyperplasia in 28-yr-old woman.



A: Fat-suppressed T2-weighted turbo spin-echo MR image shows hyperintense lesion located in right lobe of liver. Hyperintense central scar is obvious (arrowhead).
B: T1-weighted fast low-angle shot (FLASH) image shows slightly hypointense lesion in surrounding parenchyma, with more hypointense central scar (arrow).
C: Dynamic study with IV bolus injection of gadopentetate dimeglumine using T1-weighted FLASH MR sequence. Twenty seconds after bolus injection, lesion is hyperintense to surrounding parenchyma, and central scar is slightly hypointense (arrowhead).
D: Contrast-enhanced T1-weighted MR image, obtained 4 min after injection in C, shows that lesion remains hyperintense to surrounding liver, but central scar is highly enhanced (arrowhead).

Source: Mortelé KJ, et al. AJR Am J Roentgenol. 2000; 175(3):687-92 (Figure 3)

- Treatment
  - If diagnosis is firmly established
    - No further follow-up
  - If diagnosis of FNH is uncertain
    - Radiofrequency ablation
    - Surgical resection
    - Embolization

Recommendations

- Perform an MRI or CT scan to confirm a diagnosis of FNH.
  - A liver biopsy is not routinely indicated to confirm the diagnosis (Strong recommendation, low quality of evidence).
- Pregnancy and the use of oral contraceptives or anabolic steroids are not contraindicated in patients with FNH (Conditional recommendation, low quality of evidence).
- Asymptomatic FNH
  - No intervention required (Strong recommendation, moderate quality of evidence).
- Annual US for 2–3 y in women with FNH who
  - Wish to continue OCP use
  - Are not using OCP
  - Do **not** require follow-up imaging

  (Conditional recommendation, low quality of evidence).

- **Nodular Regenerative Hyperplasia** (NRH)

- Definition
  - Nodularity without fibrosis
- Demography
  - Prevalence, 2-3% (~5% in persons >80 yr)
- Pathophysiology
  - Altered blood flow → ischemia → regenerative nodules

- Associations
  - Cardiac and pulmonary disorders
  - Drugs and toxins
  - Felty Syndrome
  - Rheumatoid Arthritis
- Diagnostic Imaging
  - Does **not** establish definitive diagnosis of NRH
- Histopathology
  - Liver biopsy
    - Necessary to make diagnosis
      - Nodules of regenerative hepatocytes
      - Curvilinear compression of the central lobule
      - No fibrous septa between nodules
- Treatment
  - Treat underlying condition

Recommendations

- Perform liver biopsy to confirm the diagnosis of NRH (Strong recommendation, moderate quality of evidence).
- Pregnancy and the use of oral contraceptives / anabolic steroids
  - Not contraindicated in patients with an NRH
  (Conditional recommendation, low quality of evidence).
- Asymptomatic NRH **no** intervention required (Conditional recommendation, low quality of evidence).
- Treat any underlying predisposing disease processes (Strong recommendation, low quality of evidence).

Summary of Diagnostic Imaging of Liver in Patients with Benign Solid Hepatic Tumours

Lesion	Findings		
	Ultrasound (US)	Computed Tomography (CT)	Magnetic Resonance Imaging (MRI)
○ HCA	− Heterogeneous − Hyperechoic if steatotic − Anechoic enter if hemorrhage	− Well-demarcated − Peripheral enhancement − Usually homogenous − Hypodense if steatotic − Hyperdense if hemorrhagic	− HNF1α signal lost on chemical shift ▪ Moderate arterial enhancement ▪ Without persistent enhancement during delayed phase − IHCA markedly hyperintense on T2 with stronger signal peripherally ▪ Persistent enhancement in delayed phase − B-catenin ▪ Inflammatory subtype has same appearance as IHCA ▪ Non-inflammatory is heterogenous with no signal dropout on chemical shift − Isointense of T1 and T2 with strong arterial enhancement and delayed washout
○ THCA	Variable appearance	Hypo-/isoechoic	− T1: Heterogeneous ▪ Well-defined iso-/hyperintense mass − Strongly hyperintense, with ▪ Persistent contrast enhancement in delayed phase
○ Hemangioma	Hyperechoic, with well-defined rim and few intratumoral vessels	− Discontinuous peripheral nodular enhancement − Isoattenuation to aorta with progressive centripetal fill-in	− T1: Hypointense ▪ Discontinuous peripheral enhancement, with ▪ Centripetal fill-in − T2: Hyperintense relative to spleen

Lesion	Findings		
	Ultrasound (US)	Computed Tomography (CT)	Magnetic Resonance Imaging (MRI)
○ FNH	Usually isoechoic	−Central scar −Arterial phase −Homogeneous hypodense lesion −Returns to precontrast density during portal phase that is iso-/hypodense	− T1: Iso-/slightly isointense ▪ Gadolinium: Early enhancement with central scar dark early, enhances in delayed phase − T2: slightly hypertense or isointense
○ NRH	Iso-/hyperechoic	− Non-enhancing nodules; sometimes peripheral enhancement	−T1: hyperintense −T2: varied intensity (hypo/iso/hyperintense)

Abbreviations: CT, computed tomography; FNH, Focal Nodular Hyperplasia; HCA, Hepatocellular Adenoma; HNF1α, hepatocyte nuclear factor-1α; IHCA, Inflammatory HCA; MRI, magnetic resonance imaging; NRH, Nodular Regenerative Hyperplasia; THCA, Telangiectatic HCA

Adapted from: Marrero JA, et al. Am J Gastroenterol. 2014; 109(9): 1328-47 (Table 3)

❖ Hepatic Cysts

• Simple Hepatic Cysts

➢ Definition

- ○ Congenital exclusions of hyperplastic bile ducts

➢ Demography

- ○ ↑ prevalence with age (uncommon before age 40 yr)

➢ Pathology

- ○ Usually <1cm in size
  - − May be in multiples

- Clinical
  - Typically asymptomatic
  - Larger lesions
    - Abdominal pain
    - Fullness, intracystic bleeding, infection
- Diagnostic Imaging

- Ultrasound
  - Anechoic homogenous fluid-filled lesion
- CT
  - Well-defined water attenuated lesion
  - No internal structures; no enhancement with contrast
- MRI
  - Well-defined homogenous lesion
    - No contrast enhancement
    - Low signal intensity on T1, and
    - High intensity on T2

- Features suggestive of NON-SIMPLE CYST:
  - Internal septations
  - Irregular walls
  - Daughter cysts
  - Calcifications
    - Evaluate with F/U CT or MRI

- Treatment
  - Asymptomatic/incidentally-discovered cyst
    - No intervention
  - Symptomatic cysts
    - Those complicated by bleeding, infection, or rupture
      - Surgical cyst fenestration (aka deroofing or marsupialization), 90% successful
      - If poor surgical candidate: radiologic cyst aspiration and sclerotherapy
      - Alert A: Aspiration of cyst → recurrence

- **Polycystic Liver Disease** (PCLD)

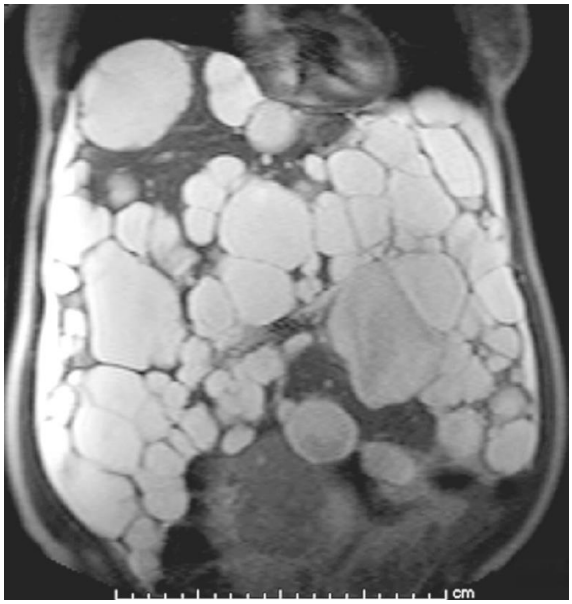
➢ Demography
  - Rare condition

➢ Definition
  - Formation of multiple liver cysts (>20) of variable size
  - Most cases occur in conjunction with autosomal dominant polycystic kidney disease (ADPKD)
    - Genes implicated with ADPKD
      - PKD-1 / PKD-2
  - Isolated PCLD has a more benign course, mostly asymptomatic
    - Genes implicated: PRKCSH, ALG8, GANAB, SEC61B
  - Cysts may be present in extrahepatic tissue: pancreas, spleen
  - Female sex hormones → ↑ size/number of cysts

➢ Clinical
  - Symptoms correlate to size/number of cysts
    - Hepatomegaly
    - Abdominal pain
    - Bloating
    - Fullness
    - Shortness of breath
  - Complications
    - Bleeding
    - Compression of surrounding structures
    - Infection
    - Rupture
    - Torsion of pedunculated cyst

➢ Laboratory
  - ↑ GGT / ↑ ALP
  - ↑ CA 19-9 (cyst aspirate)

➢ Diagnostic Imaging
  - Visualized on US, CT, or MRI
    - MRI
      - Provides more accurate information re hepatic cyst
      - Also assess possible renal cysts



Magnetic resonance imaging of the abdomen in a patient with severe polycystic liver disease. This coronal T2-weighted image shows a massively enlarged liver with numerous bright fluid-filled cysts.

Source: https://clinicalgate.com/tumors-and-cysts-of-the-liver/ (Figure 94-9)

- Treatment
  - Decompression of liver for symptomatic cysts
    - Cyst aspiration
    - Cyst fenestration (laparoscopic or open)
    - Sclerotherapy
    - Liver transplant +/- simultaneous kidney transplant

Recommendations

- Do **not** treat with mammalian target of rapamycin (mTOR) inhibitors or somatostatin analogs (Strong recommendation, low quality of evidence).
- Depending upon the patient's clinical presentation / hepatic reserve
  - Use
    - Aspiration
    - Deroofing
    - Resection of a dominant cyst

  (Conditional recommendation, low quality of evidence).

- In patients with refractory symptoms and significant cyst burden with or without kidney transplantation, consider liver transplantation (Conditional recommendation, low quality of evidence).

- **Biliary Cystadenomas** (BC)

➢ Definition

- Congenitally derived, aberrant bile duct remnants
- May be precursors to development of biliary cystadenocarcinoma (BCA)

➢ Clinical

- Usually discovered incidentally on diagnostic imaging
- Larger lesions may be symptomatic, related to their mass effect
  - Abdominal pain
  - Nausea
  - Early satiety
  - Anorexia

➢ Diagnostic Imaging

- Ultrasound
  - Irregular walls
    - Internal septations which may form loculi
- CT scan
  - Thickened cyst wall
  - Heterogenous irregular internal septations
  - Irregular papillary growths
- MRI
  - Hypointense on T1, and
  - Hyperintense on T2

➢ Aspiration / liver biopsy

- Do **not** perform aspiration/biopsy due to ↑ risk of disseminating malignancy if there is an underlying BCA

- Treatment
  - Surgical candidate
    - Resection
    - Indications
      - ↑ risk of recurrence
      - Possibility of progression to BCA
      - Inability to differentiate BC from BCA on basis of imaging alone
  - Not a surgical candidate
    - Follow-up with diagnostic imaging
    - Perform surgical resection if diagnostic

Recommendations

- Do **not** perform fluid aspiration if BCA is suspected because of
  - Limited sensitivity and
  - Risk of malignant dissemination
  (Strong recommendation, low quality of evidence).
- Imaging shows characteristics suggestive of BC or BCA, such as
  - Internal septations
  - Fenestrations, calcifications, or
  - Irregular walls
  (Strong recommendation, low quality of evidence).
- Perform complete surgical excision, by an experienced team, if BC or BCA is suspected (Strong recommendation, low quality of evidence).

- **Hydatid Cysts**

- Microbiology
  - Results from Echinococcus granulosus (tapeworm) infection
  - Transmission of hydatid larvae occurs through
    - Ingestion of food / organ meat from infected sheep/cows

- Demography
  - Occurs in patients from sheep-grazing areas (Mediterranean, South America, East Africa, Australia, New Zealand)

- Pathology
  - Cysts develop in the liver and lungs

- Clinical
  - <5 cm, asymptomatic
  - ≥5 cm, associated with
    - Abdominal pain
    - Cyst rupture → systemic inflammatory response
    - Shock
    - Peritonitis

- Diagnostic Imaging

- Ultrasound
  - Small cysts (resemble simple hepatic cysts)

- CT
  - Superior to US/MRI to demonstrate morphology of cysts

- MRI
  - Helpful for pre-surgical planning

- Treatment
  - Anti-helminthic drugs (e.g. albendazole, mebendazole), plus
  - Puncture, aspiration, injection, plus re-aspiration (PAIR)
    - Percutaneous treatment alternative to surgery
    - Indications
      - Poor operative candidates
      - Cyst recurrence post-operatively
    - Risk of anaphylaxis = 0.03%; or
  - Surgical Treatment
    - Radical pericystectomy / cyst deroofing
    - Indication
      - Complex cysts
      - Daughter cysts
      - Fistula
      - Hemorrhage
      - Multiple vesicles
      - Rupture
      - Secondary infection

Summary of Diagnostic Imaging of Liver in Patients with Benign Cystic Hepatic Lesions

Lesion	US	CT	MRI
○ Simple hepatic cysts (SHCs)	– Anechoic – Homogeneous – Fluid-filled – Smooth margins	– Well-demarcated – Water attenuated – Smooth lesion – No internal structure – No enhancement with contrast	– Well-defined, homogeneous lesion – No enhancement with contrast – T1: Hypointense – T2: Hyperintense signal intensity
○ Biliary cystadenomas (BCs)	– Irregular walls – Internal septations forming loculi	– Heterogenous septations – Internal septations – Irregular papillary growths – Thickened cysts walls	– May appear heterogeneous – T1: Hypointense signal intensity – T2: Hyperintense signal intensity
○ Polycystic liver disease (PCLD)	– Multiple hepatic cysts (similar in characteristics of SHC US findings)	– Multiple hepatic cysts, (similar in characteristics to SHC CT findings)	– Multiple hepatic cysts ▪ Similar in characteristics to SHC MRI findings
○ Hydatid cysts (HCs)	– May appear similar to SHC – Progress to develop thick, calcified walls ▪ Hyperechoic/hyperechoic content ▪ Daughter cysts in periphery	– Hypodense lesion – Hypervascular pericyst, wall – Distinct endocyst wall – Calcified walls / septa – Daughter cysts seen peripherally within mother cyst	– T1: Hypointense signal intensity of cyst contents – T2: Hyperintense signal intensity of cyst contents. Hypointense rim on T2 – Daughter cysts seen peripherally within mother cyst – Collapse parasitic membranes seen as ▪ Floating linear structures within cyst

Reproductive Health and Liver Disease

Nisha Howarth

- Normal Physiologic Changes of Pregnancy
  - GI
    - Esophageal varices
    - ↓ gallbladder motility / ↑ risk of cholelithiasis
  - CVS
    - Hyperdynamic circulatory status
  - Blood
    - ALP and AFP generation
  - Skin
    - Palmar erythema

- Demography
  - Pre-2000
    - Esophageal varices bleeding, 7% - 42%
    - Ascites, 10% - 25%
    - Mortality, 10%
  - Post-2000
    - Incidence of childbirth in women with cirrhosis
      - ↑ 8% per year over the past 2 decades
      - ↑ prognosis $1/10^6$ → $15/10^6$ (2000 vs. 2016)
    - Rates of childbirth amongst women with compensated liver disease appear comparable to the general population
    - Cirrhosis is an independent risk factor for certain maternal, fetal and liver-related adverse outcomes
    - Risk of liver-related decompensation, liver transplant, and death up to 1-yr post-partum, low (<2%)

Flemming JA, et al. Gastroenterol 2020; 159: 1752-1762.

- Fertility Issues in Women with Cirrhosis
  - ↓ hepatic metabolism of sex hormones
  - ↑ portosystemic shunting of weak androgens
  - Peripheral aromatization of androgens

  → Altered estrogen metabolism disrupts HPG axis

  → ↓ FSH, ↓ LH→ anovulation and oligo- or amenorrhea

Abbreviations: HPG, hypothalamus-pituitary gonad; LH, luteinizing hormone

- Newer epidemiological studies describing comparable or *higher* rates of reproduction in women with compensated cirrhosis
- The perceived low likelihood of conception
  - May result in differences in contraceptive counselling/prescribing/use
- Women with decompensated cirrhosis have ↓ 34% rate of childbirth, compared to the general population

Gawron LM, et al. J Gen Intern Med 2019; 35: 637-642

- Contraceptive Counselling

	COC	POP	Hormonal IUD	Copper IUD	DMPA injection	Subcutaneous implant
Compensated Cirrhosis	✓	✓	✓	✓	✓	✓
Decompensated Cirrhosis		✓	✓	✓	✓	✓

Abbreviations: COC, combined oral contraceptive; DMPA, depot-medroxyprogesterone acetate; IUD, intrauterine device; POP, progesterone only pill

- No restrictions on hormonal contraception in women with compensated cirrhosis (WHO and AASLD)

Family Planning: WHO A Global Handbook for Providers; 2018 Edition

Contraception in Patients with Liver Disease

	Copper IUD	Hormonal (Progestin) IUD	CHCs (Pill, Patch, Ring)	Progesterone-Only Pills	DMPA Injection	Subcutaneous Implant
○ Strength	– Failure rate ▪ Convenient, does **not** rely ▪ On adherence ▪ No estrogen-associated risks ▪ Effective ≥ 10 yr	– Failure rate <1% ▪ Convenient ▪ Does **not** rely on adherence ▪ No estrogen-associated risks ▪ Effective ≥ 5 yr	– Regular bleeding ▪ Lightened menses	– No estrogen-associated risks	– No estrogen-associated risks – Injections q3mon	– Failure rate <1% convenient – Does not rely on adherence – No estrogen-associated risks – Effective at least 3 yr
○ Limitations ‹ concern	– ↑ menstrual cramping and bleeding (less ideal if anemia or low platelets)	– ↑ irregular bleeding	– Typical failure rate 9% ▪ Contra-indications as denoted subsequently ▪ Interacts with P450, associated with hypertension, VTE, and (less commonly) ▪ Stroke and ▪ Rare cholestatic liver injury	– Typical failure rate 9%, requires strict daily timing ▪ Possible conversion of high-dose progestins to small amount of estrogen (unlikely relevant with modern-day, lower-dose progestin preparations) ▪ Irregular bleeding common	– Typical failure rate 6% ▪ Irregular bleeding common ▪ ↓ bone density (less favored for liver diseases associated with osteopenia/ osteoporosis	– Irregular bleeding common

CDC MEC Safety Categories / AASLD Recommendations

- Cirrhosis
  - Compensated 1/Acceptable
  - Decompensated 1/Acceptable
- BCS 2/Acceptable
- HCAs 1/Acceptable
- Post-transplant graft function
  - Normal 2/Acceptable
  - Graft failure 3/Acceptable

Abbreviations: BCS, Budd-Chiari syndrome; HCA, hepatocellular adenomas

- Inquire about sexual activity and pregnancy intentions in all reproductive-aged women with CLD or liver transplant (LT)
- Avoid estrogen-containing agents in patients with
  - Decompensated cirrhosis
  - Budd-Chiari syndrome
  - Hepatocellular adenomas
  - Transplant
- Patients using agents other than long-acting-reversible contraceptives
  - Combine these with a barrier method
  - High failure rates
- All forms of emergency contraception may be used in the setting of chronic liver disease

Shaheen AM and Myers RP. The outcomes of pregnancy in patients with cirrhosis: a population-based study. *Gut.* 2010;59(2):211–215. doi:10.1136/gut.2009.185256

Rasheed SM, et al. Prognosis and determinants of pregnancy outcome among patients with post-hepatitis liver cirrhosis. Int J Gyne & Obest 2013; 121; 247-251.

Puljic A, et al. Outcomes of pregnancies complicated by liver cirrhosis, portal hypertension, or esophageal varices. *J Matern Fetal Neonatal Med.* 2015; 29: 506-509

➢ Prognosis

- Cirrhosis and Maternal Outcomes
  - ↑ preterm birth
  - ↑ C-section
  - ↑ hypertensive complications
  - ↑ post-partum hemorrhage
  - ↑ induction of labour

- ↑ intrahepatic cholestasis of pregnancy
- ↑ puerperal infections
- ↑ gestational diabetes

- Peri-Partum Outcomes
  - Prognostic scoring systems useful in predicting peripartum outcomes
    - Predicted gestation carrying to >37 wks, ALBI cutoff -2.7
    - Predicted live birth, APRI cutoff 0.84

Gonsalkorala ES, et al. Am J Gastroenterol. 2019; 114(2):267-275.

- Maternal Cirrhosis Infant Outcomes
  - Cirrhosis has been associated with:
    - Neonatal death
    - Large/small for gestational age
    - Respiratory distress
  - No association with
    - Stillbirth
    - Aspiration of meconium
    - Neonatal jaundice

- Liver Outcomes
  - Old data
    - Women with cirrhosis
      - ↑ risk for liver events
      - Variceal hemorrhage most common liver event up to 30%
      - Death in up to 10% of pregnancies
  - Modern data
    - Variceal bleeding rate, <5%
    - Other decompensation events, 1-10%
    - Liver transplant, ≤3%
    - Death, <2%

➢ Predicting Liver-Related Outcomes

- MELD-Na
  - <6 = minimal complications anticipated
  - > 10 = predictive of hepatic decompensation during pregnancy (sensitivity, 83%; specificity, 83%)
- Post-Partum
  - No significant difference between APRI/ALBI/MELD scores pre and post-partum

Westbrook RH, et al. Clin Gastroenterol Hepatol 2011; 9(8): 694-9.

➢ Management of Chronic Liver Disease in Pregnancy

- Variceal Hemorrhage (VH)
  - Mortality rate 18-20%
  - Incidence decreasing from 33% of pregnancies to 5-8.5%
  - Screen
    - 12 mon preconception, or
    - 2nd trimester if no EGD recently
    - Platelets > 150
    - FibroScan < 20 kPa = 3 (low likelihood)
  - Screening goal
    - To detect varices of any size
    - Using LSM and PLT criteria should **not** be used to avoid endoscopy
  - Treatment
    - NSBB: EVL if high risk stigmata
    - Acute VH
      - Antibiotics
      - Fluid resuscitation
      - EVL
      - Vasoactive meds if endoscopic therapies fail +/- rescue TIPS
  - Endoscopy in pregnancy
    - Defer endoscopic procedures until after T1
    - Perform fetal monitoring during EGD in patients >24 wks gestation
    - Consult anaesthesia for sedation
    - Acceptable for use in pregnancy
      - Midazolam
      - Fentanyl
      - Propofol
    - Do **not** do EGD if obstetric complications such as
      - Placental abruption
      - Eclampsia

Abbreviations: EVL, esophageal variceal injection; NSBB, non-specific beta blocker; TIPS, transcutaneous intrahepatic portosystemic shunt

- Ascites
  - Uncommon, 7-11%
  - Avoid diuretics based on risk-benefit ratio (Spironolactone and Lasix are class C risk for fetal malformations)

- Hepatic Encephalopathy (HE)
  - Similar principles to manage HE
    - Rifaximin is a class C risk for fetal malformations
    - If encephalopathic at delivery
      - HE may influence anesthesia as certain drugs may precipitate hypotension and ↑ HE

Rahim MN, et al. United European Gastroenterol J. 2021; 9(1):110-119.

❖ Liver Diseases which Occur Only in Pregnancy

• Hyperemesis Gravidarum

➢ Demography

- Occurs in ~0.5% of pregnancies
  - More common in
    - Nulliparous, and
    - Twin pregnancies
- Early first term (T1), patients may have mild ↑ LFTs
- Liver chemistries usually normalize with hydration

➢ Treatment

- Supportive with
  - Rehydration
  - Electrolyte correction
  - Cyclizine
  - Dimenhydrinate
  - Doxylamine
  - Metoclopramide
  - Ondansetron
  - Promethazine
  - Thiamine supplementation

• Intrahepatic Cholestasis of Pregnancy

➢ Demography

- Most common liver disease specific to pregnancy
  - Occurs in T2, T3
- ↑ intracranial pressure

- Clinical
  - Mother
    - Pruritus
    - No severe in palms and soles
  - Fetal risk
    - Prematurity
    - Intrauterine fetal distress (IUFD) (1%)
      - Especially ↑ serum bile acids >100umol/L
  - Usually GGT low/normal
  - Mild elevation in other LFTs
  - Mild jaundice
  - Serum bile acids >10 µmol/L
  - Test for associations
    - HCV infection
    - Multiple gestation
    - Multiparity
    - Metabolic syndrome
    - HCV infection
    - Personal / family history of ICP
  - Treatment
    - At 37 wk, give ursodiol (UDCA) 10-15 mg/kg
    - Cholestyramine

Abbreviations: IUFA, intrauterine fetal deaths; UDCA, ursodeoxycholic aid

- **Hemolysis, elevated liver enzymes, low platelets** (HELLP) **syndrome**

- Demography
  - Occurs in ~0.4% of pregnancies
    - In T2/T3

- Risk factors
  - Hypertension
  - Multiparity
  - Diabetes mellitus
  - Age >35 yrs
  - Caucasian

- Clinical
  - Abdominal pain
  - Nausea/vomiting
  - Preeclampsia
  - Shock (from hepatic rupture)
- Diagnostic Imaging
  - Hepatic infarction + rupture, or
  - Hematoma

  } Rare
  - Mother
    - 1% maternal mortality
  - Fetal risk
    - Prematurity
    - IUGR
    - 7-20% perinatal mortality
- Treatment
  - Early delivery
  - Consider platelet transfusion (to 40-50 $x10^3$)

- **Acute Fatty Liver of Pregnancy**

- Demography
  - Rare obstetrical emergency
    - Occurs in T3 / post-partum
  - Strong association with LCHAD deficiency in the fetus
- Pathophysiology
  - Accumulation of hepatotoxic long-chain-3-hydroxyacyl metabolites that pass into maternal circulation
- Risk factors
  - Primiparity
  - Male fetus
  - Multiple gestation

- Clinical
  - Similar to preeclampsia
    - Headache
    - Nausea/vomiting
    - RUQ pain
    - Jaundice
    - Hypoglycemia

- Laboratory
  - ↑ Cr_s
  - ↑ LFTs
  - ↑ bilirubin
  - ↑ urate

- Diagnostic imaging
  - Fatty infiltration
  - Pericentral microvesicular steatosis
  - Confirmed with oil red O staining

Abbreviations: Cr, serum creatinine; LCHAD, long-chain hydroxyacyl-CoA dehydrogenase deficiency; LFT, liver function test; PP, post-partum; RUQ, right upper quadrant; T, term of pregnancy

- Diagnosis (Swansea criteria) (≥6 of below features for the diagnosis)
  - Clinical
    - Vomiting
    - Abdominal pain
    - Polydipsia/polyuria
    - Encephalopathy
  - Laboratory
    - ↑ bilirubin > 14 µmol/L
    - ↓ blood sugar < 4 µmol/L
    - ↑ uric acid level > 340 µmol/l
    - Leucocytosis > 11 x 10^9/l
    - Ascites / bright liver on ultrasound scan
    - ↑ transaminases (AST or ALT) > 42 IU/L
    - ↑ ammonia > 47 µmol/l
    - ↑ creatinine > 150 µmol/l
    - Coagulopathy: prothrombin time > 14 sec or APPT > 34 sec
    - Microvesicular steatosis

- Mortality
  - Maternal, 10%
  - Perinatal, 10-20%

➢ Treatment

- Delivery emergently
- Molecular testing for LCHAD deficiency in mother and offspring
  - AFLP may develop regardless of maternal genotype if the fetus is deficient in LCHAD and carries ≥ 1 allele for the G1528C LCHAD mutation
  - A second defect in β-oxidation has been described, deficiency of carnitine palmitoyl transferase
- Liver transplant, as indicated

Abbreviations: LCHAD, long-chain hydroxyacyl-CoA dehydrogenase deficiency;

❖ Pregnancy in the Post-Liver Transplant Patient

➢ Outcomes

- Mother
  - Time after liver transplantation when pregnancy occurs
    - < 2 yr ↓ birth weight of body
    - > 4 yr lowest rate of miscarriage (8%)
  - Immunosuppression
    - Live birth rate
      - Cyclosporin, tacrolimus, 78%
      - MMF, lower (70%)
    - Adverse effects
      - Cyclosporin
        - Renal failure
        - Hypertension
      - Tacrolimus
        - Renal failure
        - Preeclampsia
      - Mycophenolate mofetil (MMF)
        - ↑ fetal loss, T1
        - Congenital malformations
  - Outcomes
    - ↑ preeclampsia, 13-14%
    - ↑ rate of c-section, 42% vs, 32%
    - Other high risk perinatal outcomes

- Fetus
  - ↑ preterm birth rate (32% vs. 10%)
  - ↓ birthweight (vs. mean of 2.7 kg, 35% vs. 8%)
  - ↑ liver birth rate (LT subgroup), 80% vs. 65%

Valentin N, et al. Am J Gastroenterol. 2021;116(3):491-504.

