Academic Half Days

GASTROENTEROLOGY & HEPATOLOGY

Volume III

Western University
London ON

Edited by

Alan B.R. Thomson and Zaki Alhashimalsayed

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Alan B. R. Thomson

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DEDICATION

TO JEANNETTE…...WITH LOVE

FOREVER AND EVER

ALAN B.R. THOMSON

TO MY BELOVED COUNTRY FOR ITS GENEROUS SUPPORT,
TO MY FAMILY FOR THEIR UNWAVERING LOVE,
AND
TO MY TEACHERS AND MENTORS FOR SHAPING AND GUIDING MY PATH.

ZAKI ALHASHIMALSAYED

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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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When Rebecca, Maxwell, Megan, Henry, Felix, Toby, Grady, Jasper, and Laila, ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding, generous, kind and forgiving. For what I was trying to say and to do was to make my professional life focused on the four Cs and an “H”; competence, caring, compassion, and composure, as well as humor - and to make my very private personal life dedicated to family – to you all.

TABLE OF CONTENTS

ESOPHAGUS

LOS ANGELES CLASSIFICATION FOR ESOPHAGITIS

Tamoor Afzaal

- **Purpose**
  - Establishes reliable and uniform endoscopic criteria for diagnosis of esophagitis
  - Provides explicit criteria for grading of the severity of esophagitis

- **Background**
  - First presented in 1994 at the World Congress of Gastroenterology Conference in Los Angeles
    - Published in 1996 - D Armstrong et al., Gastroenterology 1996;111:85-92
    - Scoring system is used to assess severity of Reflux Esophagitis
  - An International Working Group was arranged to help formulate a classification system (the Los Angeles [LA] grading system for esophagitis) - two different studies helped validate it
    - Still Photographs - 17 different observers with 100 different images
    - Video Tapes - 42 observes with 23 different video tapes
  - Reliability of mucosal breaks
    - Interobserver agreement remains moderate to good (κ ~0.6–0.8)
    - Highest reproducibility in Grades C and D
  - Definition of mucosal breaks
    - Endoscopically visible mucosal breaks (either erosion or ulceration) are the basis for the endoscopic diagnosis of esophagitis
    - These are “an area of slough or erythema with a sharp line of demarcation from adjacent normal mucosa”
    - The two milder grades (LA A/B) are distinguished by
      - Mucosal breaks not extending between two or more mucosal folds axial extent of mucosal breaks differentiates between these grades
    - The two most severe grades (LA C/D) are defined by:
      - Mucosal breaks extending between two or more mucosal folds radial extent of mucosal folds differentiates between these grades

Modern Clinical Interpretation (Lyon Consensus 2.0, 2023)

- LA Grade C/D esophagitis constitutes conclusive evidence of GERD
- LA Grade A/B is considered inconclusive and requires supportive evidence (e.g., reflux monitoring)

Limitations of the LA Classification

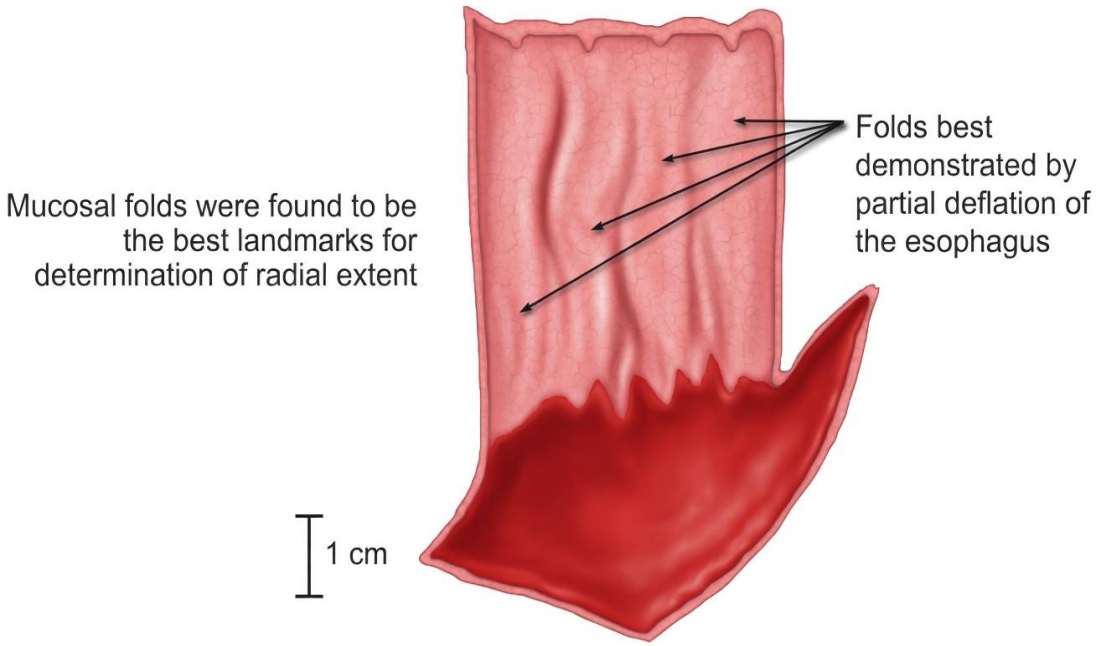
- Does not detect non-erosive reflux disease (NERD)
- Poor correlation with symptom severity in mild disease
- Findings may be influenced by: PPI use and timing of endoscopy
- Does not assess: Barrett esophagus and functional esophageal disorders

Armstrong D, et al. Gastroenterology 1996; 111: 85-92.

Los Angeles (LA) **Endoscopic Classification of Esophagitis**

Why Length Alone Is Not Reliable

- Estimation of mucosal break length:
  - Becomes unreliable beyond a few millimeters
  - Shows greater interobserver variability
- In contrast, radial extent across folds:
  - Is more reproducible
  - Better correlates with disease severity

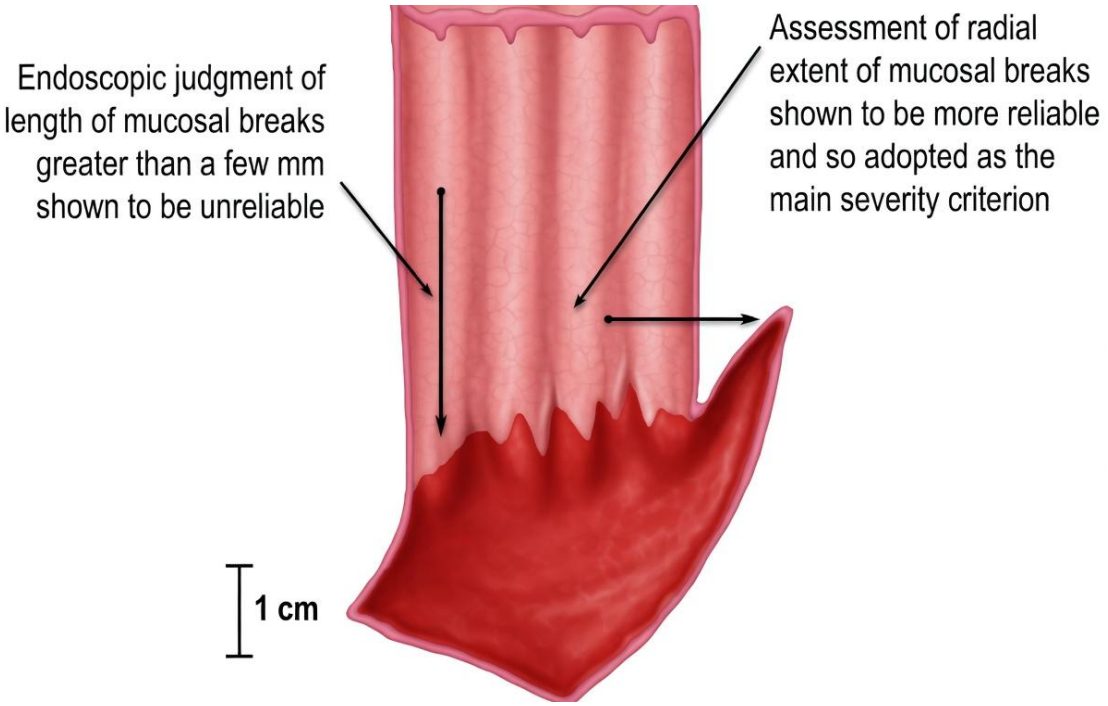


Adapted from: Armstrong D, et al., Gastroenterology 1996;111:85-92.

Los Angeles (LA) **Endoscopic Classification of Esophagitis**

Key Concept: Radial Extent Drives Severity

- The extent of mucosal involvement across mucosal folds (radial extent) is the most reliable determinant of severity
- This concept forms the basis for distinguishing:
  - Mild disease (LA A/B) → limited, non-confluent breaks
  - Severe disease (LA C/D) → confluent breaks extending across folds



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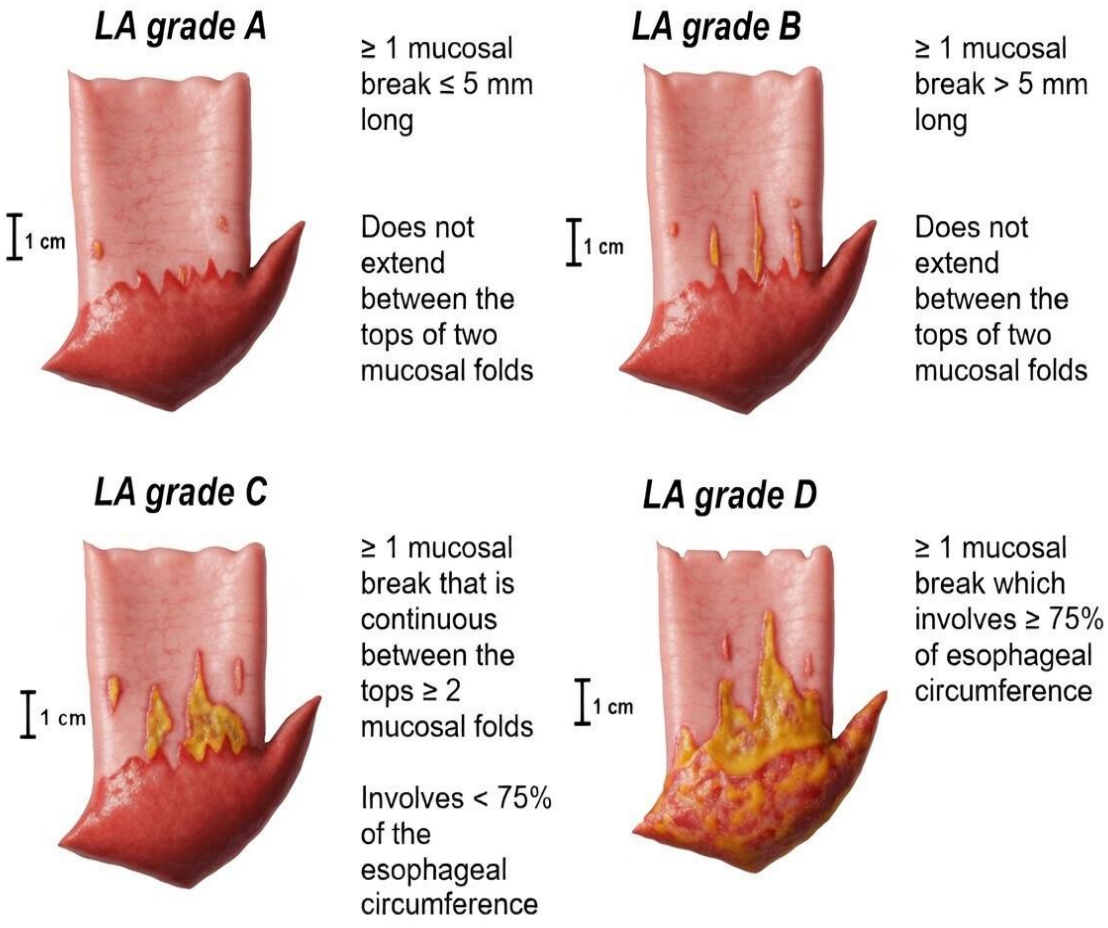
Los Angeles Classification of Reflux Esophagitis



Adapted from: Lundell et al. Gut 1999; 45:172-180.

- Importance of LA Classification in Clinical Practice
  - The LA classification has been demonstrated to have good intra- and inter-observer agreement
  - Validity of this classification scheme is demonstrated by the association with higher LA grades (LA C/D), and:
    - ↑ symptom severity
    - ↓ frequent complete healing of esophagitis on therapy
    - ↑ symptom relapse after a course of therapy

Diagnostic Significance (Lyon Consensus 2.0, 2023)

- LA Grade C/D
  - Considered conclusive evidence of GERD
  - No further diagnostic testing required in most cases
- LA Grade A/B
  - Considered inconclusive
  - Requires additional evaluation (e.g., reflux monitoring)

➢ Practice

- Practical Use
  - Describe LA grade for purposes of endoscopy dictation
    - LA grade C/D esophagitis
      - ~5% greater healing rate with PPI bid
      - Poor correlation between symptom severity and LA grade

➢ Histological Grading of GERD

- Reactive changes
  - Basal cell hyperplasia (> 15% of epithelial thickness)
  - Elongated papillae (> 60% of epithelial thickness)
  - Balloon cells
  - ↑ vascularity
- Inflammation/erosions
  - ↑ intraepithelial T-lymphocytes and eosinophils
  - T-lymphocytes may be squeezed by squamous cells, becoming elongated "squiggle cells"
  - Barrett - metaplasia, dysplasia, adenocarcinoma
- Edema (intercellular spaces), congestion, hemorrhage
- Erosion, ulceration
- Granulation tissue
- Submucosal fibrosis → stricture (peptic [esophageal] stricture)

Grade	Definition	Cell Type	Basal-Cell Hyperplasia
0	0–6 cells/HPF	Lymphocytes, plasma cells	3 cell layers or less
0.5	Small areas >6 cells/HPF	Lymphocytes, plasma cells	3 cell layers or less
1	Slight focal infiltration	Lymphocytes, plasma cells	>3 cell layers, less than 1/3 epithelial thickness
2	Moderate diffuse infiltrate	Lymphocytes, plasma cells, eosinophils	>1/3 and <2/3 of epithelial thickness
3	Severe inflammation	Lymphocytes, plasma cells, eosinophils, neutrophils	>2/3 of epithelial thickness

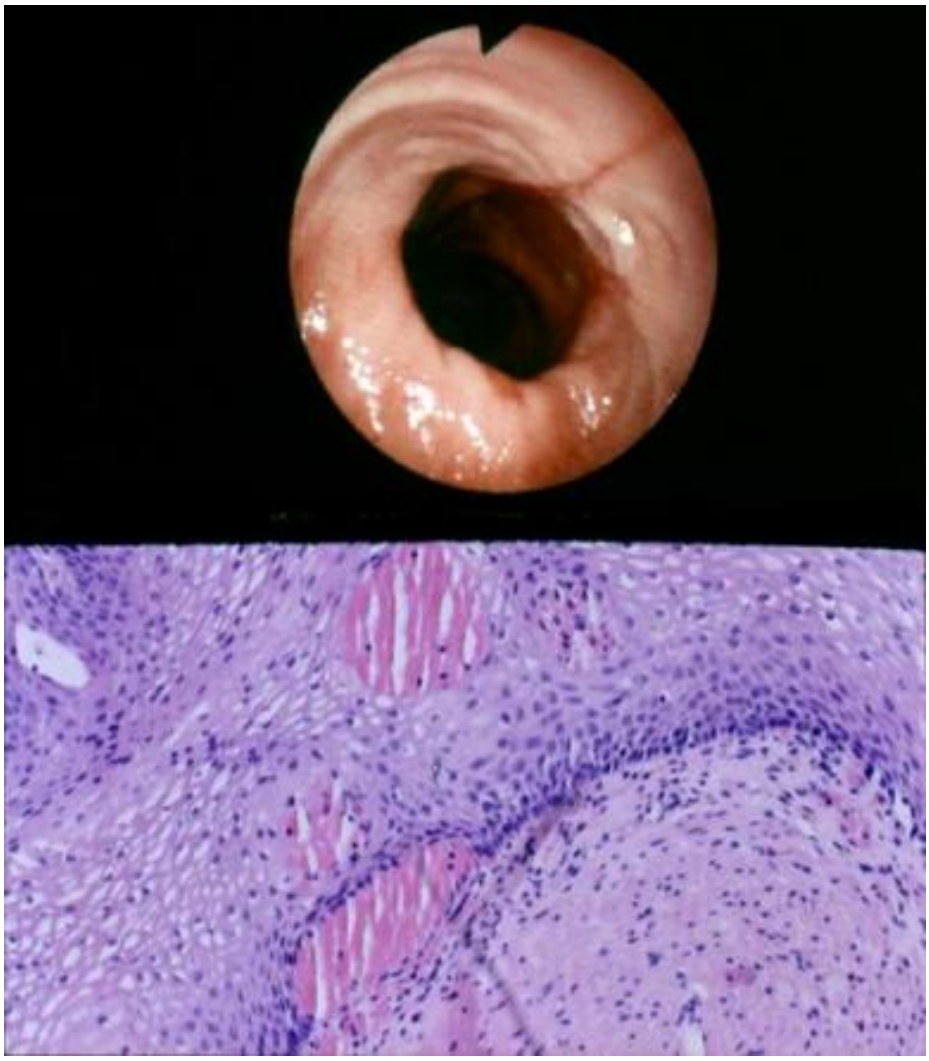
Adapted from: Vieth M. Best Pract Res Clin Gastroenterol 2008;22(4): pg. 629.

	Length of Papillae as % of Total Epithelial Thickness	Thickness of Basal Cell Layer as % of Total Epithelial Thickness
○ Normal	<15%	1–2%
○ Grade 1	15–33%	2–20%
○ Grade 2	34–66%	21–50%
○ Grade 3	>66%	>50%

Criticisms: Small number of patients; no interobserver variation; questionable control group

Adapted from: Vieth M. Best Pract Res Clin Gastroentero/ 2008;22 - GERD

Esophageal Erosion



Note the erosions of the mucosa

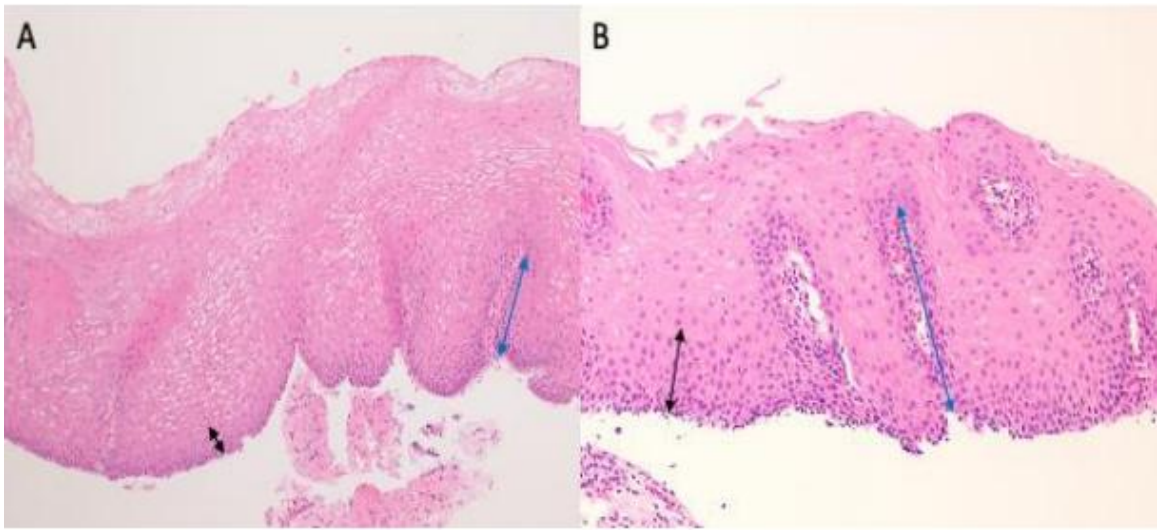
No eosinophilia

Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 1; 2021. ISBN: 9798719829074.

Endoscopic–Histologic Correlation in Reflux Esophagitis

- Reflux esophagitis is primarily a clinical and endoscopic diagnosis
- Histologic findings may support the diagnosis but are:
  - Non-specific
  - Not required in routine practice

Gastroesophageal Reflux Disease



- Normal esophageal squamous mucosa and (B) squamous mucosa with reactive changes.
- Lamina propria papillae (blue arrow) are elongated in (B) and there is basal zone hyperplasia (black arrow).

Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 1; 2021. ISBN: 9798719829074.

Abbreviations: bid, bis in die (twice daily); GERD, gastroesophageal reflux disease; HPF, high-power field (microscopy term); κ, kappa statistic (measure of interobserver agreement); LA, Los Angeles (classification/grading system for esophagitis); NERD, non-erosive reflux disease; PPI, proton pump inhibitor

GASTROESOPHAGEAL REFLUX DISEASE: PATHOPHYSIOLOGY AND MANAGEMENT

Tamoor Afzaal

- Demography
  - Worldwide pooled prevalence of onset GERD symptoms at least once a week – 13%
    - Significant geographic variation
  - Highest in South Asia, Southeast Europe
  - Lowest in Southeast Asia, Canada and France (still ~10–15%)
- Pathophysiology
  - Defensive Factors
    - Anti-reflux barriers
    - Esophageal acid clearance
    - Tissue resistance
    - ↓ Lower esophageal sphincter (LES)
    - Diaphragmatic crura
    - Phrenoesophageal ligaments
    - Intra-abdominal location of LES
    - Acute angle of His
  - Oblique entrance of the esophagus into the stomach forms sharp angle on the greater curve
    - Called the “angle of His”
  - This angle has been shown to create a flap valve effect.
  - Aggressive Factors
    - ↑ Gastric Acidity
      - Esophageal injury parallels ↑ frequency/duration of acid reflux of acid of pH < 4
    - ↓ Gastric Emptying
    - ↑ Duodenogastric Reflux
      - Retrograde movement of duodenal contents (specifically bile) into the stomach and esophagus
      - Bile acids alter integrity of mucosal barrier

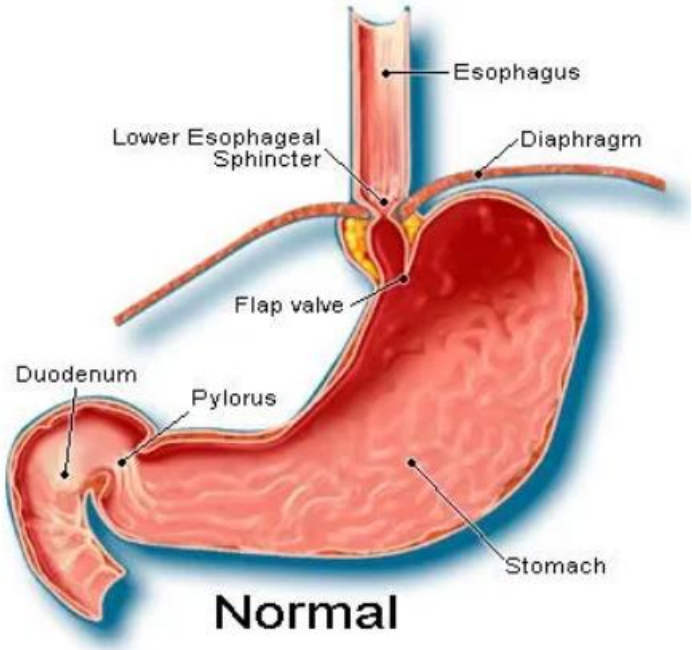
- **Mechanisms of Reflux**

- **Swallow-Induced Lower Esophageal Sphincter Relaxation** (SI-LESR)
  - About 5–10% of reflux episodes happen during swallow-induced ↓ LES tone
  - Stimulated by swallowing
    - Crural diaphragm does not relax
    - Duration of LESR is short (5–10 seconds)
    - There is peristalsis of esophagus thus reflux is prevented by oncoming peristaltic wave
  - Reflux during swallow-induced LES relaxation is more common with hiatus hernia

- **Transient Lower Esophageal Sphincter Relaxations** (TLESRs)
  - Most frequent mechanism for reflux
  - Occur independently of swallowing
    - No accompanied esophageal peristalsis
    - Persist longer (>10 secs) than swallow-induced LES relaxations
    - Associated inhibition of the crural diaphragm
    - Stimulated by proximal stomach distension
  - Account for 50–80% of reflux episodes for patients with GERD

  - Anti-Reflux Barriers
    - Determines the frequency and volume of GER (gastroesophageal reflux)
    - Anatomic region includes

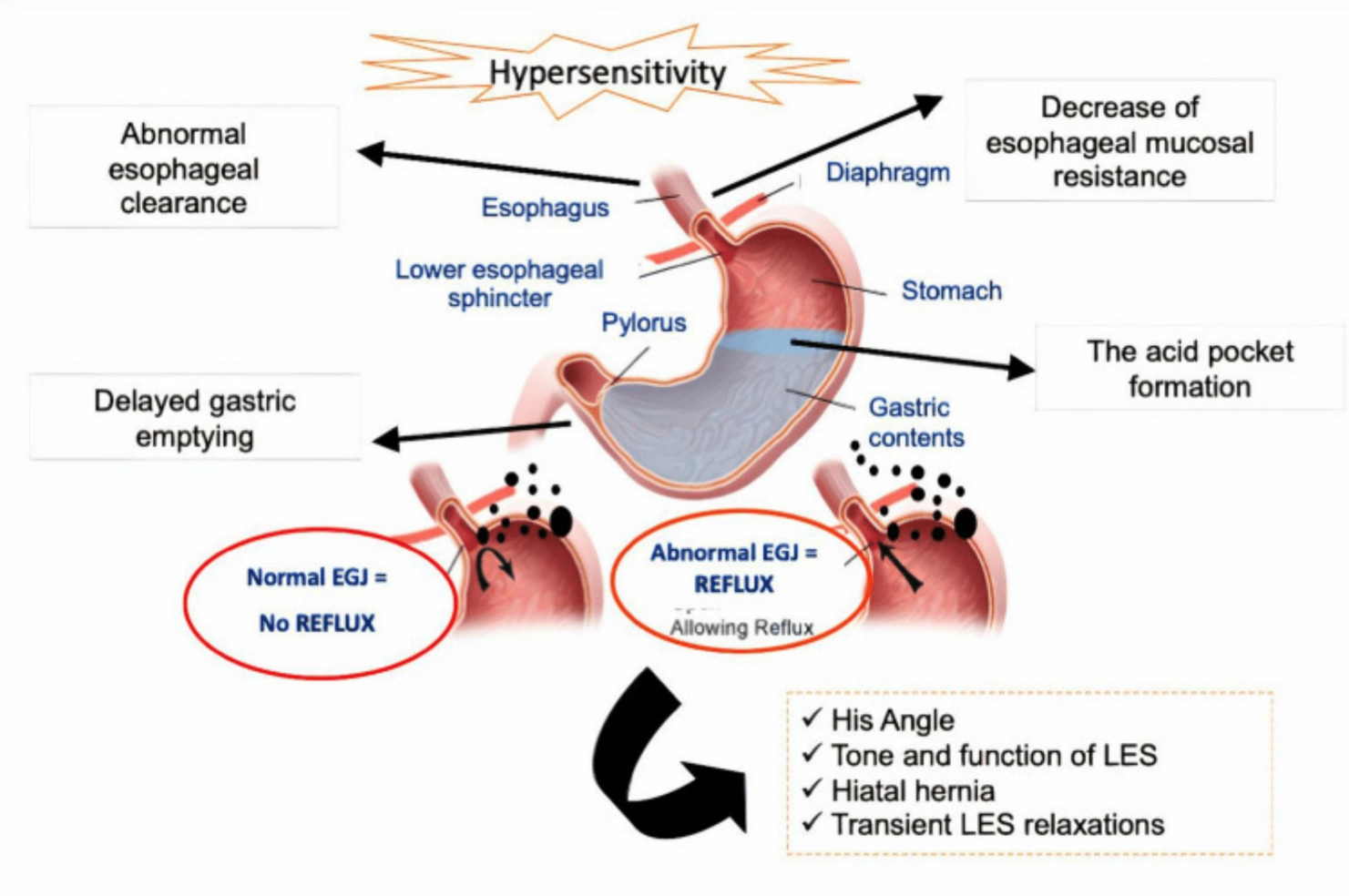
Outline of Normal Stomach



  - LES lies within the hiatus created by the right crus of the diaphragm (extrinsic squeeze to the intrinsic LES)
  - Anchored by the phrenoesophageal ligaments
    - Which insert at the level of the squamocolumnar junction