Pre-Conception Counselling: Medications (previous FDA classification)

Medications to avoid	Use with caution	Safe to use
Azathioprine (D) Lasix (C) Mercaptopurine (D) MMF (D) Prednisone (C/D) Rifaximin (C) Sirolimus (D) Spironolactone (C)	Carvedilol (C) Propranolol (C) Tacrolimus (C)	Lactulose (B) Octreotide

Maternal Outcomes

- ↑ rate preeclampsia (13% vs 4%)
- ↑ rate of C-section (42% vs 32%)

Summary

- Rates of childbirth in women with cirrhosis are climbing!
- Higher risk for certain perinatal outcomes
  - CVS
    - Hypertensive complications
  - Lung
    - Neonatal respiratory distress
  - Liver
    - Intrahepatic cholestasis of pregnancy
  - Obstetrical
    - Induction of labour
    - Preterm delivery
- Large for gestational age (LGA) and small gestational age (SGA) infants
- Neonatal respiratory distress
- Special considerations for women post-LT

Guidance Statements for in Liver Transplant Recipients Who Plan for Pregnancy

- Delayed pregnancy until ≥ 1 yr after LT, plus ≥ 6 mon of stable graft function
- Immunosuppression (in pregnancy/lactation)
  - Use calcineurins (CNIs), azathioprine/6-MP, and steroids are acceptable for use in pregnancy and lactation
  - Do **not** use MMF – use contraception with low failure rates
  - mTORs
    - Obtain calcineurin trough levels q2-4 wk during pregnancy
      - Guide-based on liver tests
- Use more frequent graft monitoring during pregnancy and postpartum period
- Mode of delivery guided by obstetric indications

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Bacterial, Parasitic and Fungal Liver Infections

Abdulaziz Alajmi

➢ Mechanism

- Liver Involvement
  - The liver is initial site of filtration of absorbed intestinal luminal contents and
    - Is particularly susceptible to contact with microbial antigens of all varieties.
  - Can be affected by
    - Spread of bacterial or parasitic infection from outside the liver
    - Systemic effects of bacterial or granulomatous infections
    - Viruses
    - Primary infection by spirochetal, protozoal, helminthic, or fungal organisms

❖ **Gram-Positive and Gram-Negative Bacterial Infections**

- **Toxic Shock Syndrome** (S. Aureus or GAS)

➢ Definition

- Toxic shock syndrome
  - Multisystem disease caused by toxic shock syndrome toxins, which are superantigens that cause T-cell activation and massive cytokine release.

➢ Risk factors

- S. Aureus TSS risk factors
  - Tampon use
  - Surgical site infection

➢ Clinical

- Typical
  - Scarlatiniform rash
  - Mucosal hyperemia
  - Hypotension
  - Vomiting
  - Diarrhea
- Liver involvement ranges from ↑ liver enzymes to jaundice / extensive hepatic necrosis

➢ Histopathology

- Microabscesses, granulomas

➢ Diagnosis

- Confirmed by culture from wound, blood, or other body sites.

- Treatment
  - Antibiotic – clindamycin for GAS, +/- IVIG (controversial)
  - Necrotizing fasciitis – surgical intervention

- Bacterial Sepsis and Jaundice
  - Jaundice may be seen in GN or GP bacterial sepsis
  - Mechanism
    - Exotoxins and endotoxin act directly or indirectly → ↓ transportation of bile acids and other organic anions across the hepatic sinusoidal and bile canalicular membranes → intrahepatic cholestasis
  - Does **not** correlate with mortality
  - Cultures of liver biopsy are usually negative

- Pyogenic Liver Abscesses

Differentiate Infections Cause of Hepatic Abscess

Parameter	Pyogenic Liver Abscess	Amebic Liver Abscess
Number	Often multiple	Usually single
Location	Either lobe of liver	Usually right hepatic lobe, near diaphragm
Clinical	Subacute	Acute
Diagnosis	US or CT; aspiration	US or CT; and serology
Treatment	Drainage (if technically feasible) and intravenous antibiotics	Metronidazole, 750 mg three times daily for 7–10 days orally or IV Tinidazole, 2 g orally for 3 days, followed by iodoquinol, 650 mg orally three times daily for 20 days; diloxanide furoate, 500 mg orally three times daily for 10 days Aminosidine (paromomycin) 25–35 mg/kg/day orally in 3 divided doses for 7–10 days

- **Actinomyces**

➢ Organism
  - Gram positive anaerobic bacterium (most commonly Actinomyces israelii)

➢ Clinical
  - Sites of infection
    - Cervicofacial infection is the most frequent
    - GI involvement in 13-60% of patients
    - Hepatic involvement in 15% - spread from other abdominal sites
    - Can get fistulization to pleural space or other surrounding tissues
  - Symptoms
    - Fever, abdominal pain, anorexia and weight loss

➢ Investigations
  - Anemia, leukocytosis, ↑ ESR, and ↑ serum ALP
  - Radiographic findings are nonspecific; multiple abscesses may be seen in both lobes of the liver

➢ Diagnosis
  - Aspirate from abscess cavity or positive culture

➢ Treatment
  - Antibiotics (penicillin or tetracycline)
  - Abscess drainage as appropriate

- **Bartonella**

➢ Microbiology
  - Primarily seen in patients with HIV or other immunodeficient states
  - Main causes
    - Bartonella henselae
    - Bartonella quintana
  - Gram negative bacilli
  - Can be associated with cat exposure

- Clinical
  - Multiple blood red papular skin lesions (Bacillary Angiomatosis)
  - Can affect liver, LN, pleura, bronchi, bones, brain, bone marrow and spleen
  - Could have persistent bacteremia and sepsis
  - Liver involvement
    - Transaminitis in absence of another explanation
    - Blood filled cysts (peliosis hepatitis)
- Histopathology
  - Inflammatory myxoid stroma containing clumps of bacilli and dilated capillaries surrounding the blood-filled peliotic cysts
- Diagnosis
  - PCR
- Treatment
  - Erythromycin +/- prolonged doxycycline for visceral infection

- **Bartonella bacilliformis**

- Microbiology
  - Gram-negative coccobacillus
  - Endemic to Colombia, Ecuador, and Peru
  - Transmitted by a sand fly
- Clinical
  - Acute febrile illness (Oroya fever)
  - Jaundice, hemolysis, hepatosplenomegaly, and lymphadenopathy.
- Histopathology
  - Centrilobular necrosis of the liver and splenic infarction may occur
- Prognosis
  - 40% of patients die of sepsis or hemolysis
- Treatment
  - Ciprofloxacin and ceftriaxone

- **Bartonella henselae**

➢ Microbiology
  - Usually affects children and young adults

➢ Clinical
  - Cat-scratch disease
  - Typical cutaneous and lymph node manifestations
  - Rarely, disseminate with visceral involvement (necrotizing granuloma in the liver and spleen)

➢ Treatment
  - Azithromycin

- **Brucella**

➢ Microbiology
  - Contracted from infected pigs, cattle, goats, and sheep (Brucella suis, Brucella abortus, Brucella melitensis, and Brucella ovis, respectively)

➢ Clinical
  - Acute febrile illness
  - Hepatic abnormalities are seen in a majority of infected persons
    - Jaundice may be present in severe cases

➢ Histopathology
  - Multiple noncaseating hepatic granulomas
  - Less often, focal mononuclear infiltration of the portal tracts or lobules is seen
  - Rarely, hepatosplenic abscesses

➢ Diagnosis
  - Isolation of the organism from a cultured specimen of liver tissue
    - Confirmed by serologic plus a history of exposure to animals

➢ Treatment
  - Streptomycin and Doxycycline
  - Surgical drainage (may be required for *Brucella* abscesses)

- **Burkholderia pseudomallei** (Melioidosis)

➢ Microbiology

- Gram negative bacterium
  - Found in soil and water
  - Predominantly in Southeast Asia

➢ Clinical

- Ranges from asymptomatic infection to
  - Fulminant septicemia with involvement of lungs GI tract and liver

➢ Histopathology

- Inflammatory infiltrates
  - Multiple microabscesses
  - Focal necrosis
- Organisms can be visualized with Giemsa stain of the liver biopsy
- With chronic disease, granulomas may be seen

➢ Diagnostic Imaging

- Some liver abscesses may demonstrate honeycombing appearance on CT

➢ Treatment

- Drain abscesses
- Antibiotics
  - Ceftazidime or meropenem, followed by a prolonged course of Septra® +/- doxycycline

- **Chlamydia trachomatis**

➢ Clinical

- Fitz-Hugh-Curtis Syndrome
  - Similar to perihepatitis caused by gonococcal infection, with RUQ pain accompanying urogenital infection such as PID

➢ Diagnosis

- Direct visualization at laparoscopy or laparotomy
  - Diagnosis supported by demonstration of endometritis, salpingitis and microbiologic detection of C. trachomatis in the GU tract
- Liver biochemistry generally normal

- Treatment
  - Follow guidelines for C. trachomatis

- **Clostridium perfringens**

- Organism
  - Mixed anaerobic infection
- Clinical presentation:
  - Rapid development of local wound pain, abdominal pain, and diarrhea
  - Skin lesions become discolored and even bullous, and gas gangrene spreads rapidly
  - Liver involvement:
    - Jaundice
      - May develop in up to 20% of patients with gas gangrene
      - Is predominantly a consequence of massive intravascular hemolysis caused by an exotoxin elaborated by the bacterium
    - Liver abscess
    - Gas in portal vein
- Prognosis
  - High mortality rate – hepatic involvement not predictive of mortality but poor prognosis in patients with cirrhosis
- Treatment
  - Antibiotics – penicillin and clindamycin
  - Surgical debridement with wide excision

- **Coxiella burnetii** (Q Fever)

- Microbiology
  - Contracted by inhalation of animal dusts
  - Q fever syndrome:
    - Relapsing fevers, headache, myalgias, malaise, pneumonitis, and culture-negative endocarditis
    - Liver involvement is common
      - ↑ ALP
      - Minimal elevations of AST or bilirubin

- Histopathology
  - Fibrin ring granulomas
- Diagnosis
  - Serologic testing for complement-fixing antibodies
- Treatment
  - Doxycycline

- **Gonococci**

- Definition
  - Disseminated gonococcal infection
    - ↑ ALP
    - ↑ AST
    - Unlikely to have jaundice
  - Fitz-Hugh-Curtis syndrome
    - Perihepatitis from direct pelvic spread of bacteria
- Clinical
  - Sudden, sharp RUQ pain
  - Risk factor
    - History of pelvic inflammatory disease
- Diagnosis
  - Culture
- Prognosis
  - Not affect by evidence of hepatitis
- Treatment
  - Antibiotics (Ceftriaxone)
    - Treat chlamydial co-infection

- **Legionella pneumophilia**

➢ Microbiology
  - Fastidious gram-negative bacterium

➢ Clinical
  - Most often causes pneumonia, but can cause abnormal liver biochemistry
    - ↑ liver enzymes, 50%
    - ↑ ALP, 45%
    - ↑ bilirubin, 20% (usually without jaundice)

➢ Histopathology
  - Microvesicular steatosis
  - Focal necrosis
  - Can occasionally see organisms

➢ Diagnosis
  - Confirmed by antibody in serum, sputum, or antigen in urine

➢ Treatment
  - Azithromycin
  - Fluoroquinolone

- **Leptospirosis**

➢ Microbiology
  - Contracted from infected feces or urine

➢ Clinical
  - Anicteric leptospirosis
    - 90% of cases
    - Biphasic illness
      - First phase: viral illness with fever, leptospiremia and conjunctival suffusion (important clue)
      - Improves clinically, then second phase involves myalgias, nausea, vomiting, abdominal tenderness and aseptic meningitis
      - A few patients have ↑ aminotransferase, ↑ bilirubin, and hepatomegaly

- Weil Syndrome
  - Liver
    - Severe icteric form of leptospirosis, 5-10% of all cases
    - First phase
      - Jaundice (can last for weeks)
    - Second phase
      - Fever
      - Hepatic and renal manifestations
      - Jaundice continues
      - Transaminitis does **not** generally exceed 5x ULN
  - Kidney
    - Acute tubular necrosis often develops and can lead to renal failure
  - Blood
    - Hemorrhagic complications from capillary injury caused by immune complexes

➢ Histopathology
- Non specific – altered mitochondria suggests toxin mediated injury
- Rarely see spirochete in liver on autopsy, can be in kidney

➢ Diagnosis
- Clinical symptoms
- Positive blood or urine culture
- Serologic testing can also confirm diagnosis if cultures are negative

➢ Treatment
- Doxycycline (most effective in first several days)
- Most patients recover without residual organ impairment

- **Listeria monocytogenes**

➢ Organism
- Uncommon to involve the liver
- Can develop abscess or acute granulomatosis hepatitis

➢ Histological
- Multiple abscesses
- Granulomas

- Risk factors
  - Immunosuppression
  - Diabetes
  - Underlying liver disease (cirrhosis, hemochromatosis, chronic hepatitis)
- Diagnosis
  - Positive blood culture, or
  - Aspirate from abscess
- Treatment
  - Antibiotics
    - Ampicillin
    - Penicillin plus gentamycin (synergy)

- **Lyme Disease**

- Microbiology
  - Causative agent: *Borrelia burgdorferi*
- Clinical
  - Cardiac, dermatologic, neurologic and musculoskeletal involvement
  - Liver involvement more common with disseminated disease, does **not** affect mortality
  - Anorexia, nausea, vomiting, weight loss, RUQ pain and hepatomegaly within days to weeks of onset of illness → ↑ transaminases and LDH in patients with these symptoms. Often had erythema migrans
- Histopathology
  - Hepatocyte ballooning
  - ↑ mitotic activity
  - Microvesicular fat
  - Mixed sinusoidal infiltrate
  - Intraparenchymal and sinusoidal spirochetes
- Diagnosis
  - Serology

- Treatment
  - Early disease
    - Doxycycline
    - Amoxicillin
    - Clarithromycin
    - Azithromycin
  - Late disease
    - Ceftriaxone for

- **Rickettsiae**

- Rocky Mountain Spotted Fever

- Clinical
  - Severe vasculitis due to microbe-induced coagulopathy and jaundice
  - Multiorgan failure = high mortality

- Histopathology
  - Portal tract
    - Inflammation
    - Portal vasculitis
    - Sinusoidal erythrophagocytosis
  - Little hepatic necrosis

- Laboratory
  - ↑ transaminases
  - ↑ ALP
  - Jaundice (bile ductular obstruction and hemolysis) → ↑ mortality

- Ehrlichia

- Microbiology
  - Parasite invades leukocytes
  - Infectious agents:
    - Human monocytic ehrlichiosis → Ehrlichia chaffeensis and Ehrlichia canis
    - Human granulocytic ehrlichiosis → Anaplasma phagocytophilum

- Clinical
  - No rash
  - ↑ transaminases
  - Can have cholestasis, hepatosplenomegaly, liver failure
    - Liver injury is due to proliferation of organisms within hepatocytes and the provoked immune response
- Histopathology
  - Focal necrosis
  - Fibrin ring granulomas, and
  - Cholestatic hepatitis
  - Mixed portal tract infiltrate and lymphoid sinusoidal infiltrate
- Treatment
  - Doxycycline

- **Shigella and Salmonella**
  - Shigella
    - Cholestatic hepatitis in response to enteric infection with shigella spp
    - Portal and periportal inflammation with PMNs, hepatic necrosis and cholestasis
    - Severe hepatic dysfunction associated with *Shigella* spp. infection has been reported
  - Salmonella typhi
    - ↑ transaminases, ↑ bilirubin mediated by
      - Bacterial endotoxin causing focal necrosis and
      - Periportal mononuclear infiltrate and Kupffer cell hyperplasia in the liver (similar to changes seen in gram negative sepsis)
    - Typhoid nodules – result of hypertrophy and proliferation of Kupffer cells
    - Complicated by cholecystitis and liver abscesses
    - Mortality rate approaches 20%, particularly with delayed treatment
    - Severe typhoid with acute liver failure
      - Jaundice and encephalopathy
      - ↑ ALP, AST>ALT, low PT, low platelets
    - Treatment
      - Ceftriaxone
      - Ciprofloxacin

- Salmonella paratyphi A and B
  - ↑ transaminases
  - Rarely complicated by liver abscesses
  - Treatment
    - 3rd generation cephalosporin, or
    - Fluoroquinolone

- **Syphilis**

- Secondary syphilis

➢ Clinical

- Non-specific
  - Anorexia
  - Weight loss
  - Fever malaise
  - Sore throat
- Pruritic maculopapular rash involving palms and soles
- Jaundice, hepatomegaly and RUQ tenderness in 50%
- Lymphadenopathy

➢ Laboratory

- ↑ transaminases
- ↑ bilirubin
- ↑ particularly elevated ALP
- Proteinuria

➢ Histology

- Focal necrosis in periportal and centrilobular regions
- Inflammatory infiltrate: neutrophils, plasma cells, lymphocytes, eosinophils and mast cells
- Kupffer cell hyperplasia may be seen
- Bile duct injury rare
- Granulomas
- Spirochetes with sliver stain in 50% of patients

- Treatment
  - Penicillin

- Tertiary syphilis

- Clinical
  - Hepatic lesions are common in late syphilis
  - Anorexia, weight loss, fatigue, fever or abdominal pain

- Histopathology
  - Characteristic lesion
    - Gumma (central necrosis, with surrounding granulation tissue consisting of lymphoplasmacytic infiltration and endarteritis
  - Can get scar tissue deposition giving the liver a lobulated appearance (hepar lobatum)
  - Can develop portal HTN with jaundice, ascites and gastroesophageal varices

- Treatment
  - Hepatic gummas may resolve after therapy with penicillin

- **TB and Mycobacteria**

- Clinical
  - Rarely get significant liver disease, occasional tender hepatomegaly

- Laboratory
  - Can get jaundice with ↑ ALP in miliary infection

- Histopathology
  - Granulomas are found in liver biopsy in
    - 25% of people with pulmonary TB, and
    - 80% with extrapulmonary TB
  - TB granulomas – central caseation, AFB present, fewer granulomas with tendency to coalesce
    - Can also be seen following BCG vaccine, particularly if immunocompromised

- Treatment
  - Guideline-based TB treatment

- **Yersinia enterocolitica**

➢ Presentation
  - In children
    - Ileocolitis
  - In adults
    - Terminal ileitis or mesenteric adenitis

➢ Clinical
  - Arthritis
  - Cellulitis / erythema nodosum
  - Septicemia
  - Risk factors for complicated disease
    - Diabetes
    - Cirrhosis / hemochromatosis (bacterial growth ↑ by iron)
  - Can present in subacute fashion with multiple abscesses diffusely in liver and spleen

➢ Prognosis
  - Mortality, 50%

➢ Treatment
  - Fluoroquinolones
  - 3rd generation cephalosporins

❖ Parasitic Infections

Classification of Parasitic Diseases of the Liver and Biliary Tract by Pathologic Process

Pathologic Process	Diseases
• Liver	
○ Granulomatous hepatitis	− Capillariasis − Fascioliasis − Schistosomiasis − Strongyloidiasis − Toxocariasis
○ Portal fibrosis	− Schistosomiasis
○ Hepatic abscess or necrosis	− Amebiasis − Toxoplasmosis
○ Cystic liver disease	− Echinococcosis
○ Peliosis hepatis	− Bacillary angiomatosis
• Reticuloendothelial Cells	
○ Kupffer cell infection or hyperplasia	− Babesiosis, Malaria − Toxoplasmosis − Visceral leishmaniasis
• Biliary Tract	
○ Cholangitis	− Clonorchiasis/Opisthorchiasis, − Fascioliasis
○ Biliary hyperplasia	− Ascariasis − Clonorchiasis − Cryptosporidiosis − Fascioliasis
○ Cholangiocarcinoma	− Clonorchiasis − Opisthorchiasis

Adapted from: Kim AY, Chung RT. Bacterial, parasitic, and fungal infections of the liver, including liver abscesses. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th ed. Vol 2. Philadelphia, PA: Elsevier; 2020:1115–1132.

- **Malaria**

➢ Demography

- Endemic areas
  - Africa
  - Asia
  - South America

➢ Microbiology

- Malaria
  - Plasmodium falciparum, P. malariae, P. vivax, P. ovale, P. knowlesi)
- Liver is affected in 2 stages
  - Pre-erythrocytic phase, then erythrocytic phase → coincides with clinical illness
- Plasmodium vivax and Plasmodium ovale is associated with a persistent exoerythrocytic stage, the hypnozoite
  - Persists in the liver and, when activated
  - Divide and mature into schizont forms
- Plasmodium knowlesi has been identified as a fifth species capable of infecting humans
  - Occasionally results in severe manifestations including jaundice, hepatic dysfunction, and acute kidney injury

➢ Pathophysiology

- Sporozoite clearance by hepatocytes; exoerythrocytic replication in the liver

➢ Cause

- Predisposing factors
  - Blood transfusion
  - IV drug use

➢ Clinical

- Erythrocytic stage (associated with clinical illness)
  - Symptoms and signs of acute infection develop within 30 to 60 days following exposure
  - Fever, malaise, anorexia, nausea, vomiting, diarrhea, myalgias
  - Jaundice caused by hemolysis

- Hepatic failure only seen with concomitant viral hepatitis or severe P falciparum infection
- Tender hepatomegaly and splenomegaly
- Cytopenia

➢ Laboratory

- Extent of hepatic injury varies with type of malarial species (most severe with P. falciparum) and severity of infection
- Unconjugated hyperbilirubinemia most commonly seen as a result of hemolysis but could also be related to hepatic dysfunction
- ↑ transaminase / ↑ 5'-nucleotidase level
- May also see synthetic dysfunction

➢ Histopathology

- Acute malaria
  - Hepatic macrophage hypertrophy
  - ↑ malarial pigment in Kupffer cells
- Hepatocyte swelling
- Centrizonal necrosis
- Reversible with treatment

➢ Diagnosis

- Thick and thin blood smear
- PCR to differentiate species

➢ Treatment

- Depends on species and chloroquine resistance patterns
- Atovaquone proguanil, or artemisinin derivatives
- P. vivax and ovale require primaquine (G6PD Def) or mefloquine to eliminate hypnozoites in liver

- P. falciparum
  - Chloroquine (chloroquine-sensitive)
  - Mefloquine
  - Quinine and either
    - Doxycycline or
    - Clindamycin; or
    - Pyrimethamine-sulfadoxine (Fansidar); or
    - Atovaquone/proguanil (chloroquine-resistant); or
    - An artemisinin
- P. malariae
  - Chloroquine
- P. vivax, P. ovale, P. knowlesi
  - Chloroquine and primaquine (chloroquine-sensitive), or
  - Mefloquine and primaquine (chloroquine-resistant)

- Hyperreactive Malarial Splenomegaly
  - Repeated exposure in endemic areas may lead to an over production of B lymphocytes, malarial antibody and increased levels of immune complexes that deposit into the liver (dense sinusoidal lymphocytosis)
  - Clinical features
    - Splenomegaly
    - Elevated antimalarial antibodies
    - Anemia
    - Variceal bleeding could happen from portal HTN
  - Treatment
    - Lifelong malarial therapy

- **Amebiasis** (Entamoeba histolytica)

➢ Demography
  - Worldwide, especially Africa, Asia, Mexico, South America

➢ Risk Factors
  - Poor sanitation
  - Sexual exposure

➢ Pathogenesis
  - Hematogenous spread
  - Tissue invasion
  - Abscess formation

- Clinical
  - Fever
  - RUQ pain
  - Peritonitis
  - Elevated right hemidiaphragm / rupture
  - Colitis
- Diagnosis
  - Cysts in stool
  - Serology (e.g., ELISA, CIE, IHA)
  - Hepatic imaging
- Treatment Option
  - Metronidazole 750 mg (oral or IV) 3× daily × 7–10 days
  - Tinidazole 2 g × 3 days followed by:
    - Iodoquinol 650 mg 3× daily × 20 days, or
    - Diloxanide furoate 500 mg 3× daily × 10 days, or
    - Aminosidine (Paromomycin) 25–35 mg/kg/day in 3 divided doses × 7–10 days

- **Babesiosis** (Babesia spp.)

- Demography
  - United States: Endemic to northeast and Midwest US
- Cause
  - Exposure to deer tick
- Pathophysiology
  - Hemolysis with multiorgan involvement
  - Disease is particularly severe in immunocompromised patients
- Clinical
  - Fever
  - Anemia
  - Hepatosplenomegaly

- Abnormal liver test results
- Hemoglobinuria
- Can get pancytopenia in rare cases
- Hepatic involvement reflects the severity of systemic illness but is generally not severe

➢ Diagnosis

- Identification of the parasite on a blood smear
- PCR

➢ Treatment

- Azithromycin 500 mg on day 1, then 250 mg daily
- Atovaquone 750 mg twice daily × 7–10 days
- Clindamycin 300–600 mg IV every 6 hrs or 600 mg every 8 hrs
- Quinine 650 mg every 8 hrs × 7–10 days |

• **Visceral leishmaniasis** (Leishmania donovani)

➢ Demography

- Endemic Areas
  - Eurasia
  - Central America
  - South America
- Consider in immigrants or returning travelers/military personnel from endemic areas

➢ Cause

- Immunosuppression (AIDS, organ transplantation)

➢ Pathophysiology

- Infection of reticuloendothelial (RE) cells
  - Amastigotes are ingested by the sand fly (Lutzomyia) and become flagellated promastigotes; these are phagocytosed by macrophages in the reticuloendothelial system where they multiply

- Clinical
  - Fever
  - Weight loss
  - Hepatosplenomegaly
  - Secondary bacterial infection
  - Skin hyperpigmentation (kala-azar)
  - Patients initially develop an ulcerated papular lesion at site of sandfly bite
  - Incubation period of 2-6 mon occurs prior to development of symptoms
- Diagnosis
  - Amastigotes seen in the spleen, liver, or bone marrow
  - Highest yield from spleen aspirate but liver biopsy is less risky and essentially just as high yield (cultures take several weeks, and serology supportive but not diagnostic)
  - Skin test is not helpful with visceral involvement
  - PCR can be used for monitoring
- Histopathology
  - Organisms found in mononuclear phagocytes of the liver, spleen, bone marrow and lymph nodes
  - Proliferation of Kupffer cells can be seen with amastigotes detected within these cells (Leishman-Donovan bodies)
  - Non-caseating granulomas
  - Hepatocyte necrosis
  - Fibrous deposition with healing
- Treatment
  - Pentavalent antimonial (stibogluconate sodium or meglumine antimoniate) 20 mg/kg/day × 28 days
    - Liposomal amphotericin B (IV) 3–5 mg/kg/day × 5, 10, 14, and 21
    - Aminosidine (paromomycin) 16–20 mg/kg/day × 20 days
    - Pentamidine isethionate 2–4 mg/kg/day for 10–15 days
    - Miltefosine 2.5 mg/kg/day × 28 days |

- **Toxoplasmosis** (Toxoplasma gondii)

➢ Demography
  - Worldwide

➢ Cause
  - Congenital infection
  - Immunosuppression (AIDS, organ transplantation)

➢ Pathophysiology
  - Replication in the liver leading to inflammation, necrosis
  - Oocysts of T. gondii in soil, water, or contaminated meat are ingested and mature in the intestinal tract of humans to become sporozoites, which penetrate the intestinal mucosa, become tachyzoites, and circulate systemically, invading a wide array of cell types

➢ Clinical
  - Fever
  - Lymphadenopathy
  - Occasionally hepatosplenomegaly
  - Atypical lymphocytosis
  - Hepatic involvement has been observed in severe, disseminated infection
  - Patients may be asymptomatic but can see atypical lymphocytes which are otherwise a usual feature of parasitic disease

➢ Diagnosis
  - Serology (IF, ELISA), isolation of the organism in the tissue
  - IgG/IgM antibody

➢ Treatment
  - Pyrimethamine 100 mg loading dose followed by 25–50 mg/day, plus
  - Sulfadiazine 2–4 g/day in 4 divided doses; or
  - Clindamycin 300 mg 4× daily, plus
  - Folinic acid 10–25 mg daily for 2–4 wk

❖ **Nematodes** (round worms)

- **Ascariasis** (Ascaris lumbricoides)

➢ Demography
  - Tropical climates

➢ Cause
  - Ingestion of raw vegetables

➢ Pathophysiology
  - Migration of larvae to the liver
  - Invasion of the bile ducts by adult worms
  - Eggs hatch in the small intestine → larvae penetrate the mucosa → enter the portal circulation → reach the liver, pulmonary artery, and lungs → grow in the alveolar spaces → regurgitated and swallowed → become mature adults in the intestine 2 to 3 mons after ingestion. Then the cycle repeats itself

➢ Clinical
  - Abdominal pain
  - Fever
  - Jaundice
  - Biliary obstruction
  - Granulomas
  - Biliary calculi
  - Small bowel
    - Obstruction
    - Intussception
    - Volvulus
    - Perforation or appendicitis
    - Biliary calculi developing on worm fragments

➢ Diagnosis
  - Ova or adult in stool, or
  - Contrast study

- Treatment
  - Albendazole 400 mg × 1 dose, or
  - Mebendazole 100 mg twice daily × 3 days, or
  - Pyrantel pamoate 11 mg/kg up to 1 g, or
  - Ivermectin 200 µg/kg × 1 dose

- **Hepatic capillariasis (Capillaria hepatica)**

- Demography
  - Worldwide
- Cause
  - Exposure to rodents
  - Acquired by ingesting contaminated food, soil or water with eggs
- Pathophysiology
  - Migration of larvae to the liver
  - Inflammatory reaction to eggs
  - Larvae released in the cecum penetrate the intestinal mucosa → enter the portal venous circulation → lodge in the liver.
    - Four weeks after infection, adult worms disintegrate → releasing eggs into the hepatic parenchyma and producing an intense inflammatory reaction with
      - Macrophages, eosinophils, and giant cells.
      - Resolution is accompanied by marked peri-egg fibrosis.
- Clinical
  - Acute, subacute hepatitis
  - Tender hepatomegaly
  - Splenomegaly
  - Eosinophilia
- Diagnosis
  - Adult worms or eggs in a liver biopsy specimen

- Laboratory investigations
  - ↑ WBC with eosinophilia
  - ↑ AST
  - ↑ ALP
  - ↑ bilirubin
  - Anemia
  - Pneumonitis on chest x-ray
- Histopathology
  - Granulomas around eggs
- Treatment
  - Supportive; possibly dithiazanine iodide, sodium stibogluconate, albendazole, or thiabendazole

- **Strongyloidiasis** (Strongyloides stercoralis)

- Demography
  - Endemic Areas
    - Asia, Africa
    - South America
    - Southern Europe
    - USA
- Cause
  - Immunosuppression (AIDS)
  - Chemotherapy
  - Organ transplantation
- Pathophysiology
  - Larval penetration from the intestine to the liver

- Clinical
  - Hepatomegaly
  - Jaundice (larvae in the portal tract or lobule)
  - Acute infection → pruritic eruption → fever, cough, wheeze, abdominal pain, diarrhea and eosinophilia
  - In immunocompromised patients, hyperinfection syndrome
    - Invasion of any organ, including liver, lung, brain
    - Consider when patient is septic with multiple organisms seen
  - Liver involvement
    - Jaundice and cholestatic biochemical tests
- Diagnosis
  - Larvae in the stool or duodenal aspirate
- Histopathology
  - Periportal inflammation, eosinophilic granulomatous hepatitis, or both.
  - Larvae may be observed in intrahepatic bile canaliculi, lymphatic vessels, and small branches of the portal vein
- Treatment
  - Ivermectin 200 µg/kg/day × 2 days
  - Albendazole 400 mg/day × 3 days

- **Trichinosis (Trichinella spiralis)**

- Demography
  - Temperate climates
- Cause
  - Ingestion of undercooked pork

- Pathophysiology
  - Hematogenous dissemination to the liver
  - Raw or undercooked pork bearing larvae → released in the small intestine, → the mucosa disseminates through the systemic circulation. Larvae can be found in the myocardium, cerebrospinal fluid, brain, and, less commonly, liver and gallbladder.
    - The larvae then re-enter the circulation and reach striated muscle, where they become encapsulated
- Clinical
  - Jaundice, biliary obstruction, larvae in hepatic sinusoids
  - High worm burden
- Diagnosis
  - History
  - Fever
  - Muscle biopsy
  - Diarrhea
  - Myalgias
  - Periorbital edema
  - Leukocytosis with marked eosinophilia
- Histopathology
  - Larvae can be seen invading hepatic sinusoids
  - Hepatic complications may be associated with fatal cases
- Treatment
  - Glucocorticoids for allergic symptoms
  - Albendazole 400 mg twice daily × 10–15 days, or
  - Mebendazole 200 mg daily × 10–15 days |

- **Toxocariasis** (Toxocara canis, T. cati)

➢ Demography
  - Worldwide

➢ Cause
  - Exposure to dogs or cats (especially for children <5 yr)

➢ Pathophysiology
  - Migration of larvae to the liver (visceral larva migrans)
  - Acquired when embryos in the soil are ingested an hatch in the small intestine
  - Larvae then penetrate the intestinal wall and enter the portal venous circulation and reach the liver via the systemic circulation
  - When vessels narrow worms migrate into tissues → provoke granuloma formation with eosinophils (liver, brain or eye most frequently)

➢ Clinical
  - Granuloma formation
  - Eosinophilia
  - Two main clinical syndromes
    - Visceral larva migrans – children with history of pica (findings of eosinophilic granulomas is specific)
      - Chronic cholestatic hepatitis and pyogenic liver abscesses, can have pulmonary and neurologic involvement
    - Occult infections with non-specific symptoms

➢ Diagnosis
  - Larvae in tissue, serology (ELISA)
  - Consider in patients with history of PICA, dog/cat exposure or persistent eosinophilia
  - Stool studies not helpful because eggs are not produced in or remain in GI tract
  - Liver biopsy may be required to differentiate from hepatic capillariasis – ELISA is supportive of diagnosis

➢ Treatment
  - Albendazole 10 mg/kg/day × 5 days
  - Mebendazole 100–200 mg twice daily × 5 days

❖ **Trematodes** (Flukes)

- **Schistosomiasis** (Schistosoma mansoni, S. japonicum)

➢ Demography

- Endemic Areas
  - Asia
  - Africa
  - South America
  - Caribbean
- Schistosoma mansoni is found in the
  - Western Hemisphere
  - Africa
  - Middle East
- S. haematobium is found in
  - Africa
  - Middle East
- S. japonicum and S. mekongi are found in
  - Far East
- S. intercalatum is found in
  - Parts of central Africa.
- The last 2 species are much less common than the other 3 and cause liver disease and colonic disease, respectively

➢ Cause

- Travelers exposed to bodies of fresh water

➢ Pathophysiology

- Fibrogenic host immune response to eggs in the portal vein
- Skin penetration from freshwater source
- Cercariae reach the pulmonary vessels within 24 hrs
  - Pass through the lungs
  - Reach the liver
  - Lodge, develop into adults, and mate
- Adult worms then migrate to their ultimate destinations in
  - The inferior mesenteric venules (S. mansoni), superior mesenteric venules (S. japonicum), or veins around the bladder (S. haematobium)

- Clinical
  - Acute: eosinophilic infiltrate
  - Chronic: hepatosplenomegaly, presinusoidal portal hypertension, granulomas
  - Site of deposition correlates with clinical complications
  - Acute toxemic schistosomiasis
    - Consequence of the host immunologic response to mature worms and eggs
    - Occurs approximately 4 to 6 wks after exposure
    - Headache, fever, chills, cough, diarrhea, myalgias, arthralgias, tender hepatomegaly, and eosinophilia.
  - Untreated acute schistosomiasis invariably progresses to chronic disease
    - Mesenteric infection leads to hepatic complications, including
      - Periportal fibrosis
      - Presinusoidal occlusion
      - Portal hypertension, as a result of the inflammatory reaction to eggs deposited in the liver.
    - Development of periportal fibrosis appears to be related to production of TNF-α
    - Lungs and central nervous system may be affected when eggs or adult worms pass through the liver into the systemic circulation, especially in S. japonicum infection; pulmonary hypertension and cor pulmonale may result
    - With severe schistosomal infection, portal hypertension becomes progressive, leading to gastroesophageal varices, splenomegaly, and rarely ascites.
  - Chronic schistosomal infection may be complicated by increased susceptibility to Salmonella infections
  - Hepatitis B or hepatitis C viral coinfection also is common in persons living in endemic areas and may accelerate the progression of liver disease and development of hepatocellular carcinoma
  - In African intestinal schistosomiasis, pseudopolyps of the colon may develop, leading in some cases to protein-losing colopathy and formation of an inflammatory mass in the descending colon

- Diagnosis
  - Ova in the stool, rectal or liver biopsy
  - Eggs cause a granulomatous response
  - Anemia from recurrent luminal GI bleeding or hypersplenism, leukocytosis with eosinophilia, an elevated erythrocyte sedimentation rate
  - ↑ serum IgE levels. Results of liver biochemical tests generally are normal until the disease is at an advanced stage

- Ultrasound and liver biopsy may demonstrate clay pipestem fibrosis, but are not used in an acute infection (will not see eggs)
- CT may show low-attenuation rings around main portal vein branches with marked enhancement with contrast

➢ Treatment

- Praziquantel 40–60 mg/kg in 1–3 divided doses × 1 day, or
- Oxamniquine for *S. mansoni* (not readily available)
- Acute toxemic schistosomiasis
  - Praziquantel 40–60 mg/kg in 2–3 divided doses × 1 day + glucocorticoids |

• **Fascioliasis** (Fasciola hepatica)

➢ Demography

- Worldwide

➢ Cause

- Cattle or sheep raising; ingestion of contaminated watercress

➢ Pathophysiology

- Migration of larvae through the liver
- Penetration of the bile ducts or surgery
- Eggs passed in the feces of infected mammals into fresh water give rise to miracidia → penetrate snails and eventually emerge as mobile cercariae → attach to aquatic plants such as watercress
- Hosts become infected when they consume plants containing encysted metacercariae → bore into the intestinal wall, enter the abdominal cavity → penetrate the hepatic capsule, and eventually settle in the bile ducts → attain maturity.
- Mature flukes release eggs that are passed in the host's feces to complete the life cycle

➢ Clinical

- Acute: fever, abdominal pain, jaundice, hemobilia
- Chronic: hepatomegaly

- Acute
  - Migration of young flukes through the liver
    - Can get urticaria with dermatographia and nonspecific GI symptoms
    - Enlarged tender liver on exam, eosinophilia
- Latent phase – settling of flukes in bile ducts – persistent eosinophilia
- Chronic obstructive phase – consequence of intrahepatic and extrahepatic bile duct inflammation and hyperplasia provoked by flukes
  - Recurrent biliary pain, cholangitis, cholestasis and biliary obstruction
  - Cholestatic findings on liver biochemistry
- Long term can lead to biliary cirrhosis and secondary sclerosing cholangitis – no definite link with malignancy

➢ Diagnosis

- Ova in the stool, flukes in the bile ducts at ERC

➢ Treatment

- Triclabendazole 10 mg/kg × 1 dose

- **Clonorchiasis and Opisthorchiasis (**Clonorchis sinensis, Opisthorchis viverrini, O. felineus)

➢ Demography

- Endemic Areas
  - Southeast Asia
  - China
  - Japan
  - Korea
  - Eastern Europe

➢ Cause

- Predisposing Factors Ingestion of raw fresh-water fish

➢ Pathophysiology

- Migration through the ampulla; egg deposition in the bile ducts
- Eggs are passed in the feces into fresh water, consumed by snails → hatch as free-swimming cercariae → seek and penetrate fish or crayfish and encyst in skin or muscle as metacercariae.

- The mammalian host is infected when it consumes raw or undercooked fish.
- The metacercariae excyst in the small intestine and migrate into the ampulla of Vater and bile ducts → mature into adult flukes
- Infection can be maintained for 2 decades or longer

➢ Clinical

- Biliary
  - Hyperplasia
  - Obstruction
  - Sclerosing cholangitis
  - Stone formation
  - Cholangiocarcinoma

➢ Diagnosis
- Ova in the stool
- Flukes in the bile ducts at ERC or surgery

➢ Treatment
- Praziquantel 75 mg/kg in 3 divided doses × 1 day

❖ **Cestodes**

- **Echinococcosis** (Echinococcus granulosus, E. multilocularis)

➢ Demography
- Worldwide

➢ Cause
- Cattle and sheep raising (E. granulosus)

➢ Pathophysiology
- Migration of larvae to the liver
- Encystment (hydatid cyst)

- Infection occurs when humans eat vegetables contaminated by dog feces that contain embryonated eggs.
  - The eggs hatch in the small intestine and liberate oncospheres
  - Penetrate the mucosa and migrate via vessels or lymphatics to distant sites.
  - The liver is the most common destination (70%), followed by the lungs (20%), kidney, spleen, brain, and bone. In these organs, a hydatid cyst develops by vesiculation → produces thousands of protoscolices.
  - The cyst wall contains 3 layers: an outer adventitial layer (host-derived and can calcify) and intermediate acellular and inner germinal layers, which are worm-derived.
  - A protoscolex is produced asexually within small secondary cysts that develop from the inner layer.
  - Rupture of the hydatid cyst releases the viable protoscolices
  - Daughter cysts in secondary sites
  - The adult Echinococcus tapeworm consists of a scolex → contains a rostellum with 20 to 50 hooklets and 4 suckers, a neck, and an immature, mature, and gravid proglottid.
  - Dogs acquire the infection by consuming organs of sheep, cattle, or other livestock bearing the hydatid cyst.

➢ Clinical

- Tender hepatomegaly, fever, eosinophilia, cyst rupture, biliary obstruction
- Most patients with hydatid cyst are asymptomatic
- Cysts can rupture spontaneously if they grow large enough causing
  - Dyspnea
  - Hemoptysis
  - Anaphylactic response
- Rare complications of hydatid cyst include
  - Pancreatitis
  - Portal HTN
  - Budd Chiari
  - Rupture into pericardial sac

➢ Diagnosis

- Serology (ELISA, IHA)
- Hepatic imaging

➢ Treatment

- Surgical resection can be curative
- Percutaneous drainage
- Perioperative albendazole 400 mg twice daily continuing × 8 wk

❖ Fungi

• Candidiasis

➢ Pathophysiology
- May cause invasive systemic infection
- Hepatic involvement in severely immunocompromised patients (most often chemotherapy patients)
  - High mortality rate
  - Can get focal candidiasis from colonization of GI tract
    - Local collections of candida collect in GI tract following onset of neutropenia and mucosal injury from high dose chemotherapy
    - Fungemia seeds the liver and can lead to formation of hepatic micro and macroabscesses

➢ Clinical
- Fever
- Abdominal pain/distention
- Nausea
- Vomiting
- Diarrhea
- Tender hepatomegaly

➢ Diagnosis
- ↑ ALP
- Liver biopsy
  - Necrosis with microabscesses
  - Yeast of hyphae
- PCR

➢ Treatment
- IV amphotericin B
- Echinocandins
- Azoles

- **Histoplasmosis**

➢ Clinical
  - A respiratory illness → spreads to the liver
  - Disseminated form seen in immunocompromised patients
  - Symptoms
    - Fever
    - Oropharyngeal ulcers
    - Hepatomegaly
    - Splenomegaly

➢ Diagnosis
  - ↑ ALT
  - ↑ AST
  - ↑ ALP
  - Liver biopsy showing organism (H and E stain)
  - Culture low yield but serology can be helpful in confirming diagnosis

➢ Treatment
  - Amphotericin B
  - Fluconazole
  - Itraconazole

❖ **Liver Abscesses**

- **Pyogenic Abscesses**

➢ Risk factors
  - Malignancy
  - Immunosuppression
  - Diabetes mellitus
  - Previous biliary surgery
  - Interventional endoscopy

- Pathogenesis
  - Infection may spread to the liver from the bile duct, along a penetrating vessel, or from an adjacent septic focus
  - May arise as a late complication of endoscopic sphincterotomy for bile duct stones or within 3 to 6 wks of a surgical biliary-intestinal anastomosis
  - Less commonly are complications of bacteremia
  - Could be initial presentation of hepatocellular or gallbladder carcinoma
- Microbiology
  - Most often polymicrobial
  - Most frequently isolated organisms are Escherichia coli and Klebsiella, Proteus, Pseudomonas, and Streptococcus species, particularly the Streptococcus milleri group
  - Most commonly identified anaerobic species are Bacteroides fragilis and Fusobacterium necrophorum
  - Pyogenic abscess associated with recurrent pyogenic cholangitis may be caused by Salmonella typhi
  - Fungal abscesses of the liver may occur in immunocompromised hosts, particularly those with a hematologic malignancy
- Clinical
  - Fevers, RUQ pain, septic shock
  - Hepatomegaly, splenomegaly
  - Could develop portal HTN if portal vein has been thrombosed
- Laboratory
  - Anemia
  - Leukocytosis
  - ↑ ALP
  - Transaminitis

- Diagnosis
  - Blood culture
  - Imaging
    - US or CT
    - MRI may be helpful for looking at small abscesses
    - ERCP if biliary stones
  - Plasma cell granuloma – benign lesion of proliferating fibrous tissue infiltrated by inflammatory cells
- Risk factors
  - Chronic inflammatory and autoimmune disorders, particularly ascending cholangitis and PSC, as well as diabetes mellitus, Sjögren's syndrome, gout, UC, Crohn disease, HIV infection, EBV infection, and acute myeloblastic leukemia.
- Treatment
  - Surgical resection
  - Antibiotics
  - Drainage

- **Amebic Abscesses**

- Risk factors
  - Travel to endemic area
  - Immunosuppressed (HIV)
- Clinical features
  - Occurs following 2 wks of symptoms
    - Bloody diarrhea, dysentery
  - Latency period following GI symptoms of years is possible
  - Liver abscess is the most common extraintestinal manifestation of amebiasis
  - RUQ pain, fever, malaise, myalgias, arthralgias, respiratory symptoms
  - Jaundice is uncommon but signals a poor prognosis

- Diagnosis
  - Amebic abscess
    - Commonly localized to the right hepatic lobe, close to the diaphragm, and is usually single
  - Available serologic tests include
    - ELISA
    - Indirect hemagglutination
    - Cellulose acetate precipitin
    - Counter immunoelectrophoresis
    - Immunofluorescent antibody, and
    - Rapid latex agglutination tests
      - High sensitivity and specificity, but can get false negatives with in first 10 days of infection
- Treatment
  - Metronidazole

Differential Infections Cause of Hepatic Abscesses

Parameter	Pyogenic	Amebic
○ Number	− Often multiple	− Usually single
○ Location	− Either lobe of liver	− Usually right hepatic lobe, near the diaphragm
○ Clinical − Jaundice	− Subacute − Mild	− Acute − Moderate
○ Diagnosis	− US or CT ± aspiration	− US or CT and serology
○ Treatment	− Drainage (if technically feasible) + IV antibiotics	− Metronidazole 750 mg TID × 7–10 days orally or IV; or − Tinidazole 2 g orally × 3 days Followed by: − Iodoquinol 650 mg orally TID × 20 days − Diloxanide furoate 500 mg orally TID × 10 days, or − Aminosidine (paromomycin) 25–35 mg/kg/day orally in 3 divided doses × 7–10 days

Hepatorenal Syndrome

Anshul Arora and Alan BR Thomson

- Demography
  - AKI very common is hospitalized patients with cirrhosis and ascites (27-52%)
  - Development of AKI associated with ↑ 30-day mortality of 29% to 44%
- Definition
  - Inappropriate and intense vasoconstriction leading to ↑ Cr_s

Revised HRS Nomenclature

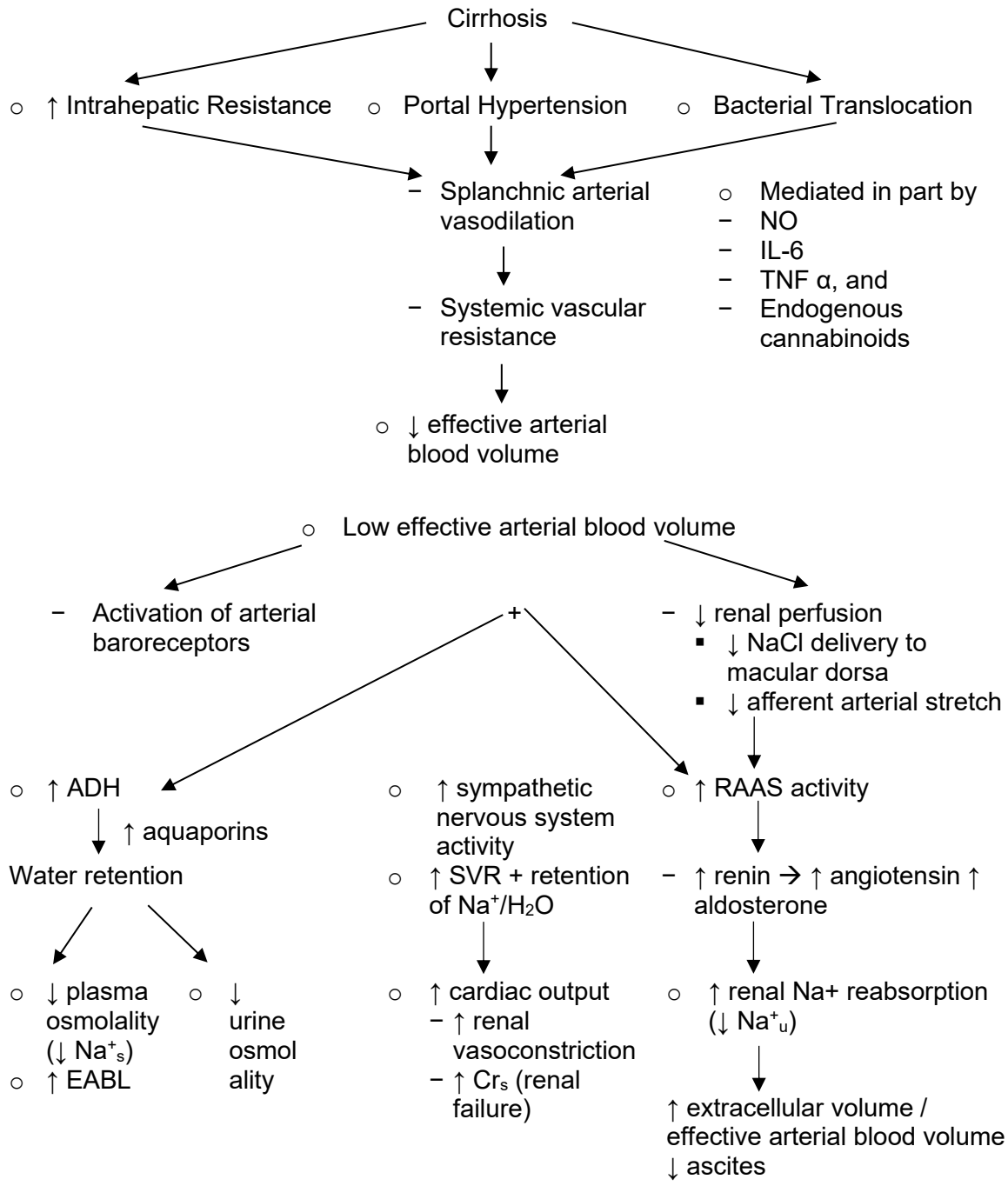
Old Classification	New Classification	Criteria
HRS-1	HRS-AKI (ICA-AKI criteria*)	▪ Absolute increase in Cr_s ≥ 26.5 µmol/L (0.3 mg/dl) within 48 hrs and/or ▪ Urinary output ≤0.5 mL/kg BW ≥6 hrs or ▪ % ↑Cr_s ≥50% using the last available value of outpatient Cr_s within 3 mon as the baseline value
HRS-2*	HRS-AKD HRS-CKD HRS-NAKI	▪ eGFR <60 mL/min per 1.73 m^2 for <3 mons in the absence of other (structural) causes ▪ eGFR <60 mL/min per 1.73 m^2 for ≥ 3 mons in the absence of other(structural) causes ▪ % Cr_s <50% using the last available value of outpatient Cr_s within 3 mon as the baseline value

* Excludes other causes of AKI in cirrhosis (HRS is a diagnosis exclusion)

Abbreviations: AKD, acute kidney disease; BW, body weight; CKD, chronic kidney disease; Cr_s, creatinine; eGFR, essential glomerular filtration rate; HRS, hepatorenal syndrome; mon, months; NAKI, non-acute kidney injury