Courtesy of: Wedro B. Hiatal hernia symptoms, location, causes, diet & treatment [Internet]. MedicineNet. Available from: https://www.medicinenet.com/hiatal_hernia_overview/article.htm

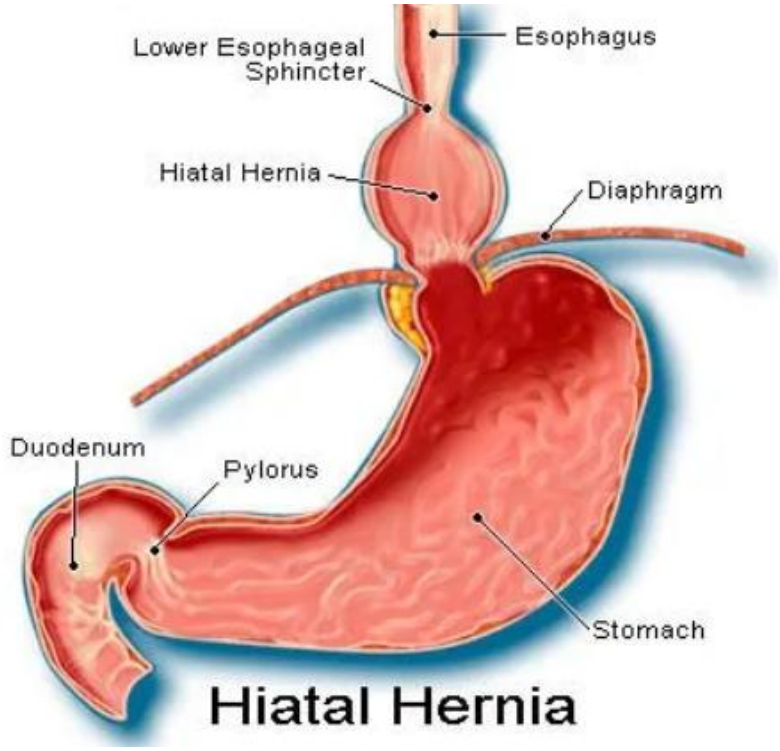
Outline of Likely Mechanisms of GERD



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

Courtesy of: Chhabra P and Ingole N. Cureus 2022; 14(8): e28563 (Figure 1)

Hiatus Hernia



- Weakened and shortened LES
- Loss of diaphragmatic support for the LES
- Loss of the intra-abdominal LES segment
- Retention of gastric fluid in hernial sac
- Stretching and rupture of the phreno-esophageal ligament
- Widened diaphragmatic hiatus

Courtesy of: Wedro B. Hiatal hernia symptoms, location, causes, diet & treatment [Internet]. MedicineNet. Available from: https://www.medicinenet.com/hiatal_hernia_overview/article.htm

Lower Esophageal Sphincter

	LES Pressure	
	Increase	Decrease
○ Hormones/ peptides	– Gastrin – Motilin, Substance P	▪ CCK ▪ Secretin ▪ Somatostatin ▪ VIP
○ Neural agents	– α-Adrenergic agonists – β-Adrenergic antagonists – Cholinergic agonists	▪ α-Adrenergic antagonists ▪ β- Adrenergic agonists ▪ Cholinergic antagonists

	LES Pressure	
	Increase	Decrease
○ Foods and nutrients	− Protein	▪ Chocolate ▪ Fat ▪ Peppermint
○ Drugs	− Antacids − Baclofen − Metoclopramide − Domperidone − Cisapride − Histamine − Prostaglandin E2	▪ Barbiturates ▪ Calcium channel blockers, ▪ Diazepam ▪ Dopamine ▪ Meperidine ▪ Morphine ▪ Prostaglandins E2 and I2, ▪ Serotonin ▪ Theophylline

- **Esophageal Acid Clearance**
  - Volume/Bolus Clearance
    - Removal of reflux material from esophagus using esophageal peristalsis
    - Esophageal peristalsis clears acid at all times aside from REM sleep
      - Broken down into
        - Primary peristalsis (swallowing) and
        - Secondary peristalsis (distension from acid)
    - Assisted with gravity – worse when supine
      - Origin of “Elevated head of bed”
  - Salivary Acid Neutralization:
    - Saliva helps restore normal esophageal pH
      - Weak base (pH 6.4–7.8)
    - Stimulated by acid in proximal esophagus (20 cm above LES)
    - Decreased during sleep
    - Some esophageal submucosal glands also secrete HCO_3^-

- **Tissue Resistance** (Cellular Level)
  - Pre-Epithelial
    - Esophageal secretions of glycoconjugate (mucin) and
    - Prostaglandin E2 (small effect)
  - Epithelial
    - Structural
      - 25–30 cell layer thick nonkeratinized squamous epithelium plus the tight junctions

- Functional
  - Ability to buffer and extrude hydrogen ions
  - Actively removes H^+ using Na^+/H^+ exchange and HCO_3^-

- Post-Epithelial
  - Blood supply/flow to epithelium delivers O_2 plus HCO_3^-
  - Removes H^+ and CO_2
  - Blood flow to esophageal mucosa increases in response to acid

- **Delayed Gastric Emptying**
  - Importance of delayed gastric emptying to GERD is controversial
  - Early studies suggested strong link; recent studies show less effect
  - ↓ gastric emptying → ↑ volume of material in stomach → ↑ volume available for reflux
  - Additionally, ↑ gastric contents → ↑ distension of proximal stomach → ↑TLESRs → ↑ GER

➢ Management of GERD

- Numerous components to management, often requiring multi-modal treatment strategies approach
  - Non-pharmacological
  - Pharmacological
  - Surgical
- Multifaceted approach
  - Symptom presentation
  - Endoscopic findings
  - Physiologic abnormalities

❖ Non-Pharmacologic Management

- Weight loss
  - ↑ intra-abdominal pressure from ↑ intraabdominal fat
  - Also, high in fat diet → ↓ LES tone
- Late Night Food
  - Avoid food < 3 hr before bed
  - ↑ gastric contents while laying supine

- Tobacco/Smoking
  - ↓ LES tone
  - Smoking cessation ↓ GERD symptoms
- Trigger Food
  - No effect on LES tone
    - Coffee, caffeine, citrus, spicy food, carbonated drinks, tomatoes
  - ↓ LES tone
    - Alcohol, tobacco, chocolate, peppermint, high fat food
- Elevate Head of Bed
  - Laying left side down more effective than right side down

❖ Pharmacologic Management

- Proton Pump Inhibitors (PPIs)
  - PPIs are superior in heartburn/regurgitation relief and healing compared to any other class of drug (particularly compared to histamine receptor antagonists (H2RA)
  - PPI therapy for 4 wk → greater rate of complete symptoms relief in patients with erosive esophagitis (EE) (70-80%) than non-erosive reflux disease (NERD) (50-60%)
  - Meta-analyses suggest similar symptom relief / mucosal healing for all available PPIs when given in the recommended doses
  - Must be taken 30-60 mins before meals
  - Empiric trial for typical heartburn or regurgitation symptoms
    - Typically, 8 wk then consider discontinuation vs on demand use of PPIs
  - Healing of erosive esophagitis
    - LA grade A/B
      - Consider intermittent PPI as needed
    - LA grade C/D Erosive Esophagitis
      - Remain on long-term PPI therapy to maintain healing
  - Barrett esophagus (BE)
    - Use long term indefinite PPI therapy as well as endoscopic follow-up (please see section on BE)

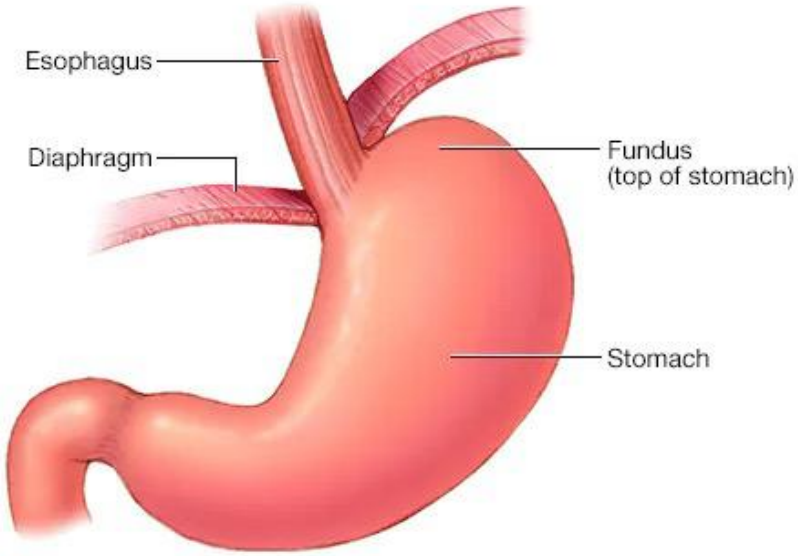
- Histamine H2 Receptor Antagonists (H2RA)
  - Suggested for patients on PPIs with persistent nocturnal symptoms (please see section on nocturnal acid breakthrough [NAB])
- Prokinetics
  - ↑ LES tone
  - ↑ esophageal peristalsis
  - ↑ gastric emptying rate
  - Not recommended for sole use for GERD
- Baclofen
  - ↓ transient LES relaxations that enable reflux episodes
  - Trial of baclofen 5–20 mg tid considered (objective evidence of continued reflux despite optimal PPI) (short term RCT evidence for this)
- Sucralfate
  - Recommendation for GERD during pregnancy (1st line)
  - Limited studies have shown similar effectiveness to H2RAs
- Alginate-Based Therapies
  - Form a mechanical barrier (“raft”) over gastric contents. Reduce postprandial reflux episodes. Particularly useful for:
    - Postprandial symptoms
    - Breakthrough symptoms despite PPI
    - Supported by randomized trials and recommended as adjunct therapy
- Potassium-Competitive Acid Blockers (P-CABs)
  - Example: Vonoprazan
  - Provide rapid and more potent acid suppression than PPIs
  - Increasing evidence for erosive esophagitis healing
  - Maintenance therapy

❖ Surgical/Endoscopic Management

- For most patients, medical management is effective for GERD (especially since PPI-era)
  - GERD is a chronic disease, and patients with severe EE may not prefer long term PPI therapy adequately
  - Note that patients who have poor benefit from PPIs usually have poor benefit from surgical fundoplication
- Choices
  - Fundoplication
  - Magnetic sphincter augmentation (MSA)
  - Roux-en-Y gastric bypass
  - Endoscopic therapies

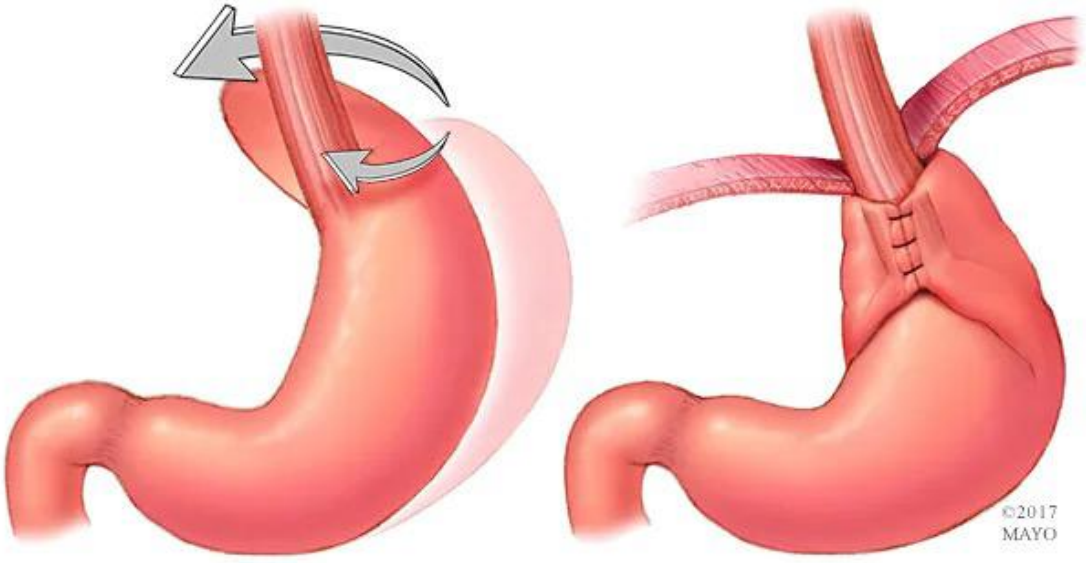
- Laparoscopic Nissen Fundoplication (NF)
  - ↓ acid / ↓ non-acid reflux → ↑ basal LES tone
  - Nissen is a complete wrap
    - Thal/Dor – anterior wrap (180 degree)
    - Toupet – posterior wrap
  - NF vs PPI-based therapy
    - Symptoms less frequent with surgery
    - Higher patient satisfaction with surgery than medical therapy
    - 16–62% of patients still needed anti-reflux medications after fundoplication and may need to continue use of PPIs

Diagram of Nissen Fundoplication



Mayo Foundation for Medical Education and Research

Steps in Nissen Fundoplication



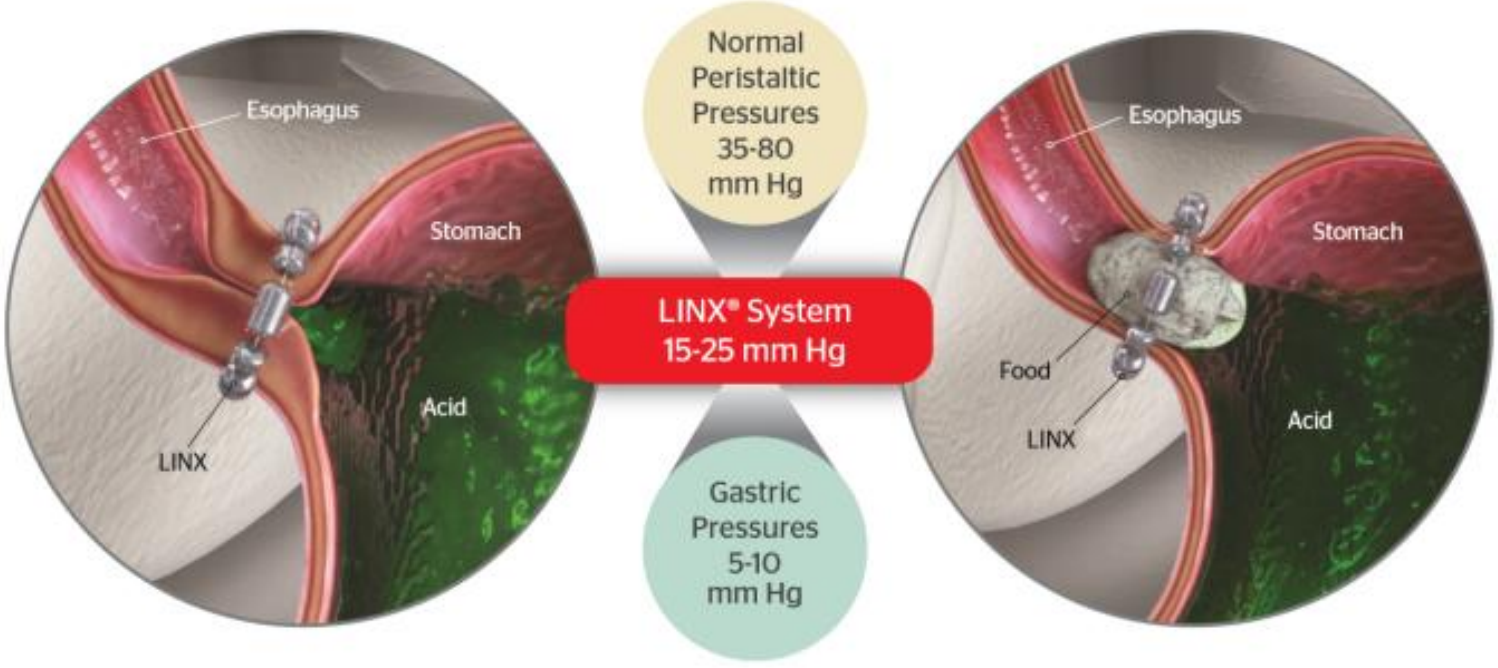
A. Fundus wrapped around back side of esophagus

B. Wrap secured with sutures to anchor lower esophagus below diaphragm

Mayo Foundation for Medical Education and Research

- Magnetic Sphincter Augmentation (MSA)
  - Titanium beads with magnetic core encircle distal esophagus to help increase LES tone
  - No head-to-head studies between fundoplication and MSA
    - Observational studies show that compared with fundoplication, MSA has:
      - ↓ operative times / ↓ hospital length of admission (LOA)
      - No significant differences in GERD symptom control
        - Postoperative PPI usage
        - Major complications
        - Dysphagia, or
        - Reoperation rates
  - Contraindications / Caution
    - Severe esophageal motility disorders
    - Large hiatal hernia (>3 cm, unless repaired)
    - Prior extensive esophageal or gastric surgery
    - Known metal allergies (rare but relevant)

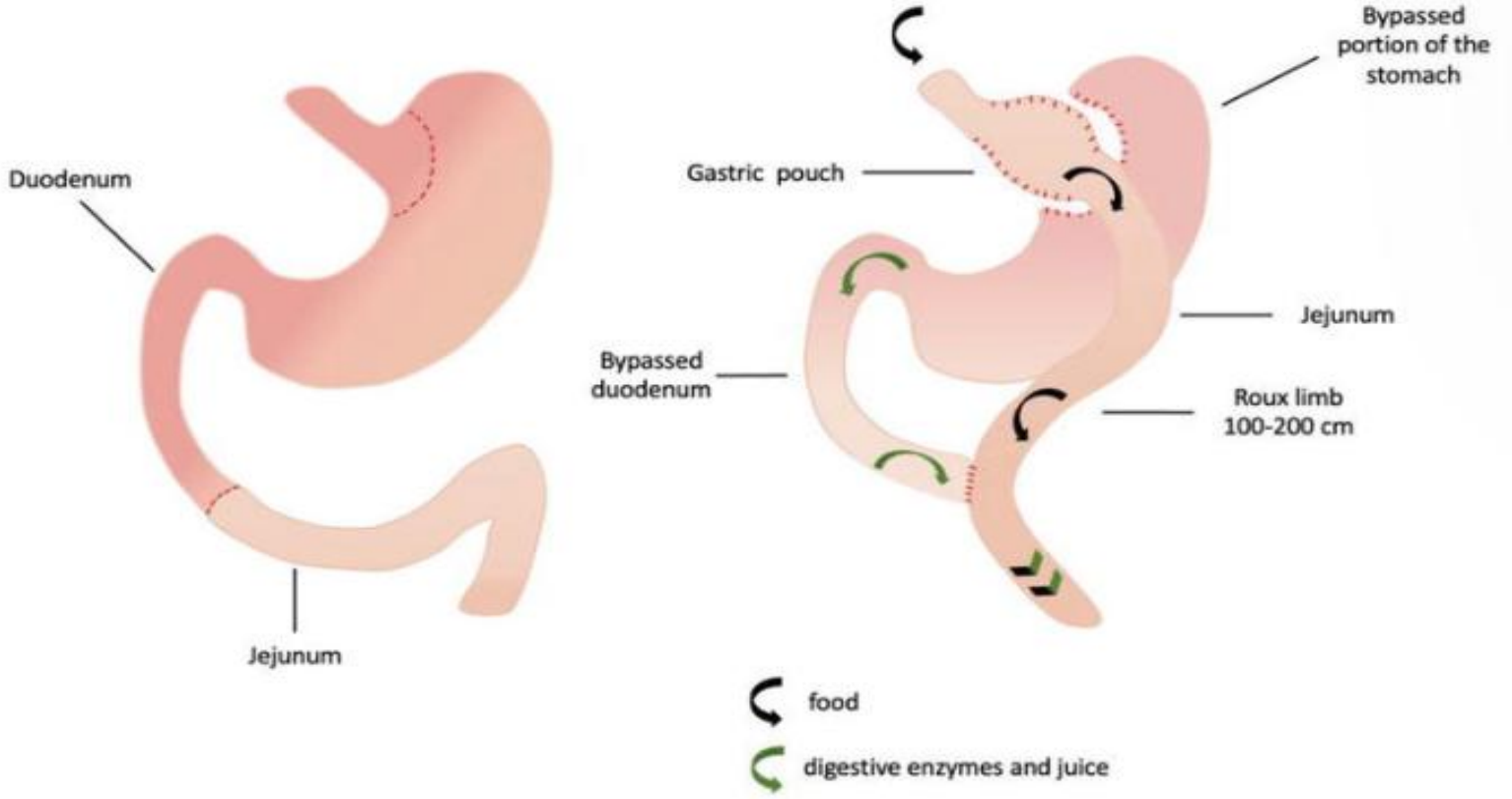
Magnetic Sphincter Augmentation (MSA)



LINX Reflux Management System is a flexible ring of small magnets placed around the LES during a minimally invasive procedure. The strength of the magnets helps keep the weak LES closed to prevent reflux. When patients swallow, LINX® opens temporarily to allow food and liquid to pass into the stomach.

Courtesy of: https://www.lincolnsurgical.com/gerd-linx

- **Roux-en-Y Gastric Bypass** (RYGB)
  - GERD is strongly associated with obesity (6× ↑ risk if BMI > 35)
  - RYGB helps with weight loss + GERD symptoms, thus surgery is of choice for obese patients
  - Some studies show fundoplication in obese patients has poor outcomes and higher complication rates
  - Small remaining gastric pouch produces far less gastric acid



Courtesy of: Baz C, et al. Duodenal Exclusion: Indications and Clinical Considerations. IntechOpen 2024. doi: 10.5772/intechopen.108516.

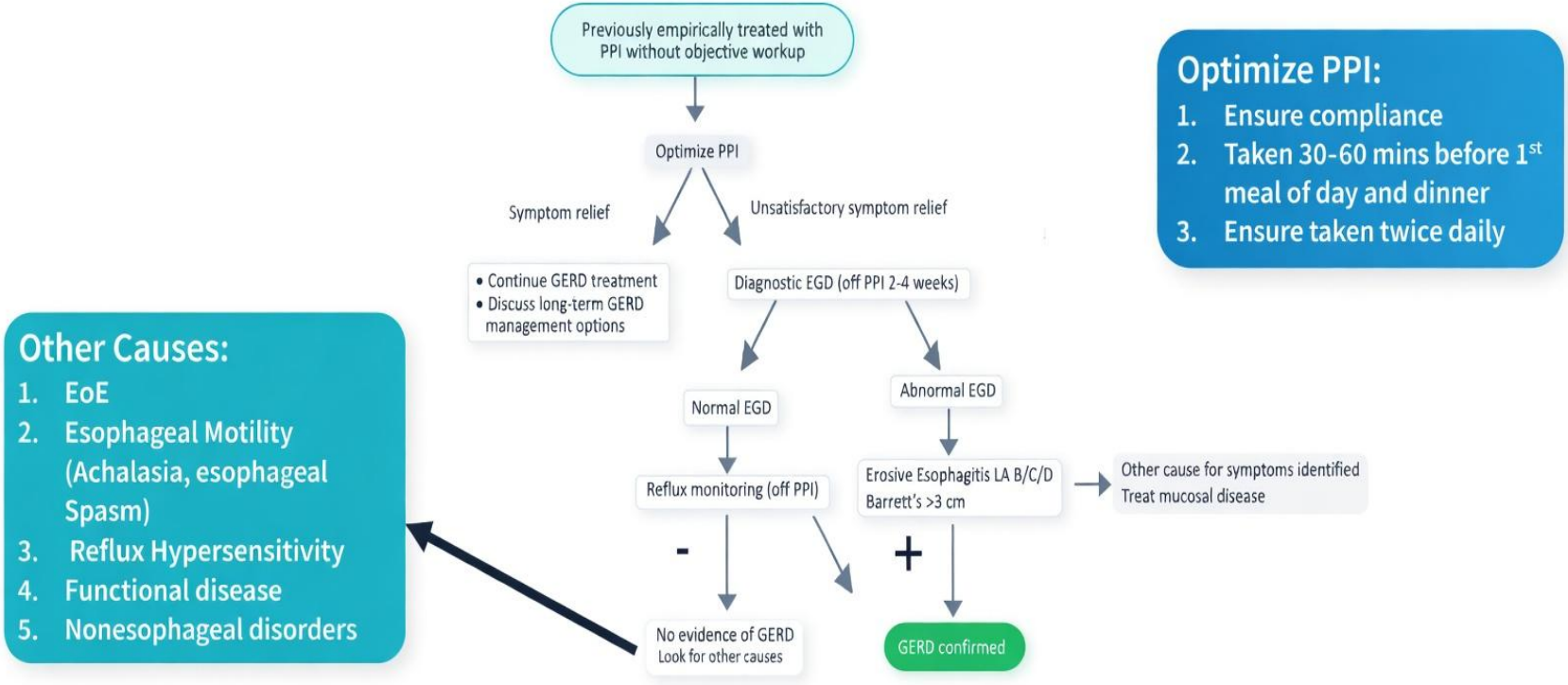
- Endoscopic Anti-Reflux Therapies (EART)
  - Numerous EARTs introduced in last 20 yr – most withdrawn due to lack of safety/efficacy
  - Currently two main procedures:
    - Radiofrequency Anti-Reflux Treatment (Stretta Procedure)
    - Transoral Incisionless Fundoplication (TIF)
      - Because data on efficacy of Stretta is inconsistent and highly variable, it is not recommended as an alternative to medical or surgical therapy (conditional recommendation, low level of evidence)
      - Consider TIF for patients with troublesome regurgitation or heartburn who do not wish to undergo 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)
  - Overall, studies for these procedures only included patients with mild disease

- Transoral Incisionless Fundoplication (TIF)
  - RCTs show TIF is effective in treating regurgitation symptoms
    - Long term benefit is questionable
  - Most serious side effects:
    - Perforation
    - Bleeding
    - Combined risk, 2.4%

Refractory GERD

➢ Definition
  - Persistent heartburn and/or regurgitation despite 8–12 wk of double-dose PPI therapy
  - Two distinct groups
    - Failed empiric therapy
      - Patients with symptoms suspected to be GERD-related who have been empirically treated with a PPI (typically once-daily then increased to twice-daily), yet remain symptomatic

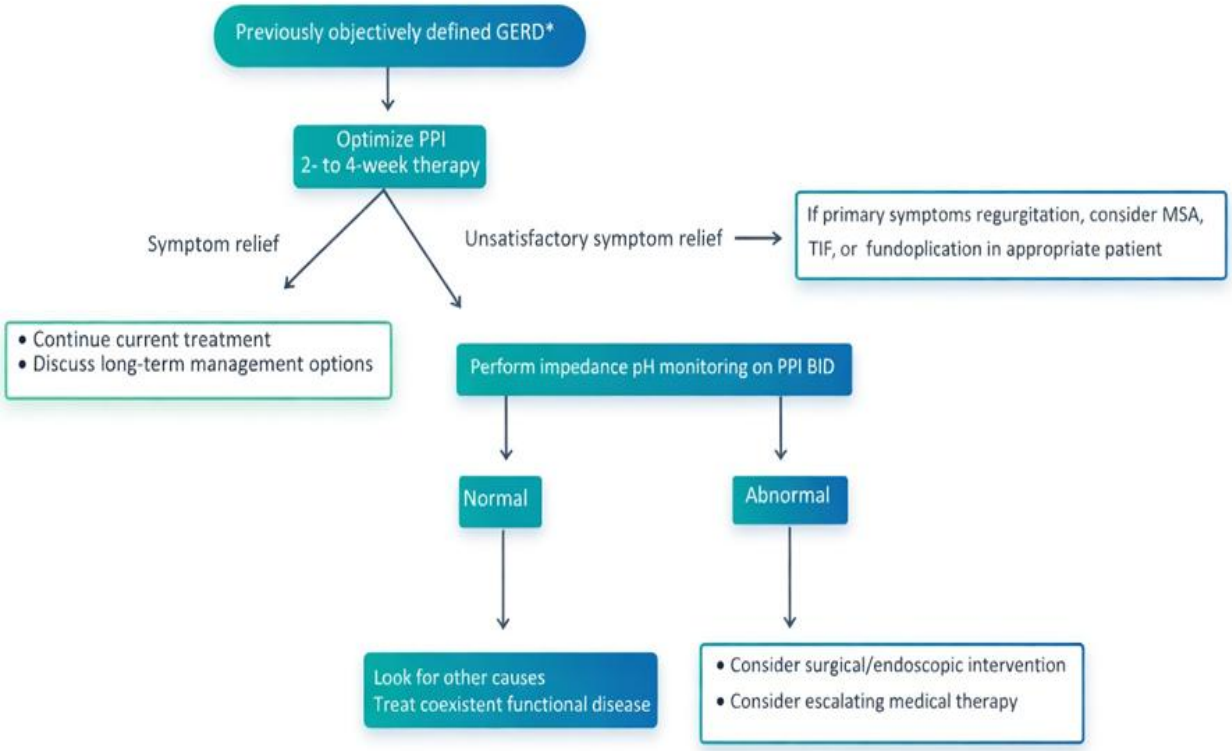
Management Algorithm of Symptoms Suspected Due to GERD Incompletely Responsive to Proton Pump Inhibitors



- Objective GERD, no/incomplete response to PPIs
  - Patients with objective evidence of GERD, with endoscopic findings of EE, or BE and/or reflux testing shows abnormal ↑ esophageal acid exposure, who have incomplete or no response to PPIs

Adapted from: Katz PO, et al. Am J Gastroenterol. 2022;117(1):27-56.

Management Algorithm of Symptoms Suspected Due to GERD Incompletely Responsive to Proton Pump Inhibitors



Adapted from: Katz PO, et al. Am J Gastroenterol. 2022;117(1):27-56.

Potential mechanisms underlying symptoms suspected due to GERD but refractory to PPI therapy

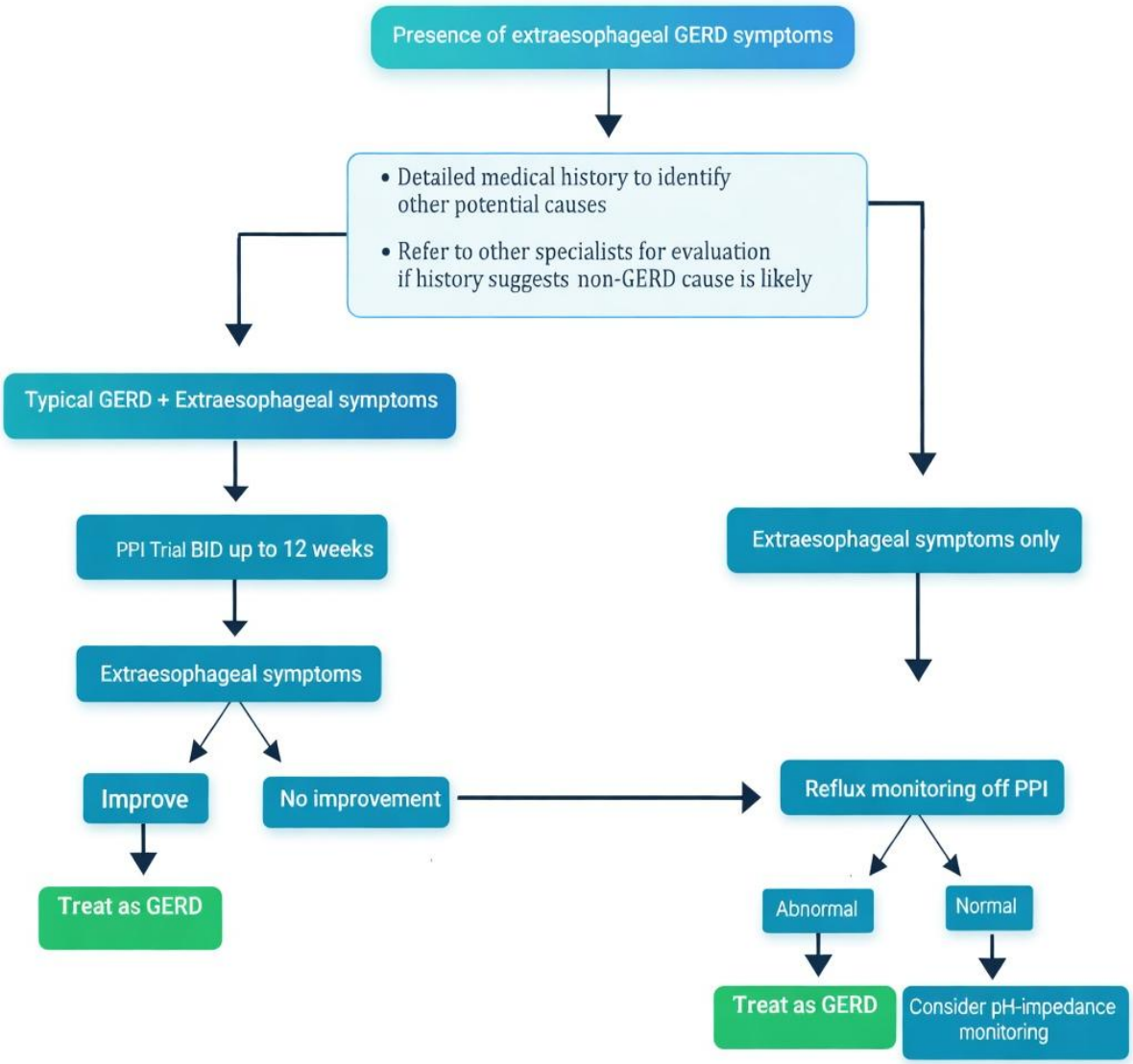
- Despite PPI therapy, abnormal acid reflux persists and is causing symptoms
- There is reflux hypersensitivity, a condition in which PPIs have normalized esophageal acid exposure, but “physiologic” reflux episodes (acidic or nonacidic) nevertheless are strongly associated with and evoke symptoms
- The symptoms are not due to GERD, but are caused by
  - Esophageal disorders other than GERD (e.g., EoE and achalasia)
  - Non-esophageal disorders (e.g., gastroparesis, rumination, and heart disease)
- The symptoms are functional (i.e., not because of GERD or any other identifiable histopathologic, motility, or structural abnormality)

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

Extra-Esophageal GERD

- Extra-esophageal symptoms of GERD may include:
  - Chronic cough
  - Throat clearing
  - Globus sensation
  - Hoarseness
  - Laryngitis

Diagnostic Algorithm for Extraesophageal Gastroesophageal Reflux Disease symptoms



Adapted from: Katz PO, et al. Am J Gastroenterol. 2022;117(1):27-56.

Abbreviations: BE, Barrett esophagus; EE, erosive esophagitis; EGJ, esophagogastric junction; EoE, eosinophilic esophagitis; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; LOA, length of admission; MSA, magnetic sphincter augmentation; NAB, nocturnal acid breakthrough; NF, Nissen fundoplication; NERD, non-erosive reflux disease; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RYGB, Roux-en-Y gastric bypass; TIF, transoral incisionless fundoplication; TLESR, transient lower esophageal sphincter relaxation; SI-LESR, swallow-induced lower esophageal sphincter relaxation.

GERD AND REFRACTORY GERD (24 HR pH STUDY INTERPRETATION)

Ricio Sedano

Gastroesophageal Reflux Disease (GERD)

- Definition
  - "GERD is a condition where the reflux of stomach contents causes troublesome symptoms or complications. It occurs due to lower esophageal sphincter (LES) dysfunction allowing acid and non-acidic contents to enter the esophagus."

Richter JE and Rubenstein JH. Gastroenterology. 2018;154(2):267-276.

- Pathophysiology
  - ↓ LES pressure → reflux of gastric contents
  - ↑LES relaxations
    - Frequent relaxations of the LES are a primary cause of GERD.
  - ↓ rate of gastric emptying → ↑ gastric pressure and reflux symptoms.
  - ↑ sensory hypersensitivity → ↑ sensitivity of the esophagus contributes to symptoms seen in the absence of significant acid exposure.

Katz PO et al. Am J Gastroenterol. 2013;108(3):308-328.

- Demography
  - GERD prevalence
    - North America, 18-28%
    - Asia, ~5%.
  - 40% of patients on proton pump inhibitors (PPIs) have persistent symptoms despite therapy.

- Clinical Symptoms
  - Typical
    - Heartburn (most common)
    - Regurgitation
    - Esophageal chest pain.
  - Atypical
    - Supraesophageal chronic cough
    - Hoarseness
    - Asthma-like symptoms

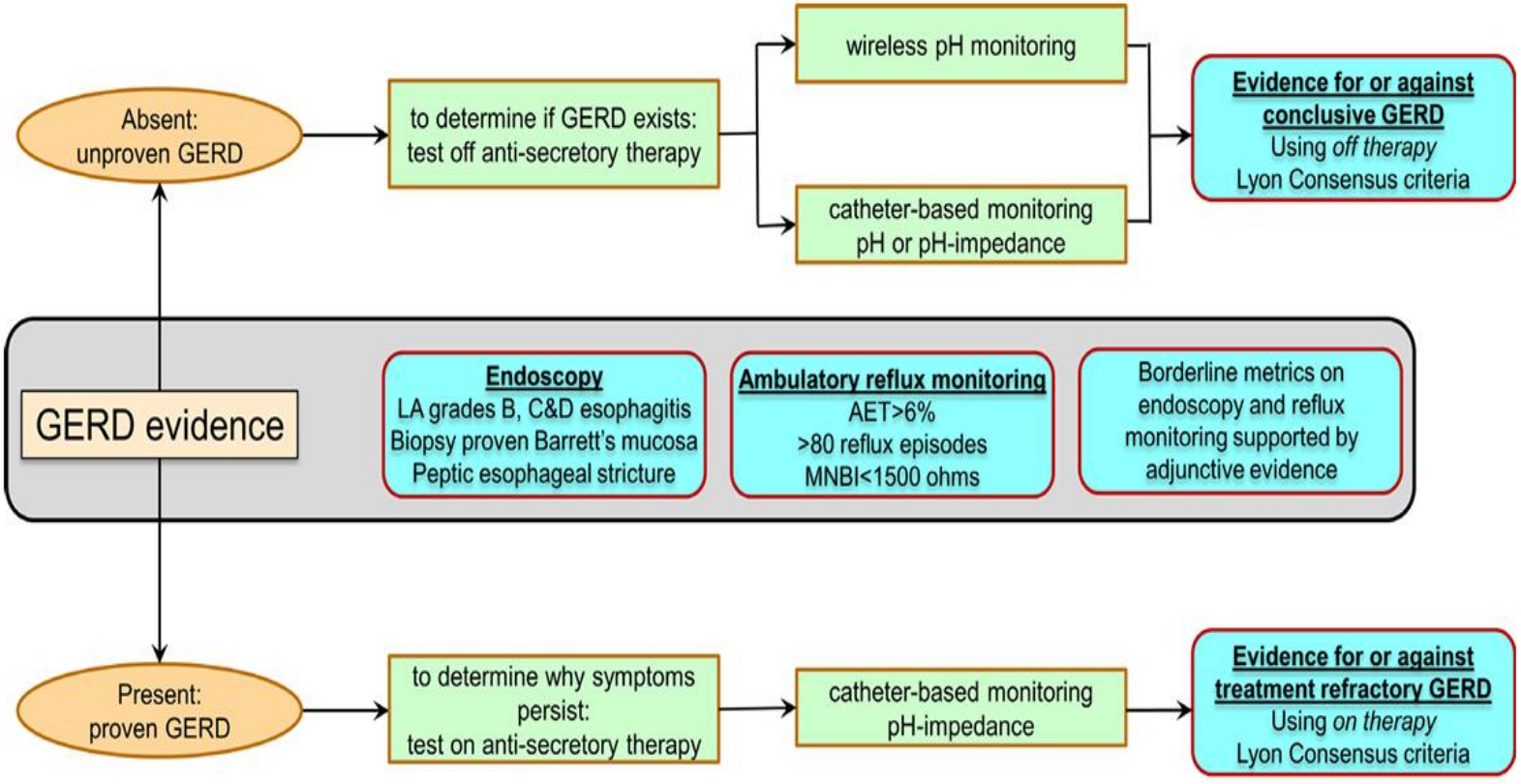
Richter JE and Rubenstein JH. Gastroenterology 2018; 154(2):267-276.
Shaqran TM, et al. Cureus 2023; 15(10):e47420.

- Risk Factors
  - Hiatal Hernia → ↓ LES function/pressure → ↑ reflux
  - Obesity → ↑ intra-abdominal pressure → ↑ reflux
  - Depression
  - Diet and Lifestyle
    - Alcohol
    - Caffeine
    - Dessert
    - ↓ gastric emptying
    - High-fat foods
    - Low-fiber diets
    - Sweets
  - Medications
    - NSAIDs
    - Calcium channel blockers
    - Anticholinergics

    } ↑ GERD symptoms

El-Serag HB, et al. Gut, 2014; 63(6):871-880.
Sadafi S, et al. BMC Gastroenterol 2024, 64 (2024).

- Diagnosis of GERD



Courtesy of: Gyawali CP, et al. Gut 2024;73:361-371.

- Diagnosis:
  - Conclusive evidence of reflux-related pathology on endoscopy and/or abnormal reflux monitoring (using Lyon consensus thresholds) in the presence of compatible troublesome symptoms.

Symptom Type	Examples	Initial Approach	Esophageal Evaluation	Adjunctive Approach
○ Typical	– Heartburn, regurgitation, chest pain	Empiric trial of anti-secretory therapy	Endoscopy, wireless pH monitoring, high-resolution manometry (HRM)	▪ Postprandial HRM, behavioral therapy
○ Atypical: Belching	– Belching*		Endoscopy, pH-impedance or wireless pH monitoring, HRM	▪ Behavioral therapy for supragastric belching
	– Chronic cough, asthma**			▪ Pulmonary evaluation***
	– Hoarseness, globus, nausea, abdominal pain			▪ Laryngoscopy for throat symptoms***

* Likelihood of GERD is low with atypical symptoms; testing is performed to identify or rule out a reflux basis.

** Laryngoscopy is typically not recommended except to rule out other causes.

*** Adjunctive approaches may precede esophageal evaluation to rule out primary pulmonary or laryngeal disorders.

Gyawali CP, et al. Gut 2024;73:361-371.

➢ Diagnosis of GERD: Clinical and endoscopic approach

- Lyon 2.0
  - LA grades B, C and D esophagitis
  - Biopsy proven Barrett esophagus
  - Peptic stricture

  → Conclusive of GERD

  - Atypical symptoms
    - Lungs
      - Chronic cough
      - Wheezing
    - Larynx
      - Hoarseness
    - GI
      - Belching
      - Globus
      - Nausea
      - Abdominal pain

  → Low likelihood of pathophysiological relationship to reflux disease

To maximize the diagnostic yield, endoscopy should be performed 2–4 weeks after discontinuation of antisecretory therapy in unproven GERD

Adapted from: Gyawali CP, et al. Gut 2024;73:361–371.

- Indications for Endoscopy in Patients with Suspected GERD
  - Symptoms
    - GERD symptoms that are persistent or progressive despite appropriate medical therapy
    - Dysphagia or odynophagia
    - Involuntary weight loss >5%
    - Evidence of GI bleeding or anemia
    - Persistent vomiting (7-10 days)
  - Complications
    - Screening for Barrett esophagus in selected patients (as clinically indicated)
  - Imaging
    - Finding of a mass, stricture, or ulcer on imaging studies
  - Procedures
    - Placement of wireless pH monitoring
  - Anti-reflux procedures
    - Evaluation of patients before or with recurrent symptoms after endoscopic or surgical

Adapted from: Muthusamy VR, et al. Gastrointestinal Endoscopy 2015; 81(6): 1305 - 1310

Non-Erosive Reflux Disease (NERD)

- Definition
  - Subtype of GERD characterized by reflux symptoms
  - No visible esophageal mucosal damage on endoscopy (EGD)
- Demography
  - 50-70% of GERD population
- Diagnosis
  - Positive symptom association with acid reflux on pH monitoring.
- Symptoms
  - Heartburn, regurgitation (similar to GERD)

* Key Differences;

  - NERD patients have no visible erosions on endoscopy.
  - Often diagnosed via ambulatory pH monitoring.

Hershcovici T and Fass R. J Neurogastroenterol Motil 2010; 16(1): 8-21.

Functional Heartburn

- Definition
  - Heartburn symptoms with no abnormal acid exposure or mucosal damage
  - No significant response to proton pump inhibitors (PPIs)
- Prevalence
  - 21%-39% of patients with heartburn refractory to PPI undergoing pH-impedance monitoring fulfill criteria for functional heartburn.
- Diagnostic Criteria
  - Normal pH monitoring
  - No correlation with reflux episodes

*Key Features:

  - Thought to be related to
    - Esophageal hypersensitivity, or
    - Visceral hyperalgesia

Fass R, et al. Gastroenterology 2020; 158(8): 2286-2293.

Feature	GERD/Erosive Esophagitis	GERD/NERD	Functional Heartburn (FH)
○ Symptoms	− Classic heartburn, regurgitation, esophageal chest pain − May include dysphagia, cough, etc. − Symptoms typically improve with PPIs	− Similar symptoms to GERD (heartburn, regurgitation, chest pain) but often less severe − Symptoms tend to persist despite normal endoscopy findings − Often PPI responsive but may show partial response	− Heartburn-like symptoms without response to PPIs − Nocturnal symptoms less common − Symptoms persist despite acid suppression
○ Endoscopic Findings	− Erosive esophagitis or complications (Barrett esophagus, strictures) − LA Grade B-D esophagitis	− Normal mucosa on endoscopy − No visible erosions or structural damage	− Normal mucosa on endoscopy − No erosions or damage, identical to NERD
○ pH Monitoring	− Abnormal acid exposure time (AET >4.5-6%) − High DeMeester score (>14.72) − Positive symptom index (SI >50%) or symptom association probability (SAP >95%)	− Abnormal acid exposure time (AET >4.5-6%) − High DeMeester score (>14.72) − Positive symptom index (SI >50%) or symptom association probability (SAP >95%)	− Normal acid exposure time (AET <4.2%) − Normal DeMeester score and no significant correlation with reflux (SI <50%, SAP <95%) − Negative SI and SAP, symptoms not linked to reflux episodes

Refractory GERD (R-GERD)

- Definition
  - Persistent evidence of pathologic reflux (abnormal ambulatory pH monitoring and/or erosive esophagitis (EE) on endoscopy) while on PPI.
  - Refractory symptoms
    - Persisting symptoms while on treatment in patients with a history of proven GERD (EGD or ambulatory pH monitoring)

Davis TA and Gyawali CP. J Neurogastroenterol Motil 2024; 30: 17-28.

➢ Demography

- Incidence of R-GERD
  - US
    - ~5-10 per 1,000 person-years (population studies)
    - ↑ incidence due to
      - ↑ obesity rates and
      - Dietary/lifestyle factors
  - Canada
    - Similar patterns observed in US (regional variations exist due to healthcare access and dietary habits)
- Prevalence of R-GERD
  - US
    - 8-33% of the general population
    - ~10-40% of GERD patients have R-GERD, i.e., symptoms despite proton pump inhibitor (PPI) therapy for ≥ 8 weeks.
    - 20-30% of patients on PPIs experience only partial relief from symptoms.
  - Canada
    - Similar patterns observed
    - ~30% of GERD patients have R-GERD.

El-Serag HB, et al. Gut 2014; 63(6): 871-80.

➢ Pathophysiology, of refractory GERD symptoms

- Key Mechanisms:
  - Persistent acid reflux despite therapy (due to inadequate dosing or nocturnal acid breakthrough).
  - Non-acid reflux: Detected by impedance-pH monitoring (~30% of refractory GERD cases involve non-acidic reflux)
  - Esophageal hypersensitivity: Exaggerated symptom response to normal esophageal acid exposure.
  - Belching can be part of reflux pathophysiology

Gyawali CP, et al. Gut 2024;73:361-371.

➢ Diagnosis of refractory GERD: Endoscopic approach

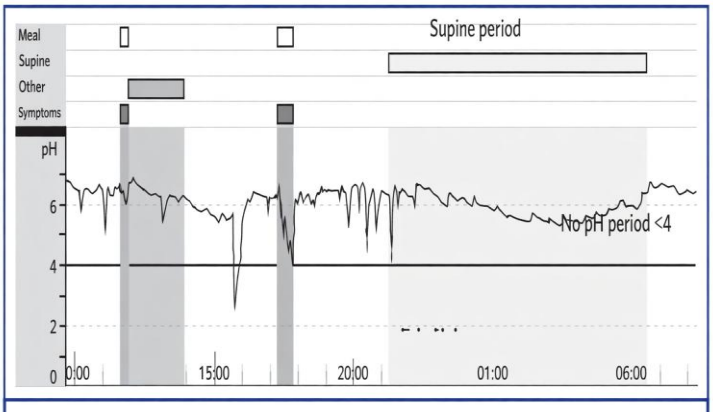
- Lyon 2.0:
  - LA grades B, C and D esophagitis
  - Recurrent Peptic stricture

  – While on optimized PPI therapy

  ▪ Conclusive of refractory GERD

Gyawali CP, et al. Gut 2024;73:361-371.

- pH Monitoring in GERD: Diagnostic utility
  - Indication
    - 24-hr pH and/or impedance-pH monitoring is critical evaluation of refractory GERD evaluation. It is used to confirm acid reflux and symptom-reflux correlation
  - Types
    - Catheter-based pH Monitoring
      - Ambulatory measures the amount of acid and non-acid reflux in 24 hours
      - Requires esophageal manometry beforehand to determine the position of the catheter



Bremner CG et al. Esophageal disease & testing. Taylor & Francis Group, 2005."

- Advantages of Impedance-pH Monitoring:
  - Differentiates between acid and non-acid reflux.
  - Detects gas reflux and can assess for reflux hypersensitivity.
- Key Metrics in pH Study Interpretation:
  - pH < 4: Defines acid reflux episodes.
  - Acid Exposure Time (AET):
    - Normal: < 4.2% of the 24-hr period spent with pH < 4.
    - Abnormal: > 6% of the time spent with pH < 4.
    - Borderline: 4.2% to 6% time spent with pH < 4.
- Reflux Episodes:
  - Normal: < 50 reflux episodes in 24 hr.
  - Abnormal: > 80 reflux episodes in 24 hr.
    - DeMeester Score: A composite score aggregate measurement that includes acid exposure time, number of reflux episodes, and duration of the longest reflux episode. A score >14.72 is considered abnormal.
- Key Parameters:
  - DeMeester score: An aggregate measure of esophageal acid exposure.
  - Reflux Episodes: Identifies the number and type (acidic/non-acidic).

- Acid Exposure Time (AET): Time pH < 4.0.
- Symptom-Reflux Correlation
  - Symptom Index (SI) and
  - Symptom Association Probability (SAP) (correlate symptoms with reflux episodes)
- Types of Reflux Episodes:
  - Supine Reflux: Occurs while lying down.
  - Upright Reflux: Occurs during an upright position (sitting or standing).

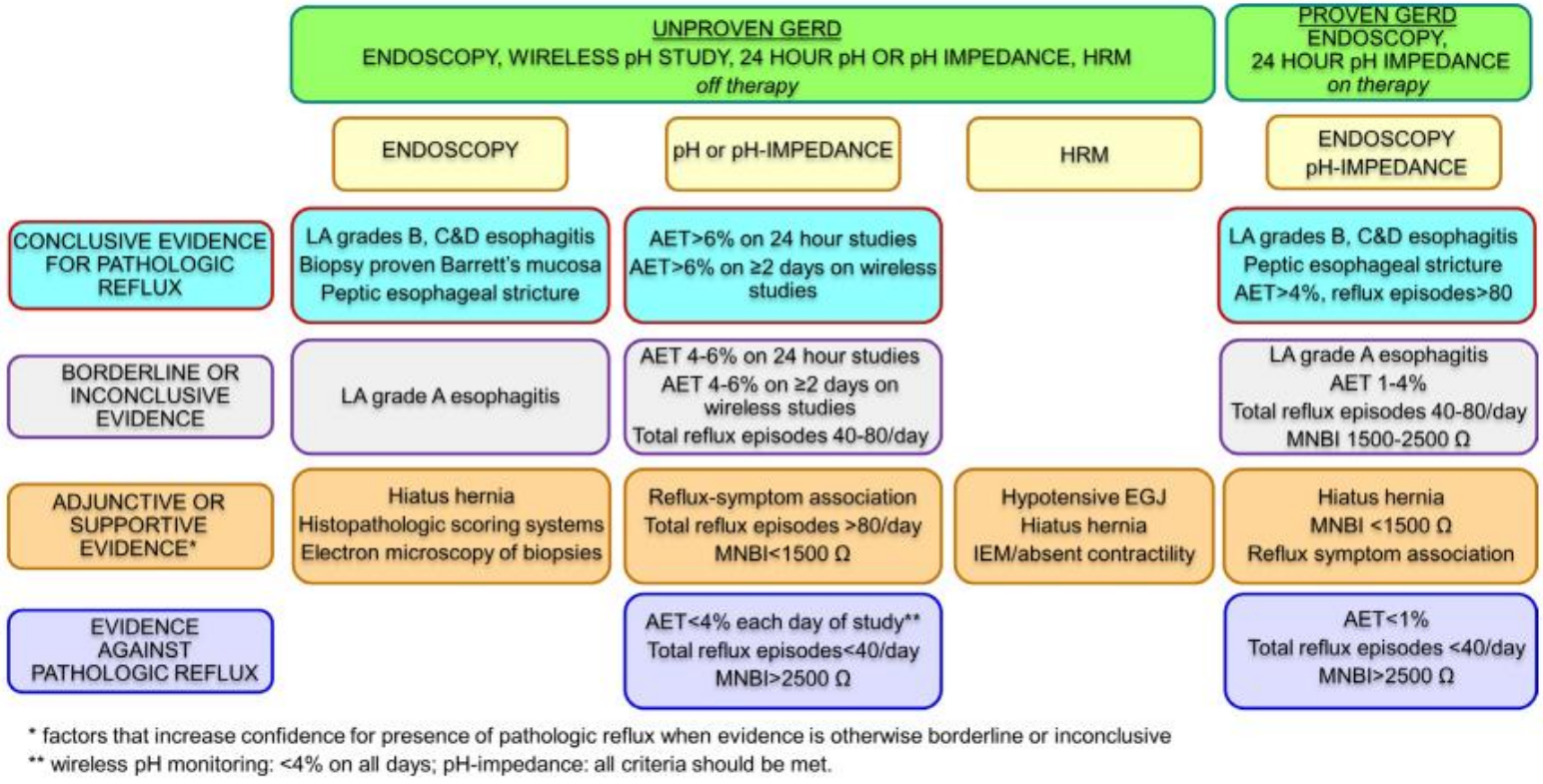
- Bravo Wireless pH Monitoring
  - Measures acid exposure for up to 96 hours of pH recording (without a nasoesophageal catheter)
  - Wireless pH-sensing capsule (6 mm × 5.5 mm × 25 mm)
  - Endoscopic or manometry guidance (5 cm above proximal border of LES).
  - Falls after 4-10 days

Bredenoord AJ, et al. Gut 2005; 54(12): 1810-7

Components of the Bravo Capsule System

Courtesy of: https://manchestergastrospecialists.com/bravo-for-reflux-monitoring/#

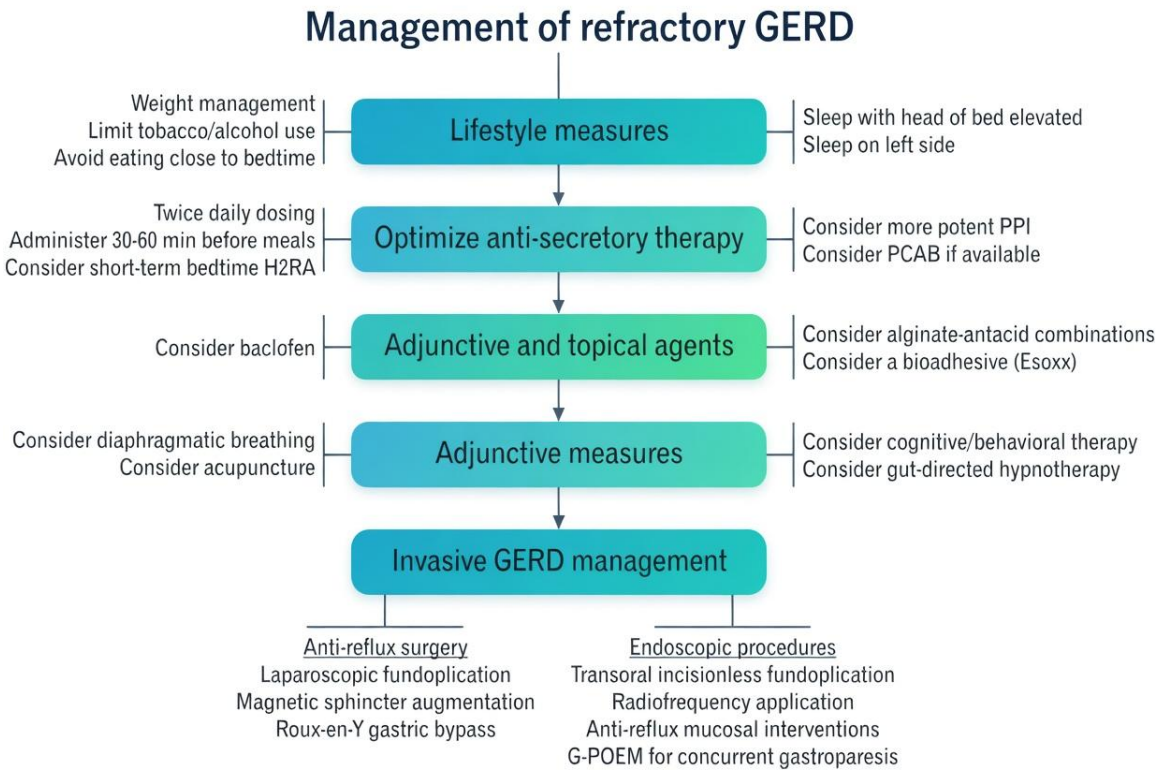
Suspected vs. Proven GERD



Findings that establish conclusive evidence for gastroesophageal reflux disease (GERD) can be acquired from endoscopy and/or ambulatory reflux monitoring off therapy in unproven GERD. When evidence is borderline, adjunctive evidence on endoscopy, pH-impedance monitoring and manometry can sway confidence towards or away from conclusive GERD. Findings on pH-impedance monitoring can establish absence of GERD, especially when endoscopy is also normal. Similar levels of conclusive, borderline and adjunctive metrics are described for endoscopy and pH-impedance monitoring performed on optimised antisecretory therapy.