➢ Pathophysiology

Physiological Effects of Cirrhosis on Kidneys



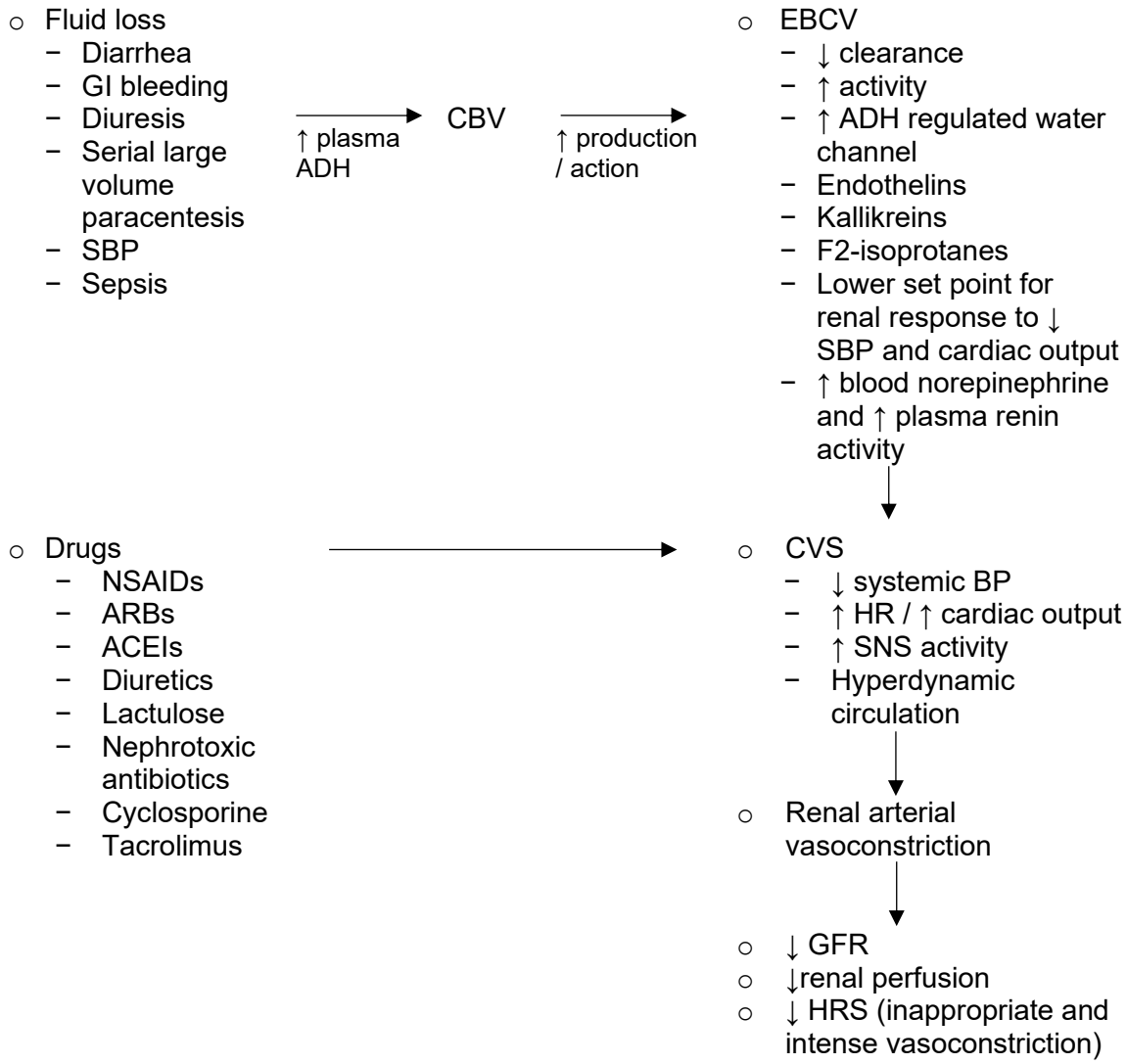
- When there is cirrhosis
  - Infection
  - Inflammation
  - Vasoactive mediators → ↑ vasodilation, ↑ NO, ↑ CO, ↑ Glucagon, ↑ prostacyclin, ↑ adrenomedullin, ↑ endogenous opiates
  - Splanchnic and peripheral vasodilation
  - CVS
    - ↓ systemic BP
    - ↑ HR / ↑ cardiac output
    - ↑ SNS activity
    - Hyperdynamic circulation
  - EBCV
    - ↓ clearance
    - ↑ activity
    - ↑ ADH regulated water channel
    - Endothelins
    - Kallikreins
    - F2-isoprotanes
    - Lower setpoint for renal response to ↓ SBP and cardiac output
    - ↑ blood norepinephrine and ↑ plasma renin activity
  - Fluid loss
    - Diarrhea
    - GI bleeding
    - Diuresis
    - Serial large volume paracentesis
    - SBP
    - Sepsis
  - Drugs
    - ARBs
    - ACEIs
    - Cyclosporine
    - Diuretics
    - Lactulose
    - Nephrotoxic antibiotics
    - NSAIDs
    - Tacrolimus
  - Renal arterial vasoconstriction
  - ↓ GFR
  - ↓ renal perfusion
  - ↓ HRS (inappropriate and intense vasoconstriction)
  - Cirrhotic cardiomyopathy
    - Hyperdynamic circulation → LV hypertrophy → diastolic dysfunction → ↓B-adrenergic signaling
    - ↓ cardiomyocyte function
      - ↑ QTC

Renal

Ascites
SBP
↓ Na^+_s

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ADH, antidiuretic hormones; ARBs, angiotensin receptor blockers; BP, blood pressure; CO, carbon monoxide; CVS, cardiovascular system; GFR, glomerular filtration rate; HR, heart rate; HRS, hepatorenal syndrome; LV, left ventricle; Na^+_s, serum sodium concentration; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; SBP, systolic blood pressure

- When there is no cirrhosis



Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ADH, anti-diuretic hormone; ARBs, angiotensin receptor blockers; CBV; cerebral blood volume; CO, carbon monoxide; CVS, cardiovascular system; GFR; glomerular filtration rate; GI, gastrointestinal; HR; heart rate; HRS, hepatorenal syndrome; LV; left ventricular; Na+, sodium ion; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; QTc, corrected QT interval; SBP, systolic blood pressure; SNS, sympathetic nervous system.

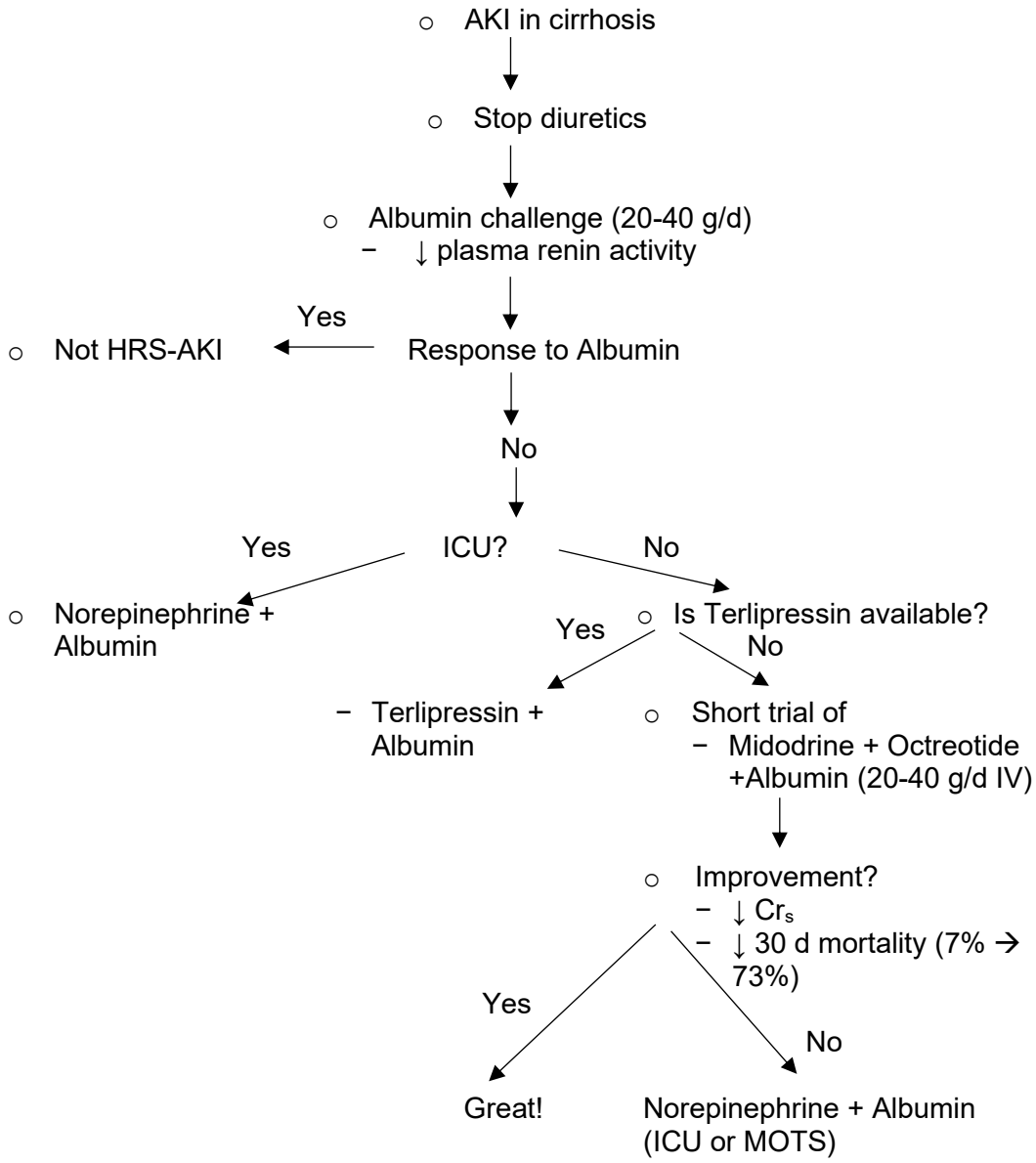
- Diagnostic criteria for HRS-AKI
  - Cirrhosis with Portal HTN
  - Acute Kidney Injury (ICA AKI Criteria)
  - Not Volume Responsive (to Albumin)
  - No clear alternative explanation (differential diagnosis)
    - No evidence of glomerular disease (hematuria or significant proteinuria
    - No recent Nephrotoxic mediations (NSAIDS, iodinated contrast)
    - No shock

Differential Diagnosis of AKI in Cirrhosis

- Pre-renal
  - Volume depletion
  - Hepatorenal syndrome
  - Cirrhotic cardiomyopathy
- Intra-renal
  - Acute tubular necrosis (ATN)
  - Cholemic nephropathy
  - Glomerulonephritis (IgA MPGN)
- Post-renal
  - Obstruction

- Essentially make the diagnosis of HRS
  - ↑ urine osmolarity
  - ↓ Na^{+}_{u}
  - ↓ FABV / ↓ Renal perfusion

- Treatment Algorithm Approach



- Terlipressin

Terlipressin vs. Placebo – Clinical Outcome Comparison

Outcome	Terlipressin (n=199)	Placebo (n=101)
HRS Reversal	32% *	17%
Mortality Rate	51%	45%
Liver Transplant Required	23%	29%
Respiratory Failure (adverse effect)	14%	5%

*P = 0.006 (statistically significant for HRS reversal)

Respiratory failure higher with terlipressin plus total albumin exposure

< 423 g, 12.9%

≥ 423 g, 16.5%

- Vasopressin analogue with affinity for body
  - V1 receptors – vascular smooth muscle (systemic, splanchnic, renal and coronary circulations)
  - V2 receptors – distal convoluted tubule and medullary collecting ducts in the kidney (regulate aquaporins)

- Terlipressin (3-12 mg/d) plus albumin (20-40 g/d) superior to midodrine (7.5 – 12.5 mg tid) pus octreotide (100-200 µg tid) plus albumin (20-40 g/d)

	Response	
Combination	Complete	Partial/Complete
TER + Alb	58	70
MID + OCT + Alb	5	30

- Confirm RCT multicentre, prospective, randomization: Terlipressin (1-2 mg IV q6hr plus albumin (20-49 g/d) vs. albumin (20-40 g/d) in Type 1 HRS

Cavallin M, et al. Hepatology. 2015; 62(2): 567–574.
Wong F, et al. N Engl J Med 2021;384(9):818–828.

- Norepinephrine
  - α-/β-agonist
  - Norepinephrine continuous infusion
    - 0.5 mg/hr, titrate to maintain MAP ≥ 10 mmHg maximum dose 3 mg/hr plus albumin 20 g/d is non-inferior to terlipressin (0.5 – 2 mg IV q6hr) plus albumin 20 g/d
  - Norepinephrine has fewer AEs than TER

Nassar AH, et al. PLoS One 2014;9(3): e93297.

- Transjugular intrahepatic portosystemic stent (TIPS) procedure for HRS
  - Steady
    - ↓ Na^+_s
    - ↑ Na^+_u

    } Over 6 mon

Rössle M, Gerbes AL. Gut. 2010;59(7):988–1000.

- Renal replacement therapy (RRT, aka renal dialysis) (Allegretti AS, et al. Clin J Am Soc Nephrol 2019;14(12):1763–1772)
  - RRT is frequently initiated in HRS patients, but outcomes are poor without liver transplantation.
  - Timing of RRT initiation did not significantly affect survival, suggesting that early dialysis may not improve prognosis in the absence of transplant.
  - Continuous RRT (CRRT) was more commonly used than intermittent modalities, reflecting hemodynamic instability in HRS patients.
  - Transplant candidacy is the key determinant of whether RRT offers meaningful benefit
    - Patients not eligible for liver transplant had markedly worse outcomes.
  - High mortality rates were observed in HRS patients receiving RRT without subsequent liver transplantation.

- Liver transplant
  - The only definitive treatment for HRS-AKI in 2021 is liver transplantation.
  - Do **not** forget “Comfort focused care”

COVID-19 and Chronic Liver Disease

Chris Lavalle

➢ Clinical course of COVID-19 in CLD

- 4 died during the observation period
  - Perforated duodenal ulcer
  - Massive GIB
  - Hemoperitoneum post paracentesis
  - Cholangitis
- Cholangitis
  - 5 patients considered for transplant
    - 1 living donor transplant
    - 2 died before transplant
    - 2 declined or ineligible

- Susceptibility
  - Unclear
    - Does **not** seem markedly increased
    - CLD is not more prevalent in hospitalized patients in a meta-analysis of 73 studies with almost 25000 patients
      - 3%, in keeping with the general population
    - Possibly better adherence to social distancing guidelines and vaccination

- Disease severity in CLD
  - CLD is an independent risk factor for mortality from COVID-19
  - TriNetX Registry (USA) Gastroenterology 2020; 159(2): 768
    - Patients > 10 yr, 2780 patients, 250 with liver disease, 50 with cirrhosis
    - Propensity matching for comorbidities (hypertension, diabetes), age, race, nicotine
    - 30-day mortality, 12% vs 4%
  - Other registry studies have placed mortality rates higher in CLD (J Hepatol 2020;73(3):705)
  - ↑ CP stage →
    - ↑ hospitalization
    - ↑ IUC
    - ↑ invasive ventilation

Mortality Rates by Cirrhosis Stage and Clinical Setting

Condition	CLD without cirrhosis	CP-A	CP-B	CP-C
○ Once hospitalized	8%	22%	39%	54%
○ Once admitted to ICU	20%	40%	62%	79%
○ Once receiving ventilation	21%	52%	74%	90%

Abbreviations: CP, Child-Pugh; CLD, chronic liver disease; ICU, intensive care unit

Adapted from: Marjot T, et al. Nat Rev Gastroenterol Hepatol 2021; 8: 348–364.

- Patients with cirrhosis face elevated risks during COVID-19 due to a cascade of systemic and immune dysfunctions. These mechanisms include:
  - Systemic Inflammation
    - Cirrhosis triggers chronic immune activation.
    - This leads to widespread inflammation, which can destabilize hepatic function and promote multi-organ stress.
  - Hypercoagulation
    - Inflammatory signals increase clotting tendency.
    - This raises the risk of thrombotic events, including pulmonary embolism and portal vein thrombosis.
  - Acute Hepatic Decompensation & ACLF
    - COVID-19 can precipitate sudden liver failure in cirrhotic patients.
    - This includes worsening encephalopathy, jaundice, and systemic collapse.
  - Organ-Specific Complications
    - Ascites: Fluid accumulation due to portal hypertension and hypoalbuminemia.
    - Hepatic encephalopathy: Neurocognitive decline from ammonia buildup.
    - Respiratory failure: Resulting from systemic inflammation, fluid overload, and impaired oxygen exchange.
  - Immune Dysfunction
    - ↓ T lymphocyte frequency and proliferation: Weakens cellular immune defense.
    - ↓ Antigen-dependent responses: Reduces ability to mount targeted immune reactions.
    - ↓ B lymphocyte frequency and $CD24^{+}$ memory cells: Impairs antibody production and long-term immunity.
    - Defective vaccine response: Cirrhotic patients show poor immunogenicity, limiting vaccine protection

Adapted from: Marjot T, et al. Nat Rev Gastroenterol Hepatol 2021; 8: 348–364.

- Liver related features of acute infection
  - Patients often present with elevated aminotransferases
    - Up to 50% of cases
  - Usually mild
    - < 5x ULN
    - AST greater than ALT
      - COVID-19-related mitochondrial dysfunction
      - SARS-CoV-2-induced hepatic steatosis
      - Altered hepatic perfusion secondary to microthrombotic disease
  - Can transition to severe acute hepatitis
    - However, debate on association between degree of enzyme elevation and disease outcome
      - Shock, ICU admission, Mechanical ventilation
      - More lab values in those more ill
      - AST/ALT > 5x ULN has been associated with increased mortality
  - Acute hepatitis has been reported in asymptomatic patients
    - Rare, only a few case reports, although unknown prevalence

- Clinical: Liver related Chronic complications

Faruqui et al; Am J Gastroenterol 2021; 116(7): 1414-1425

- Cholangiopathy
  - Retrospective review of all admitted COVID-19 patients with hepatology consultation over a 6 mon period
    - Identified 12 patients with cholangiopathy as a late complication of infection
      - M, 11; F, 1; mean age 58; represented 0.6% of all admitted Covid patients
      - ↑ ALP peak, medium ↑ AST, GGT, ↑ ALP
    - Mean time from COVID-19 diagnosis to diagnosis of cholangiopathy was 118 days
  - MRCP
    - Beading of intrahepatic ducts (11/12, 92%)
    - Bile duct wall thickening with enhancements (7/12, 58%)
    - Peribiliary diffusion high signal (10/12, 83%)
  - ERCP
    - 4 patients underwent ERCP
      - Limited due to predominance of diffuse intrahepatic abnormalities unlikely to be conducive to intervention
    - 11 received ursodiol: no convincing evidence of therapeutic benefit

- Biopsy
  - Acute and chronic large duct destruction
  - No definitive bile duct loss
  - Mild fibrosis of some portal tracts
  - Generally, in keeping with sclerosing cholangitis (PSC/SSC

➢ Histopathology Findings

- Non specific
  - Moderate micro-vesicular steatosis
  - Mixed lobular and portal activity
  - Focal necrosis
  - Hepatic vascular involvement
    - Possible Italian Group

➢ Treatment

- COVID-19 and Specific Liver Disease
  - Pooled recommendations from AASLD/EASL/APASL
    - NAFLD
    - HBV and HCV
    - AIH
    - Transplant

- NAFLD
  - Continue Treatment of Hypertension with ACE/ARB
  - Prioritize admission
    - High mortality in CLD and likely comorbidities
    - Otherwise, no specific recommendations

- HBV and HCV
  - Chronic hepatitis B or C have not been associated with increased mortality from COVID-19
  - HBV
    - Defer initiation of treatment until after recovery if possible
    - Continue treatment for chronic HBV or HCV if already receiving
    - Initiate therapy if clinical suspicion of HBV flare or when initiating immunosuppression
  - HCV
    - Defer treatment until recovery from COVID-19

- Autoimmune hepatitis
  - Largest cohort of patients with AIH and SARS-CoV-2 infection (n = 70) showing equivalent risk of death compared to propensity score-matched patients with other aetiology of liver disease and patients without liver disease (Marjot T, et al. J Hepatol. 2021; 74(6):1335-1343)
  - Do **not** discontinue corticosteroids, use stress doses as needed
    - Consider budesonide for management of acute flare of AIH to limit systemic glucocorticoids
  - In those without infection do **not** ↓ immunosuppression
  - In those with mild symptoms continue immunosuppression
  - In severe infection consider lowering antimetabolites

- Liver Transplant
  - Prioritize LT for patients with
    - Acute liver failure
    - Acute-on-chronic liver failure (ACLF)
    - High MELD score and
    - HCC at upper limits of the Milan criteria
  - Test everyone for LT
    - Consideration for Covid
  - In SARS-CoV-2-positive transplant candidates
    - Consider transplantation at least 14-21 d after symptom resolution and 1 or 2 negative SARS-CoV-2 diagnostic tests
  - In posttransplant patients with COVID-19
    - Consider lowering overall immunosuppression (particularly antimetabolite therapy)

❖ **Covid Specific therapy and the liver**

- **Monoclonal Antibody Preparations for Treatment of Mild to Moderate COVID-19**
  - Monoclonal antibodies that target the SARS-CoV-2 spike protein have received emergency use authorization for treatment of mild to moderate COVID-19.
    - Casirivimab + imdevimab (Regeneron).
    - Sotrovimab (Vir Biotechnology and GSK).
    - Bamlanivimab alone and bamlanivimab + etesevimab (Eli Lilly).

- Criteria for treatment include the following:
  - Mild to moderate proven COVID-19.
  - Patients ≥12 yrs and weighing ≥40 kg.
  - At high risk for progressing to severe COVID-19 or hospitalization.
  - Not currently hospitalized for COVID-19 (allowed if hospitalized for another reason).
  - Not requiring oxygen therapy or increase in baseline oxygen therapy.
  - Must be administered in setting allowing treatment of infusion reactions.
- Data indicates that when given early in the course of COVID-19 (within 10 days of onset of symptoms but preferably earlier)
  - Monoclonal antibodies ↓ need for hospitalization and death (up to 85% reduction), and
  - ↓ viral load

- **Remdesivir**
  - Patients ≥12 yrs, and ≥40 kg with COVID-19 requiring hospitalization.
  - No mortality benefit has been demonstrated, but
    - ↓ duration of illness
    - ↓ hospitalization, and
    - Most effective when given to patients on supplemental oxygen within 10 days of symptom onset
  - No benefit observed in those requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
  - Elevations in aminotransaminase levels have been observed in patients and healthy volunteers treated with remdesivir
  - Discontinue if ALT >10x ULN elevation and signs or symptoms of liver inflammation

- **Dexamethasone**
  - Dexamethasone (6 mg daily for up to 10 days)
    - ↓ mortality in hospitalized patients with COVID-19 requiring supplemental oxygen.
    - The greatest benefit was seen in patients requiring mechanical ventilation
    - A trend toward harm was observed in patients who did not require supplemental oxygen
    - No benefit was seen in those more than 7 days from onset of symptoms.

- **IL-6 inhibitors**
  - Tocilizumab and sarilumab are IL-6 inhibitors approved by the FDA for treatment of autoimmune diseases (e.g., rheumatoid arthritis) and chimeric antigen receptor T cell (CAR-T) induced cytokine release syndrome.

- Early in the COVID-19 pandemic, case series suggested that IL-6 inhibition of the inflammatory state occurring in some patients with COVID-19 might improve outcomes.
- Multiple randomized trials have been reported with mixed results.
  - Overall, when added to dexamethasone, tocilizumab (less data available for sarilumab), may
    - ↓ mortality
    - ↓ duration of critical illness, and
    - ↓ need for mechanical ventilation in patients with recent (24 hrs), or
    - ↓ need for mechanical ventilation and elevated markers of inflammation (e.g., CRP levels > 7.5 mg/L).
- Tocilizumab is suggested for use in those not responding to steroids alone with high levels of inflammation (e.g., CRP >7.5 mg/L) and progressive oxygen requirements.
- Immunosuppressed patients who receive both corticosteroids and tocilizumab ↑ risk for both routine and opportunistic infections and careful monitoring is required.
- ↑ aminotransaminase elevations and drug-induced liver injury have been observed in patients treated with tocilizumab.
- Not recommended in patients with active hepatic disease, particularly if AST or ALT >1.5x ULN

Suggested Reading:

AASLD Expert Panel Consensus statement (Updated Nov 2021)
https://www.aasld.org/sites/default/files/2021-11/AASLD%20COVID-19%20Expert%20Panel%20Consensus%20Statement%20Update%2011.02.2021.pdf

Most recent Ontario Vaccination Guidelines (Dec 31, 2021)
https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/vaccine/COVID-19_vaccination_rec_special_populations.pdf

Review article to early 2021 with a look at mechanism of disease severity in CLD
https://www.nature.com/articles/s41575-021-00426-4#ref-CR92

Assessing Surgical Risk in Patients with Cirrhosis

Tamoor Afzaal

- Overview
  - 1.5 billion cases of Chronic Liver Disease (CLD) worldwide (all stages)
  - With ↑ rates of alcohol use worldwide, burden of ALD expected to increase
  - Modeling studies estimate of NASH prevalence will ↑ over the next 10 yrs
  - Patients with cirrhosis are living longer with more advanced disease because of improved medical and surgical management.
  - Important to be able to assess the risk of surgery which might be needed in our patients with chronic liver disease
  - Cirrhotic patients are at risk of other diseases and morbidities that patients with cirrhosis may not have experienced in the past including emergent or elective surgeries

Cheemerla, S. and Balakrishnan, M. Clinical Liver Disease 2021; 17:365-370
Northup PG, et al. Clin Gastroenterol Hepatol. 2019; 17(4): 595-606.

For Surgery in Patients with Cirrhosis – Estimates over the years of post-operative mortality

- 1984
  - Garrison et al. Abdominal Surgery (n= 100)
    - 30% total mortality
    - CP-A = 10%, CP-B = 31%, CP-C 76%
- 1997
  - Mansour et al. Abdominal Surgery (n = 92)
    - 26% total mortality
    - CP-A = 10%, CP-B = 30%, CP-C 82%
- 2010
  - Talem et al. Abdominal Surgery (n = 100) (many laparoscopic procedures)
    - 7% total mortality
    - CP-A = 2%, CP-B = 12%, CP-C 12%
  - Modi et al. Cardiac surgery (n = 210)
    - Systematic Review and Meta-analysis
    - 17% total mortality
    - CP-A = 5%, CP-B = 35%, CP-C 70%

- 2011
  - Neff et al. Abdominal Surgery (N = 138)
    - 28% total mortality
    - CP-A = 10%, CP-B = 17%, CP-C 63%

Garrison RN, et al. Ann Surg 1984; 199(6): 648-55.
Mansour A, et al. Surgery 1997; 122,4: 730-5 discussion 735-6.
Telem DA, Clin Gastroenterol Hepatol. 2010; 8(5): 451-7.
Neeff H, et al. J Gastrointest Surg 2011; 15(1):1-11.
Modi A, et al. Interact Cardiovasc Thorac Surg. 2010; 11(5): 630-4.

➢ Pathophysiology

- Hemodynamic changes
  - Hemodynamic changes that ↓ hepatic perfusion AT BASELINE
    - Systemic Vascular Resistance
    - ↓ Vascular Autoregulation
    - Arteriovenous Shunting
    - Splanchnic Vasodilation

Friedman LS. Trans Am Clin Climatol Assoc. 2010; 121: 192-204.
Northup PG, et al. Clin Gastroenterol Hepatol. 2019; 17(4): 595-606.

- Intraoperative Risks
  - ↑ Intraoperative Bleeding/Hemorrhage
  - ↑ Anesthetic Agents (e.g., Propofol)
  - ↑ Positive Pressure Ventilation
  - ↑ Pneumoperitoneum

    ↓

    ↓↓↓ hepatic perfusion

- Synthetic Protein Dysfunction
  - As cirrhosis progresses the degree of protein synthetic dysfunction progresses →
    - Results in Malnutrition and sarcopenia syndrome → ↓ wound healing / ↓ physical recovery (deconditioning) in the post operative period

- Bleeding Risk
  - ↑ risk of surgical bleeding (especially bleeding from the splanchnic system in thoracic / abdominal surgeries
  - Splenic sequestration → potential thrombopoietin deficiency leads to peripheral thrombocytopenia → ↓ primary hemostasis

- **Hypoxemia Risk**
  - Intra-operative hypoxemia from
    - Ascites
    - Hepatic hydrothorax
  - Post operatively
    - Ascites
    - Hepatic encephalopathy (HE)
    - Anesthetic agent pharmacodynamics
    - ↑ risk of aspiration
  - Hepatopulmonary syndrome (HPS) in 5-32% patients with cirrhosis

Friedman LS. Trans Am Clin Climatol Assoc 2010; 121: 192-204; discussion 205.
Northup PG, et al. Clin Gastroenterol Hepatol. 2019; 17(4): 595-606.