Printed with permission: Gyawali CP, et al. Gut 2024;73:361-371

➢ Treatment



Adapted from: Davis T. et al. J Neurogastroenterol Motil 2024; 30(1): 17-28 (Figure 2)

- Lifestyle and Dietary Modifications
  - Lifestyle Changes
    - Weight loss in patients with obesity → ↓intra-abdominal pressure.
    - Tobacco cessation in smokers
    - Head-of-bed elevation → ↓ nighttime reflux
    - Avoid lying down within 3 hr after meals
  - Dietary Recommendations
    - Avoid “trigger foods”
      - Alcohol
      - Caffeine
      - Spicy foods
    - Smaller, more frequent meals.

Adapted from: Maret-Ouda J, et al. JAMA. 2020;324(24):2536–2547.

- Non-competitive Pharmacological
  - Proton Pump Inhibitors (PPI)
    - PPIs irreversibly inhibit hydrogen-potassium ATPase in the parietal cells of the stomach → ↓ acidity of the gastric contents.
    - Common PPIs: Omeprazole, Esomeprazole, Pantoprazole, Lansoprazole, Rabeprazole.
    - Patients with LA grade C or D erosive esophagitis / Barrett esophagus
      - Should remain on long-term PPI therapy to maintain healing.
    - Consider on-demand PPI for patients with NERD
    - Use the lowest effective dose
  - H2RAs
    - Effective as adjunct therapy, especially at night
    - Provide an additional ↓ nocturnal acid breakthrough
  - Sucralfate
    - Coats the esophageal lining and protects it from acid exposure.
    - Used as an adjunct in selected cases of refractory GERD

- Competitive Pharmacological (Vonoprazan [P-CAB])
  - Mechanism of Action
    - ↓ H+/K+ ATPase (proton pump) by competing with potassium ions → faster and more sustained acid suppression compared to PPIs.
  - Advantage
    - Does not require activation in acidic conditions
    - This is effective at neutral pH
    - Provides rapid onset and long-lasting acid suppression.
  - Pharmacokinetics
    - Faster onset of action compared to PPIs (peak action within hours).
    - Longer duration of action, allowing for consistent acid suppression
    - Particularly beneficial for patients with nocturnal acid breakthrough.
  - Adverse Effects
    - Generally well-tolerated
    - Some mild side effects reported
      - Headache
      - Diarrhea/constipation
      - Abdominal pain
    - Long-term safety: No significant ↑ in adverse events compared to PPIs in trials lasting up to 12 mon

Adapted from: Sugano K. Therapeutic Advances in Gastroenterology. 2018;11: 1756283X17745776.

- Endoscopic: Transoral Incisionless Fundoplication (TIF):
  - Creates a new anti-reflux valve at the gastroesophageal junction (GEJ)
    - Symptom improvement in 75%
  - Indicated for patients with refractory GERD who do not respond to medical therapy.

Adapted from: Richter JE. Clin Gastroenterol Hepatol 2013;11(5):465–471.
Moore M, et al. World J Gastrointest Surg 2016; 8(1): 77–83.

- Surgical Procedures
  - Indication
    - For patients failing medical therapy or with anatomical issues (e.g., large hiatal hernia)
  - Types
    - Nissen Fundoplication
      - Involves wrapping the fundus around the esophagus to augment ↑ LES.
      - High rates of symptom resolution long term
      - Dysphagia may occur in 10-15% of cases (gas/bloat syndrome)
    - Roux-en-Y bypass (RYGB)
      - Patients with morbid obesity following RYGB lose weight → ↓ GERD symptoms (94% resolution at 9 mon)

Adapted from: Richter JE. Clin Gastroenterol Hepatol 2013;11(5):465–471.
Moore M, et al. World J Gastrointest Surg 2016; 8(1): 77–83.

➢ Conclusion

- Refractory GERD is a multifactorial condition that requires a combination of clinical assessment, advanced diagnostic techniques (e.g., impedance-pH monitoring), and individualized therapy (ranging from PPIs to endoscopic procedures and surgical interventions).
- Early and accurate diagnosis is crucial for better outcomes, and preventing complications (Barrett esophagus, adenocarcinoma)
- Emerging therapies (e.g., Vonoprazan) are showing promise in refractory cases.

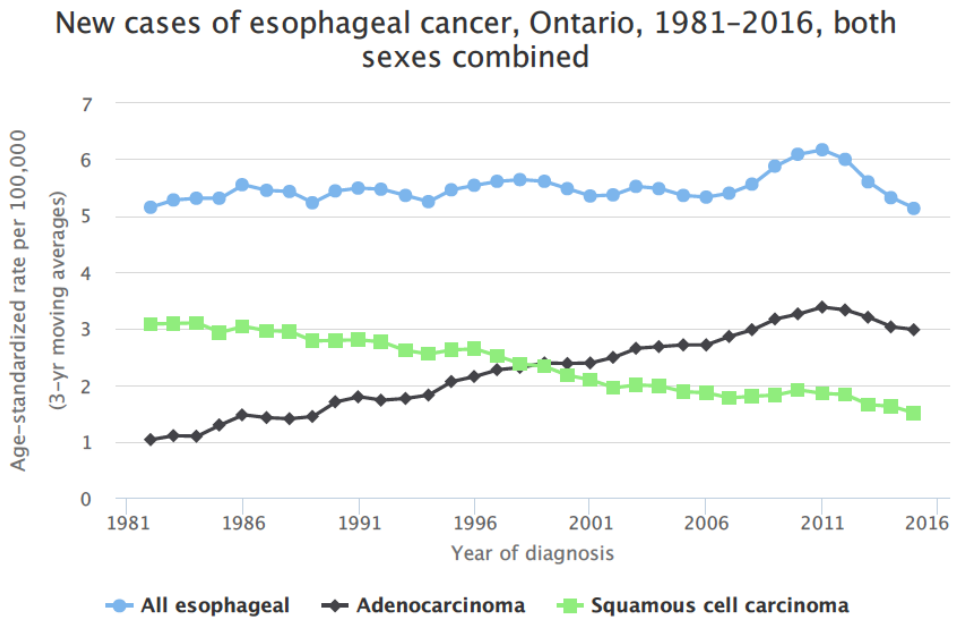
Abbreviations: AET, acid exposure time; EE, erosive esophagitis; EGD, esophagogastroduodenoscopy; FH, functional heartburn; GEJ, gastroesophageal junction; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; IEM, ineffective esophageal motility; LA, Los Angeles (classification/grading system for esophagitis); LES, lower esophageal sphincter; MNBI, mean nocturnal baseline impedance; NERD, non-erosive reflux disease; PPI, proton pump inhibitor; R-GERD, refractory gastroesophageal reflux disease; RYGB, Roux-en-Y gastric bypass; SAP, symptom association probability; SI, symptom index

BARRETT ESOPHAGUS: AN UPDATE

Brian Yan

➢ Demography

- Ontario Data

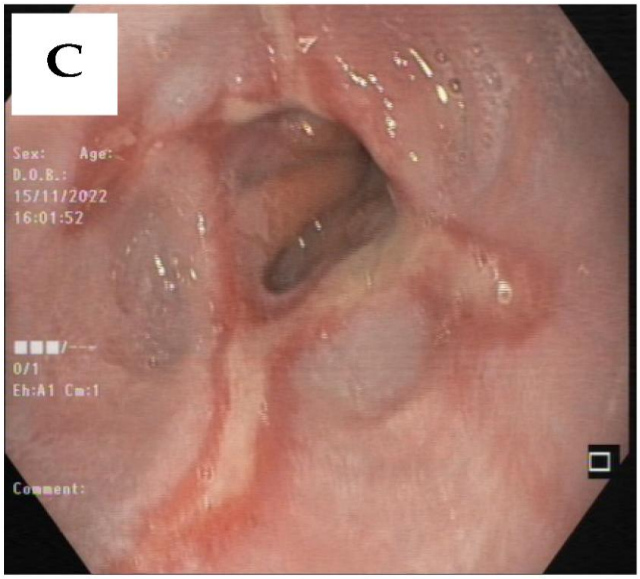


Courtesy of: Canadian Cancer Registry and National Cancer Incidence Reporting System Databases at Statistics Canada

- Esophageal adenocarcinoma (EAC)
  - Incidence of ↑ 500% since 1970
    - Lifetime risk
      - Men 1:116
      - Women 1:314
    - ↑ 2%/year between 1998-2016
    - Barrett esophagus → 50x ↑ risk of EAC (compared to general population)
  - Projected age standardized incidence rates of new cases (all esophageal) in Ontario for 2019:
    - Males: $8.7/10^5$
    - Female: $2.4/ 10^5$

Courtesy of: Canadian Cancer Registry and National Cancer Incidence Reporting System Databases at Statistics Canada

Barrett Esophagus



Endoscopic image of Barrett esophagus visible as a salmon-coloured metaplastic epithelium (columnar) replacing the normal bright-pink epithelium of the distal squamous esophagus.

Courtesy of: Sheikh M, et al. Cancers. 2023; 15(3):765.

➢ Diagnosis

Recommendations

- (1) The diagnosis of BE requires
  - Finding of intestinal metaplasia in the tubular esophagus
- (2) Columnar mucosa ≥ 1 cm in length
  - (2a) Patients with a normal-appearing Z line
  - (2b) In the absence of any visible lesion, patients with a Z line demonstrating < 1 cm of proximal displacement from the top of the gastric folds, and no visible lesions.
- (3) Take ≥ 8 endoscopic biopsies be obtain in screening examinations with endoscopic findings consistent with possible BE, with the Seattle protocol followed by segments of longer than 4 cm
- (4) Confirm dysplasia of any grade detected on biopsies of BE should by a second pathologist with expertise in GI pathology.

8 biopsies increase yield of IM to 94%

Shaheen NJ, et al. Am J Gastroenterol 2022; 117: 559-587.

- Barrett < 1cm
  - Reliability of Prague Classification is poor (0.22)
    - Follow up biopsies are negative for intestinal metaplasia (IM) >50% of times (Thota PN, et al. 2017)
  - Progression to high-grade dysplasia (HGD) / esophageal adenocarcinoma (EAC) is extremely low (Thota PN, et al. 2017; Jung KW, et al. 2011)
  - Don't biopsy if there is no visible lesion (e.g., tongues of salmon-pink mucosa, or mucosal nodule(s)

Thota PN, et al. Gastroenterol 2017; 152: 987 – 992
Jung KW, et al. Am J Gastroenterol 2011; 106: 1447 – 1455

➢ Screening and Surveillance

- Barrett prevalence of BE
  - General population, 1-2%
  - Chronic GERD, 7-10%
  - Patients having a screening colonoscopy who also have an EGD, BE in 10%
- However, screening programs limited to patients with symptomatic gastroesophageal disease (GERD) miss 50% of patients with short segment BE
- No RCTS
  - < 10% of esophageal adenocarcinomas (EAC) have a prior diagnosis of BE
  - Current practices have failed to identify the majority of patients
  - 40% of EAC pts have no history of GERD

Qumseya B, GIE 2019; 90: 335 – 359
Chak A, et al. Cancer 2006;107:2160-6.

➢ Guidelines on BE

- Many societies, over many years
  - ACG (American College of Gastroenterology
  - AGA (American Gastroenterological Association)
  - ASGE (American Society for Gastrointestinal Endoscopy)
  - AASLD (American Association for the Study of Liver Diseases)
  - BSG (British Society of Gastroenterology)
  - CCO (Cancer Care Ontario) (Canada-based guideline body for oncology)
  - CSSLD (Chinese Society of Liver Diseases) (used in some regional contexts; not a global standard)
  - EASL (European Association for the Study of the Liver)
  - GESA (Gastroenterological Society of Australia)
  - PCSG, Primary Care Society for Gastroenterology

➢ Screening

- Canadian Association of Gastroenterology (CAG) Guidelines 2004
  - Statement 52: Endoscopic screening for Barrett in patients with longstanding GERD has not been shown to reduce mortality from esophageal adenocarcinoma (Level III, C)
  - Statement 53: Endoscopy to detect Barrett esophagus with dysplasia may be considered in adults with GERD symptoms for more than 10 years (Level III, C)

- ASGE (American Society of Gastroenterology), 2019 (Qumseya B, GIE 2019; 90: 335-59)
  - There is insufficient evidence on the effectiveness of screening for BE.
  - However, if screening endoscopy for BE is performed, we suggest
    - A screening strategy that identifies an at-risk population, defining “at-risk” individuals as
      - Those with a family history of EAC or BE (high risk) or patients with GERD, plus
      - At least 1 other risk factor (moderate risk)

- ESGE (European Society for Gastrointestinal Endoscopy), 2017 (Weusten B, et al. Endoscopy 2017; 49: 191-8)
  - Endoscopic screening for BE is not recommended.
    - However, screening can be considered in patients with
    - Longstanding GERD symptoms (i. e. > 5 years) and
      - Multiple risk factors (age ≥ 50 years, white race, male sex, obesity, first-degree relative with BE or EAC)

➢ Risk Factors for BE

- High Risk: Family history (1st or 2nd deg relative) of EAC/BE
- Moderate Risk
  - GERD plus one of:
    - Male
    - Age >50
    - Obesity
    - Smoking

Association between various risk factors and BE base on literature review

Risk Factor	Effect Estimate
Family history of BE or EAC	OR = 12, adjusted for age, sex, and obesity
GERD	OR = 2.9 (4.5 in 12 studies with GERD for at least 2 wks)
Male	Male-to-female ration = 2.13
Obesity	OR = 1.15 (0.89-1.47), adjusting for GERD
Central adiposity	OR = 1.44 (1.2-1.74), adjusting for GERD
Smoking	OR = 1.42 (1.15-1.76, ever smoked vs. population control OR = 1.06 (1.14-2;73), adjusted for confounders

RF's are additive: add 1.2% risk of barrett's risk for each factor

Chak A, et al. Gut 2002;51:323–328
Qumseya B, GIE 2019; 90: 335 – 359

- CCO (Cancer Care Ontario) Guidelines 2019: GERD based
  - Patients present to health care provider with daily GERD >10y. Consider screening in men with chronic (>5y) and/or frequent (weekly or more) symptoms of GERD plus ≥ 2 of the following factors:
    - Age > 50 yr
    - Caucasian
    - Central obesity (waist circumference >102 cm or waist to hip ratio >0.9)
    - History of smoking
    - 1st degree relative with ERC

- ACG (American College of Gastroenterology), 2022
  - These are all conditional, and low to very low evidence
  - Screening
    - (5) Do single screening endoscopy in patients with chronic GERD symptoms plus ≥ 3 additional risk factors for BE, including male sex, age > 50 yr, white race, tobacco smoking, obesity, and family history
    - (6) A swallowable, non-endoscopic capsule device combined with a biomarker is an acceptable alternative to endoscopy for screening for BE
    - (7) Do not repeat screening in patients who have undergone an initial negative screening examination by endoscopy.

Shaheen NJ, et al. Am J Gastroenterol 2022; 117: 559-587

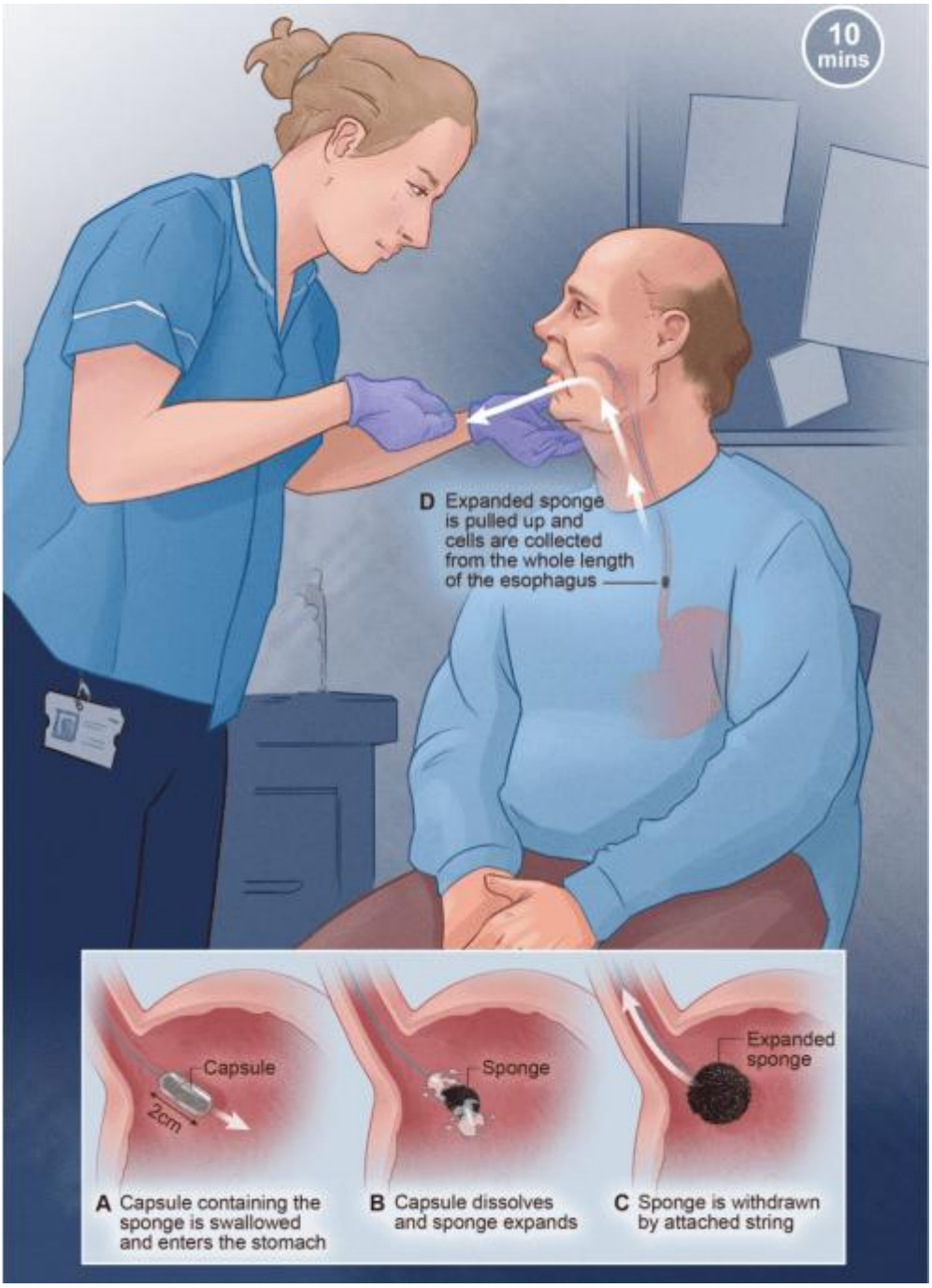
- Less invasive methods for screening
  - "Electronic Nose" Devices – exhaled volatile compounds
    - Cytosponge®, EsophaCap®, Esocheck®
  - Esophageal Capsule
  - "Liquid biopsy": circulating microRNA
  - Oral Microbiome
  - Tethered Capsule Endomicroscopy
  - Unsedated TransNasal Endoscopy (uTNE)

Spechler SJ, Katzka DA, Fitzgerald RC. Gastroenterology 2018;154:1594-601.
Shaheen NJ, et al. Am J Gastroenterol 2022; 117: 559-587

Cytosponge ®

Courtesy of: https://heartburncanceruk.org/latest-updates/research/cytosponge/

Non-Endoscopic Sampling of Esophageal Mucosa for Barett Esophagus



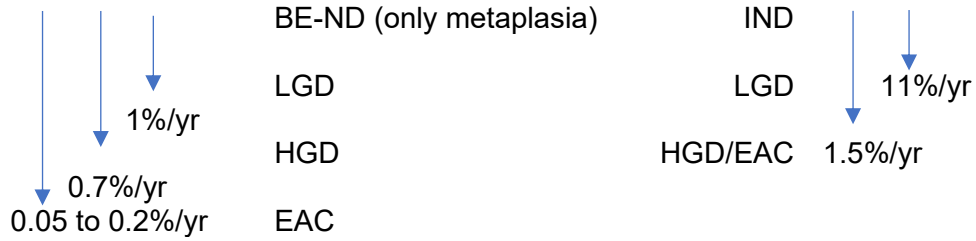
Courtesy of: https://heartburncanceruk.org/latest-updates/research/cytosponge/

- Collect cells to stain for the biomarker Trefoil Factor 3 (TFF3, a secretory protein from mucin-producing cells, which differentiates Barrett's cells from gastric cardia and squamous cells)
- 3 large scale studies
  - Sensitivity for Barrett
    - > 1 cm, 75%
    - > 2 cm, ~93%
    - Specificity, ~93%
- Can ↓ cost by up to 30% compared to EGD

Trindade AJ, et al. Gastrointest Endosc 2019;90(3):325-334
Sanghi V and Thota PN. Ther Adv Chronic Dis 2019; 10:2040622319837851.

➢ Progression of BE to Low Grade Dysplasia (LGD), High Grade Dysplasia (HGD), and Esophageal Adenocarcinoma (ECA)

- BE-No Dysplasia (BE-ND)



Abbreviations: BE-ND, Barette esophagus with no dysplasia; EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; IND, indefinite for dysplasia; LGD, low grade dysplasia;

Krishnamoorthi R, et al. Gastroenterol Endosc 2020; 91: 3-10.

- Risk factors for Progression

Risk Factor		Odds Ration (95% CI)
Patient	– Age	1.03 (1.01-1.05)
	– Male	2.16 (1.84-2.53)
	– Smoking (ever)	1.47 (1.09-2.53)
BE	– Length	1.25 (1.16-1.36)
	– LGD	4.25 (2.58-7.0)
Medication	– PPI use	0.55 (0.32-0.96)
	– Statin use	0.48 (0.31-0.73)

Krishnamoorthi R, et al. Gastroenterol Endosc 2018; 16: 1046-55.

- Other risk factors
  - Patient
    - Caucasian
    - Family history
    - BMI > 30 (especially central obesity)
  - Intake
    - Alcohol
    - NSAIDs
  - EGD risk factors

Wani S. Gastroenterology 2011; 141(4): 1179-1186
Shaheen N, et al. Am J Gastroenterol 2016; 111: 30-50

- Length of BE
  - Modest ↑ risk of BE-ND, LGD, IND → EAC, < 0.1%/yr
  - ↑↑↑ HGD → EAC, 0.5%/yr

Wolf WA, et al. Gastroenterology. 2015;149(7):1752-1761.e1.

- Medications
  - PPI, low dose / high dose plus ASA, 15% have EAC in 10 yr
  - PPI, high dose plus ASA 10% have EAC in 10 yr

Jankowski JAZ, et al. Lancet 2018; 392: 400-408 (AspECT Trial)

- Surveillance may reduce EAC and all cause of mortality
  - Regular surveillance → ↓ lower EAC-related / all-cause mortality (RR 0.60; 95% CI 0.50 – 0.71)
  - ↓ EAC-related and all-cause mortality among patients with surveillance-detected EAC vs. symptom-detected EAC
    - RR = 0.73 (95% CI, 0.57–0.94)
    - Patients with surveillance are more likely to be diagnosed with early stage EAC compared to no/inadequate surveillance (RR 2.11)
  - Single RCT currently underway: Barrett's Oesophagus Surveillance Study (BOSS) Trial in UK
    - 100 hospitals, 3400 BE pts, EGD q2y vs no surveillance

Codipilly DC et al. Gastroenterology. 2018;154(8):2068-2086

- Surveillance Cost Effectiveness
  - 3 independent population-based models
  - 60y individuals with BE in USA, followed until death w/o surveillance or treatment (natural progression) vs 78 patients with different strategies for patients with NDBE or LGD
  - Surveillance EGD in 3y for males, 5y for females with NDBE, and treatment for LGD after confirmation
    - ICER $53 000/QALY men, $36 000/QALY for females

Omidvari AH, et al. Clin Gastroenterol Hepatol 2019

- American College of Gastroenterology (ACG) 2022

Care algorithm for patients noted to have columnar mucosa in the tubular esophagus.

- Initial Endoscopy Finding
  - Salmon-coloured mucosa extending proximally from the gastroesophageal junction (GEJ)
- Step 1: Assess Length of Mucosa
  - If < 1 cm salmon-coloured mucosa or irregular Z-line OR regular Z-line → No biopsy
  - If ≥ 1 cm salmon-coloured mucosa → Obtain at least 8 endoscopic biopsy samples
- Step 2: Biopsy Results
  - Negative for Intestinal Metaplasia → Repeat endoscopy with biopsy in 1–2 yr
  - Intestinal Metaplasia
    - No Dysplasia
      - < 3 cm BE segment → Repeat surveillance EGD in 5 yr
      - ≥ 3 cm BE segment → Repeat surveillance EGD in 3 yr
    - Indefinite for Dysplasia (IND)
      - Confirm by 2nd pathologist with GI expertise
      - PPI BID → Repeat EGD with biopsy within 6 months
    - LGD / HGD / Early EAC
      - Confirm by 2nd pathologist with GI expertise
      - Refer to flowchart for BE-related neoplasia

Note the stratification of surveillance interval by length of nondysplastic BE.

Abbreviations: BE, Barrett esophagus; EAC, esophageal adenocarcinoma; GEJ, gastroesophageal junction; GI, gastrointestinal; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Adapted from: Shaheen N, et al. Am J Gastroenterol 2022; 117: 559 – 587 (Figure 2).

- Recommended endoscopic surveillance intervals based on degree of dysplasia and segment length (ACG, 2022)

Baseline Endoscopic Finding	Suggested Endoscopic Surveillance
Nondysplastic BE of	
– <3 cm length	▪ EGD q5 yr
– ≥3 cm length	▪ EGD q3 yr
BE indefinite for dysplasia, any length (confirmed by a second pathologist)	– Repeat EGD within 6 mon after increasing PPI to twice-daily dosing, if not already on high-dose PPI

Baseline Endoscopic Finding	Suggested Endoscopic Surveillance
	▪ If repeat EGD yields diagnosis of NDBE or LGD, treat using that algorithm ▪ If repeat EGD demonstrates BE indefinite for dysplasia, EGD annually
○ BE with LGD (confirmed by second pathologist and opting for endoscopic surveillance)	− EGD at 6 mon from diagnosis − EGD at 12 mon from diagnosis − EGD annually thereafter

Abbreviations: BE, Barrett esophagus; EGD, esophagogastroduodenoscopy; LGD, low-grade dysplasia; NDBE, nondysplastic BE; PPI, proton pump inhibitor.

Adapted from: Shaheen N, et al. Am J Gastroenterol 2022; 117: 559 – 587

Overview of BE Surveillance 2023

- Non-dysplastic BE
  - Repeat EGD in 3-5 years
- Dysplastic BE
  - Confirm with 2nd GI pathologist
  - Eradicate with Endoscopic Therapies (LGD and HGD)
  - ASA may help prevent progression (assess patient for possible need for preventive therapy [PPI] against ASA-mucosal damage)

Wani S, et al. Gastroenterol 2022; 162: 366-372

- Consider risk/benefit ratio re ASA-associated intracerebral / GI bleeding, +/- PPI prophylaxis
- PPI may need to be given bid for optimal protection of LGD/HGD progression.
- Quality Esophagogastroduodenoscopy (EGD)
  - Thus, these is a need to improve and maintain quality of EGDs performed for screening/surveillance of BE
- Pool prevalence of post-endoscopy UGI cancer is 10.7% based on meta-analysis of 25 studies

Sawas T, et al. Clin Gastroenterol Hepatol 2022; 20(2): e31-e50

- Special attention to ↑ risk area for BE
  - Right wall of esophagus on EGD, at 12 to 4 o'clock positions
    - Biopsy examination
    - High-definition white light
    - Chromoendoscopy / virtual chromoendoscopy
    - Distal attachment CAP
    - WATS, PB-CLEM, VLE, AI (please see below)
- Procedure
  - Identity landmarks
  - Use water jet to ↓ mucus / debris
  - Insufflation / deflation
  - Adequate time of inspection to identify SCF, GEJ, pinch sign of hiatus hernia
  - Describe BE using Prague system
  - Interactive online education modules → ↑ detection of dysplasia by 46%

Gupta N, et al, Gastrointest Endosc 2012; 76: 531-5382.
Enestvedt BK, et al. Gastrointest Endosc 2013; 78: 462-467.
Bergman, JJGMH et al. Gastroenterology 2019; 156:1299.e3–1308.e3.
Parasa S, et al. Gastrointest Endosc 2022; 95: 239-245 (ACQUIRE STUDY)

- Use standard classifications
  - Prague for maximal length (M) and EGD type
  - Paris, maximal circumference height (C), neoplasia
  - LA, GERD lesion severity
  - Seatle protocol for taking mucosal biopsies

Shaheen N, et al. Am J Gastroenterol 2022; 117: 559 – 587
Wani, S, et al. Gastroenterol 2022; 162: 366 – 372

Measurements:
M = length from GEJ to maximal height of metaplasia
C = length from GEJ to maximal extent of circumferential metaplasia

GEJ to C of 2 cm, and GEJ to M of 5 cm → C2M5

SO YOU WANT TO BE A GI PATHOLOGIST!

- Give standardized classification systems used to describe and to classify grade of disorders seen on EGD. Name the disorders, and the grading systems used in these classifications.

Conditions seen on EGD	Classification	Grade
○ Erosive esophagitis	Los Angeles[1]	A, B, C, D
○ Barrett esophagus	Prague[2]	Circumferential extent, maximal extent
○ Eosinophilic esophagitis	Endoscopic reference score[3]	EREFS
○ Caustic esophagitis	Zagar[4]	I, II, III, IV
○ Esophageal varices	Baveno[5]	I, II, III
○ Hiatal hernia	Hill[6]	I, II, III, IV
○ Ulcer bleeding	Forrest[7]	Ia, Ib, IIa, IIb, IIc, III
○ Duodenal adenomas in patients with FAP	Spigelman[8]	0, I, II, III, IV
○ Neoplasia	Paris[9]	0-Ip, 0-Is, 0-IIa, 0-IIb, 0-IIc, 0-III

[1] Armstrong D, et al. Gastroenterology 1996; 111:85–92.
[2]Alvarez Herrero L, et al. Endoscopy 2013; 45: 876–882.
[3]Hirano I, et al. Gut 2013; 62: 489–495.
[4]Cheng HT, et al. BMC Gastroenterol 2008;8:31.
[5]de Franchis R; Baveno VI Faculty. J Hepatol 2015; 63: 743–752.
[6]Kahrilas PJ, et al. Best Pract Res Clin Gastroenterol 2008; 22: 601–616.
[7]Forrest JA, et al. Lancet 1974; 2: 394–397.
[8]Spigelman AD, et al. Lancet 1989; 2: 783–785.
[9]Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005; 37:570–578.

- Seattle Protocol
  - First described in 1993
  - (Jumbo) biopsy forceps
  - 4 quadrant biopsies
  - Take biopsies every 1-2 cm from the top of gastric fold (TOGF) to squamocolumnar junction (SCJ)
  - Only represents 5-10% of Barrett epithelium
  - Biopsy visible lesions separately
  - Worldwide adherence to Seatle protocol ~49% !!!!

Roumans CAM, et al. Endoscopy 2020; 52: 17 - 28

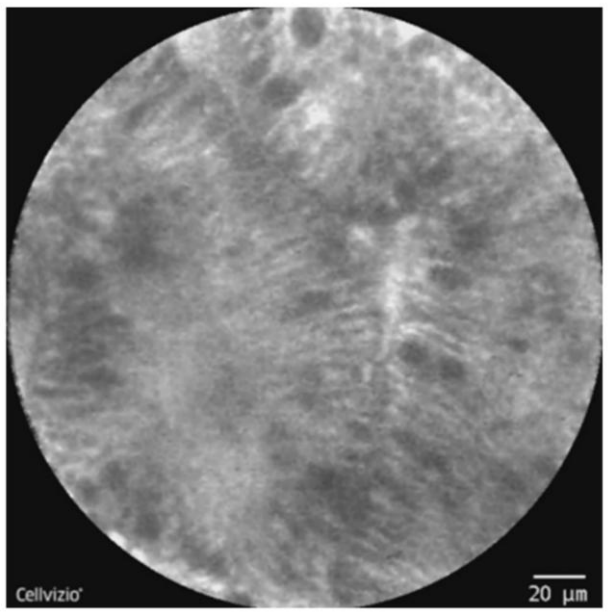
- Chromoendoscopy (acetic acid, Lugol's iodine)
- Narrow band imaging (NBI)

Consensus-Driven NBI Classification of Barrett's Epithelium

Morphologic Characteristic	Pattern Description	Classification
○ Mucosal pattern	− Circular, ridged/villous, or tubular patterns	Regular
	− Absent or irregular patterns	Irregular
○ Vascular pattern	− Blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long, branching patterns	Regular
	− Focally or diffusely distributed vessels not following normal architecture of the mucosa	Irregular

- Barrett's International NBI Group (BING) Criteria (Sharma P, et al. Gastroenterology. 2016; 150(3):591-8)

Probe Based Confocal Laser Endomicroscopy



- ○ pCLE view
  - − Intestinal metaplasia of the esophageal epithelium, columnar cells with dark goblet cells

Courtesy of: Vaculová J, et al. Diagnostics. 2022; 12(7):1616 (Figure 2)

- Volumetric Laser Endomicroscopy (VLE)
  - Optical Coherence Tomography
  - Real time 360deg images
  - 1200 cross sectional scans over 6 cm, in 90s, imaging depth of 3 mm, resolution of 10 μm
  - Scans are viewed in real time – cross sectional, transverse, or longitudinal views
  - Superficial laser marking to target suspicious areas

Trindade AJ, et al. Gastrointest Endosc 2019; 90(3): 479–486.e2.
Trindade AJ, et al. Gastroenterology. 2019;157(2):303–305.

- Argos Consortium
  - Automatically detects and localizes early neoplastic lesions on White Light Endoscopic images
  - For other examples of AI use in detection of BE, please see
    - Its is estimated that up to 25% of esophageal adenocarcinomas in patients with BE are missed within 1 year of index

de Groof J, et al. United European Gastroenterol J 2019; 7(4): 538-547
Hashimoto R, et al. Gastrointest Endosc. 2020; 91(6): 1264–1271.e1.

- Wide Area Transepithelial Tissue Sampling (WATS)
  - 19 mm highly abrasive stiff brush to sample <5cm segment
  - Thick specimen: Computer assisted 3D analysis (WATS-3D)
  - Average of 10^5 cells obtained for cytological analysis

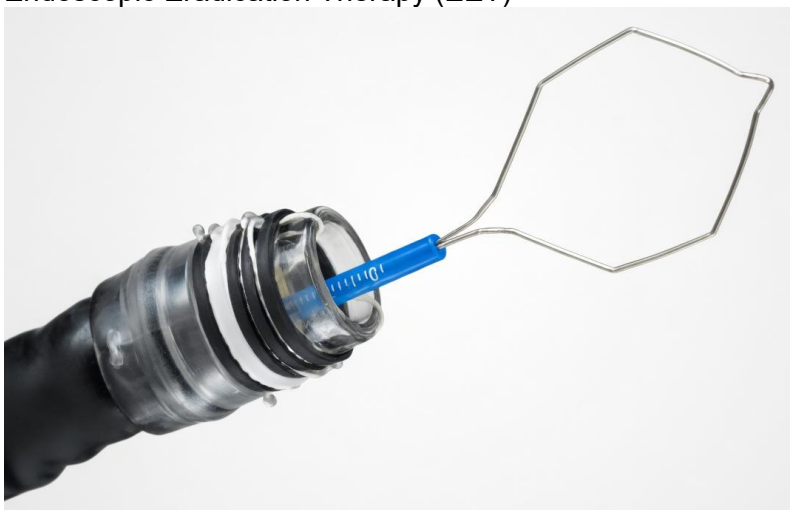
Trindade AJ, et al. Gastrointest Endosc 2019; 90(3): 479–486.e2.

- Endoscopic Eradication Therapy (EET) for HGD and IMC (<T1b SM2)
  - No Difference between EET and esophagectomy with regard to overall 1,3, and 5 year survival and EAC mortality

Standards of Practice Committee, Wani S, et al. Gastrointest Endosc 2018; 87:907–31.
Wu J, et al. Gastrointest Endosc 2014;79:233–41.

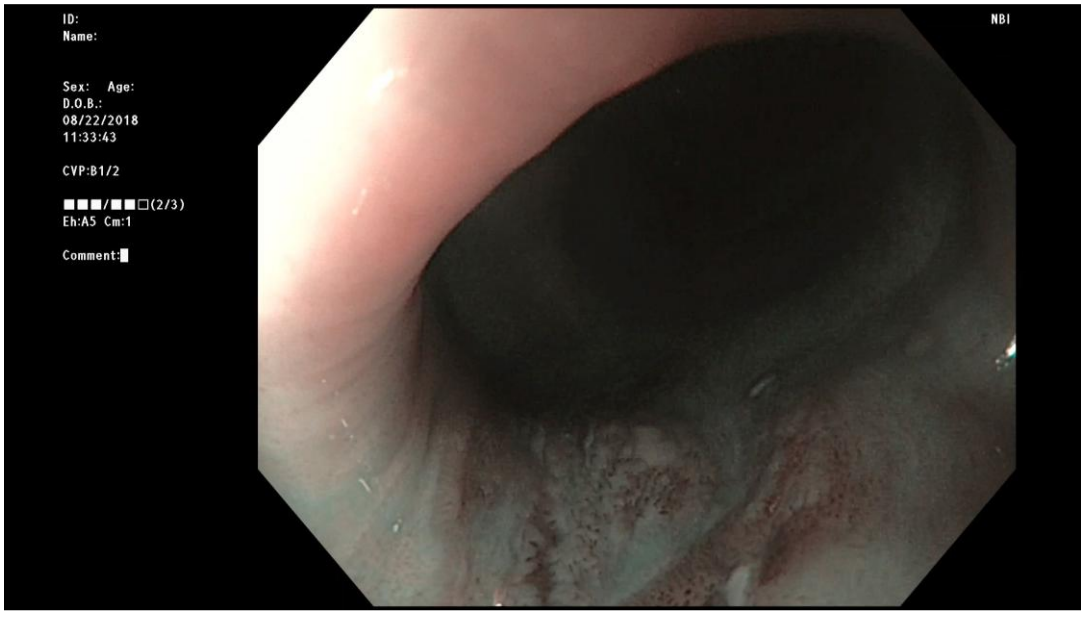
- Band Assisted EMR

Endoscopic Eradication Therapy (EET)

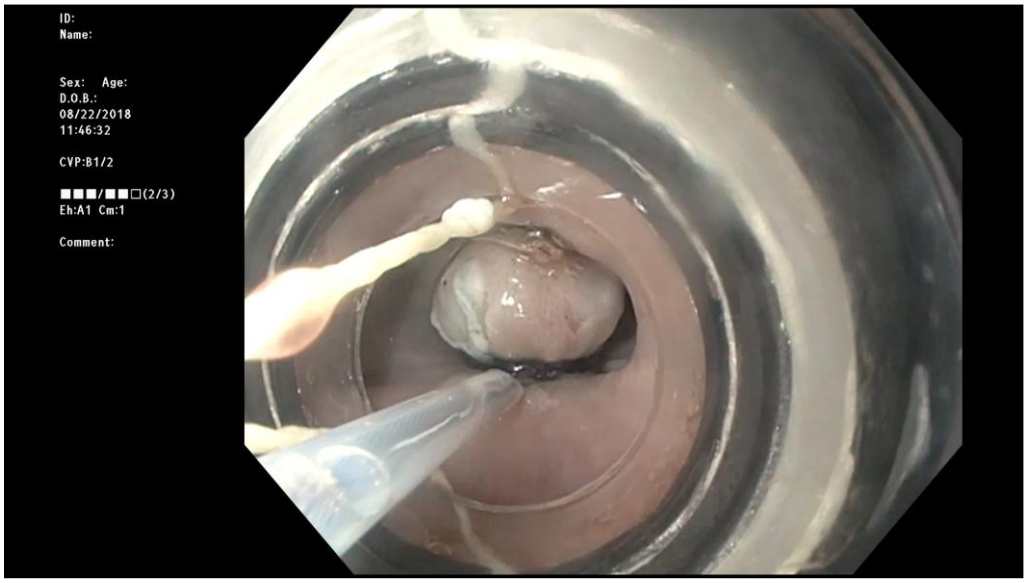


Courtesy of: https://www.cookmedical.com/products/esc_duette_webds/

Marking Abnormal Area of Esophageal Mucosa: Resection



Cutting Biopsy to Abnormal Esophageal Mucosa



- Safety (in “Experienced hands”)
  - Perforation rate: 2%
  - Bleeding: 2-3%
  - Dysphagia/stricturing: up to 50% with “stepwise radical endoscopic resection

Gerke H, et al. Gastrointest Endosc 2009; 69: 153-154.
May A, et al. Gastrointest Endosc. 2003;58(2):167-75.
Pouw RW, et al. Gut 2010; 59:1169-77.
Alvarez Herrero L et al. Endoscopy. 2011; 43:177-83.
Ortiz-Fernando-Sordo J, et al. World J Gastrointest Endosc 2011; 3: 171 – 182

- Benefits of EMR: determine
  - Presence or absence of malignancy
  - Depth of Invasion
  - Degree of differentiation
  - Presence of lymphovascular invasion
  - Adequacy of resection (curative intent)

- Radiofrequency Ablation (RA)
  - The equipment
    - Uses focal ablation catheter
    - Circumferential application of radiofrequency
  - Efficacy

Outcome	RFA	Sham (placebo)	RR (95% CI)	NNT
Complete eradication of intestinal metaplasia (all patients), 12 mon				
− Intention-to-treat	65/84 (77%)	1/43 (2%)	33.3 (4.6–52.1)	1.3
− Per-protocol	65/78 (83%)	1/29 (3%)	32.5 (4.6–52.5)	1.2
Complete eradication				
− LGD	42 (80%)	22 (20%)		
− HGD	42 (80%)	21 (18%)		

Abbreviations: CI, confidence interval; NNT, number needed to treat; RFA, radiofrequency ablation

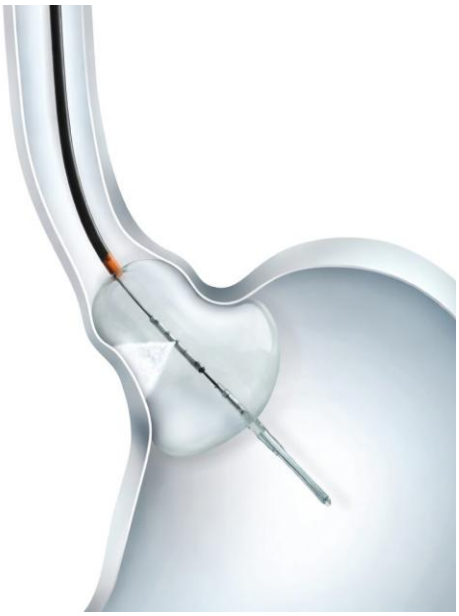
Shaheen NJ et al. N Engl J Med 2009; 360: 2277-2288

  - Overall ablation
    - CE-HGD/IMC, 96%
    - CE- Dysplasia, 87-97%
    - CE-IM, 64-88%
    - Timeframe to achieve CR, 12-36 mon
  - Safety
    - Stricture, 5-9%
    - Bleeding, 0.2-3%
    - Hospitalization, 2%
    - Perforation, 0.6%
  - Durability
    - 5 yr dysplasia/IM free: 90%
    - Progression to EAC
    - 2-4% at 1 yr
    - ~10% at 5 yr

- Freeze Therapy
  - First report, 2005
  - Cycles of rapid cooling and thawing
  - Liquid N2 (-196 ℃), N2O (-85 ℃), or CO_2 (-78 ℃)
  - Mechanism of action
    - Cell membrane destruction
    - Thrombi in blood vessels
    - Induction of apoptosis / ischemia
  - 3 Systems:
    - truFreeze® (CSA Medical): liquid N2 spray
    - Polar Wand® (GI supply): liquid CO2 spray
    - C2 Cryoballoon® (Pentax): liquid N2O into balloon → HC approved (Oct 2022)

Johnston MH, et al. GIE 2005; 62: 842-848

Freeze Therapy: C2 Cryoballoon®



Courtesy of: https://device.report/manual/3561199
https://sites.pentaxmedical.com/pentax-cryoballoon-endocast-registration/p/1

- Conclusion
  - Endoscopic therapy is the standard of care for the treatment of dysplasia in Barrett esophagus
    - Nodular segments or short segments of Barrett's Endoscopic mucosal resection (EMR)
    - Highly effective to treat HGD/LGD → Radiofrequency ablation (RFA) (intent of complete eradication of metaplasia)
    - Potential for first line therapy or adjunct/rescue to RFA → Cryoablation

- Recurrence of BE after achieving Complete Endoscopic Intestinal CE-IM by EET
  - 1/5 to 1/3 of those achieving CE-IM will have BE recurrence within 15 mon of EET

Cotton CC, et al. Gastroenterol 2017; 153; 681-688

  - This includes recurrence of →
    - Non-dysplastic Barrett esophagus
    - Low-grade dysplasia
    - Indefinite for dysplasia
    - High-grade dysplasia
    - Intramucosal adenocarcinoma

Cotton CC, et al. Gastroenterol 2018; 155; 316-326

  - Development of EAC after RFA
    - Non-dysplastic Barrett Esophagus
    - Low grade dysplasia, <2% at 4 yr
    - Indefinite dysplasia
    - High grade dysplasia, 10% at 4 yr

Wolf WA, et al. Gastroenterology. 2015; 149(2): 307–315.e1.

- Surveillance Protocol post complete eradication of intestinal metaplasia (CE-IM)
  - ACG recommends endoscopic surveillance intervals following CEIM (based on worst pretreatment histology)

Worst pretreatment histology	Suggested endoscopic surveillance
Low-grade dysplasia	1 yr following CEIM 3 yr following CEIM Every 2 yr thereafter
High-grade dysplasia	3 mon following CEIM 6 mon following CEIM 12 mon following CEIM Annually thereafter

Worst pretreatment histology	Suggested endoscopic surveillance
○ Intramucosal carcinoma	− 3 mon following CEIM − 6 mon following CEIM − 12 mon following CEIM − Annually thereafter |

- ○ Four quadrant biopsies are taken in the high cardia just below the Z line from the top of the gastric folds.
  - − Four quadrant biopsies are additionally taken from each third of the distal 2–3 cm of neosquamous epithelium.
  - − Biopsies taken of normal-appearing tissue above the Z line, even in previously long-segment disease, have not been demonstrated to have substantial yield and are not suggested for standard biopsies.

➢ Summary

- ○ Surveillance time after complete eradication of intestinal metaplasia is dependent on worst pathology
- ○ (Usually) treat
  - − LGD with risk factors (dependent on resources)
  - − HGD with endoscopic therapy
    - ▪ EMR/ESD
    - ▪ RFA
    - ▪ Cryotherapy

} Combination endoscopic therapy is safe and effective in eradicating BE and dysplasia

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; AASLD, American Association for the Study of Liver Diseases; ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett esophagus; BE-ND, Barrett's esophagus with no dysplasia; BING, Barrett's International NBI Group; BMI, body mass index; BSG, British Society of Gastroenterology; CCO, Cancer Care Ontario; CI, confidence interval; CSSLD, Chinese Society of Liver Diseases; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; EET, endoscopic eradication therapy; EMR, endoscopic mucosal resection; EoE, eosinophilic esophagitis; ESGE, European Society for Gastrointestinal Endoscopy; ESD, endoscopic submucosal dissection; GEJ, gastroesophageal junction; GI, gastrointestinal; HGD, high-grade dysplasia; IM, intestinal metaplasia; IMC, intramucosal carcinoma; IND, indefinite for dysplasia; LGD, low-grade dysplasia; LOA, length of admission; NBI, narrow band imaging; NDBE, nondysplastic Barrett's esophagus; NNT, number needed to treat; OR, odds ratio; PB-CLEM, probe-based confocal laser endomicroscopy; PPI, proton pump inhibitor; RFA, radiofrequency ablation; RR, relative risk; SCJ, squamocolumnar junction; TFF3, trefoil factor 3; uTNE, unsedated transnasal endoscopy; VLE, volumetric laser endomicroscopy; WATS, wide area transepithelial tissue sampling.

EOSINOPHILIC ESOPHAGITIS

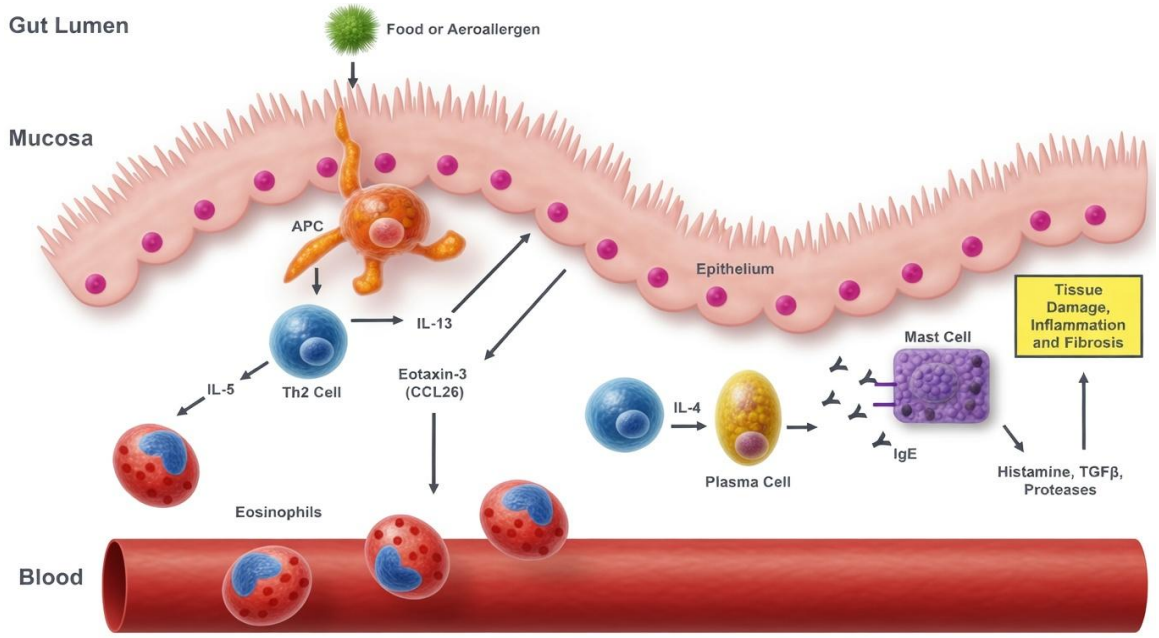
Mohammed Alsager

- Demography
  - Prevalence of 55 per 10^5
  - Atopic male (M:F ratio >3:1)
  - Presents in childhood or 30–40s
  - Mean age of diagnosis 34 yr
  - Seen across racial/ethnic groups
  - Possible predominance in non-Hispanic white persons

- Definition
  - Chronic, immune/antigen-mediated esophageal disease
    - Characterized by esophageal dysfunction from eosinophilic-predominant inflammation: ≥15 eos/hpf
  - Eosinophil-predominant inflammation on esophageal biopsy:
    - Isolated to esophagus
    - May persist after 8-week PPI trial
    - ↑ eosinophils in both middle and distal esophagus
  - Secondary causes excluded
  - Response to treatment (PPI, dietary elimination, topical corticosteroids)
    - Supports, but is NOT required for diagnosis
  - Eosinophils release major basic protein, a cytotoxic cationic protein that → direct damage to the esophagus → esophageal dysfunction
  - Eosinophils in blood 50%
  - Eosinophilic infiltration on biopsies in a patient without symptoms
    - Not sufficient to make a diagnosis of EoE
  - Symptoms + eosinophilic infiltration >15/HPF on biopsy after PPI trial = EoE in proper clinical setting
  - ↑ numbers of mast cells, B cells, and IgE-bearing cells
  - Subepithelial and lamina propria fibrosis and inflammation
  - Basal cell hyperplasia / Papillary lengthening
  - Eosinophils
    - ↑ number mid/distal 1/3 of esophagus
    - Sheets
    - Microabscesses
    - Extracellular (eosinophil) granules

- Pathophysiology

Esophageal Mucosa and Eosinophilic Esophagitis (EoE)



- Barrier integrity is essential in the gastrointestinal tract to protect against inappropriate inflammation.
  - Impaired barrier defenses and allergic sensitization to food and aeroallergens can then initiate inflammation in the esophageal epithelium.
  - Tissue resident antigen-presenting cells are thought to process and present allergenic peptides to CD4+ T lymphocytes, activating and skewing T cell differentiation towards T helper type 2 (Th2) lymphocyte development.
  - When activated by antigen, Th2 cells produce pathogenic and inflammatory cytokines, IL-13, IL-5, and IL-4. IL-13 induces non-traditional immune cells, like the epithelium, to produce chemoattractant cytokines.
  - One chemokine, CCL26 (also called Eotaxin-3) attracts and recruits eosinophils to the esophageal tissue.
  - IL-5 promotes eosinophil maturation, differentiation, and activation, leading to the release of allergic mediators.
  - IL-4 activates B cells to differentiate into plasma cells, undergo class switching, and produce antigen-specific IgE.
  - IgE can then bind to Fc receptors on mast cells, triggering degranulation and release of histamine and proteases.
  - Activated mast cells also produce TGF-β, a key cytokine implicated in fibrotic processes that lead to stenotic disease and esophageal narrowing

Courtesy of: Lambert KA, et al. J Transl Genet Genom 2018;2:11.