➢ Prediction Scored for Surgical Risks in Patient with Cirrhosis

- **The Child-Turcotte Pugh Score (CTP): 1980**
  - Numerous retrospective studies have shown good correlation between Child-Pugh (CP) Turcott class and surgical mortality

Parameter	Score 1	Score 2	Score 3
○ Albumin (g/L)	> 35	28 – 35	< 28
○ Ascites	Absent	Slight	Moderate
○ Bilirubin (µmol/L)	< 34.2	34.2 – 51.3	> 51.3
○ Encephalopathy	None	Grade 1 – 2	Grade 3 – 4
○ PTT – Seconds over control – INR	< 4 < 1.7	4 – 6 1.7 – 2.3	> 6 > 2.3

Score	Class	Surgical Mortality
5-6	A	10%
7-9	B	30%
10-15	C	76-82%

- **Model for End Stage Liver Disease (MELD) Score**
  - Addresses some limitations of the CP score
    - All objective variables only (no ascites, hepatic encephalopathy)
    - Variables weighted differently
    - No arbitrary cut-offs
    - Not continuous (result of MELD score is a continuous variable instead of 3 classes)
  - MELD Score (original, pre-2016, Model for End-Stage Liver Disease): Calculates the MELD score to quantify end-stage liver disease for transplant planning
    - Dialysis at least twice in the past week
    - Creatine (normal, 62-115 µmol/L
    - Bilirubin (normal, 5.13-32.42 µmol/L
    - INR (normal, 0.8-1.2)

Calculation of MELD Score = 3.78 x ln (serum bilirubin in mg/dL) + 11.2 x ln (INR) + 9.57 x ln (serum creatinine in mg/dL) + 6.43

Perkin L, et al. Clin Gastroenterol Hepatol 2004; 2(8); 719-23
Suman A, et al. Arch Surg 2005; 140: 650-4.
Befeler AS, et al. Arch Surg 2005; 140(7): 650-4; discussion 655.

  - Abdominal, orthopedic, cardiovascular, and urologic procedures (140 patients)
    - MELD mean 18.0
  - MELD score was the only statistically significant predictor of 30-day mortality
    - ~1% ↑ mortality risk for each 1-point ↑ MELD score (5 to 20)
    - 2% ↑ mortality risk for each 1-point increase in the MELD score >20

Northup PG, et al. Ann Surg 2005; 242(): 595-606.

- Largest retrospective study of predictors of perioperative mortality in patients with cirrhosis (n = 772)
  - Included abdominal (non-laparoscopic-cholecystectomy), orthopedic, cardiac surgeries
  - MELD score
  - Patients age
  - ASA class
  - On multivariable analysis statistically significant predictors of mortality
  - No patients < 30 died within 90 days of surgery
  - Age >70 added 3 MELD points to mortality
  - ASA Class strongest predictor of 7-day mortality (ASA class IV added equivalent of 5.5 MELD points to patients' mortality rate). 100% (10 patients) ASA Class V died within 90 days
- MELD was best predictor of 30-day, 90-day post operative mortality for all types of surgery
  - Mortality at 1 yr for those who survived after surgery was no different than the controls
  - Relative risk of 30-/90-day mortality ↑ 14% with each 1-point ↑ in MELD

	Predicted Mortality (%)
MELD ≤ 7	~6
MELD 8-11	~10
MELD 12-15	~25

Overall, increase in RR of death was very linear for MELD scores > 8: MELD scores of 30 on day 20/90 were ~70%

Teh S, et al. Gastroenterol 2007; 132(4): 1261-9

- **Mayo Risk Score (MRS): 2011**
  - Variables
    - Age
    - ASA class
    - MELD score (Bili, Cr, INR)
    - Gives out 7-day, 30-day, 90 day and 1-yr post-op mortality risk
    - Cirrhosis etiology
      - Alcoholic cholestatic
      - Viral/other
  - Mortality rate at days 7, 30, 90, and at 1 yr post-operative

- Retrospective, 160 patients (surgeries from 1996-2006)
- Multivariate analysis and c statistic did show MRS were significantly associated with mortality
  - 30-, 90-day mortality c statistic was 0.832, 0.803 for MRS in this cohort
  - 1-yr mortality was significantly different
    - 1-yr mortality (22.6±12.0%) using MRS was significantly higher than that from observed in the cohort (8.9±1.4%, P<0.01)

Kim SY, et al. Liver Int 2011; 31: 222-8

- **VOCAL-Penn Score: 2020**
  - Variables
    - Patient
      - Age
      - BMI ≥ 30
      - NAFLD
      - Emergency surgery
    - ASA class
    - Surgical type (abdominal)
      - Laparoscopic
      - Open
      - Wall
    - Vascular
    - Major orthopedic
    - Chest/Cardiac
  - Retrospective cohort study using data from the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) cohort
    - Data from 128 US hospitals
    - 129,000 total patients in this cohort, with cirrhosis (2008-2016)
  - Excluded hepatic surgeries
    - Received liver transplant prior to surgery
    - Preoperative ASA 5
    - CNS procedures excluded (<50 surgeries)
  - Categorized surgeries as
    - Abdominal wall
    - Vascular
    - Major orthopedic
    - Chest/cardiac
    - Abdominal – laparoscopic
    - Abdominal – open

- Randomly divided the analytic cohort into a derivation (80%) and validation cohort (20%) – total 3,785 patients
  - Patients 97% males, 63% white
  - Surgery
    - Abdominal wall, 28%
    - Major orthopedic, 28%
  - MELD
    - Median 8
    - MELD-Na, median 10
  - CTP, 88% class A
  - Cause of liver disease
    - Alcohol, 35%
    - Alcohol plus HCV, 30%
  - ASA-class
    - 68% class 3
    - 28% class 4
- Multivariable regression to model
  - 30-, 90-, and 180-day post operative mortality
  - 90-day risk of decompensation
- Then compared the VOCAL-Penn score to:
  - Child-Turcotte Pugh (CTP) scores
  - Mayo Risk Score (MRS)
  - MELD / MELD-Na
- When considering all surgeries declining calibration of the MRS over time for both 30 and 90 day post operative mortality
- When considering cardiovascular, orthopedic and major abdominal surgeries it was better for cohorts from 2008-2010 but as years progressed the calibration declined substantially
- Possible reasons for declining calibration resulted from overestimation of post operative mortality versus observed mortality
- Advances in surgical and post operative care
- No account for surgery type
- Many surgeries included in MRS were from 1980-1990
- MRS derived from single center data

Mahmud N, et al Hepatology 2021; 73; 204-218.

➢ Major predictors for post-op mortality

- Patient

Approximate rates of survival 180 d post-operative

- ASA Score
  - 2 99%
  - 3 95%
  - 4 80%
- Type of surgery
  - Abdominal ~95%
  - Vascular 90%
  - Orthopedic (major) 85%
  - Chest/cardiac 80%

- ASA Class

Classification	Description
ASA 1	Healthy patients
ASA 2	Mild to moderate systemic disease caused by ▪ The surgical condition, or ▪ Other pathological processes, and medically well controlled
ASA 3	Severe disease process which limits activity but is not incapacitating
ASA 4	Severe incapacitating disease process that is a constant threat to life
ASA 5	Moribund patient not expected to survive 24 hrs with or without an operation
ASA 6	Declared brain-dead patient, whose organs are being removed for donor purposes

- Type of surgery
  - Emergency surgery (OR 2.53 for 30-day mortality, 95% CI 1.54–4.16, p<0.001)
  - Chest/cardiac surgeries had a 6.64x increase odds of death for 30 day mortality, (95% CI 1.20–36.64), relative to laparoscopic abdominal surgeries

- Type of liver disease
  - NAFLD Cirrhosis (OR 2.29 for 30-day mortality, 95% CI 1.37–3.82, p=0.002)
  - NAFLD increasing post op mortality
    - NAFLD is a surrogate for ↑ cardiovascular risk
    - Patients with metabolic syndrome associated liver disease likely have ↑ vascular risk factors which ↑ their post op risk (HTN, DLD, T2DM etc.)

Approximate rates of survival 180 d post-operatively

- NAFLD
  - Present 83%
  - Not present 90%

- Older age
- Obesity (BMI > 30) (BMI > 30 being protective post operatively) (30-day OR 0.47, 95% CI 0.30–0.74, p=0.001)
  - "Obesity paradox"
    - Patients with cirrhosis who have ↑ nutritional reserve fare better after an acute stressor
- Laboratory
  - Hyperbilirubinemia
  - Hypoalbuminemia
  - Platelet count

VOCAL-Penn Score: **Preoperative Risk Assessment Form**

- Age (yrs)
- Albumin (g/L)
- Total Bilirubin (µmol/L)
- Platelet Count (×10⁹/L)
- BMI ≥30 Yes / No
- NAFLD Yes / No
- ASA Score 2 / 3 / 4
- Emergency Yes / No
- Surgery Type

- Comparison of VOCAL-Penn Score vs. Others
  - For all time points (30-, 90, and 180-day mortality) the VOCAL Penn score (using both the derivation and validation cohorts) had better discrimination of post operative mortality when compared to MELD, MELD-Na, and CTP
    - VOCAL- Penn was better at 30-, and 90-day morality compared to MRS
  - Discrimination (C-statistics) of Post-Operative Mortality Models at 30, 90, and 180 Days
    - Derivation Cohort

Model	30-Day	90-Day	180-Day
▪ VOCAL-Penn	0.872 (0.836–0.908)	0.839 (0.805–0.873)	0.817 (0.792–0.842)
▪ Mayo Score	0.771 (0.713–0.830)	0.741 (0.705–0.777)	–
▪ MELD	0.724 (0.674–0.774)	0.682 (0.642–0.718)	0.664 (0.640–0.689)
▪ MELD-Sodium	0.740 (0.690–0.790)	0.705 (0.667–0.743)	0.684 (0.660–0.709)
▪ CTP	0.652 (0.596–0.709)	0.599 (0.552–0.646)	0.594 (0.563–0.625)

    - Validation Cohort

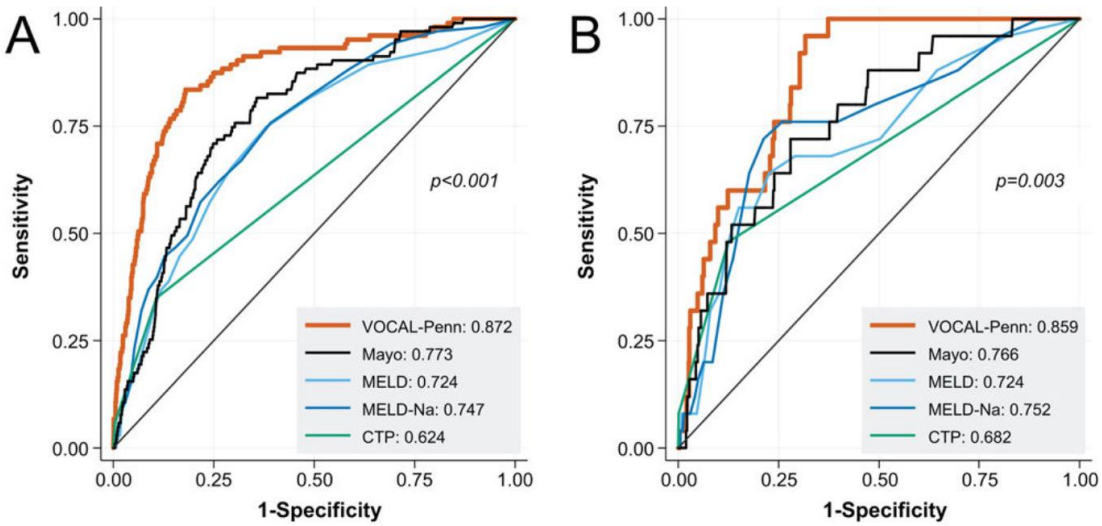
Model	30-Day	90-Day	180-Day
▪ VOCAL-Penn	0.859 (0.809–0.909)	0.822 (0.768–0.875)	0.803 (0.743–0.849)
▪ Mayo Score	0.775 (0.702–0.848)	0.741 (0.677–0.805)	–
▪ MELD	0.712 (0.651–0.854)	0.682 (0.626–0.738)	0.660 (0.620–0.700)
▪ MELD-Sodium	0.754 (0.687–0.821)	0.720 (0.662–0.778)	0.693 (0.652–0.734)
▪ CTP	0.682 (0.580–0.785)	0.659 (0.587–0.731)	0.657 (0.607–0.707)

VOCAL-Penn Score

- Overall, strong paper to suggest VOCAL-Penn score is the best score at predicting 30-, 90- and 180-day post-op mortality for patients with cirrhosis
  - Numerous surgeries with varying types
  - Multi center cohort with large sample size
  - Diverse etiology of liver disease (externally valid)
  - Model relies on readily available laboratory work and information easily attainable

C-statistic (95% CI) for Postoperative Mortality Prediction Scores

Prediction Score	30-Day Mortality	90-Day Mortality
VOCAL-Penn	0.84 (0.78–0.90)	0.82 (0.77–0.87)
Mayo	0.84 (0.79–0.89)	0.79 (0.74–0.84)
MELD	0.80 (0.75–0.86)	0.79 (0.74–0.84)
MELD-Na	0.80 (0.74–0.85)	0.78 (0.73–0.83)



30-Day Post-Operative Mortality in Derivation (A) and Validation Cohorts (B)

- Potential Limitations of VOCAL-Penn Study
  - Large dataset so possibility of misclassification of exposures and outcomes
    - Although dataset is manually adjudicated
  - Cohort/Dataset may not generalize well to all population
    - Largely males
  - Possibly higher burden of psychosocial comorbidities
  - Inclusion of patients who have not had pre operative optimization (TIPS, nonselective beta blocker)
  - Observed closely for hepatic encephalopathy, ascites and jaundice
  - Consider venous thromboembolism (VTE) if platelets > 50,000

- Hemostasis
  - "rebalanced" hemostasis, in which multiple abnormalities that increase risks of hypo- and hypercoagulability may co-exist in an individual patient
  - Can give Vitamin K to patients with suspected vitamin K deficiency (as a result of poor nutritional status or cholestatic disease)
  - Plasma or cryoprecipitate should not be administered to "correct" elevated INR
  - Replace platelets in severe thrombocytopenia (< 50) or if requiring neuraxial anesthesia
- Patients with known esophageal varices should receive appropriate prophylactic treatment
- Ascites
  - ↑ risk of wound dehiscence and abdominal wall herniation → ↑ postoperative mortality (↑ risk independent of the MELD score)
  - Treat aggressively prior to surgery (medical) or consider therapeutic paracentesis prior to surgery
- Metabolic Replacement
  - Correct electrolyte abnormalities, particularly potassium to ↑ risk of the
    - Cardiac arrhythmias, and
    - Hepatic encephalopathy
  - Evaluate and optimize renal function
- Nutritional replacement
  - Perioperative nutritional support → ↓ frequency of postoperative complications and short-term mortality
- No data on patients with cirrhosis who had an indication for surgery but did not receive it (↑ perioperative risk)
  - This might explain lower MELD and CTP A patients in the cohort, as presumably patients with severe derangements in MELD parameters, for example, rarely proceeded to surgery

Treatment of Chronic Hepatitis B Viral (HBV) Infection and Its Reactivation

Navneet Natt

- Guidelines for Initiation of Treatment

CASL/AMMI 2018	AASLD 2018	WHO 2024
○ Cirrhosis ○ Extrahepatic manifestations of HBV ○ HBV DNA > 2000 IU/mL + ↑ ALT persistent ALT elevation above ULN x 3-6 mon − Regardless of eAg status (+/-) ○ Pregnancy: HBV DNA > 200 000 IU/mL in late 2nd/early 3rd trimester (24-32 wk gestation) (T2/T3))	○ Cirrhosis ○ Extrahepatic manifestations of HBV ○ HBV DNA > 2000 IU/mL + ALT > 2x ULN in HBeAg negative ○ HBV DNA > 20 000 IU/mL + ALT>2x ULN in HBeAg positive ○ Pregnancy: HBV DNA > 200 000 IU/mL in T3	○ Evidence of ≥F2 fibrosis regardless of ALT or HBV DNA levels ○ Extrahepatic manifestations of HBV ○ HBV DNA > 2000 IU/mL + ↑ ALT above ULN x3-6 mon ○ Pregnancy: HBV DNA > 200 000 IU/mL or HBeAg positive in T2 ○ Co-infections (HIV, HCV, HDV) ○ Family history of liver cancer or cirrhosis ○ Comorbidities (e.g. MASLD) or immunosuppressed

Abbreviations: AASLD, American Association for the Study of Liver Disease; AMMI, Association of Medical Microbiology and Infectious Disease Canada; CASL, Canadian Association for the Study of the Liver; HCC, hepatocellular cancer; MALD, metabolism associated liver disease; T, trimester of pregnancy; ULN, upper limit of normal; WHO, World Health Organization

Phases of Chronic Hepatitis B Infection

Parameter	Phase 1 $HBeAg^+$ Chronic Infection (Immune Tolerance)	Phase 2 $HBeAg^+$ Chronic Hepatitis (Immune Active)	Phase 3* $HBeAg^-$ Chronic Infection (Inactive Carrier)	Phase 4 $HBeAg^-$ Chronic Hepatitis	Phase 5 $HBsAg^-$ or OHB
○ HBsAg	+	+	+	+	-
○ HBsAb	-	-	-	-	+/-
○ HBeAg	+	+	-	-	-
○ HBV DNA IU/mL*	Often $>10^7$	10^4 - 10^7	Often <2,000 (sometimes >2,000)	10^3 - 10^7	- (or trace)
○ ALT	Normal	↑ / fluctuating	Normal	Often fluctuating	Normal
○ Phase	Mostly in young patients but could extend to 40-50	Young patients to 50 yr with active hepatitis	Variable duration with HBV immune control	Mostly in older patients with intermitten t flare	Immune clearance of HBV or immune control of the virus with OHB
○ Non-invasive fibrosis assessment or biopsy	Normal (may be at ↑ risk HCC)	Abnormal	Normal / Mildly abnormal	Abnormal	Normal
○ Treatment	No	Yes (if not signs of spontaneous seroconversio n because prolonged duration of hepatitis ↑ fibrosis risk)	No	Yes	No (except during immunosuppression)

*Phase 3: HbeAg-negative chronic infection / inactive carrier state

- Low, / undetectable viral DNA
- No histologic evidence of inflammation and normal ALT
- Favourable long-term prognosis
- Low risk of developing cirrhosis / HCC

Adapted from: Loomba R and Liang TJ. Gastroenterology. 2017;152(6):1297-1309.

Hepatitis B Reactivation

- Definition
  - Chronic Hepatitis B (HBsAg+, anti-HBc+)
    - ↑ HBV DNA level > baseline[1]
  - Resolved Hepatitis B (HBsAg-, anti-HBc+)
    - Re-appearance of HBV DNA in serum, or
    - Conversion to HBsAg+ (reverse seroconversion)

[1]AASLD 2018 Definition:
(i) a ≥2 log (100-fold) increase in HBV DNA compared to baseline
(ii) HBV DNA ≥3 log (1,000) IU/mL in a patient with previously undetectable level, or
(iii) HBV DNA ≥4 log (10,000) IU/mL if the baseline is not available

Terrault NA, et al. Hepatology 2018; 67(4): 1560-1599.

- Stages

	Silent Reactivation	HBV-associated Hepatitis	Fulminant Liver Failure
Clinical	-	+	+
↑ ALT	-	+	+
↑ HBV DNA load	+	++	++
↑ Bili, INR, ↓ Ala	-	+/-	+
Histopathology hepatitis	-	+	+
Ascites/HE	-	-	+

- Risk Factors
  - Host Factors
    - Male
    - ↑ age
    - Cirrhosis
    - Co-morbidities (e.g. cancer)
  - Virus
    - $HBsAg^+$
    - $HBeAg^+$ (or precore mutant $HBeAg^-$)*
    - High baseline HBV DNA Viral Load
    - Non-A HBV Genotype

- Immunosuppression (IS) (type and duration of immunosuppressants modify risk)
  - Chemotherapy
  - Biologics
  - Corticosteroids*

Loomba R and Liang TJ. Gastroenterology 2017; 152(6): 1297-1309.

- **Immunosuppression**

	High Risk (>10%)	Moderate Risk (1–10%)	Low Risk (<1%)
Chronic Hep B Infection			
○ $HBsAg^+$ plus $Anti\text{-}HBc^+$	– B-cell depleting agents (e.g., rituximab) – Anthracycline derivatives ▪ Doxorubicin ▪ Epirubicin – Steroid therapy ≥4 wk (prednisone equivalent >10–20 mg/day)	– TNF-α inhibitors – Cytokine/integrin inhibitors (e.g., ustekinumab, vedolizumab) – Tyrosine kinase inhibitors (e.g., imatinib) – Steroid therapy ≥4 wk (prednisone equivalent >10–20 mg/day)	– Immunomodulators: azathioprine, 6-MP, methotrexate – Intra-articular corticosteroids – Steroid therapy for ≤ 1 wk
○ $HBsAg^-$ and $Anti\text{-}HBc^+$	B-cell depleting agents (e.g., rituximab)	– Anthracycline derivatives ▪ Doxorubicin ▪ Epirubicin – TNF-α inhibitors – Cytokine/integrin inhibitors (abatacept, ustekinumab, natalizumab) – Tyrosine kinase inhibitors – Steroid therapy ≥4 wk (prednisone equivalent >10–20 mg/day)	– Immunomodulators: azathioprine, 6-MP, methotrexate – Intra-articular corticosteroids – Steroid therapy ≥4 wk (prednisone equivalent <10 mg/day)

- **Take Home Points**
  - Chronic steroid therapy (>10 mg prednisone for ≥4 wks) poses moderate / high risk of HBV reactivation
  - High risk (>10%): Chronic HBV (HBsAg+)
  - Moderate risk (1-10%): Resolved HBV (HBsAg -, HBcAb+)

- **Society Guideline Recommendations**
  - EASL 2017 (J Hepatol. 2017;67(2):370-398)
    - All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression (Evidence level I, grade of recommendation 1).
  - CASL/AMMI 2018 (Coffin CS, et al. Can Liver J 2018; 1(4): 156-217)
    - All patients undergoing immunosuppression or chemotherapy should be screened for HBsAg, anti-HBc, and anti-HBs before therapy (Strong recommendation; Class 2, Level A)
  - AASLD 2018 (Terrault NA, et al. Hepatology 2018; 67(4): 1560-1599)
    - HBsAg and anti-HBc (total or immunoglobulin G) testing should be performed in all persons prior to initiation of any immunosuppressive, cytotoxic, or immunomodulatory therapy."

➢ Prevention of Hep B Reactivation (prophylactic anti-viral therapy recommended, regardless of baseline HBV DNA level

- Drugs with High Risk (>10%)
  - Drugs of choice
    - TDF, TAF, ETV
  - Initiation
    - As soon as possible ***before*** initiating immunosuppression (AASLD 2018)
  - Duration
    - Continue 6-12 mon after cessation of the immunosuppressive regimen
    - 18 mon for rituximab (EASL 2017)
  - Monitoring
    - ALT, HBV DNA, +/- HBsAg q3mon

Abbreviations: ETV, entecavir; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate;

- Drugs with Moderate Risk (1-10%)
  - Chronic HBV (HBsAg+)
    - Treat with TDF, TAF, ETV
  - HBsAg+, anti-HBc+
    - Monitor labs q3mon
    - Consider HBV prophylaxis

- Drugs with Low Risk (<1%)
  - Prophylaxis not required
  - Monitoring q3mon during and up to 12 mon after cessation of immunosuppression
    - HBV DNA
    - Liver enzymes
    - +/- HBsAg in those who are HBsAg (for reverse seroconversion)
  - Consider pre-emptive therapy if
    - ↑ HBV DNA level, or
    - Liver enzymes

➢ Treatment of Reactivated Hepatitis B

- Please see recommendations on first full page
- WHO 2024 treatment guidelines (2024)
  - Nucleoside analogs with high barrier to resistance including TDF, TAF, and ETV recommended in latest
  - Do ALT / HBV DNA q3mon while on therapy

➢ Summary

- Everyone receiving steroid therapy (>10-20 mg prednisone equivalent) ≥ 4 wk at
  - Screened chronic hepatitis B for HBsAg+ or anti-HBe+
    - Give anti-HBV therapy TDF, TAF, ETV for prophylaxis against reactivation

Suggested Reading:

Coffin CS, et al. Management of Hepatitis B Virus Infection: 2018 Guidelines from the Canadian Association for the Study of Liver Disease and Association of Medical Microbiology and Infectious Disease Canada. Can Liver J 2018; 1(4): 156-217.

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection. J Hepatol 2017; 67(2): 370-398.

Loomba R and Liang TJ. Hepatitis B Reactivation Associated with Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. Gastroenterology. 2017; 152(6): 1297-1309.

Terrault NA, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018; 67(4): 1560-1599.

World Health Organization (WHO). Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. March 2024. Available from: https://www.who.int/publications/i/item/9789240090903

PANCREAS

Acute Pancreatitis

Mathew Cheah

Acute Pancreatitis

- Definition
  - Two of the following three items
    - Epigastric pain) consistent with pancreatitis
    - ↑ serum amylase / lipase >3xULN
    - Diagnostic imaging (CT or MRI) consistent with pancreatitis

- Demography
  - Incidence 5-75 /10^5 (in US)
  - ↑ as population is increasingly obese
  - Mortality rate <5%

- Grades and Severity (**2012 Atlanta Classification Revision)**
  - Mild Acute
    - No organ failure
    - No local / systemic complications
  - Moderately Severe
    - Transient organ failure (<48 hrs), +/-
    - Local or systemic complications* without persistent organ failure
  - Severe Acute
    - Persistent organ failure (>48 hrs)—single organ or multiorgan

*Local complications are peripancreatic fluid collections, pancreatic necrosis and peripancreatic necrosis (sterile or infected), pseudocyst, and walled-off necrosis (sterile or infected).