- Histopathology
  - 2–4 mucosal biopsies should be taken from distal and from proximal esophagus to determine presence of eosinophilia
  - Duodenal biopsies should be biopsied at the same time
  - Other causes of ↑ esophageal eosinophils must be ruled out
  - Normal
    - Stratified squamous epithelial surface
      - Few lymphocytes / no other leukocytes
  - Inflammation
    - ↑ eosinophils
    - Epithelial → hyperplasia (accumulates eosinophils)

- Associations
  - Achalasia and other disorders of esophageal dysmotility
  - Allergic rhinitis
  - Asthma
  - Atopic dermatitis
  - Autoimmune disorders and vasculitides
  - Connective tissue disorders
  - Crohn disease with esophageal involvement
  - Dermatologic conditions with esophageal involvement (e.g., pemphigus)
  - Drug hypersensitivity reactions
  - Environmental allergies
  - Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
  - Food allergies
  - Gastroesophageal reflux disease (GERD)
  - Graft vs host disease (GVHD)
  - Hypereosinophilic syndrome (HES)
  - Hypermobility syndromes
  - Infections (fungal, viral)
  - Mendelian disorders (Marfan syndrome type II, hyper-IgE syndrome, PTEN hamartoma tumour syndrome, Netherton syndrome, severe atopy metabolic wasting syndrome)
  - Pill esophagitis

- Clinical
  - Dysphagia (most common)
  - Food impaction/foreign body requiring endoscopic removal (33–55%)
  - Esophageal stricture (30%)
  - Refractory heartburn (25%)
  - Chest pain – centrally located burning that does not respond to antacids

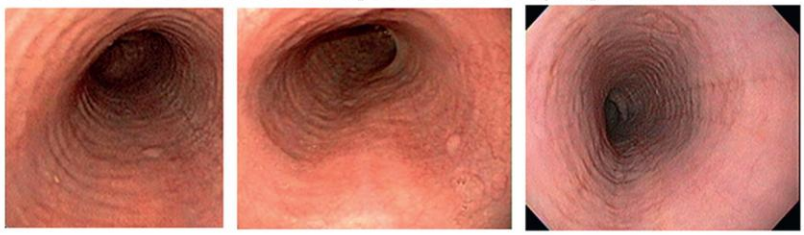
- Diagnostic Imaging

- Barium Study
  - Strictures
  - Multiple fixed ring-like indentations (ringed esophagus)
    - Rarely, esophageal intramural diverticulosis
  - Endoscopy is usually not helpful for diagnosis usually but
    - May provide information on length and diameter of strictures for planning therapeutic dilation

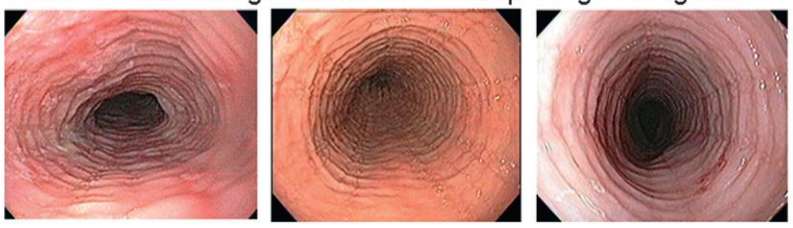
- Endoscopy
  - Individual endoscopic features suggestive of eosinophilic esophagitis →
    - ↓ sensitivity, 15–50%
    - ↑ specificity, 90–95%
  - Stacked circular rings (“feline” esophagus) = trachealization = corrugated appearance (sensitivity 44%)
  - ↓ subepithelial vascular pattern from edema (sensitivity 40%)
  - Longitudinal furrows: linear furrowing, may extend entire length of esophagus (sensitivity 48%)
  - Whitish papules/exudate/plaques (eosinophil microabscesses) (27%)
  - Small caliber esophagus = diffuse narrowing (10%)
  - Strictures (particularly proximal strictures) (21%)
  - Mucosal fragility = friability laceration with passage of endoscope

EoE Reference Score for Endoscopic Abnormalities (EoE-EREFs)

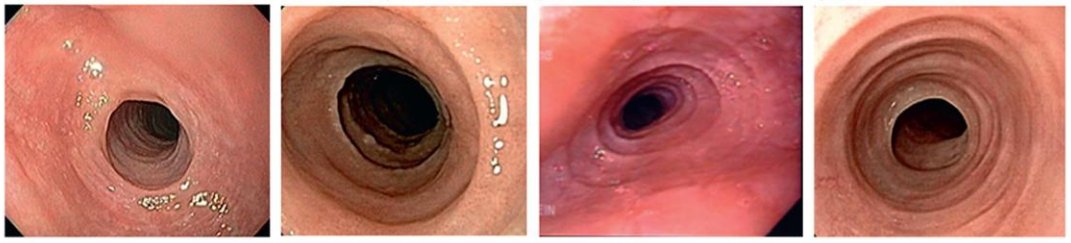
A **Mild:** Subtle circumferential ridges seen on esophageal distension



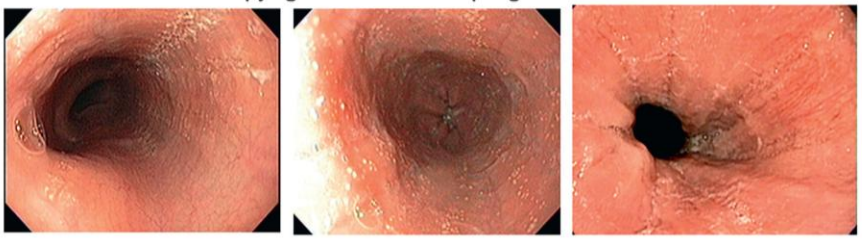
Moderate: Distinct rings that do not occlude passage of diagnostic endoscope



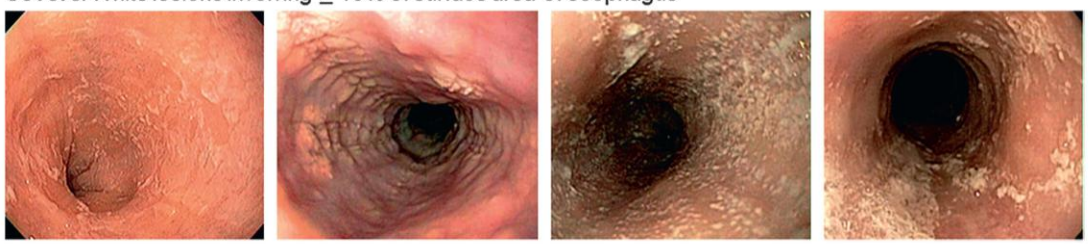
Severe: Distinct rings that do not permit passage of diagnostic endoscope



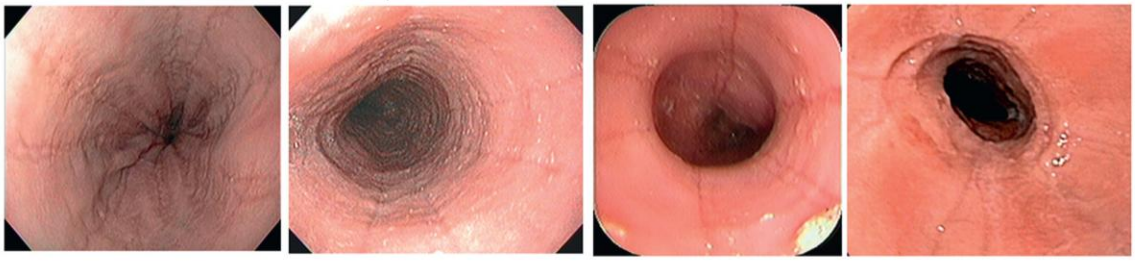
B **Mild**: White lesions occupying < 10% of the esophageal surface area



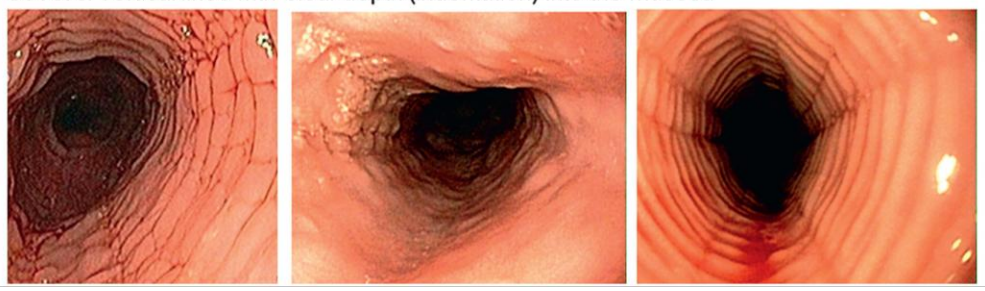
Severe: White lesions involving ≥ 10% of surface area of esophagus



C **Mild**: Vertical lines without visible depth

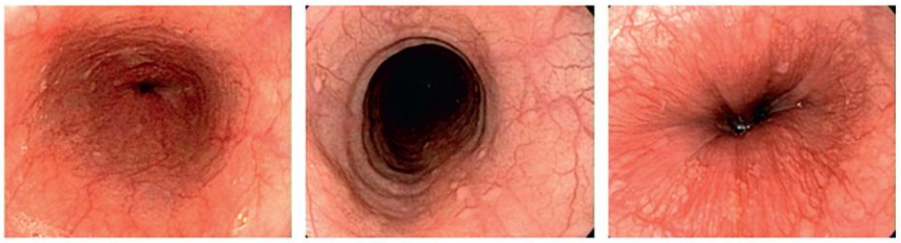


Severe: Vertical lines with clear depth (indentation) into the mucosa

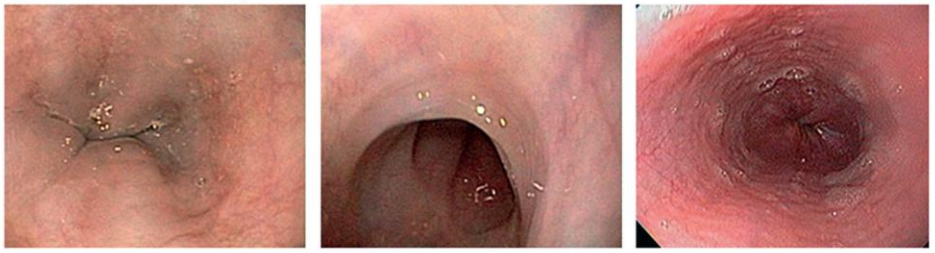


D

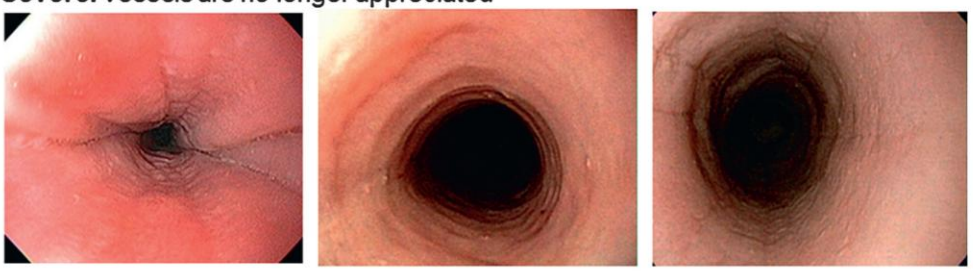
Normal: Distinct vasculature

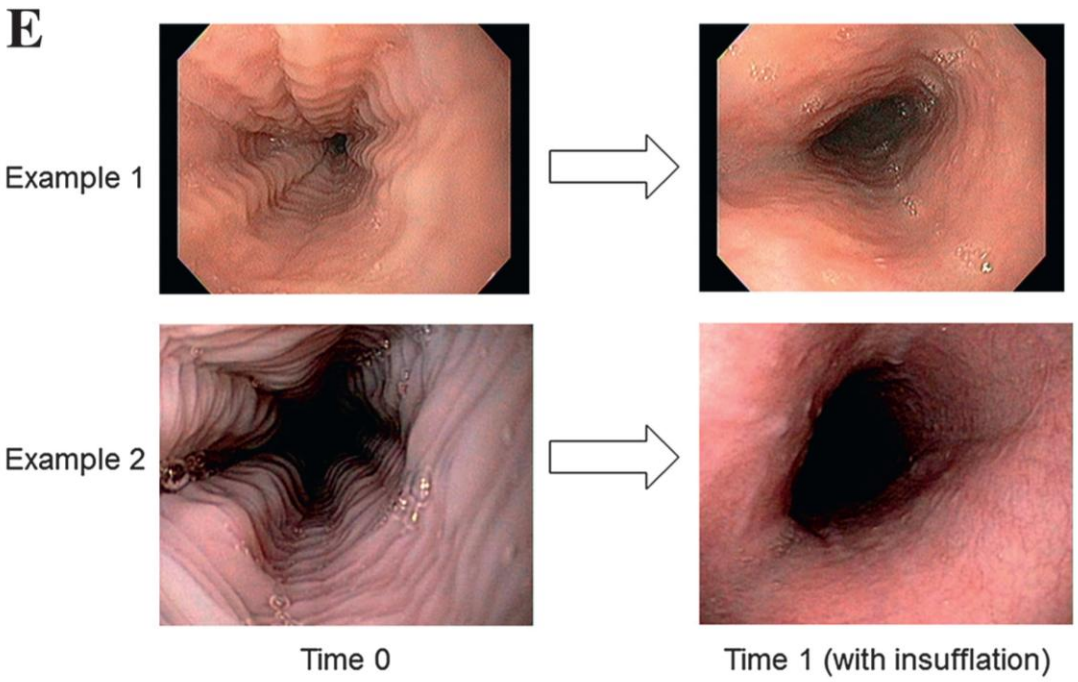


Mild: Decrease clarity of vessel



Severe: Vessels are no longer appreciated





- Grading system for the endoscopic assessment of the esophageal features of eosinophilic esophagitis.
- Categories for each feature are listed in box 1.
  - (A) Fixed esophageal ring (trachealisation, ringed oesophagus, corrugated oesophagus).
  - (B) Exudates (plaques).
  - (C) Furrows (vertical lines).
  - (D) Edema (decreased vascular markings).
  - (E) Transient oesophageal rings (feline oesophagus).
  - (F) Crepe paper oesophagus (mucosal fragility).

Printed with permission: Hirano I, et al. Gut 2013; 62: 489-495 (Figure 1)

Box 1 Original classification and grading system for the endoscopic assessment of the esophageal features of eosinophilic oesophagitis

Major features

- Fixed rings (also referred to as concentric rings, corrugated esophagus, corrugated rings, ringed esophagus, trachealisation)
  - Grade 0: none
  - Grade 1: mild (subtle circumferential ridges)
  - Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8e9.5 mm))
  - Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)
- Exudates (also referred to as white spots, plaques)
  - Grade 0: none
  - Grade 1: mild (lesions involving <10% of the oesophageal surface area)
  - Grade 2: severe (lesions involving >10% of the oesophageal surface area)
- Furrows (also referred to as vertical lines, longitudinal furrows)
  - Grade 0: absent
  - Grade 1: mild (vertical lines present without visible depth)
  - Grade 2: severe (vertical lines with mucosal depth [indentation])
- Edema (also referred to as decreased vascular pattern, mucosal pallor)
  - Grade 0: absent (distinct vascularity present)
  - Grade 1: mild (loss of clarity of vascular markings)
  - Grade 2: severe (absence of vascular markings)
- Stricture
  - Grade 0: absent
  - Grade 1: present

Minor features

- Feline esophagus (transient, concentric mucosal rings observed spontaneously or during belching, retching or swallowing that disappear with air insufflation)
  - Grade 0: absent
  - Grade 1: present
- Narrow calibre oesophagus (reduced luminal diameter of the majority of the tubular esophagus)
  - Grade 0: absent
  - Grade 1: present
- Crepe paper esophagus (mucosal fragility or laceration upon passage of diagnostic endoscope but not after esophageal dilation)
  - Grade 0: absent
  - Grade 1: present

Printed with permission: Hirano I, et al. Gut 2013; 62: 489-495 (Box 1)

- Diagnostic Criteria (AGREE Conference – Gastroenterology [2018])
  - Symptoms of esophageal dysfunction
    - ↑ suspicion
      - Atopy
      - Endoscopic findings
  - Isolated esophageal eosinophilia of ≥15 eos/HPF (≥2 biopsies at ≥2 levels)
  - Exclusion of non-EoE disorders that cause or contribute to esophageal eosinophilia
- Treatment
  - Targets
    - Clinical: ↓ symptoms and ↓ complications
    - Endoscopic: ↓ eosinophilic inflammation

- Diet
  - Elimination diets should be done with assistance of a registered dietician
    - Elemental Diet (Total Elimination): elemental or amino acid-based formula with 95–98% resolution of symptoms and histology
    - Targeted Elimination: guided by skin prick or patch allergy testing
    - Empiric 6-food Elimination Diet: milk, wheat, soy, nuts, egg, seafood
      - 94% symptomatic improvement
      - 70% histologic improvement
      - 2–4 food elimination variants: milk (60%), wheat (50%), egg, soy
  - Food triggers identified by sequential food challenge after response to the FFGED
    - Milk
    - Wheat
    - Egg
    - Legumes

- Endoscopy
  - Dilation of strictures (treatment response >1 yr)
  - Complications: chest pain (75%), bleeding, perforation

- Pharmacological Therapy
  - High rate of recurrence after discontinuation
  - Topical Steroids (8-week course)
    - 50% complete and 95% partial response
      - Fluticasone 880–1760 mcg/day in divided dose
      - Oral viscous budesonide 1 mg BID
  - Prednisone
    - Higher histologic response
    - Higher risk of side effects (40%)

Abbreviations: AGREE, Appraisal of Guidelines for Research and Evaluation; BID, bis in die (twice daily); CD4+, cluster of differentiation 4 positive T lymphocytes; CCL26, chemokine ligand 26 (Eotaxin-3); EoE, eosinophilic esophagitis; EoE-EREFs, eosinophilic esophagitis endoscopic reference score; Fc, fragment crystallizable receptor; GERD, gastroesophageal reflux disease; GVHD, graft-versus-host disease; HES, hypereosinophilic syndrome; HPF, high-power field; IgE, immunoglobulin E; IL, interleukin; PPI, proton pump inhibitor; Th2, T helper type 2 lymphocyte; TGF-β, transforming growth factor beta.

FOREIGN BODIES AND FOOD BOLUS MANAGEMENT

Pavithra Parthasarathy

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

Birk M, et al. Endoscopy 2016;48(5):489–496.

GI Divisional Policy – London Health Science Center (LHSC)

- All interactions with the patient should be automatic and consistent with each presentation
- Minimize number of endoscopies performed overall and after hours
  - Patient assessed by ER team at presentation (Psychiatry care plan expands on this)
    - If patient shows signs of distress, obstruction, GI bleeding, Peritonitis/perforation, the appropriate services will be emergently involved
      → Emergent involvement of GI, General Surgery, Thoracics as required
  - If patient is stable and minimally symptomatic, they can safely wait, and may wait and not even need EGD
    - Endoscopy performed per ASGE Guidelines:
      i. Emergent endoscopy: Esophageal obstruction, sharp object, or button/disk battery in esophagus
      ii. Urgent endoscopy: Item in esophagus not in above category, or item in stomach >6 cm long / >2.5 cm wide, sharp or magnet. Batteries can be watched for 48 hr
    - 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 be contracted the following day if Emergent EGD is not required.

- **Approach to the Patient with Suspected Foreign Body** (FB) **Ingestion**

  - Clinical
    - Ingestion
      - Nature
      - Time
      - Number of items
    - Anatomic risks

- Typical Patient Groups
  - Children
    - Accidental ingestion
  - Adults
    - Developmental delay
    - Intoxication
    - Psychiatric illness
    - Secondary gain
- Symptoms
  - Chest or abdominal pain
  - Dysphagia
  - Dyspnea
  - Hypersalivation
  - Odynophagia
  - Retrosternal pain
  - Stridor
  - Wheezing
- Physical Exam
  - ABCs
  - Abdominal exam for obstruction/peritonitis
  - Auscultation for wheezing and aspiration
  - Check for visible FB in oral cavity
  - Subcutaneous emphysema in chest

Birk M, et al. Endoscopy 2016; 48(5): 489–496. doi:10.1055/s-0042-100456
Demiroren K Pediatr Gastroenterol Hepatol Nutr 2023; 26(1): 1–9.

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

➢ **Diagnostic Imaging**

- Chest X-ray (CXR) and abdominal X-ray
  - To assess for foreign bodies [FB] and free air)
  - 87% false negative rate in food bolus impaction (87%)
  - ESGE
    - Does **not** recommend
      - X-rays for nonbony food bolus
      - Barium swallow due to aspiration risk and interference with endoscopic view

Birk M, et al. Endoscopy 2016; 48(5): 489–496. doi:10.1055/s-0042-100456
Demiroren K Pediatr Gastroenterol Hepatol Nutr 2023; 26(1): 1–9.

- Upper Esophagogastroduodenoscopy (EGD)
  - Endoscopic management is ~96% successful in retrieving foreign bodies
    - No significant complications
  - Can treat associated complications
  - 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 hr for
    - Esophageal obstruction
    - Sharp objects in esophagus
    - Batteries
    - Other esophageal items/incomplete obstruction: 2-24 hr
      - For stomach: <24 hr for sharp items/batteries, nonurgent (72 hr) for medium-sized blunt objects
  - Food bolus
    - Do not delay endoscopy for medical treatment; attempt to gently push food into stomach
      - 90% success
    - Pushing bolus into stomach is superior to retrieval
    - When pushing watch for significant resistance
      - Do not to use excessive force; consider en bloc vs piecemeal retrieval

Birk M, et al. Endoscopy 2016; 48(5): 489–496.
Demiroren K Pediatr Gastroenterol Hepatol Nutr 2023; 26(1): 1–9.
Skok P and Skok K. Zeitschrift für Gastroenterologie 2020; 58(03): 217-223.

- **Timing of Endoscopic Intervention in Foreign Body Ingestions**

	Object Type	Timing
Esophagus	Battery	Emergent
	Magnet	Urgent
	Sharp-pointed foreign body	Emergent
	Blunt and small foreign body <2–2.5 cm	Urgent
	Blunt and medium-sized foreign body >2–2.5 cm	Urgent
	Large foreign body >5–6 cm	Urgent
	Food bolus	Emergent (Urgent if without symptoms or without complete obstruction)
Stomach / Small Bowel	Battery	Urgent
	Magnet	Urgent
	Sharp-pointed foreign body	Urgent
	Blunt and small foreign body <2–2.5 cm	Nonurgent
	Blunt and medium-sized foreign body >2–2.5 cm	Nonurgent
	Large foreign body >5–6 cm	Urgent

- Urgent, preferably within 2 hours, but at latest within 6 hr; urgent, within 24 hr; nonurgent, within 72 hr.

Adapted from: Birk M, et al. Endoscopy 2016; 48(5): 489–496.

- Foreign Body Retrieval Tools (Images courtesy of Olympus America https://medical.olympusamerica.com/procedure/foreign-body-retrieval)

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

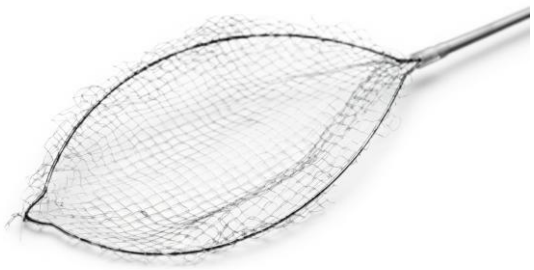
Rat Tooth Alligator Jaw Grasping Forceps

Retrieval Basket (FG-460YR)

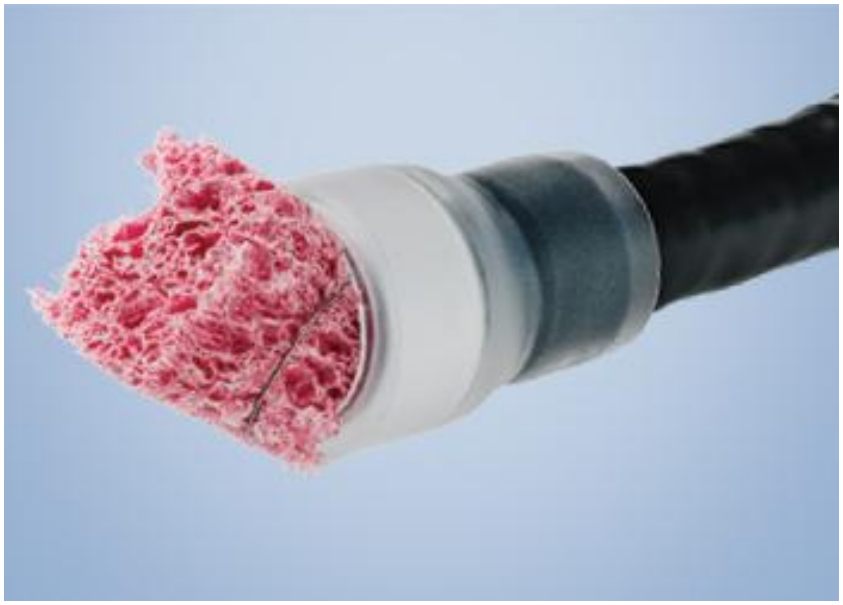
eSuction

EVIS EXERA III GIF-1TH190

SwirlNet



Friction on Wall of Esophagus



➢ **ESGE Recommendations** (2016)

- **Non-endoscopic Measures**
  - Do diagnostic evaluation based on patient history and symptoms.
  - Do a physical exam should assess general condition and signs of complications. (Strong recommendation, low quality evidence)
  - Do not do radiological evaluation for nonbony food bolus impaction without complications.
  - Do plain radiography only if radiopaque object suspected or object type unknown (Strong recommendation, low quality evidence)
  - Do CT scan for suspected perforation or complications requiring surgery. (Strong recommendation, low quality evidence)
  - Do barium swallow (risk and interference with endoscopic view. (Strong recommendation, low quality evidence)
  - Do clinical observation without endoscopy for asymptomatic ingestion of blunt/small objects (except batteries, magnets).
  - Do outpatient management, if feasible. (Strong recommendation, low quality evidence)
  - Do close observation in asymptomatic individuals who have concealed packets of drugs by swallowing
  - Do not do endoscopic retrieval
  - Do surgical referral in cases of suspected packet rupture, failure to progress, or intestinal obstruction (Strong recommendation, low quality evidence)

- **Endoscopic Measures**
  - Do emergent (preferably within 2 hr, but at the latest within 6 hours) therapeutic esophagogastroduodenoscopy for
    - Foreign bodies inducing complete esophageal obstruction
    - Sharp-pointed objects or batteries in the esophagus
  - Do urgent (within 24 hr) 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 unsuccessful, retrieval considered (Weak recommendation, low quality evidence)
    - The effectiveness of medical treatment of esophageal food bolus should not delay endoscopy (Strong recommendation, low quality evidence)

- In cases of food bolus impaction, 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.
  - Do non-urgent (within 72 hr) therapeutic EGD for medium-sized blunt foreign bodies in the stomach (Strong recommendation, low quality evidence)
- Use protective device to avoid esophagogastric/pharyngeal damage and aspiration during endoscopic extraction of sharp-pointed foreign bodies.
  - Endotracheal intubation should be considered if high aspiration risk (Strong recommendation, low quality evidence)
- Use suitable extraction devices according to type and location of ingested foreign body.
  (Weak recommendation, low quality evidence)
- After successful and uncomplicated endoscopic removal of ingested foreign bodies
  - The patient may be discharged if f foreign bodies are not or cannot be removed, a case-by-case approach is suggested depending on size and type
  (Weak recommendation, low quality evidence)

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; CXR, chest X-ray; EGD, esophagogastroduodenoscopy; ESGE, European Society for Gastrointestinal Endoscopy; FB, foreign body; GI, gastrointestinal; LHSC, London Health Science Center; SAGES, Society of American Gastrointestinal and Endoscopic Surgeons

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(05): 489–496.
- Demiroren K. Management of gastrointestinal foreign bodies with brief review of the guidelines. Pediatric Gastroenterology, Hepatology & Nutrition 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.
- 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. Zeitschrift für Gastroenterologie 2020; 58(03): 217–223.
- https://medical.olympusamerica.com/procedure/foreign-body-retrieval

STOMACH

GASTROPARESIS, CANNABIS HYPEREMESIS, CYCLIC VOMITING AND RUMINATION SYNDROMES

Maytham Hussain

Gastroparesis

- Definition
  - The word “gastroparesis” comes from the ancient Greek language:
    - Gaster = stomach
    - Paresis = partial paralysis
  - Gastroparesis is the objective evidence of delayed gastric emptying in the absence of mechanical obstruction.

- Demography
  - A systematic review in 2023 concluded:
    - Prevalence
      - 14 to 268 per 10^5 adults
      - Females > males

- Gastric Physiology
  - Components
    - Gastric motor function depends on 3 levels of control:
      - Autonomic nervous system (ANS)
      - Parasympathetic via vagal nerve
      - Sympathetic system
      - Enteric neurons and interstitial cells of Cajal (ICC)
      - Smooth muscle cells
  - Terminology
    - Peristaltic reflex, the propulsion of food from the stomach to the intestine has two components:
      - Ascending contraction secondary to distention from food bolus (via Acetylcholine)
      - Descending inhibition below the level of distention, to allow the bolus to travel down (via Nitric Oxide [NO] and vasoactive intestinal peptide [VIP])
  - The “Rule of the intestine”
    - A peristaltic wave is comprised of
      - An initial relaxation followed by
      - Contraction

- Pathophysiology
  - Each region of the stomach may be affected:
    - Fundus
      - Vagal nerve injury
      - Diabetes mellitus

- Antrum
  - Friction
  - Grinding
  - Mixing
  - Emptying

  } Solids from the stomach

  - ↓ antral contractions/function caused by neuropathic and infiltrative disease (i.e., systemic sclerosis)
  - Autonomic neuropathy and hyperglycemia
- Pylorus
  - Idiopathic hypertrophic pyloric stenosis (loss of inhibitory NO)
  - Diabetic gastroparesis: ↑ pyloric tonic/phasic pressure activity

➢ Causes/Associations

- Most Common

Diagnosis	Incidence (%)
○ Idiopathic gastroparesis (IGP)* (20% have obstructive gastroparesis)	40
○ Diabetic gastroparesis (type 1 and 2 diabetes mellitus) (20% obstructive)	35
○ Postsurgical gastroparesis (antrectomy, vagotomy, fundectomy, fundoplication)	20
○ Ischemic gastroparesis	1
○ Miscellaneous causes	4

*may be
- Infection, post-viral (Norwalk, Rotavirus)
- Inflammation
  - Enteric nerves
  - Intestinal cells of Cajal
  - Smooth muscle

Modified from: Parkman HP and Hasler WL. Gastroparesis. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 11th ed. Philadelphia, PA: Elsevier; 2020: Table 50.3, p.754.

- Idiopathic gastroparesis (IGP, 40%)
  - Most common cause of gastroparesis (1/3 of patients)
  - Infection
    - Post viral, i.e. Norwalk, Rotavirus → dysautonomia
- Drug-Induced
  - GLP 1 agonists
  - Narcotics
  - TCAS (Tricycle Antidepressants)
  - CCBS (Calcina Channel Bokens)
  - Octreotide
  - Dopamine agonists
- Diabetic gastroparesis (20%)
  - Cumulative incidence over 10 yr
    - DM1, 5%
    - DM2, 1%
  - ↓ Interstitial cells of Cajal (ICC)
  - ↑ abnormal enteric nerve endings, leading to
  - Abnormal postprandial proximal gastric accommodation/contraction
  - ↓ frequency of antral contractions
  - ↓ pylorospasm
- Functional pyloric obstruction
  - Secondary
    - ↓ coordination of n=antral contraction and pyloric relaxation → ↓ normal gastric peristaltic waves emptying chyme into duodenum (particles ≤ mm)
- Post-surgical (20%)
  - Intended or accidental injury to vagal nerve
  - Vagotomy
  - Fundoplication
  - Billroth 1, Billroth 2, Roux-en-Y
  - Post radiofrequency (RFA) for atrial fibrillation
  - Botulinum toxin infection for achalasia treatment
- Ischemic gastroparesis (< 1%)
  - Secondary to chronic mesenteric ischemic from underlying ie atherosclerosis.
- Systemic diseases
  - Neurological
    - Multiple sclerosis (MS)
    - Parkinsonism
    - Amyloid neuropathy
  - Autoimmune GI dysmotility

- Clinical
  - History
    - Nausea/Vomiting
    - Early satiety / Post-prandial fullness / Bloating
    - Abdominal pain
    - ↓ Body weight
  - Examination
    - Abdominal tenderness / distension
    - Succession splash.
    - Volume depletion / poor nutrition
    - Features of systemic disease

- Laboratory
  - Hemoglobin
  - Fasting plasma glucose
  - HbA1c
  - Serum total protein
  - Albumin
  - TSH
  - ANA (ANNA-1 or anti-Hu antibody in search for paraneoplastic gastroparesis)
  - Evidence of
    - Nutrient deficiency
    - Electrolyte disturbance

- Endoscopy
  - Upper GI endoscopy (esophagogastroduodenoscopy [EGD]
    - Retained food after an overnight fast (supportive of a diagnosis of gastroparesis, but is **not** diagnostic)

- Diagnostic Imaging
  - CT/MR enterography to rule out mechanical obstruction
  - Barium swallow
    - If CT/MRE not available))
  - Scintigraph (nuclear medicine) (gastric emptying study)
  - Wireless motility capsule (WMC)

- Electrogastrogram
  - Assess for electrical postprandial signals
    - Bradygastria
    - Tachygastria, or
    - Mixed
- Manometry
  - Neuropathic (abnormal contractile response) vs myopathic process (low amplitude contractions)
  - Contractile response
    - Abnormal, neuropathic
    - ↓ amplitude, myopathic

- Instructions to patient
  - Avoid/stop drugs that can cause delayed gastric emptying for at least 48 hr.
  - Control blood glucose (BG) < 10 mmol/L
  - Low fat radiolabeled egg-white meal and imaging immediately after it, then at 1, 2, 4 hours following ingestion

- Classification (used to guide pharmacological treatment)
  - Positive for Gastric retention
    - Mild, 10% to 15%
    - Moderate, 15% to 35%
    - Severe, > 35%

➢ Treatment

- Diet and Lifestyle Modifications
  - Registered dietician consultation
  - Avoid
    - Fatty
    - Spicy food
    - Non-digestible fiber
      - Soluble fiber can be found in foods such as oat bran, barley, nuts, seeds, beans, lentils, fruits (citrus, apples), strawberries and many vegetables
      - Insoluble fiber is found in foods such as whole wheat and whole grain products, vegetables, and wheat bran
    - Carbonated drinks
    - Smoking and alcohol
    - Glycemic control

- Blended food for mild to severe gastroparesis
  - In diabetic patient
    - Maintain normal fluid and electrolyte balance
    - Control blood glucose concentration
- Nutrition support
  - Mild gastroparesis
    - Usually normal diet, perhaps small meals frequently, and avoiding foods which are bothersome to patient)
  - Moderate
    - Liquid diets (rare to use jejunostomy feeding tube [JFT])
  - Severe
    - Liquid diets per JFT

- Parenteral nutrition
  - For continued refractory gastroparesis
  - For correction / maintenance malnutrition as needed

- Prokinetics
  - 1st line: metoclopramide
    - D2 receptor antagonist, a 5-HT4 agonist, and a weak 5-HT3 receptor antagonist →
      - ↑ gastric antral contractions and ↓ postprandial fundus relaxation
    - FDA approved for use <12 wk
    - Metoclopramide 10 mg po tid-qd, taken 10 to 15 min AC (may be given subcutaneously, 5-10 mg tid AC)
    - Consider drug holiday for patients drugs use for other purpose, and which might cause/aggravate other causes of gastroparesis
    - Adverse effects:
      - Hyperprolactinemia
      - QTc prolongation (↑ risk)
      - Extrapyramidal signs (i.e., tardive dyskinesia and dystonia, which may be non-reversible)
  - 2nd line: Domperidone
    - D2 peripheral receptor antagonist 10 mg tid
    - Adverse effects
      - Hyperprolactinemia
      - QTc prolongation (↑ risk)
  - 3rd line: Macrolides
    - GI use for
      - Gastroparesis
      - Upper GI tracts before EGD for bleeding

  - (i.e., erythromycin or azithromycin with longer half-life)
  - Motilin agonist
  - ↑ fundic contractility
  - ↓ accommodation response of proximal stomach after food ingestion
  - Use limited to <4 wk (tachyphylaxis → ↑ resistance to drug → ↓ benefit)
  - Adverse effects
    - QT prolongation
    - GI toxicity
    - Ototoxicity
    - ↑ resistance (tachyphylaxis)
- Antiemetics **(**Add-on therapy for nausea and vomiting symptoms)
  - Dimenhydrinate: 12.5 mg PO q6–8h PRN
    - H1 and muscarinic receptor inhibitor
  - Ondansetron: 4–8 mg TID/PRN
    - 5HT3 antagonist
  - Prochlorperazine
    - 5–10 mg po tid, or
    - 5–25 mg po tid

- **Endoscopic approaches**
  - Balloon dilatation of pylorus
  - Laparoscopic pyloroplasty
  - Gastric endoscopic pyloromyotomy (G-POEM)
  - Transpyloric stent
  - Botox injections of lower esophageal sphincter (LES)
  - G-tube for venting and decompression with J-tube for enteral feeding (± small volume liquid meals via mouth)
    - Confirm tolerance of feeding (~80 cc/hr) via nasogastric tube (NGT) prior to placement

- **Cyclic Vomiting Syndrome / Hyperemesis Syndrome**

➢ Definition
  - Stereotypical episodes of clustered, recurrent vomiting in absence of other etiology

➢ Risk factors
  - Cannabis use
  - History of migraines

- Clinical
  - Acute nausea/vomiting lasting hours-days plus symptom free intervals
  - Personal history or family history of migraine headaches
- Diagnostic criteria
  - Rome Criteria
    - Criteria must be fulfilled for ≥ 3 mon plus symptom onset ≥ 6 mon prior to diagnosis
    - Stereotypical vomiting episodes (< 1 wk duration)
    - ≥ 3 discrete episodes in last 12 mon
    - 2+ episodes in last 6 mon (at least 1 wk apart)
    - No vomiting episodes
    - regarding onset (acute) and duration (less than 1 week)
- Treatment
  - Treat associated
    - Anxiety
    - Depression
    - Dehydration
  - Prophylaxis
    - Beta blockers
    - Cyproheptadine
    - Erythromycin
    - Naloxone
    - SSRIs
    - TCAs
    - Valproic acid
  - Prodrome
    - Antimigraine meds (5HT1 blockers)
    - Conventional antiemetics
    - Benzodiazepines
    - Hydration management

- **Cannabinoid Hyperemesis Syndrome (**CHS)

- Clinical
  - CB1 receptors: brain, GI tract
  - CB2 receptors: lymphoid tissue
  - CB1 stimulation inhibits HPA axis and sympathetic response, modulates gastric motility/sensation
  - Chronic cannabis use downregulates CB1; sensitivity returns after cessation

- Diagnostic criteria
  - Must include all of the following:
    - Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 wk)
    - At least three discrete episodes in the prior year and two episodes in the past 6 mon, occurring at least 1 wk apart
    - Absence of vomiting between episodes, but other milder symptoms can be present between cycles

- Supportive remark
  - May be associated with pathological behaviour (prolonged hot bath or shower)

- Treatment
  - Stop use of cannabis
  - As for cyclic vomiting syndrome (CVS)
    - Complications
    - Anxiety
    - Depression
    - Drugs
      - Cessation of cannabis
      - Topical capsaicin cream
      - CVS prophylactic treatments may be used

- **Rumination Syndrome**

- Definition
  - Repetitive, effortless regurgitation of recently ingested food into the mouth, plus re-chewing, re-swallowing, or expulsion of regurgitated material

- Clinical
  - No
    - Nausea/vomiting
    - Hypersalivation
    - Sweating
  - Regurgitant contains recognizable food, may taste pleasant
  - Criteria fulfilled for last 3 mon with symptom onset ≥6 mon prior

- Diagnosis
  - Esophageal and gastroduodenal manometry plus pH impedance → detect sharp phasic pressure spikes in antrum/duodenum

- Treatment
  - Behaviour modification: diaphragmatic breathing, biofeedback
  - Reassurance and explanation of the phenomenon allow patients to develop control over rumination
  - If associated GERD
    - ↓ HCl production: proton pump inhibitors (PPIs)
  - ↑ lower esophageal pressure (LES) to ↓ reflux: baclofen
- Curiosity
  - Process ceases when regurgitated material becomes acidic

Abbreviations: ANA, antinuclear antibody; ANNA-1, anti-neuronal nuclear antibody type 1; BG, blood glucose; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; CCBS, calcium channel blockers; CHS, cannabinoid hyperemesis syndrome; CVS, cyclic vomiting syndrome; DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; EGD, esophagogastroduodenoscopy; G-POEM, gastric peroral endoscopic myotomy; GI, gastrointestinal; HbA1c, glycated hemoglobin; HPA, hypothalamic–pituitary–adrenal axis; ICC, interstitial cells of Cajal; IGP, idiopathic gastroparesis; JFT, jejunostomy feeding tube; LES, lower esophageal sphincter; MS, multiple sclerosis; NGT, nasogastric tube; NO, nitric oxide; PPI, proton pump inhibitor; RFA, radiofrequency ablation; SB, small bowel; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal peptide; WMC, wireless motility capsule.

Suggested Reading:

Uptodate: https://www.uptodate.com/contents/gastroparesis-etiology-clinical-manifestations-and-diagnosis

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

https://theromefoundation.org/rome-iv/rome-iv-criteria/

FEEDING AND EATING DISORDERS

Zaki Alhashimalsayed

- Importance to Gastroenterologists
  - The patient with feeding/eating disorders may present with GI symptoms
  - The gastroenterologist must be aware that esophagogastric, colonic and nutritional presentations of patients in their practice may be due to / associated with GI disorders.
  - The take-home message for the patient with GI disorders, always have feeding/eating disorders in your differential and approach.

- Definition
  - Eating disorders are serious mental disorders characterized by persistent disturbances in body image, weight control, and dietary patterns.
  - Anorexia Nervosa
    - Characterized by severe food restriction, intense fear of weight gain, and distorted body image.
  - Bulimia Nervosa
    - Involves episodes of binge eating followed by compensatory behaviors such as purging.
  - Binge-Eating Disorder
    - Recurrent episodes of eating large amounts of food with feelings of lack of control.
  - Other Specified Disorders
    - Includes avoidant/restrictive food intake disorder, pica, and rumination disorder.

- Demography
  - Prevalence Rates
    - Anorexia nervosa:1.7–3.6% lifetime prevalence.
    - Bulimia nervosa: 2.6% lifetime prevalence.
    - Binge eating disorder: 0.62–3.6% point prevalence.
  - Gender Distribution
    - All eating disorders are more common in women.
    - Men account for less than 10% of anorexia and bulimia cases, but up to 40% of binge-eating disorder cases.
  - Risk Factors
    - Multifactorial causes include psychodevelopmental, sociocultural, and genetic contributions. Body dissatisfaction and dieting are key risk factors.

- Clinical
  - Identify Warning Signs
    - Up to 50% of cases go unrecognized in clinical settings.
    - Patients often reluctant to disclose symptoms.
    - GI complaints may precede eating disorder diagnosis.
  - Conduct Targeted Assessment
    - Directed clinical interview about restrictive or binge eating and compensatory measures.
    - Physical examination for signs of malnutrition or purging.
  - Determine Diagnosis
    - Apply diagnostic criteria while recognizing overlap in symptoms.
    - Exclude medical causes of weight changes and GI symptoms.
  - Onset
    - Anorexia and bulimia typically begin in adolescence.
    - Binge eating disorder usually manifests in early 20s.
  - Comorbidity
    - High psychiatric comorbidity
      - 56.2% for anorexia
      - 94.5% for bulimia
      - 63.6% for binge-eating disorder.
  - Recovery
    - About 47% of anorexia patients achieve normal eating behavior.
    - Up to 50% of treated individuals remain symptomatic in follow-up. (Partial recovery, and chronically symptomatic)
  - Condition
    - Multidisciplinary approach
    - Psychotherapy
    - Pharmacotherapy

- Classification

- Major

- Anorexia Nervosa
  - Key Features
    - Significantly low weight, fear of gaining weight despite being thin, and disturbed body perception.
    - Often denies or minimizes fear of weight gain.

- Diagnostic Challenges
  - Diagnosis may be delayed when patients present with GI complaints without disclosing weight concerns.
  - May state desire to gain weight while restricting.
- Subtypes
  - Restricting type: primarily controls weight through dieting, fasting, or exercising.
  - Binge eating/purging type: routinely purges calories or binge eats.
- Treatment
  - No approved medications
  - Olanzapine may help weight gain, but evidence is inconsistent.
  - Antidepressants not effective in underweight AN.
  - Hormonal therapy (e.g., estrogen) may improve BMD in adolescent girls but not full catch-up.
  - Supplement on calcium, vit D

- Bulimia Nervosa
  - Binge Eating
    - Consuming unusually large amounts of food during discrete periods with feeling of loss of control
  - Body Image Concerns
    - Self-image excessively influenced by weight and shape
  - Recurrent Pattern
    - Behaviors occur at least weekly for three months
  - Compensatory Behaviors
    - Purging, excessive exercise, fasting. or medication misuse to prevent weight gain
  - Patients may use various compensatory methods including self-induced vomiting, laxative abuse, diuretics, insulin under-dosing, and excessive exercise. Many describe emotional numbing during binge episodes.
  - Treatment
    - Fluoxetine is FDA-approved: moderate symptom reduction.
    - CBT > pharmacotherapy: combination may be helpful.
    - Other agents: topiramate, ondansetron, and SSRIs – limited by side effects or evidence.
    - Bupropion not recommended due to seizure risk.

- Binge-Eating Disorder (BED)
  - Recurrent Binge Episodes
    - Eating large amounts of food with loss of control, at least weekly for three months
  - Associated Features
    - Eating rapidly, eating when not hungry, eating alone due to embarrassment. feeling disgusted afterward
  - No Compensatory Behaviors
    - Unlike bulimia, no regular inappropriate compensatory behaviors to prevent weight gain
  - Marked Distress
    - Significant emotional distress about binge eating pattern
  - Patients frequently present without specific physical findings except overweight or obesity.
  - Many seek help for weight concerns rather than binge eating behaviors.
  - Treatment
    - Lisdexamfetamine is FDA-approved for moderate-severe BED.
    - Orlistat, topiramate, SSRIs, and SNRIs (e.g., duloxetine) show variable results.
    - Monitor for cardiovascular risks and psychiatric side effects.

❖ Minor

- Atypical Anorexia
  - Fear of fatness and body image disturbance without low weight. May occur after substantial weight loss while still in normal weight range.
- Purging Disorder
  - Recurrent purging to influence weight or shape without binge eating. More common in women, with peak onset around age 20.
- Night Eating Syndrome
  - Recurrent episodes of night eating. No clear diagnostic criteria, but characterized by morning anorexia, evening hyperphagia, sleep disturbances. More common in obese individuals.
  - These presentations fall short of criteria for major eating disorders but cause significant distress or impairment. They include subthreshold forms of anorexia, bulimia, and binge eating disorder.

❖ **Avoidant/Restrictive Food Intake Disorder** (ARFID)

➢ Definition

- A DSM-5 eating disorder involving restrictive intake leading to nutritional or psychosocial issues; not due to body image concerns.
- Physical Manifestations
  - Significant weight loss or growth delay; nutritional deficiency; dependence on supplements/enteral feeding
- Common Triggers
  - Sensory sensitivity; fear of adverse effects (e.g., choking); lack of interest in eating
- Diagnosis & Comorbidities
  - Requires detailed dietary history; often associated with intellectual disability and autism; more common in males

- **Pica**
  - Repeated ingestion of non-food items (e.g., chalk, paper, paint chips).
  - Not diagnosed if developmentally normal (e.g., toddlers) or culturally accepted.
  - Unique: Only eating disorder (ED) that can co-occur with another ED.

- **Rumination Disorder**
  - Repeated, voluntary regurgitation of food for 21 mon, not due to a medical issue.
  - Food may be re-chewed, re-swallowed, or spit out
  - Seen in both children and adults.
  - Diagnosis not made if explained by AN or BN, though behavior may co-occur.

➢ Treatment

- No pharmacologic agents with strong evidence.
- Treatment is non-pharmacologic, focusing on nutritional rehab + therapy (Severely malnutrition patients)

- Distinguishing Features of Feeding & Eating Disorders (DSM-5)

Disorder	Weight/Nutritional Deficit	Restrictive Eating	Binge Eating	Purging	Body Image Concern
○ AN	Underweight	Yes	May occur	Up to 50%	Yes
○ ARFID	Underweight or deficiency	Yes (sensory /trauma)	No	No	No
○ BED	Often overweight	No	Yes (≥1x/week)	No	Yes
○ BN	Normal/overweight	May occur	Yes (≥1x/week)	Yes	Yes
○ Pica	No	No	No	No	NO
○ Rumination	No	No	No	Not for weight	No

- Medical Complications of Eating Disorders

System	Weight Loss / Restriction: AN. OSFED USFED!	Purging / Refeeding (AN, BN, OSFED USFED)
○ Cardiovascular	− Bradycardia, hypotension, orthostasis. arrhythmias. heart failure	Palpitations. edema, prolonged QT. cardiomyopathy: ipecac;
○ Dermatologic	− Dry skin, hair loss. lanugo. acrocyanosis, brittle nails	Russell sign: knuckle lesions)
○ Endocrine/ Metabolism.	− Amenorrhea, low testosterone, osteopenia. hypoglycemia. hypothermia	Electrolyte abnormalities. metabolic alkalosis acidosis
○ GI	− Delayed gastric emptying, constipation. GERD. hepatic pancreatic issues	Bloating. GERD. esophagitis, rectal prolapse. pancreatitis
○ Genitourinary	− Amenorrhea, infertility, atrophic vaginitis, kidney stones	Amenorrhea, azotemia
○ Hematologic	− Anemia. leukopenia, thrombocytopenia	-
○ Neurologic	− Cognitive decline. cortical atrophy, peripheral neuropathy	Stroke (ephedra). gag reflex loss, ipecac neuropathy
○ Oral/Pharyngeal	− Cheilosis, halitosis	Dental erosion, parotid swelling, trauma, vocal fold pathology
○ General	− Irritability. mood issues	Mood changes, weight fluctuations

- Gastrointestinal Complications
  - Motility Issues
    - Delayed gastric emptying, slow colonic transit, constipation
  - Esophageal Problems
    - GERD, esophagitis, Mallory-Weiss tears, Barrett esophagus
  - Severe Complications
    - SMA syndrome, gastric dilation, rupture, pancreatitis
  - Liver Abnormalities
    - Elevated enzymes, steatosis, hypoglycemia
  - GI symptoms are reported in 78–98% of hospitalized eating disorder patients. Symptoms often relate to the duration or presence of active eating disorder behaviors.

➢ Laboratory

Test	Purpose
Complete Blood Count	Assess for anemia, neutropenia. leukopenia, thrombocytopenia
Electrolytes	Check for hypokalemia, hypochloremia, hyponatremia
Metabolic Panel	Evaluate glucose, renal and liver function
Cardiac Assessment	ECG to identify QTc prolongation and arrhythmias
Bone Health	DEXA scan to assess bone density in anorexia

- Laboratory results may be normal despite severe malnutrition in anorexia. Those who binge and purge often show metabolic abnormalities. Monitor for refeeding syndrome during nutritional rehabilitation.

➢ Treatment

- Multidisciplinary Treatment Approach
  - Medical Care
    - Monitor and treat physical complications, manage weight restoration
  - Psychiatric Treatment
    - Psychotherapy and medication management for eating disorder and comorbidities
  - Nutritional Therapy
    - Dietary planning, nutritional rehabilitation, normalized eating patterns
  - Family Support
    - Education and involvement of family members in treatment process

- Optimal management includes integration of mental health, nutrition, and primary care. A treatment agreement establishes goals and criteria for adjusting care intensity.

- Evidence-Based Psychotherapies
  - First-Line Treatments
    - CBT is first-line for bulimia and binge eating disorder
  - Alternative Approaches
    - IPT, DBT, and family-based therapy are effective alternatives
  - Self-Help Options
    - Guided self-help with evidence-based manuals can be beneficial
  - Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have received the most research attention. Family-based therapy is effective for adolescents. Treatment choice depends on diagnosis, comorbidities, and patient preferences.

- GI Symptom Management in Eating Disorders
  - Common GI Symptoms & Constipation
    - Bloating, constipation, early satiety, nausea often due to restrictive eating or purging
    - Manage with osmotic agents, fiber, and addressing underlying ED
  - Delayed Gastric Emptying
    - Common in AN and during refeeding process
    - May persist despite weight normalization
    - Treatment: nutritional rehabilitation, possibly prokinetics, psychological support
  - GERD & Functional Symptoms
    - May require PPIs or H2 blockers if symptomatic
    - Most symptoms improve with weight restoration
    - Patient reassurance is important part of treatment
  - Serious Complications & Approach
    - Rare but critical: SMA syndrome, acute gastric dilation, rectal prolapse
    - Start with nutritional rehabilitation + psychotherapy

Abbreviations: AN, anorexia nervosa; ARFID, avoidant/restrictive food intake disorder; BED, binge-eating disorder; BMD, bone mineral density; BN, bulimia nervosa; CBT, cognitive behavioral therapy; DBT, dialectical behavior therapy; DEXA, dual-energy X-ray absorptiometry; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG, electrocardiogram; ED, eating disorder; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IPT, interpersonal therapy; PPI, proton pump inhibitor; SMA, superior mesenteric artery; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; USFED/OSFED, unspecified/other specified feeding or eating disorder.