Factors Associated with Severe Pancreatitis

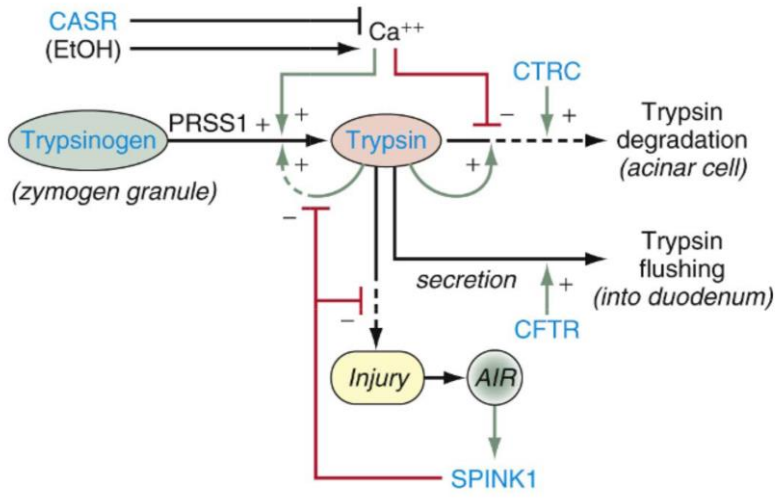
- Clinical
  - Age > 55 yrs
  - Obesity (BMI > 30 kg/m²)
  - Altered mental status
  - Comorbid disease
  - Systemic inflammatory response syndrome (SIBS)
    - Two or more of the following:
      - Pulse > 90/min
      - Respirations > 20/min or $PaCO_2$ < 32 mm Hg
      - Temperature > 38° or < 36°C
      - WBC count > 12,000 or < 4000/mm³ or > 10% band forms

- Laboratory Findings
  - BUN > 20 mg/dL
  - Rising BUN
  - Hematocrit > 44%
  - Rising hematocrit
  - Elevated serum creatinine level
  - Note: WBC count noted above in definition of SIRS
- Diagnostic Imaging
  - Pleural effusions
  - Pulmonary infiltrates
  - Multiple or extensive extrapancreatic fluid collections

➢ Natural History

- Phase 1: Interstitial phase
  - Usually > 1 wk
  - Acinar Cell Injury → SIRS → Extrahepatic organ failure
- Phase 2: Necrotizing phase
  - Up to 20% develop more protracted course
  - Duration: wk to mon
- Mortality: 2 peaks
  - Half of deaths occur in the first 2 wk (MOF)
  - After wk 2, remaining deaths from infection

➢ Pathophysiology



- Pathogenesis
  - ↑↑ trypsin overcomes protective mechanisms >> protective
  - Initial step within acinar cells:
    - Trypsinogen → Trypsin → activate pro-enzymes / PLA2, Carboxypeptidase
    - May also activate complement and kinase systems
  - Uncontrolled Acinar injury → local inflammation → SIRS +/- Sepsis

- Protective Mechanisms
  - Intrapancreatic Enzymes
    - Pancreatic secretory trypsin inhibitor (SPINK1)
    - Mesotrypsin, Enzyme Y, Trypsin
    - Non-specific anti-proteases
      - α1-AT
      - α2-macroglobulin
  - Other mechanisms
    - Sequestering pancreatic enzymes within intracellular compartments of acinar cell during synthesis and transport
    - ↓ Ca^{2+}_i (intracellular calcium)

- Pathophysiologic mechanisms include:
  - Microcirculatory injury
  - Leukocyte chemoattraction
  - Release of pro- and anti-inflammatory cytokines
  - Oxidative stress
  - Leakage of pancreatic fluid
  - Bacterial translocation to the pancreas and systemic circulation

- Genetics
  - R122H, N291
    - Trypsin resistant to lysis or premature trypsinogen activation (gain of function mutation)
  - CFTR
    - Anion channel allows flushing of enzymes into duodenum
  - SPINK1
    - Inhibits prematurely activated trypsin

- Gallstone Pancreatitis
  - Initiating factors
    - Bile acid reflux into pancreatic duct (PD)
      - Common channel theory
    - PD obstruction
      - Stones/edema from passed gallstone

➢ Risk Factors (predisposing conditions)

- Obstructive
  - Gallstones
    - Microlithiasis/Sludge
  - Tumours
  - Parasites
  - Structures
    - Annular pancreas
    - Choledochocele

- Alcohol and Toxins
  - Ethyl Alcohol
  - Methyl Alcohol
  - Scorpion Venom
  - Organophosphorus Insecticides

- Drugs/Medications
  - Please refer to lasts of probable/possible medications associated with acute pancreatitis (Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th ed. Elsevier; 2020 (Box 58.4)

Examples of Drug-Induced Acute Pancreatitis Based on Drug Class

Class Ia	Class Ib	Class II	Class III	Class IV
• Aminosalicylates • Azathioprine • Didanosine • Enalapril • Estrogens • Furosemide • Hydrochlorothiazide • L-asparaginase • Mercaptopurine • Mesalamine • Pentamidine • Procainamide • Sulfasalazine • Sulindac • Tetracycline • Trimethoprim/ sulfamethoxazole • Valproic acid	• 6-amino-nicotinic acid • Amiodarone • Carbamazepine • Cisplatin • Cytarabine • Dexamethasone • Erythromycin • Ethambutol • Furosemide • Interferon-alpha • Lamivudine • Lisinopril • Methimazole • Methyldopa • Metronidazole • Omeprazole • Olsalazine • Oxaliplatin • Pentamidine • Phenformin • Pravastatin • Prednisone • Simvastatin • Sulfasalazine • Tetracycline • Valproic acid	• Acetaminophen • Amitriptyline • Asparaginase • Chlorothiazide • Cimetidine • Dexamethasone • Doxycycline • Estrogens • Ethambutol • Interferon-alpha • Isoniazid • Lamivudine • Lisinopril • Methimazole • Metronidazole • Omeprazole • Olsalazine • Oxaliplatin • Pentamidine • Phenformin • Pravastatin • Prednisone • Simvastatin • Sulfasalazine • Tetracycline • Valproic acid	• Allopurinol • Atorvastatin • Carbamazepine • Chlorpromazine • Cimetidine • Ciprofloxacin • Doxycycline • Enalapril • Erythromycin • Ethambutol • Hydrochlorothiazide • Interferon-alpha • Isoniazid • Lamivudine • Lisinopril • Methimazole • Metronidazole • Omeprazole • Olsalazine • Oxaliplatin • Pentamidine • Phenformin • Pravastatin • Prednisone • Simvastatin • Sulfasalazine • Tetracycline • Valproic acid	• Acetaminophen • Amitriptyline • Asparaginase • Chlorothiazide • Cimetidine • Dexamethasone • Doxycycline • Estrogens • Ethambutol • Interferon-alpha • Isoniazid • Lamivudine • Lisinopril • Methimazole • Metronidazole • Omeprazole • Olsalazine • Oxaliplatin • Pentamidine • Phenformin • Pravastatin • Prednisone • Simvastatin • Sulfasalazine • Tetracycline • Valproic acid

- Metabolic Disorders
  - Hypertriglyceridemia (TG > 11 mmol/L)
  - Diabetes Mellitus
  - Hypercalcemia
- Infection
  - Viral
    - CMV
    - Coxsackievirus
    - EBV
    - Hep A/B/C
    - HSV
    - Mumps
    - VZV
  - Bacteria
    - Brucellosis
    - Legionella
    - Mycoplasma
    - Salmonella
    - TB
  - Fungal
    - Aspergillus
    - Candida
  - Parasitic
    - Ascaris
    - Clonorchis
    - Cryptosporidia
    - Toxoplasma
- Vascular Disorders
  - Pancreatic Ischemia
    - Atheromatous embolization following angiography (post-TACE)
    - Interoperative hypotension
    - Hemorrhage/post-cardiac arrest / post-shock
    - Ergotamine overdose
  - Vasculitides
    - Systemic lupus erythematosus (SLE)
    - Polyarteritis nodosa (PAN)

- Trauma and Post-Operative State
  - Trauma
  - Post-operative state (cardiopulmonary bypass, Liver transplant)
  - Post-ERCP (endoscopic retrograde cholangiopancreatogram)
    - Asymptomatic hyperamylasemia (35-70%)
    - Rates:
      - Up to 5% of diagnostic ERCP
      - Up to 7% therapeutic ERCP
      - Up to 25% in those with suspected sphincter of Oddi dysfunction (SOD)

- Hereditary Pancreatitis
  - Autosomal Dominant Disorder
  - Variable Penetrance

- Controversial
  - Pancreas Divisum
    - Most common congenital malformation of pancreas (5-10%)
  - Sphincter of Oddi Dysfunction (SOD)
    - Basal Sphincter Pressure > 40 mmHg

- Other Causes
  - Immune
    - Crohn disease (4x ↑ risk)
    - Autoimmune Pancreatitis (AIP)
      - Acute pancreatitis (AP) from AIP is associated with granulocyte epithelial lesions
  - Idiopathic

➢ Clinical
  - Rapid onset of severe epigastric pain
  - Radiating to back
  - Nausea/vomiting

- Laboratory
  - Complete blood count (CBC)
  - Electrolytes
  - Glucose
  - Liver Panel including bilirubin
  - Lipase
  - Amylase
  - Immunoglobulins
  - Genetic testing (< 30 yr, family history, no other cause apparent)

- Laboratory
  - Abdominal ultrasound
  - Contrast enhanced computed tomography (CT)
  - Magnetic resonance imaging (MRI)

- Diagnosis
  - Symptoms (epigastric pain) consistent with pancreatitis
  - Serum amylase or lipase > 3x ULN (upper limit of normal)
  - Imaging (CT or MRI) consistent with pancreatitis

- Predicting Disease Severity
  - Ranson criteria
    - Sn 40-88%, Sp 43-90%
    - PPV 50%, NPV 90%
    - Takes 48 hrs to complete, only validated up to this
  - APACHE-II
    - Most patients survive APACHE ≤ 9 in first 48 hrs
  - Bedside Index for Severity in Acute Pancreatitis (BISAP)
    - Simple to calculate and can be done at presentation

Abbreviations: BISAP, Bedside Index for Severity in Acute Pancreatitis; Sn, sensitivity; Sp, specificity

Algorithm for the Management of Acute Pancreatitis at Various Stages in its Course

- Early Course Management (0–72 hrs)
  - If no organ failure
    - Admit to medical/surgical floor
    - NPO (nothing by mouth)
    - IV hydration: 250–400 cc/hr
    - Nasal oxygen
    - Frequent evaluation of oxygen saturation
    - Hematocrit daily, BUN twice daily for 48 hrs
    - Serum electrolytes daily
    - Pain control
  - If organ failure present
    - Admit to ICU
    - Same orders as above
    - Central line placement
    - Evaluate need for assisted ventilation
    - Assess for bile duct obstruction
    - If bilirubin is rising, consider urgent ERCP
- Later Course Management (>72 hrs)
  - If no evidence of severe disease or organ failure
    - Begin early refeeding
    - Evaluate etiology:
      - If gallstones: early cholecystectomy
      - If alcohol: address psychosocial issues
      - If high serum triglycerides: initiate medical therapy
    - If CT shows interstitial pancreatitis without peripancreatic necrosis:
      - Continue supportive care
      - Observation
  - If evidence of severe disease or organ failure
    - Transfer to ICU if not already there
    - Assess for biliary sepsis; if present, consider emergency ERCP
    - Begin enteral feedings (nasojejunal or nasogastric)
    - Perform CT to evaluate for necrosis
    - If pancreatic or peripancreatic necrosis is present:
      - Continue supportive care
      - Maintain enteral feedings
      - If infection is suspected, consider antibiotics

- Late Course Management (7–28 days and beyond)
  - 7–28 days
    - If patient is improving:
      - Consider oral refeeding
    - If patient is not improving:
      - If on antibiotics: consider FNA (fine-needle aspiration) of pancreas for culture and adjust antibiotics
      - If not on antibiotics and FNA is negative: avoid antibiotics
  - Beyond 28 days
    - If patient is improving:
      - Consider refeeding
      - If unable to tolerate feedings: consider necrosectomy
    - If not improving:
      - Consider necrosectomy via endoscopic, radiologic, or surgical approach

Adapted from: Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th ed. Elsevier; 2020 (Figure 58.5)

- Role of ERCP in Patient with Acute Pancreatitis
  - Biliary obstruction
  - Acute cholangitis within 24 hrs
  - Minimize risk of Post-ERCP Pancreatitis
    - PD stent placement
    - Rectal indomethacin
    - Ringers Lactate

➢ Factors That Increase the Risk of Post-ERCP Pancreatitis

- Patient-Related
  - Female gender
  - History of post-ERCP pancreatitis
  - Normal serum bilirubin level
  - Recurrent pancreatitis
  - Suspected SOD (Sphincter of Oddi Dysfunction)
  - Young age
- Procedure-Related
  - Balloon dilation
  - Difficult cannulation
  - Pancreatic duct injection
  - Pancreatic sphincterotomy
  - Precut access

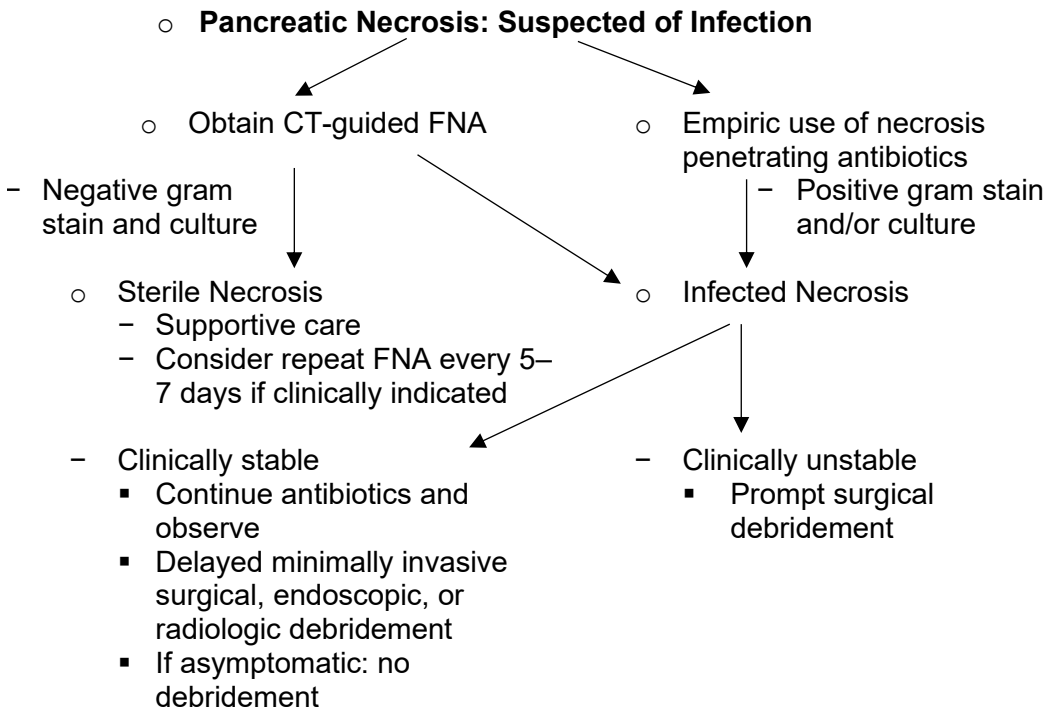
- Operator or Technique-Related
  - Trainee (fellow) participation
  - Non-use of a guidewire for cannulation
  - Failure to use a pancreatic duct stent in a high-risk procedure

- Role of Surgery
  - Cholecystectomy as soon as patient has recovered from acute inflammation
  - Necrotizing pancreatitis
    - Defer until alter inflammation subsides and fluid collections resolve

➢ Complications

- Pseudocyst
  - ↑↑↑ pancreatic enzymes
  - Tissue debris
    - Usually sterile
  - Complications
    - Infection, hemorrhage, rupture
  - Treatment
    - Asymptomatic → no treatment
    - Cyst-gastrostomy-duodenostomy
    - Roux-en-Y cysts jejunostomy
    - Pancreatic resection (if in tail)
    - Percutaneous drainage

- Necrotizing Pancreatitis
  - >30% non-enhancement of pancreas on CECT or MRI with gadolinium
  - Generally sterile for first week
  - Infection occurs after 10th day of hospitalization
    - Bacterial translocation from colon
    - Suspect with deterioration or failure to improve after 7-10 d
    - Antibiotics
      - Carbapenems
      - Quinolones,
      - Metronidazole
    - Ideally delay drainage >4wks



- Other Local Complications
  - Splenic
    - Pseudocyst
    - Splenic vein thrombosis
    - Infarction and necrosis of spleen
    - Spleen rupture
    - Hematoma
  - Bowel compression or fistulization

- Systemic Complications
  - Organ dysfunction
    - Respiratory insufficiency
      - ARDS
      - Atelectasis
      - Pleural effusions
      - Pneumonia
    - Renal failure
      - Hypovolemia
      - Hypotension

- Hyperglycemia
  - Transient secondary to Islet cell necrosis
- Disseminated intravascular coagulopathy (DIC)
- Fat necrosis
  - Bone
  - Pericardium
  - Peritoneum, mediastinum
  - Pleura
  - Retroperitoneal tissue
  - Subcutaneous tissue
  - Usually resolve days to weeks
- Abdominal compartment syndrome
  - Sustained intra-abdominal pressure >20 mmHg associated with organ dysfunction
  - Urinary bladder catheter pressure measurements
  - Treatment
    - Percutaneous / surgical decompression
  - Mortality rate, 30-60%
- Pancreatic Encephalopathy
  - Agitation
  - Coma
  - Confusion
  - Disorientation
  - Hallucinations
- Purtsher retinopathy
  - Microembolization in choroidal and retinal arteries
  - Flame shaped hemorrhages with cotton wool spots
    - Can cause sudden blindness

Chronic Pancreatitis

Navneet Natt

- Definition
  - Exposure to known risk factors
  - Genetic susceptibility
  - Compatible clinical symptoms: abdominal pain, exocrine insufficiency (steatorrhea), endocrine insufficiency (diabetes mellitus)
  - Pancreatic exocrine or endocrine function abnormalities
  - Structural changes on imaging
  - +/- histological changes demonstrating chronic inflammation, fibrosis, and/or destruction of ductal, acinar, or islets of Langerhans cells
- Demography
  - M > F, age > 40 yrs
  - Increasing incidence rate – ≥ $5/10^5$ in the USA
  - Chronic alcohol abuse accounts for 50% of cases of CP and is associated with increased mortality
  - Survival further reduced in those with older age and concurrent smoking
  - Cause of death is not the pancreatitis itself but complications (e.g. pancreatic adenocarcinoma, post-operative complications) and downstream consequences of smoking/alcohol abuse
  - 10-yr survival = 70%; 20-yr survival = 45%
  - Significant morbidity results from chronic pain and reduced quality of life
- Pathology

- Early Chronic Pancreatitis
  - Patchy uneven histologic changes
  - Interlobular fibrosis with infiltration of lymphocytes, plasma cells, mast cells, and macrophages
  - Eosinophilic protein plugs may be seen in the pancreatic ducts
  - Acinar cells start to be replaced by fibrosis
  - Features of acute pancreatitis may be seen: acute edema and inflammation of pancreas with acinar cells and fat necrosis

- Later Stages
  - More widespread fibrosis in and between the lobules
  - Progressive fibrosis and dilation of pancreatic ducts
  - Calcification of the ductal protein plugs which can cause downstream obstruction
  - Islets of Langerhans cells become destroyed late in the disease course

➢ Pathophysiology

- Environmental insult (e.g. alcohol use, smoking, gallstones) in a genetically predisposed individual causes physiologic stress to pancreatic acinar and ductal cells
  - Stress → cellular injury → necrosis / inflammation
  - Once the physiologic stress is removed, this process should be self-limiting i.e. acute pancreatitis (AP)
- In those with continued cell oxidative stress, repeated ductal/acinar cell injury leads to inflammation and activation of pancreatic stellate cells which lay down extracellular matrix and are implicated in fibrosis
  - Fibrosis → acinar cell ischemia → additional inflammation and fibrosis
  - This explains high risk of chronic pancreatitis in those with recurrent acute pancreatitis

➢ Causes

- Toxic-Metabolic
  - Alcohol
  - Tobacco
  - Hypercalcemia
  - Hypertriglyceridemia
  - Chronic renal failure
- Idiopathic
  - Tropical calcific pancreatitis
  - Idiopathic pancreatitis diabetes
  - Early-onset idiopathic
  - Late-onset idiopathic

- Genetic
  - Autosomal dominant
    - Hereditary pancreatitis (PRSS1 mutations)
  - Associated disorders or modifier genes:
    - CFTR mutations
    - SPINK1 mutations
    - Trypsinogen C mutations
    - Calcium sensing receptor gene
    - Carboxypeptidase A1
    - Other
- Autoimmune Pancreatitis**
  - IgG4-related systemic disease, type 1
  - IgG4-related pancreatitis, type 2
- Recurrent and Severe Acute Pancreatitis
  - Post-necrotic acute recurrent pancreatitis
  - Vascular diseases/ischemia
- Obstructive
  - Benign pancreatic duct obstruction
    - Traumatic stricture
    - Structure after severe acute pancreatitis
    - Ampullary obstruction
      - Sphincter of Oddi stenosis
      - Celiac disease
      - Crohn disease
    - Duodenal wall cyst
    - Pancreas cancer
  - Malignant pancreatic duct obstruction
    - Ampullary carcinoma
    - Duodenal cancer
    - Inflammatory disease or modified papilla
    - Neuroendocrine and intraductal papillary mucinous neoplasm
- Asymptomatic Pancreatic Fibrosis
  - Asymptomatic acute necrosis
  - Old age
  - Chronic kidney disease
  - Diabetes mellitus
  - Previous radiotherapy

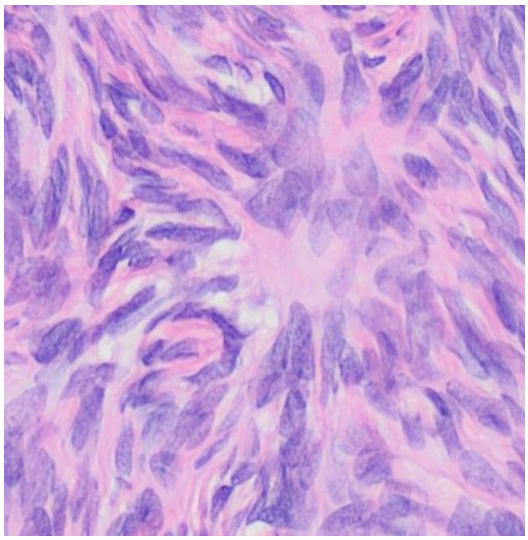
- **Alcohol**
  - Alcohol accounts for 50% of CP cases
  - Risk increases with rising alcohol use though no threshold value defined
    - Typically requires at least 4-5 drinks per day for at least 5 yrs

- Pathophysiology
  - Alcohol metabolites cause direct toxic injury to pancreatic acinar and ductal cells
  - Alcohol stimulates release of protein-rich pancreatic juice which can form protein precipitates in the ducts
- Histologic evidence of CP usually develops before clinical symptoms
- Only 5% of heavy alcohol users develop CP thus other genetic and environmental factors likely implicated (e.g. tobacco smoking in 90% of those with alcohol CP)
- Prognosis of alcohol CP tends to be poorer compared to other etiologies

- **Autoimmune Pancreatitis (AIP)**
  - Immune-mediated inflammatory and fibrosing diseases of the pancreatitis
    - Two sub-types: Type 1 and Type 2 AIP
  - Clinical Presentation
    - Most common = painless obstructive jaundice due to biliary compression by enlarged inflammatory mass at the head of the pancreas
      - Clinically resembles pancreatic cancer
    - Weight loss
    - Nausea/vomiting
    - Least common = acute pancreatitis
  - Imaging
    - Diffusely enlarged sausage-shaped pancreas +/- focal swelling / hypoechoic mass that may mimic pancreatic malignancy
    - Irregularity or narrowing of the PD can be seen on MRCP or ERCP
  - Treatment
    - Prednisone 0.6-1.0 mg/kg (typically 40 mg once daily)
    - Assess for clinical and radiographic response at 2-4 wks, if improved then start taper by 5-10 mg weekly to complete treatment course in 10-12 wks
    - In case of relapse: repeat prednisone course, azathioprine, rituximab

- **Type 1 AIP**
  - Commonly occurs in middle-aged men (mean age of presentation = 70yo)
  - Characterized by infiltration of pancreas with plasma cells and CD4+ T cells
  - Pancreatic biopsy reveals “storiform fibrosis” – whirling spokeswheel pattern
  - Often associated with IgG4 elevation (>2 x ULN)
    - >10 IgG4+ plasma cells per HPF

- Can occur in isolation, or more commonly with extra-pancreatic IgG4 disease
  - IgG4 sclerosing cholangitis
  - Tubulointerstitial nephritis
  - Retroperitoneal fibrosis
  - Sialadenitis
- 30-50% of patients may have disease relapse after glucocorticoid therapy



https://www.pathologystudent.com/what-exactly-does-storiform-mean/

International Consensus Diagnostic Criteria for Type 1 Autoimmune Pancreatitis":

Criteria	Level 1 Evidence	Level 2 Evidence
P: Parenchymal Imaging	− Typical imaging − Diffuse enlargement of pancreas with delayed enhancement − With or without rim-like enhancement or pancreas	− Indeterminate imaging − Segmental or focal enlargement of pancreas − With delayed enhancement
D: Ductal Imaging (ERCP or MRCP)	− Long (>1/3 the length of pancreatic duct) stricture, or − Multiple strictures without upstream dilation of pancreatic duct	− Segmental or focal narrowing of pancreatic duct − Without marked (> 5 mm) upstream dilation of pancreatic duct

Criteria	Level 1 Evidence	Level 2 Evidence
○ S: Serology	− IgG4 >2× upper limit of normal	− IgG4 1-2x > upper limit of normal
○ OOI: Other Organ Involvement	− Histology of extrapancreatic organ involvement (at least 3 of 4 below) ▪ Marked lymphoplasmacytic infiltration with fibrosis ▪ Obliterative phlebitis ▪ Storiform phlebitis ▪ Abundant IgG4-poisitive cells Or − Imaging evidence of extrapancreatic organ involvement (any) ▪ Segmental/ multiple proximal or proximal and distal bile duct strictures ▪ Retroperitoneal fibrosis	− Histology of extrapancreatic organ involvement, including bile duct or ampullary biopsies ▪ Marked lymphoplasmacytic infiltration and Abundant IgG4-positive cells, or − Physical or radiologic evidence ▪ Symmetrically enlarged salivary or lacrimal glands ▪ Renal involvement consistent with AIP
○ E: Histology	− Lymphoplasmacytic sclerosing pancreatitis on core biopsy or resection specimen (at least 3) ▪ Periductal lymphoplasmacytic infiltrate without granulocytic infiltration ▪ Obliterative phlebitis ▪ Storiform fibrosis ▪ Abundant (> 10 cells/HPF) IgG4-positive cells	− Lymphoplasmacytic sclerosing pancreatitis on core biopsy (at least 2) − Periductal lymphoplasmacytic infiltrate without granulocytic infiltration − Obliterative phlebitis − Storiform fibrosis − Storiform fibrosis − Abundant (> 10 cells/HPF) IgG4-positive cells
○ Rt: Response to Steroids	− Rapid (2 wk) radiological demonstrable resolution or marked improvement in pancreatic / extrapancreatic manifestations	

Diagnosis	Primary Basis of Diagnosis	Imaging Evidence	
○ Definitive type 1 AIP	− Histology	− Typical/indeterminate	
	− Imaging	− Typical/indeterminate	− Any non-D level 1/ level 2 − Two or more from level 1
	− Response to steroids	− Indeterminate	− Level 1 S/OOI or level 1 D + level 2 S/OOI/H
○ Probable Type 1 AIP		− Indeterminate	− Level 2 S/OOI/H + Rt

- **Type 2 AIP**
  - Accounts for <20% of AIP cases, mostly affecting young adults and children
  - 15-30% of patients have concomitant IBD
  - Neutrophilic infiltration of the pancreas with microabscesses
  - Histologic pattern = idiopathic duct centric pancreatitis
  - No associated serologic markers; usually requires biopsy
  - Excellent long-term outcome with remission sustained after treatment with steroids (very rare relapse)

Feature	Type 1 AIP	Type 2 AIP
○ Histologic features	− Lymphoplasmacytic infiltration − Dense periductal infiltrate without damage to ductal epithelium − Storiform fibrosis − Obliterative phlebitis − Infiltration of duct IgG4-positive cells (>10 cells/HPF) − Fibroinflammatory process may extend to peripancreatic region	− Lymphoplasmacytic and neutrophilic infiltration around ducts − Destruction of duct epithelium by neutrophils (granulocytic epithelial lesion) − Obliterative phlebitis rare − No IgG4-positive cells
○ Average age at presentation	− 60–70 yrs	− 40–50, but may present in young adults and even children
○ Gender predominance	− Male	− Equal
○ Usual clinical presentations	− Obstructive jaundice (50%) − Acute pancreatitis (30%)	− Obstructive jaundice (50%) − Acute pancreatitis (25%)

Feature	Type 1 AIP	Type 2 AIP
○ Pancreatic imaging	− Diffuse pancreatic enlargement (40%) − Focal pancreatic enlargement (40%)	− Diffuse pancreatic enlargement (15%) − Focal pancreatic enlargement (85%)
○ IgG4	− ↑ in serum (~2/3 of patients) − Positive in staining of involved tissues	Not associated
○ Other organ involvement	− Biliary stricture − Sialoadenitis − Retroperitoneum fibrosis − Pseudotumours ▪ Kidney ▪ Lung ▪ Others	Not associated
○ Associated diseases		IBD
○ Long-term outcome	Frequent relapses	Rare relapses

- Other Etiologies
  - Tobacco
    - Smoking is both an independent and additive risk factor for CP
    - Implicated in more rapid development of pancreatic calcifications
    - Smoking cessation after the development of histologic CP reduces risk of subsequent calcifications
    - Increased risk of progressing to pancreatic cancer in those who smoke
  - Tropical Pancreatitis
    - Most common in southwest India
    - Mean age of onset = 24 yr, 90% of cases before age 40
    - Associated with severe malnutrition and trace element/micronutrient deficiencies though exact pathophysiology is unclear
    - Endocrine and exocrine insufficiency is a common end complication
  - Genetics
    - *PRSS1* is the only gene mutation sufficient to cause hereditary pancreatitis
      - Increased risk of pancreatic cancer
    - Other implicated gene mutations may modify risk in predisposed individuals but would not necessarily lead to CP in and of themselves:
      - *CFTR, SPINK1*, *CTRC*, CPA1, CLDN2/MORC
    - These mutations are in genes that code for digestive enzymes and can lead to their premature activation in acinar cells

- Obstruction
  - Chronic obstruction of the main PD can result from tumours, strictures, CBD stones, duodenal wall cysts, or stenosis of the papilla
  - Strictures can be malignant or benign
    - Benign strictures can occur after an episode of acute severe pancreatitis or following blunt/penetrating trauma
  - Pancreas divisum and sphincter of Oddi dysfunction are associated with acute or recurrent pancreatitis but not typically a cause of chronic pancreatitis
- Recurrent or Severe Acute Pancreatitis
  - 10% of patients with acute pancreatitis, especially those with significant pancreatic necrosis, may go on to develop chronic pancreatitis
- Asymptomatic Pancreatic Fibrosis
  - In older adults, histologic evidence of pancreatitis and fibrosis may be found without any clinical symptoms of chronic pancreatitis or exocrine/endocrine insufficiency
- Idiopathic
  - Accounts for 10-30% of chronic pancreatitis cases, most commonly in women

➢ Clinical Features

- Abdominal Pain
  - Most common clinical symptom with greatest impact on QoL
  - Pain is the most common reason for hospitalization, endoscopic intervention, and surgery
  - Associated with reduced appetite, weight loss, and malnutrition
  - Epigastric pain radiating to the back +/- nausea or vomiting
  - May improve with leaning forward
  - Pain often post-prandial or nocturnal
  - Initially pain is episodic but may become continuous
  - Mechanisms of pain:
    - Increased pressure within the pancreatic duct → tissue ischemia
    - Injury to peripheral and central nociceptive nerves
    - Increased sensitization to pain
- Endocrine Pancreatic Insufficiency
  - Occurs in longstanding chronic pancreatitis (median disease duration ranges from 6-26 yrs)
  - Pancreaticogenic diabetes (type 3c) is characterized by low levels of insulin, glucagon, and pancreatic polypeptide due to destruction of both islet cells and alpha cells
    - Risk of both hyperglycemia and hypoglycemia
    - 50% of patients will go on to require insulin

- Exocrine Pancreatic Insufficiency
  - Occurs late in disease course
  - Steatorrhea occurs when pancreatic lipase secretion is reduced to <10% of the maximum output due to acinar cell destruction
  - Bulky foul-smelling tools +/- oil droplets
  - Associated deficiency of fat-soluble vitamins (A, D, E, K)
  - Azotorrhea = protein maldigestion due to reduction of protease secretion, less common

➢ Physical Examination

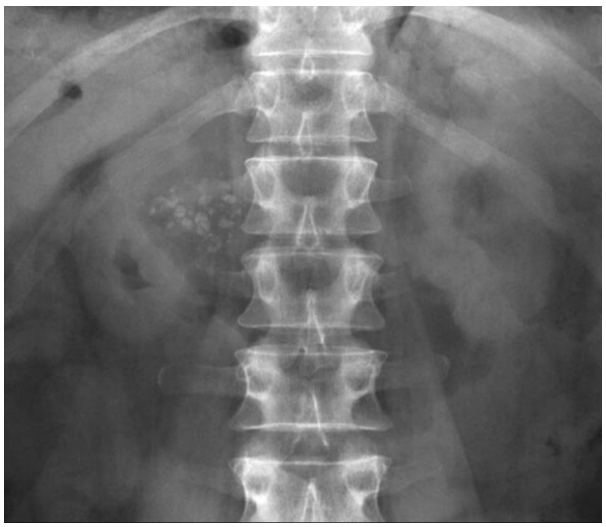
- General Appearance
  - BMI
  - Jaundice
  - Signs of sarcopenia / malnutrition (Subjective Global Assessment)
  - Signs of autoimmune disease (e.g. parotid gland enlargement, lymphadenopathy) in case of AIP
- Abdominal Exam
  - Palpable mass if pseudocyst present
  - Splenomegaly if complicated by splenic vein thrombosis

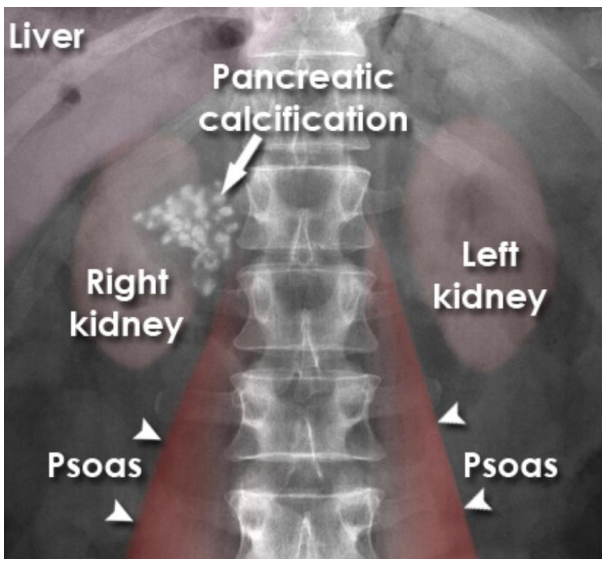
➢ Diagnosis

Tests of Pancreatic Structure	Tests of Pancreatic Function
○ Endoscopic Ultrasound (EUS)	− Direct hormonal stimulation (with pancreatic stimulation by secretin or cholecystokinin or both): ▪ Using oroduodenal tube ▪ Using endoscopy
○ MRI with MRCP, with or without secretin stimulation	− Fecal elastase
○ CT	− Serum trypsinogen (trypsin)
○ ERCP	− Fecal chymotrypsin
○ Abdominal Ultrasound	− Fecal fat
○ Plain Abdominal X-ray	− Blood glucose level

*Ranked in estimated order of decreasing sensitivity of each category

- Plain Abdominal X-Ray
  - May see diffuse or focal pancreatic calcifications in advanced disease
  - Specific but not sensitive
  - Bottom Line: May suggest CP in the appropriate patient population and prompt further workup but should NOT be used as first line test for investigation or diagnosis of CP





Source: https://www.radiologymasterclass.co.uk/gallery/abdo/abdominal_xray_calcification/pancreatic

- Abdominal Ultrasound
  - Sensitivity: 50-80%, specificity: 80-90%
  - Findings of CP:
    - Dilation of pancreatic duct*
    - Pancreatic ductal stones
    - Gland atrophy*
    - Irregularity of gland margins
    - Increased pancreatic echogenicity*
    - Pseudocyts

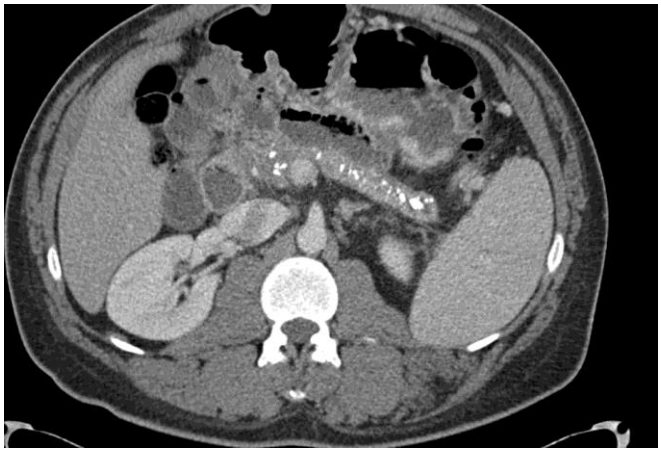
*may be seen as age-related changes

  - Limitations: visualization may be limited in patients with elevated BMI or due to overlying bowel gas

Bottom Line:

- US best used to evaluate for complications of CP or exclude mimickers such as cholelithiasis
- Normal pancreas or marked changes of advanced CP may be diagnostic but everything in between can be hard to interpret
- Should not be used as initial screening evaluation for someone with suspected CP

- CT Scan
  - Sensitivity: 75-90%, Specificity: >85%
  - Preferred over US due to higher sensitivity and specificity, which increased with more advanced disease
  - Radiographic features of CP
    - PD duct dilation > 4 mm
    - Irregularity of PD
    - Increased echogenicity of PD
    - Intraductal filling defect / stricture
    - Pancreatic calcifications
    - Cavities
    - Irregular contour of gland
    - Focal necrosis / loss of parenchyma



Abdominal computed tomography scan of patient with chronic pancreatitis, showing calcifications and dilation of the pancreatic duct, especially in the tail

Printed with permission: Hines OJ and Pandol SJ. BMJ 2024; 384: e070920 (Figure 2).

- MRI/MRCP
  - Superior visualization of subtle ductal changes in the tail of the pancreas or side branches
    - At least as accurate as CT if not more
  - Secretin-enhanced MRI/MRCP
    - Functional test that measures output of pancreatic fluid into the duodenum after administration of IV secretin
    - Measures quantitative change in main PD diameter and qualitative change in the amount of fluid in the duodenum as an indirect estimate of pancreatic secretory function
    - Limited availability

Coronal maximum intensity projection reformat showing stricture of Main pancreatic duct with upstream dilatation in a case of chronic pancreatitis.

Source: Kumar A, et al Front. Med. Technol 2023; 5:946555 (Figure

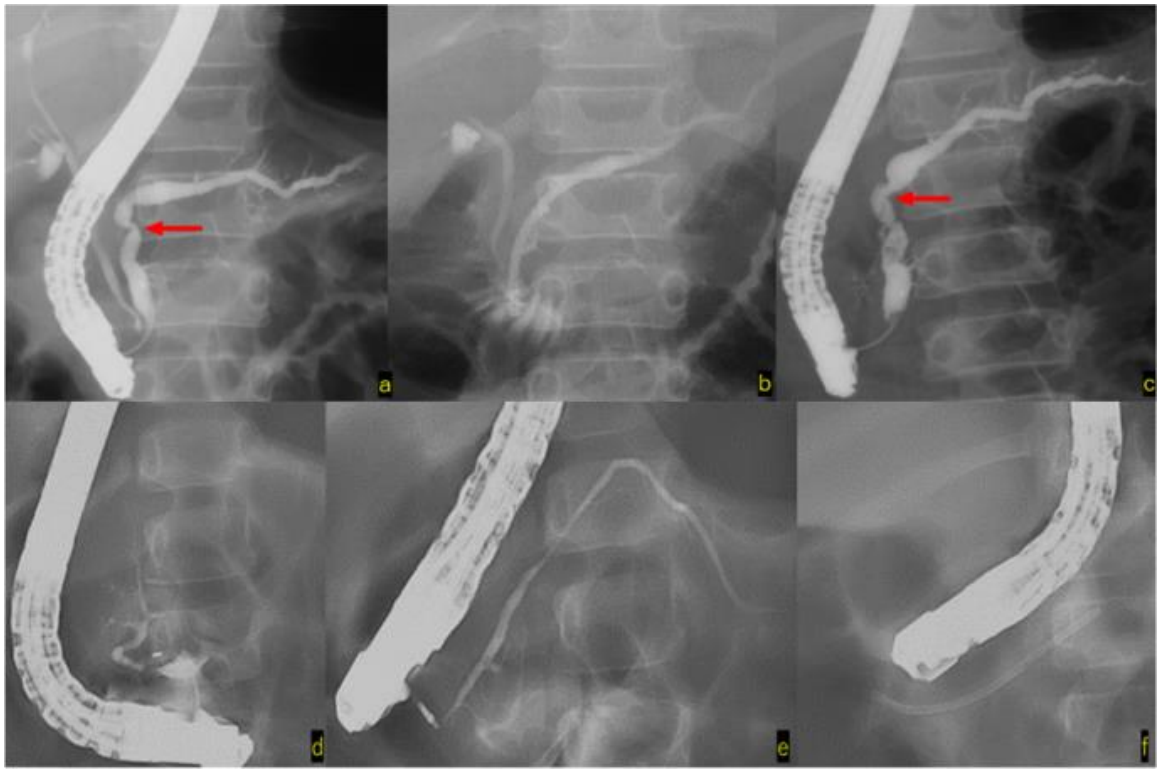
- ERCP
  - Benefits
    - Sensitivity, 70-90%, Specificity, 80-100%
    - ERCP in both diagnostic and therapeutic (e.g. pancreatic duct stenting / stone extraction)
    - Advanced CP
      - Mild changes to the duct may be non-specific and lead to overcalling of diagnosis of chronic pancreatitis
  - Limitations
    - Invasive with risk of complications = 5%
    - Interpretation relies on adequate duct filling and limited motion artifact
      - Substantial intraobserver and interobserver variability (up to 53%)
  - Bottom Line
    - Do **not** use ERCP as a primary diagnostic tool for diagnosing CP
    - Use less invasive modalities, i.e. MRI/MRCP and EUS
    - Do use ERCP if endoscopic therapy is planned

Cambridge Grading of Chronic Pancreatitis on ERCP

Grade	Main Pancreatic Duct	Side Branches
Normal	Normal with filling of main pancreatic duct to side branches	Normal
Equivocal	Normal	<3 Abnormal
Mild	Normal	≥3 Abnormal
Moderate	Abnormal	≥3 Abnormal
Severe	Abnormal with at least one of the following: − Large cavity (>10 mm) − Obstruction or stricture − Filling defect(s) − Severe dilatation or irregularity	≥3 Abnormal

Adapted from: Axon ATR, et al. Pancreatography in chronic pancreatitis: international definitions. Gut 1984; 25:1107–12.

ERCP of Patients with CP

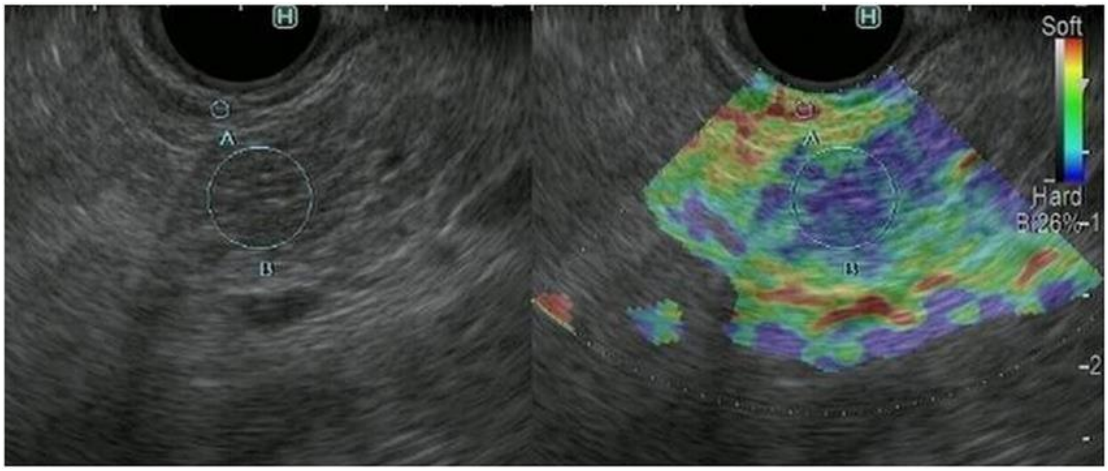


A. Pancreatic duct stenosis due to chronic inflammation and fibrosis.
B. Stent placement across the stenotic segment to restore ductal flow.
C. Post-stent image showing improved ductal patency.
D. Disruption of the main pancreatic duct (Wirsung) with contrast leakage.
E. Contrast injection via accessory papilla to visualize caudal duct segment.
F. Stent placed from accessory papilla to bypass disrupted duct.

Source: Makita S, et al. BMC Pediatr 2022; 22, 134 (Figure 5)

- **Endoscopic Ultrasound** (EUS)
  - Of all above tests of pancreatic structure, EUS is most sensitive
    - Provides highly accurate assessment of pancreatic parenchyma and duct
  - However, detection of subtle pancreatic changes may lead to overcalling of CP diagnosis
    - Unlike ERCP, moderate interobserver variation and intraobserver agreement is high

- Highly accurate for detecting advanced disease
  - EUS Score > 5 as per MST criteria is very specific for CP
  - Normal-near normal EUS makes severe CP very unlikely
- Dilated PD with
  - Hyperechoic margins
  - Surrounding hyperechoic strands
  - Foci on radial EUS probe



Representative EUS strain elastography images in a patient with chronic pancreatitis. EUS strain elastography measurements in pancreatic parenchyma are shown mainly in blue, indicating hardness.

Source: Yamashita Y, et al. Front. Physiol 2022; 12: 800516 (Figure 3)

➢ Grading System for EUS Diagnosis of CP

- Standard MST EUS Grading System
  - Parenchymal
    - Hyperechoic foci
    - Hyperechoic strands
    - Lobularity of contour
    - Cysts
  - Ductal Abnormalities
    - Main duct
      - Dilatation
      - Irregularity
    - Hyperechoic duct walls
    - Visible side branches
    - Calcification

- Rosemont Criteria for EUS Diagnosis
  - Major Features
    - Hyperechoic foci without shadowing (Major A)
    - Main pancreatic duct calculi (Major A)
    - Lobularity with honeycombing (Major B)
  - Minor Features
    - Lobularity without honeycombing
    - Hyperechoic foci with shadowing
    - Stranding
    - Cysts
    - Irregular main pancreatic duct contour
    - Main pancreatic duct dilatation
    - Hyperechoic duct margin
    - Dilated side branches

Interpretation of Rosemont Criteria

Most Consistent with Chronic Pancreatitis	1 Major A feature and ≥3 minor features, or 1 Major A feature and 1 Major B feature, or 2 Major A features
Suggestive of Chronic Pancreatitis	1 Major A feature and <3 minor features, or Major B feature and ≥3 minor features, or ≥5 minor features
Indeterminate for Chronic Pancreatitis	3–4 minor features, or Major B feature with <3 minor features
Normal	≤2 minor features

  - Overview
    - All diagnostic tests are most useful in patients with advanced disease once structural changes become apparent
    - Mild ductal / parenchymal changes should be interpreted with caution in the absence of compatible clinical symptoms or risk factors for CP, because these may be related to normal variant changes seen in aging, tobacco, alcohol, diabetes mellitus, CKD, etc.

- **Direct Hormonal Stimulation Tests**
  - Directly measure output of pancreatic enzymes and bicarbonate in response to hormonal stimulation (CCK or secretin)
  - Performance characteristics
    - Sensitivity 74-97%
    - Specificity 80-90%

- Procedure:
  - IV secretin → measure (bicarbonate [HCO_3-]) in pancreatic secretions collected from duodenum either via oroduodenal tube or endoscopy q15 mins x 60 mins post administration
  - Abnormal value is HCO_3- < 80 mEq/L
  - Variation of test involves ERCP to collect pancreatic secretions after administration of secretin
  - Can alternatively measure [enzymes] in response to IV CCK
- Drawbacks
  - Pancreas must have 30-50% damage before test is abnormal
  - Limited availability across centers
  - Not well standardized

- Indirect Tests
  - Tests that measure the effects of pancreatic enzymes in blood or stool
  - Serum trypsin/trypsinogen level
    - Trypsinogen which is produced / stored in the pancreas is reduced in patients with advanced CP, leading to ↓ levels of trypsin
  - Fecal chymotrypsin
    - False positives of ↓ fecal chymotrypsin with malabsorption secondary to Crohn disease, celiac disease, etc.
      - Fecal levels may be diluted secondary to diarrhea
  - Fecal elastase
    - Easier to measure and more stable passage in stool
    - Level < 200 µg/g of stool is abnormal and
    - < 100 is essentially diagnostic of exocrine insufficiency
  - 72-hr fecal fat
    - Abnormal only after 90% of pancreatic lipase secretory capacity is lost
    - Patient needs to be on high-fat diet for 3 days prior and post-test (at ≥100 g/day)
    - Fecal smear, stained ≥6 globules of fat per high powered field (hpf) (Sudan III stain)
    - Blood glucose test to assess endocrine dysfunction (islet cells) is a positive test

➢ Diagnostic Strategy

Abdominal pain syndrome +/- exocrine or endocrine insufficient

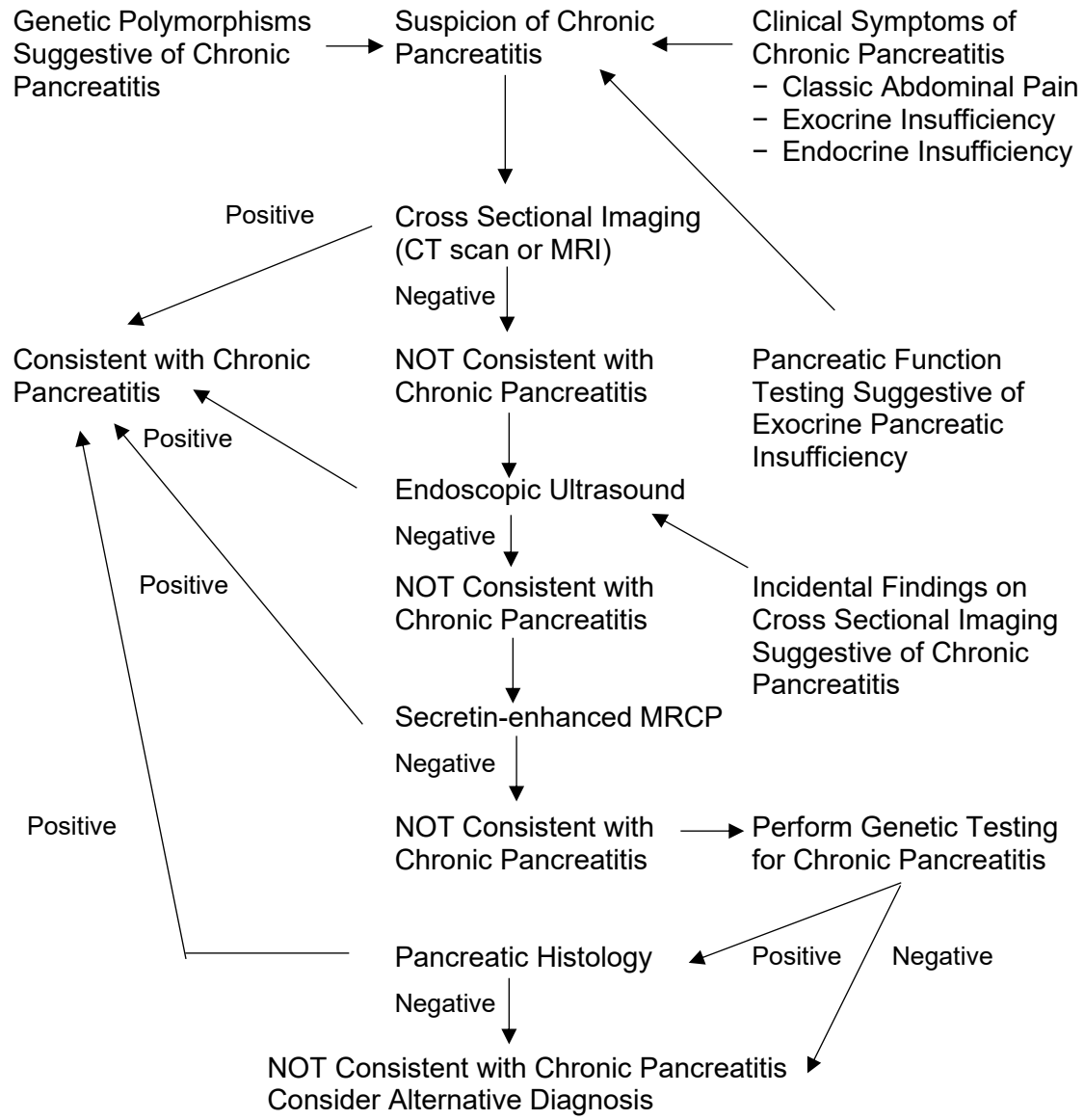
↓

CT (pancreatic protocol) or MRI/MRCP

↓

EUS

Tests of pancreatic function (if available)



➢ Treatment

- **Abdominal Pain**
  - Exclude secondary causes of abdominal pain for which specific therapies exist.
  - This usually requires use of cross-sectional imaging to exclude
    - Cholelithiasis/cholecystitis
    - Pancreatic pseudocyst
    - Duodenal or bile duct compression
    - Pancreatic cancer
  - Medical Therapy
    - Lifestyle Interventions
      - No alcohol
        - May ↓ chronic abdominal pain from 53% of consensus, to 26% of those who are abstinent
      - Smoking cessation
    - Analgesics
      - Acetaminophen
      - Tricyclic antidepressants (TCAs)
      - Selective norepinephrine receptor inhibitors (SNRIs)
      - Gabapentinoids
      - Opioids
      - Celiac plexus block with local long-lasting anesthetic (e.g. bupivacaine and steroid)
        - Injection guided by EUS > CT
        - Not recommended, due to unpredictable, short-lived response
    - Antioxidants and Pancreatic Enzymes
      - CP associated with free radical and oxidant stress → may further exacerbate inflammation and damage to the pancreas
        - Selenium, beta-carotene, Vitamin C, Vitamin E, methionine combination antioxidant was used in a placebo-controlled trial in India that showed less painful days with use of antioxidants
      - CCK stimulation of the pancreas may ↑ pain by ↑ intrapancreatic ductal pressure
        - Oral administration of pancreatic enzymes may denature CCK-releasing factor (CCK-RF) and thus ↓ pancreatic secretion, to ↓ pain
      - Data to support their role in pain relief is limited.
        - Consider their use on a patient-to-patient basis, and weigh costs of therapy against limited potential benefit.

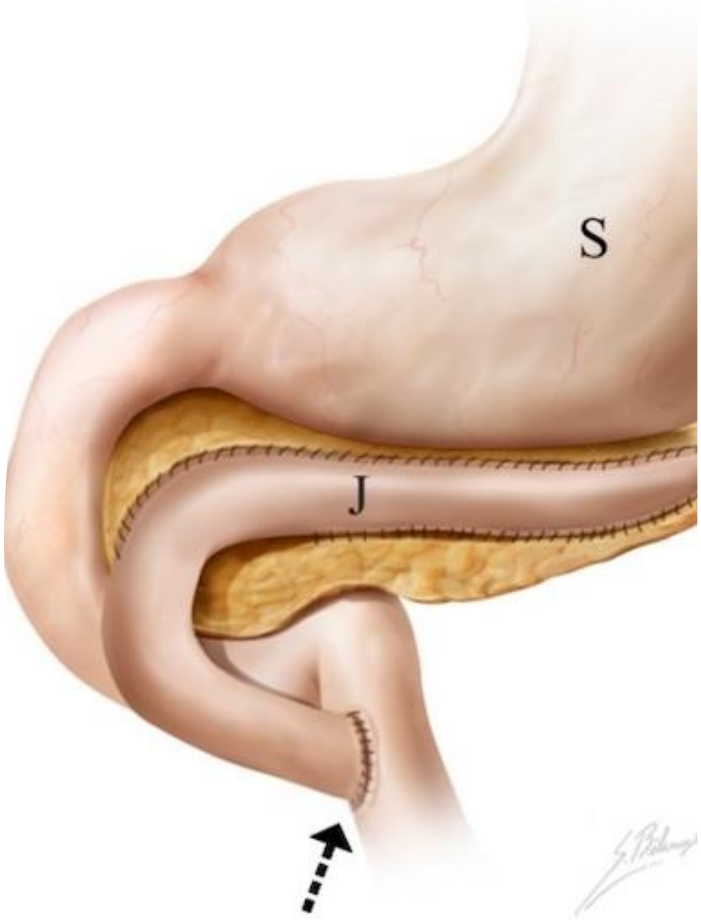
Summary of Medical Therapy (ACG 2020)

- Stop alcohol and smoking in patients with CP (Strong recommendation, very low quality of evidence)
- Use of antioxidant therapy for CP with pain, although the benefit of pain reduction is likely limited
  (Conditional recommendation, moderate quality of evidence)
- Do **not** use pancreatic enzyme supplements to improve pain in CP
  (Conditional recommendation, low quality of evidence)
- Use opiates to treat painful CP only in patients in whom all other reasonable therapeutic options have been exhausted.
- Use celiac plexus block for treatment of pain in CP (Conditional recommendation, very low quality of evidence).

- Endoscopic Therapy
  - Goal: improve pancreatic drainage in patients with PD obstruction
  - Indications
    - Candidates: dilated PD (>5 mm), obstructive stone or stricture in the *head* of the pancreas
  - Therapies:
    - PD sphincterotomy usually used in concert with stent placement or stone removal; limited data to do this prophylactically alone
    - PD stent placement used to bypass and dilate stricture
    - Complications: obstruction of PD, migration, ductal perforation
    - PD stone removal using endoscopic extraction or lithotripsy (extracorporeal shockwave or. intraductal lithotripsy)
- Surgical Therapy
  - Indications:
    - Intractable abdominal pain with failure of medical therapy
    - Complications of CP (e.g. pseudocyst) that have failed endoscopic or radiologic intervention
    - Need to exclude pancreatic malignancy
  - Therapies:
    - Ductal drainage procedures for those with PD >5 mm (e.g. Modified Puestow procedure / lateral pancreaticojejunostomy)
    - Pancreatic resection for those with PD >5 mm, plus inflammatory mass at head of pancreas
    - Rarely, total pancreatectomy with islet cell auto-transplantation in those with non-dilated PD

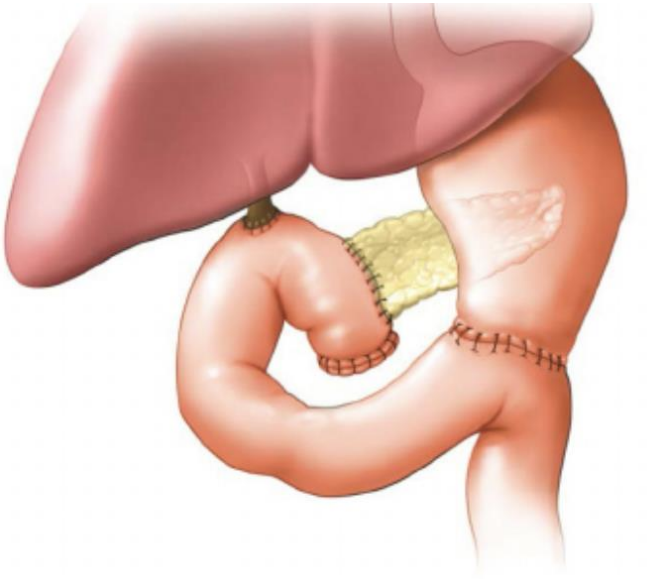
Modified Puestow Procedure

- PD is opened longitudinally and anastomosed to a limb of jejunum
- At time of PD incision, strictures and stones can be removed as needed
- Jejunal limb can be used to decompress any pseudocysts

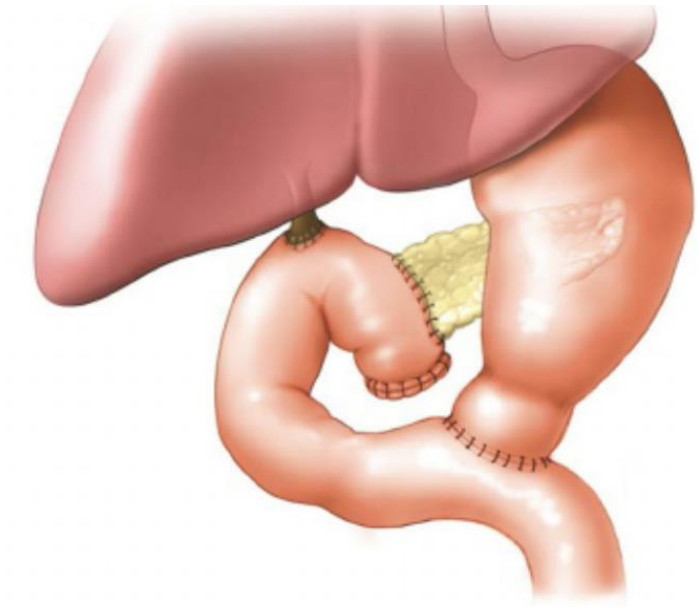


Source: https://operativereview.com/pancreatic-drainage-procedures/

Head of Pancreas Resection



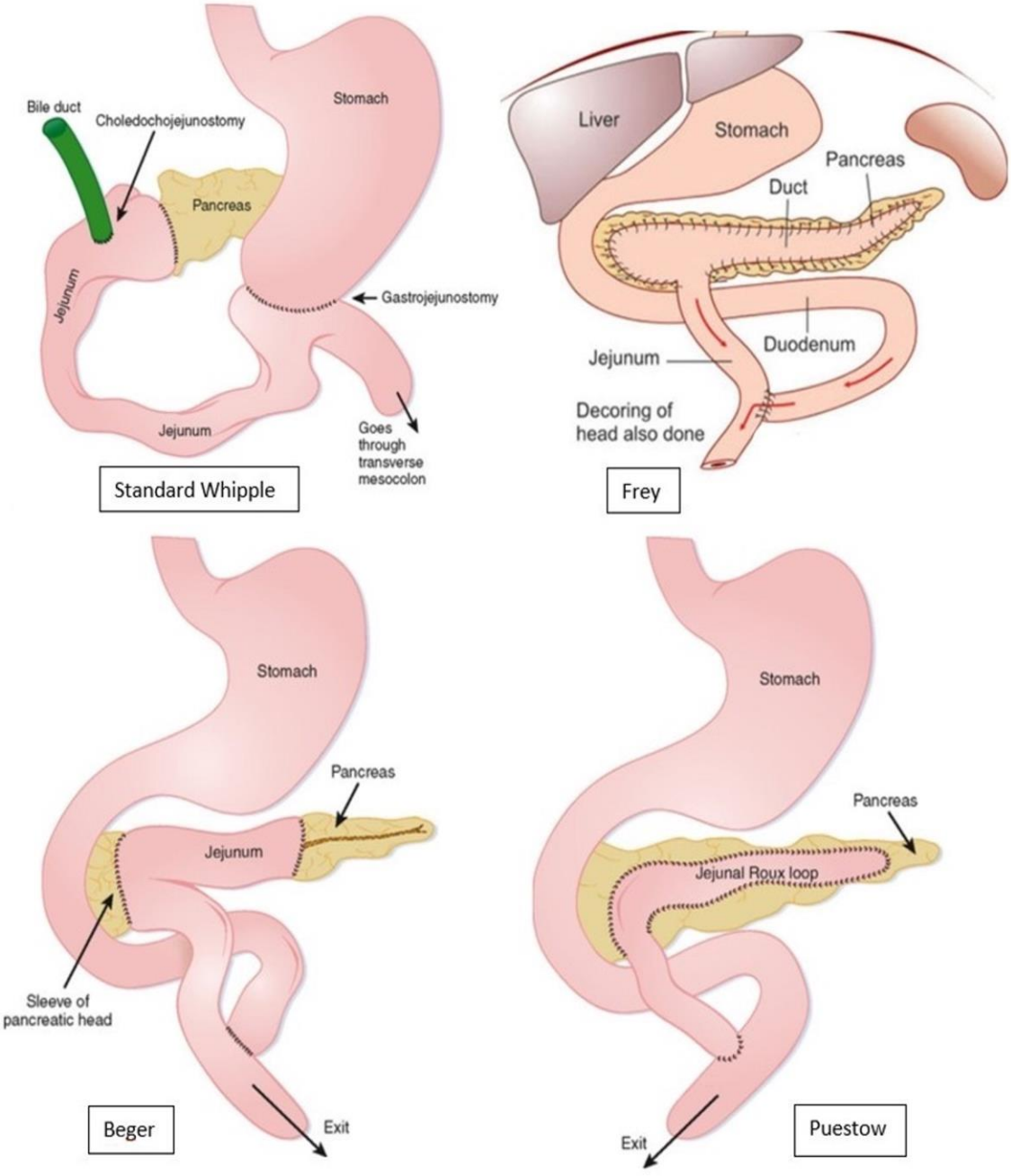
Standard Whipple Procedure (Pancreaticoduodenectomy)



Pylorus-Preserving Whipple Procedure

Source: Bartel MJ, et al. Pancreatic exocrine insufficiency in pancreatic cancer: A review of the literature. Digestive and Liver Disease 2015: 47(12), 1013–1020.

Depiction of the final gross anatomical changes associated with the Whipple, Frey, Beger, and Puestow procedures.



Source: Ashraf H, et al. A Clinical Overview of Acute and Chronic Pancreatitis: The Medical and Surgical Management. Cureus 2021; 13(11): e19764 (Figure 1)

Endoscopic vs. Surgical Therapy

- Requires careful selection of appropriate candidates based on co-morbidities, ductal anatomy (i.e. dilated PD >5 mm and obstructing stone/stricture) and exclusion of other complications that may be contributing to pain
- In large case series, endoscopic therapy is effective in about 2/3 of patients, but recurrence of pain is common and there is need for repeat endoscopic intervention
- Based on data from small trials, surgical therapy is associated with more durable and effective response than endoscopic therapy

Recommendations from ACG 2020

- We recommend surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful (Strong recommendation, moderate quality of evidence).
- Total pancreatectomy with islet autotransplant (TPIAT) should be reserved for highly selected patients with refractory chronic pain in which all other symptom control measures have failed.

- **Steatorrhea and Maldigestion**

Product	Lipase Content/Pill or Capsule (USP Units)
Creon (Enteric-coated porcine capsule)	3,000, 6,000, 12,000, 24,000, 36,000
Zenpep (Enteric-coated porcine capsule)	3,000, 5,000, 10,000, 15,000, 20,000
Pancreaze (Enteric-coated porcine capsule)	4,200, 10,500, 16,800, 21,000, 23,000
Pertzye (Enteric-coated porcine capsule with bicarbonate)	4,000, 8,000, 16,000
Viokace (Non-enteric coated porcine tablet)	10,440, 20,880

- Requires co-treatment with a histamine-2 receptor antagonist or proton pump inhibitor to avoid denaturation of enzymes by gastric acid.

- The total dosage of lipase per meal should be titrated based on response, but
  - Usually requires 40,000 to 90,000 units of lipase per meal and half that amount with snacks.
    The dosage should be split equally during the meal.
- If ineffective, consider changing brands, adding acid suppression, raising enzyme dose, and working up other malabsorptive diseases
  (e.g. SIBO, celiac)

Recommendations from ACG 2020

- We suggest pancreatic enzyme replacement therapy in patients with CP and exocrine pancreatic insufficiency to improve the complications of malnutrition (Conditional recommendation, low level of evidence).
- Patients with CP should have periodic evaluation for malnutrition, including tests for osteoporosis and fat-soluble vitamin deficiency
  - Fat soluble vitamins (Vitamin A, D, E, K)
  - Zinc and magnesium deficiency
  - No guidance given frequency of surveillance
  - Recommendation also includes small frequent meals without fat restriction

- **Diabetes Mellitus** (DM)
  - Monitor patients with CP with annual HbA1C + fasting blood glucose
  - Treat DM as per Diabetes Canada guidelines once it develops
    - Screen for microvascular and macrovascular complications
    - Patients will often need insulin but usually at lower doses than patients with T1DM

- **Summary**
  - Treatment is targeted towards modifying underlying risk factors to reduce progression of disease and manage clinical symptoms
  - Important to set patient expectations from the outset, given frequency of symptom recurrence

➢ **Complications**

- **Pancreatic Pseudocysts** (PP)

➢ Definition
  - Walled-off fluid-filled pancreatic fluid collection

➢ Diagnosis/Differentiation
  - Use EUS ± FNA to differentiate PP from other types of pancreatic cysts
  - Presence
    - Acute pancreatitis → PP may resolve
    - Chronic pancreatitis → PP may persist
  - In CP, pseudocysts are more likely to persist than in acute pancreatitis
  - Complications (20–40%):
    - Hemorrhage → GI bleeding
    - Gastric/duodenal obstruction → nausea and vomiting
    - Fistula
    - Bile duct compression → jaundice
    - Infection → fevers, sepsis, abdominal pain

➢ Treatment
  - Monitor if asymptomatic
  - If symptomatic, rapidly enlarging, or complications develop

- Endoscopic guided drainage:
  - EUS-guided cystogastrostomy or cystojejunostomy (80–90% success, 10% complication rate)
  - Use transpapillary drainage for PP at head of pancreas

- Surgical drainage:
  - Often combined with PD drainage (e.g., cyst decompression plus modified Puestow)
  - Long-term success rate, 90%

- Percutaneous drainage:
  - Falling out of favor due to low success rate, frequent re-accumulation, and fistula risk

- **Upper GI Bleeding**

➢ Differential diagnosis:
  - Esophagitis/Gastritis/
  - Peptic ulcer disease
  - Varices (alcohol cirrhosis)
  - Bleeding into pseudocyst (Hemosuccus pancreaticus)
  - Pseudoaneurysmal bleeding
  - Portal/splenic vein thrombosis → gastric varices

- **Pseudoaneurysm**

➢ Pathophysiology
  - Pancreatic enzymes digest arterial wall → aneurysmal dilation (splenic > gastroduodenal or pancreaticoduodenal)
    - Rupture risk → GI bleeding (5–10%)
    - High mortality rate

➢ Clinical
  - Sentinel bleed → brisk bleed
  - Unexplained anemia
  - Abdominal pain

➢ Diagnosis
  - Upper GI endoscopy
  - CT angiography

➢ Management
  - Angiographic embolization

- **Splenic Vein Thrombosis**

➢ Pathophysiology

Inflammation of pancreas
↓
Splenic or portal vein thrombosis
↓
Non-cirrhotic portal hypertension
↓
Gastric varices
↓
Variceal bleeding

- **Common Bile Duct** (CBD) **Obstruction**

➢ Pathophysiology
  - CBD may be compressed
    - Extrinsically by inflamed head of pancreas or
    - Internally intrinsically by ductal strictures secondary to CP

➢ Symptoms
  - Fever
  - Jaundice
  - Abdominal pain
  - Transaminitis

➢ Diagnosis
  - US
  - CT
  - MRCP
  - ERCP
  - EUS

➢ Treatment
  - If cholangitic
    - Manage short-term with ERCP stents, or
    - Definitively with surgical biliary bypass

- **Duodenal Obstruction**

➢ Pathogenesis
  - Inflammatory mass at head of pancreas

➢ Clinical
  - Nausea/vomiting
  - Abdominal pain

➢ Diagnosis
  - CT scan

➢ Treatment
  - Trial of conservative therapy allowing for inflammation to settle.
  - Definitive therapy involves gastrojejunostomy bypass surgery

- **Pancreatic Fistulas**

External Fistulas

➢ Clinical
  - Occurs in setting of post-surgical or percutaneous PP drainage

➢ Treatment
  - Octreotide, 100 µg SC q8hr
  - Endoscopic stenting
  - Surgical fistulojejunostomy
    - Resection of affected portion of pancreas

Internal Fistulas

➢ Clinical
  - Occurs in setting of pseudocyst rupture or trauma
  - Presents as
    - Pancreatic ascites (low SAAG, amylase > 4000)
    - Peripancreatic fistulas due to fluid tracking into adjacent cavity

- Treatment
  - NPO
  - TPN
  - Paracentesis/thoracentesis prn to remove fluid ± octreotide,
    - Consider endoscopic PD stent
    - If leak is from distal pancreas, then surgical drainage/resection

- **Malignancy**

- Demography
  - Lifetime pancreatic duct adenocarcinoma (PDCA) in CP, 4%
    - Highest in
      - Hereditary pancreatitis, and
      - Concurrent risk factors (smoking or diabetes mellitus)

- Clinical
  - Signs/symptoms overlap with pancreatic cancer (i.e., abdominal pain, weight loss)
    - Have low threshold for CT and CA 19-9
    - EUS is best for malignancy detection and obtain simultaneous fine needle core biopsies
  - Extra-pancreatic cancers may be related to heavy alcohol use or smoking
    - Head/neck
    - Lung
    - Liver (hepatocellular cancer [HCC])

ACG 2020 Pancreatic Cancer Screening

- There is a lack of evidence to suggest that performing screening examinations on patients with CP to detect pancreatic malignancy is beneficial.
  - No RCTs, systematic reviews, or meta-analyses to support screening
  - Difficult to interpret imaging tests in context of chronic morphologic changes in CP
  - Questionable benefit as there are often limited options to intervene once pancreatic cancer is detected

- **Gastroparesis**

- Causes/Associations
  - Effects of chronic opioid use
  - Peri-gastric inflammation
  - ↑ plasma CCK
  - Post-surgical changes

MISCELLANEOUS

GLP-1 Receptor Agonists (GLP-1 RAs)

Nisha Howarth

- Background
  - Use of GLP-1 receptor agonists (GLP-1 RAs) dramatically ↑ since approval in 2005 for type 2 diabetes (T2DM)
  - More recently approved for weight loss
    - Up to 20% weight loss with utilization

- Pharmacological / Physiological Effects
  - Brain
    - ↑ Appetite
    - ↑ Satiety
    - ↑ Energy expenditure
    - Modulate of areas of the brain involved in appetite regulation and caloric intake
  - Heart
    - ↓ Blood pressure
    - ↑ Heart rate
    - ↑ Myocardial contractility
  - Kidney
    - ↑ Natriuresis
  - Pancreas
    - ↓ Post-prandial and inappropriate glucagon secretion
    - ↑ Glucose-dependent insulin secretion
    - ↑ Insulin biosynthesis
    - ↑ β-cell proliferation
  - GI Tract
    - ↓ Gastric emptying
    - ↓ GI motility
    - ↓ Acid secretion
  - Liver
    - ↓ Hepatic glucose production
  - Adipose Tissue
    - ↑ Lipolysis
    - ↑ Free fatty acid (FFA) synthesis
    - ↑ Glucose uptake
  - Muscle
    - ↑ Glycogen synthesis
    - ↑ Glucose oxidation

- Indications for use
  - T2DM—typically 2nd line therapy but can be utilized as 1st line when concomitant atherosclerotic CVD or when weight loss or avoidance of hypoglycemia is a primary consideration
  - Atherosclerotic cardiovascular disease (ASCVD)
  - Obesity and metabolic syndrome with or without diabetes

- Formulations
  - Semaglutide, dulaglutide, exenatide—sc, weekly
    - Half-life of injectable GLP1-RAs is 7 d (reaches steady state at 4-5 wk)
    - Liraglutide—sc daily
    - Orforglipron—po daily; investigational small molecule

- GI Side effects
  - Nausea and vomiting
  - Diarrhea / constipation
  - Allow gastric emptying causing possible aspiration (to be discussed below)
  - Published case studies showing that GLP-1 RA use associated with
    - ↑ gastric retention of solids not liquids, and
    - ↑ gastric residue with weekly vs. daily injections
    - Previous observational studies have associated insulin treatment with ↑ gastric residue in EGD
  - Gastric ultrasound was performed on patients receiving GLP-1 RAs and showed ↑ gastric residual contents after >10 h of fasting, as compared to controls
    - Inferred increased risk of aspiration
  - A case report published in the Canadian Anaesthesiologists' Society (2023) described a 42-yr-old male undergoing repeat EGD with propofol sedation for ablative therapies for dysplastic Barrett epithelium, who had substantial gastric content despite 18 hr of fasting
    - He was taking weekly injectable Semaglutide
    - He required endotracheal intubation, and gastric contents were removed from trachea and bronchi with bronchoscopy

- Statement from Specialists
  - Insufficient evidence regarding safety of GLP-1 RAs in the perioperative setting for a robust systematic review and guideline
  - American Society of Anesthesiologists published consensus-based guidance on June 29, 2023
    - Acknowledges lack of scientific data but rising anecdotal and observational evidence to suggest increased risk of aspiration during GA and deep sedation
  - Suggestions
    - If the patient has GI side effects (nausea/vomiting) while on GLP-1 RA, with endoscopy
    - This ↑ likelihood of residual gastric contents.
      - Proceed with caution
        - Hold GLP1-RA on day of procedure (daily dosing)
          - Hold 1 wk prior (weekly dosing) irrespective of indication.
          - Consider endocrinology consultation if taking for DM
          - Consider gastric US if GLP-1 RA not held as advised. Consider delaying if stomach is full or US inconclusive
          - Consider delaying procedure if the patient is having GI symptoms such as N/V/retching, bloating, abdominal pain

- Statement from

- Canadian Journal of Anaesthesia (2023)
  - Acknowledges lack of evidence other than case reports and observational data
  - Suggestions
    - If taking GLP-1 RA for weight loss
      - Consider holding drug for 3 half-lives (approximately 3 wks for semaglutide)
    - If taking GLP-1 RA for T2DM
      - Consider endocrinology consult regarding risks/benefits of holding for 3 half-lives
    - Prolonging the fasting time unlikely to be required/reasonable given negative perioperative effects of fasting and limited evidence to suggest a safe duration
    - Perform rapid-sequence intubation if GLP1-RAcannot hold for 3 half-lives.
      - Consider prokinetic drugs if no intubation planned, ensure preparedness to obtain airway with cuffed ET tube.
    - Consider POCUS of stomach to assess for residual content

- Remarks
  - High quality evidence urgently required to assess safety of this medication in the perioperative setting
  - Shared decision-making principles must be utilized when discussing risks/benefits of moving forward with a procedure in this population

Source: Jones PM, et al. Can J Anaesth. 2023; 70(8): 1281-1286.

- GI societies

AGA Rapid Clinical Practise Update, November 7, 2023:

- AGA does **not** endorse all patients stopping GLP-1 RAs prior to endoscopy, given lack of data
- An individualized approach should be adopted
  - If GLP-1 RA given for obesity
    - Likely little harm in holding the drug
    - Unclear if holding for 1 dose will be reliably adequate for an individual's gastric motility to return to normal
    - If DM, GLP-1 RA given for glycemic control is important before sedation
- Proceed with upper and/or lower endoscopy in patients taking GLP-1 RAs who
  - Have followed standard fasting procedures (8-hr for solid, 2-hr for liquid fast) and
  - Do **not** have symptoms of nausea, vomiting, dyspepsia, abdominal distension
  - If patient is symptomatic, can consider gastric US (but insufficient evidence to support this)
- Consider placing patients on a liquid diet in lieu of holding daily GLP-1 RAs

Source: Hashash JG, et al. Clin Gastroenterol Hepatol 2024; 22(4): 705-707.

Multi GI Society Statement Regarding GLP-1 RA and Endoscopy, August 11, 2023 (AASLD, ASGE, AGA, ACG, NASPGHAN (pediatric GI and hepatology society)

- Recognition that this class of medication is associated with delayed gastric emptying
- Acknowledges concern that GLP-1 RAs might be associated with safety issues regarding sedation and endoscopy
  - However, also acknowledges that there is little data regarding the relative risk of complications from aspiration
- Given that GIs and Hepatologists are familiar with safety risks of endoscopy, proceed with best practises when performing endoscopy on this population

- Cautionary notes
  - More data needed to understand when these medications should be held
  - Work with anaesthesia and endocrinology collaboratively to develop necessary evidence to inform medication adjustments in this setting

Source: https://www.aasld.org/news/gi-multi-society-statement-regarding-glp-1-agonists-and-endoscopy

- Important
  - What is the evidence that GLP-1 RAs are associated with aspiration?
  - Are pre-procedural changes necessary for patients taking GLP-1 RAs?
    - Do suggested pre-procedural changes truly mitigate periprocedural aspiration?
  - Do we need to make changes to our local practise regarding patients taking GLP-1 RAs?

- Implications of modifying approach to patients on GLP-1 RAs
  - Pre-procedure:
    - Physicians and secretaries to identify patients on GLP-1 RA and notify them to hold depending on dosing schedule
    - Consider
      - ↑ fasting duration?
      - Suggesting fluid only diet
      - Giving a prokinetic agent

    Change to patient handout
    Education of secretaries
    Possibly additional prescriptions

  - Day of Procedure
    - Nurses to inquire about GLP-1 RA on checklist and assess for symptoms of slow gastric emptying
    - Access if necessary for anaesthesia gastric US

    Changes to nursing documentation
    Education of nursing staff
    Access to equipment
    Competency in gastric US

  - System Implications:
    - Cancellation and resource costs may incur

- Summary and future steps
  - Case reports (retrospective studies along with anecdotal evidence have a limited ability to inform clinical care)
  - It is possible that this evidence is flawed and that there is no cause-effect relationship between GLP-1 RAs and aspiration

- However—early signals of safety problems with novel drugs should trigger this cascade of investigation
- This is reasonable to invoke precautionary action regarding these drugs when the consequences of their use can be life-threatening → assume drug is unsafe→ act accordingly

Suggested Reading:

Dungan K, and Anthony D. UpToDate:Glucagon-like Peptide 1-Based Therapies for the Treatment of Type 2 Diabetes Mellitus." Www.uptodate.com, Wolters Kluwer, 9 Nov. 2023, www.uptodate.com/contents/glucagon-like-peptide-1-based-therapies-for-the-treatment-of-type-2-diabetes-mellitus?search=glp%201%20agonist&source=search_result&selectedTitle=2~134&usage_type=default&display_rank=1#H1 Accessed 1 Nov. 2023.

Hashash JG, et al. aga rapid clinical practice update on the management of patients taking GLP-1 receptor agonists prior to endoscopy: Communication. Clin Gastroenterol Hepatology 2024; 22: 705–707

https://www.aasld.org/news/gi-multi-society-statement-regarding-glp-1-agonists-and-endoscopy

Jones PM, et al. Anesthesia and glucagon-like peptide-1 receptor agonists: proceed with caution. Can J Anaesth 2023; 70(8): 1281-1286.

Joshi GP, et al; American Society of Anesthesiologists Task Force on Preoperative Fasting. Consensus-based guidance on preoperative management of patients (adults and children) on glucagon-like peptide-1 (GLP-1) receptor agonists. American Society of Anesthesiologists. Published July 25, 2023. https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative

Klein SR and Hobai IA. Semaglutide, delayed gastric emptying, and intraoperative pulmonary aspiration: a case report. Can J Anesth/J Can Anesth 2023; **70**: 1394–1396

Kobori T, et al. Association of glucagon-like peptide-1 receptor agonist treatment with gastric residue in an esophagogastroduodenoscopy. J Diabetes Investig 2023; 14(6):767-773.

Raven LM, et al. Delayed gastric emptying with perioperative use of glucagon-like peptide-1 receptor agonists. Am J Med 2023; 136(12): e233-e234.

Sherwin M, et al. Influence of semaglutide use on the presence of residual gastric solids on gastric ultra- sound: a prospective observational study in volunteers without obesity recently started on semaglutide. Can J Anaesth 2023; 70: 1300–1306.

Silveira SQ, et al. Relationship between perioperative semaglutide use and residual gastric content: a retrospective analysis of patients undergoing elective upper endoscopy. J Clin Anesth 2023; 87: 111091.

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