DYSPEPSIA AND PEPTIC ULCER DISEASE

Pavithra Parthasarathy

❖ Dyspepsia

- Demography
  - 10-45% of general population have dyspepsia
  - Higher incidence
    - Women > men
    - Smokers
    - NSAID users;

- Definition
  - Difficult digestion (Greek dys + pepse)
  - Rome IV Consensus Committee definition:) symptoms that are considered to originate from the gastroduodenal region

- Symptoms
  - Anorexia
  - Belching
  - Early satiety
  - Epigastric burning
  - Epigastric pain
  - Heartburn
  - Nausea
  - Postprandial fullness
  - Regurgitation
  - Upper abdominal bloating
  - Vomiting
  - Affects quality of life, causes patients to be concerned for serious underlying disease

- Symptoms
  - Organic vs. functional
  - Uninvestigated (no esophagogastroduodenoscopy [EGD]) vs. investigated (EGD performed)

- Causes/Associations
  - Luminal GI Tract
    - Chronic gastric volvulus
    - Chronic gastric or intestinal ischemia
    - Food intolerance
    - Gastric infections
      - Cytomegalovirus (CMV) Infection
      - Fungus
      - Tuberculosis
      - Syphilis
    - Gastric or esophageal neoplasms
    - Gastroesophageal reflux

- Gastroparesis
  - Diabetes mellitus
  - Post-vagotomy
  - Scleroderma
  - Chronic intestinal pseudo-obstruction
  - Post-viral, idiopathic
  - Irritable bowel syndrome
- IBS
- Infiltrative gastric disorders
  - Ménétrier disease
  - Crohn disease
  - Eosinophilic gastroenteritis
  - Sarcoidosis
  - Amyloidosis
- Parasites
  - Giardia lamblia
  - Strongyloides stercoralisrom
- Peptic ulcer disease (PUD)

- Medications
  - Acarbose
  - Aspirin, other NSAIDs (including COX-2 selective agents)
  - Colchicine
  - Digitalis preparations
  - Estrogens
  - Ethanol
  - Gemfibrozil
  - Glucocorticoids
  - Iron
  - Levodopa
  - Narcotics
  - Niacin
  - Nitrates
  - Orlistat
  - Potassium chloride
  - Quinidine
  - Sildenafil
  - Theophylline

- Pancreaticobiliary Disorders
  - Biliary pain: cholelithiasis, choledocholithiasis, SOD
  - Chronic pancreatitis
  - Pancreatic neoplasms

- Systemic Conditions
  - Adrenal insufficiency
  - Diabetes mellitus
  - Heart failure
  - Hyperparathyroidism
  - Intra-abdominal malignancy
  - Myocardial ischemia
  - Pregnancy
  - Renal insufficiency
  - Thyroid disease

- **Functional Dyspepsia (FD)**
  - Rome IV
    - Early satiety
    - Postprandial fullness
    - Epigastric pain
    - Epigastric burning in the absence of organic
    - Systemic, or metabolic disease

    } Likely to explain the symptoms
  - Symptoms usually intermittent
  - Subtypes (use aggravation of symptoms with meals as a distinction
    - Postprandial distress syndrome (PDS)
    - Epigastric pain syndrome (EPS)
    - Impaired gastric emptying

➢ Pathophysiology

- ↓ gastric emptying
- ↓ gastric accommodation to food
- Visceral hypersensitivity
  - Some evidence of hypersensitivity to isobaric gastric distension
  - Duodenal hypersensitivity to lipids or acid
- Low-grade mucosal inflammation in the duodenum
  - ↑ duodenal mucosal mast cell and eosinophil counts
  - Most associated with early satiety
  - ↑ mucosal permeability
  - Altered expression of tight junction proteins
  - Neuronal changes
- Infection
  - H pylori infection
  - Post-infectious
- Pathogenic factors (genetic predisposition
  - G-protein beta polypeptide 3 gene
- Psychosocial factors
  - Symptom burden

➢ Approach to Patient with Dyspepsia

- History & physical
  - Distinguish EPS vs PDS
  - Assess for systemic disorder (e.g., DM, IBD)
  - Red flag symptoms
  - Medications
  - Physical examination findings

- Laboratory testing
  - No particular tests unless directed by history/physical
- Difficult to distinguish organic vs. functional
  - EGD if risk factors for organic cause, including age > 60 yr (rule out esophageal/gastric adenocarcinoma)
  - H pylori assessment
    - Active infection
      - Urea breath test (UBT)
      - Stool antigen
      - EGD mucosal biopsies
    - Exclude present/past H. pylori infection by finding negative serology
  - Empiric antisecretory therapy

➢ Treatment Algorithm

- EGD to rule out organic causes and treat as appropriate, in the right population
  - Caveat EGD is expensive and may still lead down same treatment algorithm
- Test and treat H pylori (non-invasive)
  - RCT evidence that it does not worsen GERD
- Empiric antisecretory therapy (H2RA, PPI)

- Dyspepsia Diagnostic and Treatment Pathway
  - Uninvestigated Dyspepsia
    - Empirical therapy:
      - "Test and treat"
      - Proton pump inhibitor (PPI)
      - Consider prokinetic agent
    - If no response → Endoscopy
  - Functional Dyspepsia (≈70%)
    - Postprandial Distress Syndrome
      - Prokinetic agent (can add PPI)
      - Acotiamide if available
      - 5-HT_1A agonist if early satiation
      - Mirtazapine if weight loss
      - If refractory:
        - Gastric emptying study
        - If delayed → Treat as gastroparesis
    - Epigastric Pain Syndrome
      - Eradicate if positive for Helicobacter pylori and not already treated
      - PPI therapy (consider adding prokinetic agent)
      - Amitriptyline or other tricyclic antidepressant (TCA)

        - If refractory:
            - Hypnotherapy and/or psychotherapy
            - Nutritional support
    - Organic Dyspepsia (≈30%)
        - Peptic ulcer
        - Esophagitis
        - Celiac disease
        - Giardiasis
        - Pancreatitis
        - Biliary disease
        - Other rare causes

➢ Treatment

- Acid suppression (H2RAs, PPI)
- Eradication of H pylori (prove eradication with repeat test for acute infection)
- Prokinetic agents
- Agents that improve gastric accommodation
    - Buspirone
    - 5HT1A agonist)
- Centrally-acting neuromodulators
    - Amitriptyline (improves gastric accommodation)
- Psychologic interventions (insufficient data)
- Lifestyle modifications
    - Dietary changes not studied rigorously
    - Certainly reasonable to exclude foods which they have found to be bothersome

- **Peptic Ulcer Disease** (PUD)

➢ Definition

- Ulcer
    - EGD ≥ 5mm break in mucosal lining with appreciable depth at endoscopy, or
    - Histologic evidence of submucosal extension
- Erosion: ≤ 5mm break, limited to mucosa
- "Peptic" when ulcer/erosion in stomach/duodenum is ultimately due to action of proteolytic enzyme pepsin at acidic pH
- Complications of bleeding, obstruction, perforation and ulcer perforation
- ↑ symptoms/ ↑ complications of " two kit" etiology, e.g., NSAIDs use plus H. pylori infection

- Pathophysiology
  - Defensive factors
    - Mucosal integrity depends on a delicate balance between aggressive and defensive factors. When mucosal defense mechanisms are overwhelmed, ulceration may occur.
  - Aggressive factors
    - Lumen
      - Bile acids
      - Mucus
      - Pancreas enzymes
    - Wall
      - Growth factors
      - H_2S
      - HCO_3^-
      - Lipid-protein membrane (phospholipids)
      - Muscle (emptying) activity
      - Regulatory peptides
      - ROS
      - Tight junctions

Abbreviations: CA, carbonic anhydrase; CGRP, calcitonin gene-related peptide; H2S, hydrogen sulfide; HCO_3^-, bicarbonate; NO, nitric oxide; ROS, reactive oxygen species.

  - H pylori
    - Antrum-predominant gastritis
      - ↑ gastric acid secretion → duodenal ulcers, and gastric metaplasia in duodenal bulb → focal duodenitis → erosion → ulceration
    - Pan-gastritis
      - ↓ mucosal defense predisposes to gastric ulceration
  - NSAIDs
    - Damage mucosa via
      - ↓ mucus
      - ↓ phospholipids
      - Damaged cell membranes
      - Uncoupling mitochondrial oxidative phosphorylation
      - ↓ prostaglandin synthesis (COX-1)

- Other Ulcer Etiologies
  - Drugs
    - Bisphosphonates
    - Cocaine and methamphetamine (mucosal ischemia)
    - Glucocorticoids + NSAIDs / COXIBs
  - ↑ H^+
    - Zollinger-Ellison syndrome (SES); ↑↑gastrin → ↑↑ H^+)
    - Systemic mastocytosis (↑↑ histamine → ↑↑ H^+)

- Association
  - Alpha-1-antitrypsin deficiency, COPD, CKD
  - ↑ Alcohol
  - Chronic liver disease
  - Psychological
  - Type A personality
  - Smoking
  - Stress
  - Chronic obstructive pulmonary disease (COPD)
  - Chronic kidney disease (CKD)
  - Alcohol-related disorder (ARD)
  - Idiopathic

- Features
  - Symptoms
    - Epigastric pain/discomfort associated with
      - Hunger
      - Occurring at night
      - Relieved by food/antacids
    - Some definitions of dyspepsia include heartburn (GERD)

- Diagnosis
  - EGD first line for first/second line diagnosis, (much superior to UGI series with barium)
    - Biopsy gastric mucosa to rule out H pylori
    - Biopsy edge of gastric ulcers (risk of gastric cancer)
    - Gastric ulcers (GU): repeat EGD in 8 weeks to confirm healing - up to 4% of biopsy-benign GU are found to be malignant at a later time
  - H pylori test-and-treat; part of dyspepsia workup
  - Alarms (↑ risk of malignancy)
    - Patient
      - > 60 yr
      - Anemia/bleeding (unexplained)
      - Dysphagia
      - Vomiting, chronic/unexplained
      - Weight loss, unexplained
    - Family
      - History of esophageal / gastric cancer
    - These features should prompt EGD and often other testing to establish a definitive diagnosis

- Treatment
  - Acid suppression
    - Antacids
    - Antisecretory agents
      - H2Ras
      - PPIs
      - Potassium-competitive acid blocker
  - Mucosal protective agents
    - Sucralfate (sulfate anions bind to positively-charged proteins in damaged tissue
    - Bismuth
  - H pylori treatment, and proven eradiation
  - Treatment of
    - Underlying cause, if relevant
    - Contributing factors
      - Alcohol overuse
      - Drugs: ASA, NSAIDs, COXIBs
      - Smoking
  - Lifestyle modifications
    - Particularly if dyspepsia due to GERD

Abbreviations: AN, anorexia nervosa; ARFID, avoidant/restrictive food intake disorder; BED, binge-eating disorder; BMD, bone mineral density; BN, bulimia nervosa; CBT, cognitive behavioral therapy; DBT, dialectical behavior therapy; DEXA, dual-energy X-ray absorptiometry; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG, electrocardiogram; ED, eating disorder; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IPT, interpersonal therapy; PPI, proton pump inhibitor; SMA, superior mesenteric artery; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; USFED/OSFED, unspecified/other specified feeding or eating disorder.

Suggested Reading:

Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 11th ed. Philadelphia, PA: Elsevier; 2020, Chapter 14, 51, and 53.

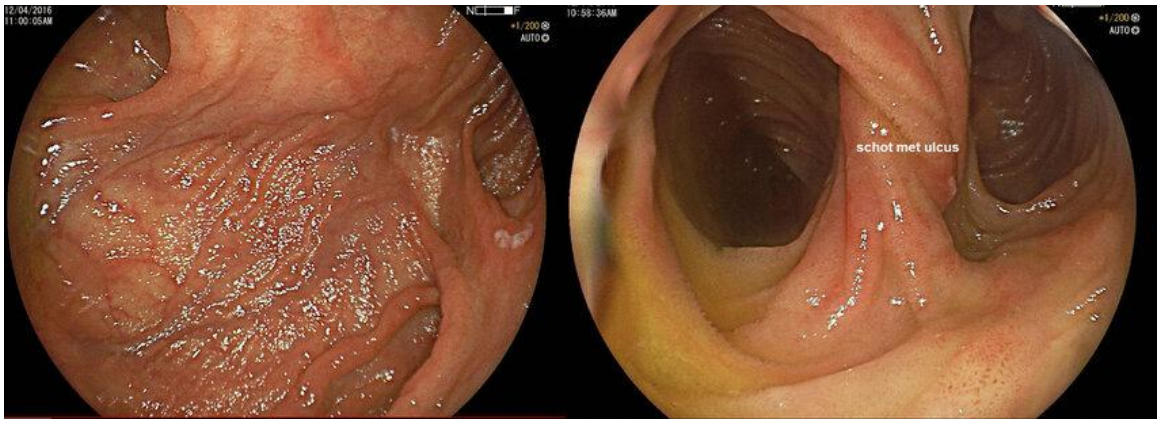
SMALL BOWEL

ILEAL POUCH DISORDERS

Abdulaziz Alajmi

- Anatomy

Ileal Pouch



  - Endoscopy in a pouch demonstrating intussuscepting septa surrounded by connecting openings
    - The tip of the J pouch
    - Owls' eyes appearance in the pouch body
    - Afferent limb
    - Anal transition zone leading to rectal cuff

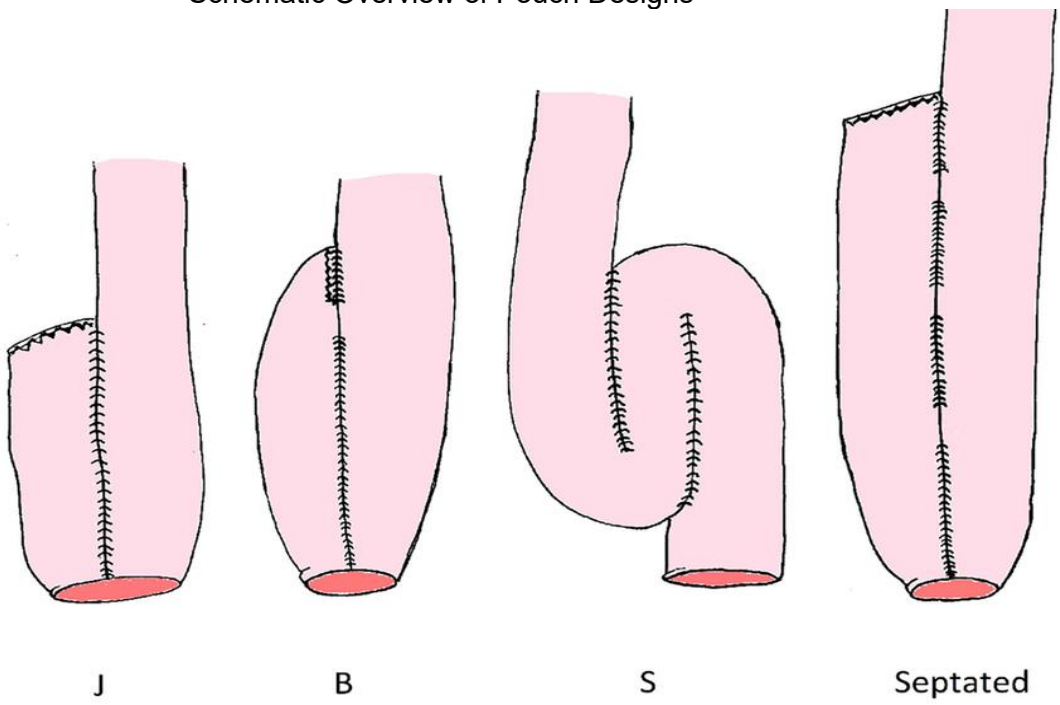
Courtesy of: Reijntjes MA, et al. Int J Colorectal Dis 2022; 37, 2491–2499.

- Indications
  - Ulcerative Colitis (UC)
  - Classic Familial Adenomatous Polyposis (FAP)
  - Colonic Crohn disease (CD) (although generally contra-indicated, IPAA can also be proposed in highly selected patients)

Ileal Pouch

- Variations

Schematic Overview of Pouch Designs



(a): J-pouch, (b): B-pouch, (c): S-pouch, (d) Septated pouch

Courtesy of: Reijntjes MA, et al. Int J Colorectal Dis 2022; 37, 2491–2499.

Ileal Pouch Anal Anastomosis (IPAA)

- Long term Functional Outcome of IPAA
  - Bowel regulating medication may be helpful
  - Bowel movements/24 hr vary widely
  - Bowel movements during night time
    - Vary widely (usually at least once a wk)
    - Never, 14%
  - Delay of bowel movement vary widely
    - <15 min
    - <30 min
    - 30 min

- Fecal incontinence
  - Daytime
    - Never or seldom
    - Sometimes – 25 (13%)
    - Frequently – 12 (6.5%)
  - Nighttime – 72 (39%)
- Functional score (median/IQR)
  - OS – 6 (4–8)
  - PFS – 6 (3–11)

van Overstraeten, Ade B, et al. J Crohn and Colitis 2014; 8: 1261-1266.

➢ Classifications

Inflammatory	Postsurgical	Functional	Neoplastic
Idiopathic Pouchitis	Leak	Irritable Pouch Syndrome	Dysplasia or cancer of pouch
CD of the pouch	Pelvic abscess		Dysplasia or cancer of anal transition zone
PSC-associated	Pouch sinus	Dyssynergic defecation	
Ischemic	Pouch fistula		
Infectious	Stricture		
Cuffitis			

Quinn KP, et al. Inflamm Bowel Dis 2019; 25(3): 460-471

➢ Pathogenesis

- Inherited
  - Genetic susceptibility
- Infection
  - Microbiota
    - Colonic type composition
    - Dysbiosis
    - Sulfate-reducing bacteria

- Inflammation
  - Mucosal immune response
    - Innate: dendritic cells
    - Adaptive
    - Increased mucosal permeability
- Ischemia
  - Mechanical factors
    - Ischemia
- Mucosal adaptation
- Colonic metaplasia

➢ Clinical

- ↑ stool frequency
- Urgency/ Incontinence
- Hematochezia
- Abdominal pain
- Perianal pain
- Notes
  - Symptoms alone **not** sufficient to make a definitive diagnosis

➢ Laboratory tests

- Blood
  - Hemoglobin, white blood cell count
  - C-reactive protein (CRP)
  - Liver enzymes
  - Celiac serologies
  - Stool
    - Culture/ sensitivity, ova/parasites (O/P), C. difficile ELISA / PCR testing
  - Iron studies
  - Vitamin B12 and D

➢ Diagnostic Imaging

- CT/MR enterography
- Pelvic MRI
- Water-soluble contrast pouchogram

- Defecography
  - Barium
  - MRI

➢ Functional Assessment

- MR defecography
  - Barium
  - MR
- Barium defecography
- Anorectal manometry
- Balloon expulsion test

➢ Endoscopy

- The mainstay of pouch evaluation
- Most helpful in suspected inflammatory, mechanical, and dysplastic pouch disorders
- Important to correctly identify pouch landmarks (afferent limb and pouch inlet, tip of the J, efferent limb, pouch outlet, and rectal cuff)
- Histologic evaluation of biopsies provides further information regarding presence of granulomas, viral inclusion bodies, and dysplasia

Idiopathic Pouchitis

➢ Types of Pouchitis

❖ Structural Disorders

- **Idiopathic**
  - Most common
  - Up to 80% will have an episode of idiopathic pouchitis (UC patients)
  - Recurrence is common

- Treatment (Acute Idiopathic Pouchitis)
  - Typically responds to antibiotics
  - Metronidazole, Ciprofloxacin, Tinidazole, and Rifaximin
    - First line: 2 wk of
      - Metronidazole (15-20 mg/kg/d) or
      - Ciprofloxacin (1g/d)
    - Doses
      - Tinidazole: 500 mg every 12 hours
      - Rifaximin: 550 mg every 12 hours

Agent	Duration	Outcome
Metronidazole 1.4 g/d vs placebo	1 wk	↓ in stool frequency, more in study group than in placebo
Rifaximin 1.2 g/d vs placebo	4 wk	Remission in 25% of study group; 0% in control (P = .206)
Ciprofloxacin 1 g/d vs metronidazole 20 mg/kg/d	2 wk	↓ in PDAI score: ciprofloxacin −6.7; metronidazole −5.9

  - Recurrence
    - Repeat Antibiotics
    - Rifaximin
    - Probiotics

- **Crohn Disease (CD) of a Pouch**
  - De novo CD is the most common
  - May be diagnosed in colectomy specimens in patients with preoperative diagnosis of UC or Indeterminate colitis
  - Type of CD
    - Inflammatory
    - Fibrostenotic
    - Fistulizing
  - Endoscopy features
    - Mucosal ulcerations
    - Fistulae
    - Strictures (afferent limb)

- **Primary Sclerosing Cholangitis (PSC)-Associated Pouchitis**
  - ↑ risk of developing pouchitis
  - Distinct clinical phenotype
  - Endoscopic
    - Long-segment inflammation of afferent limb
- **Ischemic Pouchitis**
  - Caused by tension on mesenteric vessels
  - More common
    - Males
      - Weight gain
  - Less common
    - In S pouch
  - Endoscopic features
    - Asymmetric distribution of inflammation, plus sharp demarcation
- **Infectious Pouchitis**
  - Common
    - C. difficile and CMV
  - Uncommon
    - Campylobacter
    - Salmonella
    - Candida
  - Consider testing in patients with recurrent/chronic pouchitis)
  - Endoscopy: nonspecific/pseudomembranes

➢ Treatment

- Antibiotic combinations
- Rule out secondary causes
  - C. difficile → vancomycin / FMT transplant for refractory
  - CD of the pouch → CD management
  - CMV pouchitis → ganciclovir
  - Cuffitis → topical 5-ASA / topical steroids
  - IPS → diet modification, anti-diarrhea agents, tricyclic antidepressants (TCA)
  - Ischemic pouchitis → allopurinol
  - NSAIDs associated → Stop NSAIDs – use selective COX-2 inhibitors
  - PSC-associated → steroids / immunomodulators / anti-TNF agents

Zezos P and Saibil F. World J Gastroenterol 2015; 21(29): 8739-8752

- Anti-TNF and Anti-Integrin
  - Clinically relevant remission
    - Infliximab, ~42%
    - Adalimumab, ~38%
    - Vedolizumab, ~58%

Adapted from: Verstockt B, et al. United European Gastroenterol J 2019;7(9):1215-1225.

- Vedolizumab

Time, mon	Response	Remission
3	40%	12%
6	42%	18%
12	28%	18%

- Ustekinumab for CARP
  - Retrospective study of UC patients with IPAA, who developed CARP and received Ustekinumab
    - CD of the pouch was excluded
    - 24 patients included
    - 12 patients (50%) had a clinical response

- Prophylaxis (probiotics, RCTs)
  - Primary

Agent	Duration	Outcome
Probiotics 3 g/d vs placebo	12 mon	Pouchitis in 10% of study group; 40% in placebo ($P < .05$)

  - Secondary

Agent	Duration	Outcome
Probiotics 6 g/d vs placebo	9 mon	Relapse in 15% of study group; 100% in placebo ($P < .001$)
Probiotics 6 g/d vs placebo	Up to 1 y	Relapse in 15% of study group; 94% placebo ($P < .0001$)

- **Cuffitis**
  - Recurrence of UC in the residual cuff of rectal mucosa after IPAA
  - Symptoms overlap with pouchitis
  - Bleeding more common
  - Endoscopy
    - Inflamed residual rectal mucosa

➢ Treatment

  - Similar to treatment of ulcerative proctitis
    - Topical 5-ASA or topical steroids
  - Cuffitis refractory to topical treatment
    - Suspected to other perianal and peri-pouch diseases

➢ Postoperative Complications

- Leaks, sinus, fistulae
  - Common site of postoperative complications include:
    - Leaks at the posterior pouch-anal anastomosis or tip of J
    - Sinuses at the pouch-anal anastomosis that extend into the pre-sacral space forming an abscess
    - Pouch-vaginal fistulae

Quinn KR, et al. Inflamm Bowel Dis 2019; 25(3): 460-471

- Strictures
  - Common, up to 16%
  - Arise from
  - Most common in pouch-anal anastomosis (PAA)
  - Cause/Associations
    - Anastomotic tension
    - CD of the pouch
    - Ischemia
    - NSAIDs
    - Pelvic sepsis

- Pouch Dysplasia and Neoplasia
  - Develop in
    - Anal transition zone, and
    - Ileoanal pouch
  - Adenocarcinoma is the most common
  - Two-thirds at the anal transition zone

- **Irritable Pouch Syndrome** (IPS)
  - Diagnosis of exclusion
  - Clinical
    - ↑ bowel movement frequency with change in consistency,
      · abdominal perianal/pelvis/pain discomfort in absence of a structural or inflammatory pouch disorder
  - Dyssynergic defecation
    - May develop from maladaptive learning because of
      - The voluntary holding of stool, and
      - Recurrent recruitment of pelvic floor muscles in the setting of frequent defecation
  - Symptoms of Pouch Dysfunction
    - Increased stool frequency
    - Urgency
    - Tenesmus
    - Abdominal/pelvic pain
    - Hematochezia
  - Diagnostic Step
    - Pouchoscopy ± biopsy
  - Inflammation Present?
    - **No**
      - Assess for symptoms of pouch evacuation disorder:
        - Straining
        - Incomplete evacuation
        - Manual maneuvers to facilitate defecation
      - If no evacuation disorder symptoms:
        - Testing:
          - CT or MR enterography
          - ± Pelvic MRI
        - Results:
          - No structural abnormality → Irritable Pouch Syndrome
          - Structural abnormality → Mechanical/post-surgical complication

        - If evacuation disorder symptoms present:
            - Testing:
                - Anorectal manometry (ARM) and balloon expulsion test (BET)
                - ± MR defecography
            - Results:
                - Abnormal → Pouch evacuation disorder
                    - Treatment: Biofeedback therapy
                - Normal → Antibiotic-responsive
                    - Treatment: Repeat antibiotic course if symptoms recur
    - **Yes**
        - Cuffitis
            - Treatment: Topical 5-ASA or corticosteroid
        - Pouchitis
            - Treatment: Oral ciprofloxacin or metronidazole for 2–4 weeks
            - If antibiotic-dependent or refractory:
                - Exclude secondary causes:
                    - Clinical: NSAID use
                    - Laboratory: Celiac serologies, liver enzymes, stool studies for Clostridioides difficile infection
                    - Imaging: CT/MR enterography, pelvic MRI
                    - Functional testing: ARM, BET, MR defecography
                    - Repeat pouchoscopy: Assess for Crohn disease of the pouch, ischemia
                    - Histology: Evaluate for CMV, granulomas

Abbreviations: ARM: anorectal manometry; BET: balloon expulsion testing

Adapted from: Quinn KP, et al. Inflamm Bowel Dis. 2019;25(3):460–471.

- Classification of Pouchitis
    - Site/type (structural, functional, complications)
    - Duration of symptoms
        - Acute: < 4 wk
        - Chronic: > 4 wk
    - Response to antibiotic therapy
        - Antibiotic-responsive
        - Antibiotic-dependent
        - Antibiotic-refractory

- Summary
  - IPAA is the procedure of choice for medically refractory UC and FAP
  - Pouchitis represent a wide spectrum of diseases and conditions
  - Diagnosis of pouchitis need symptoms, imaging, and endoscopy evaluation
  - Secondary causes of pouchitis must be ruled out
  - Antibiotics are the mainstay treatment of idiopathic pouchitis
  - Biologics have a role for chronic antibiotic-refractory pouchitis

Abbreviations: ARM, anorectal manometry; BET, balloon expulsion test; CD, Crohn disease; CMV, cytomegalovirus; COX-2, cyclooxygenase-2; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; FAP, familial adenomatous polyposis; IQR, interquartile range; IPS, irritable pouch syndrome; IPAA, ileal pouch–anal anastomosis; JFT, jejunostomy feeding tube; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; O/P, ova and parasites; OS, overall score; PAA, pouch-anal anastomosis; PFS, pouch functional score; PSC, primary sclerosing cholangitis; RCT, randomized controlled trial; TNF, tumour necrosis factor; UC, ulcerative colitis; WBC, white blood cell.

CELIAC DISEASE HISTOPATHOLOGY: MARSH CLASSIFICATION

Pavithra Parthasarathy

- Introduction
  - Celiac Disease (CD) is an immune-mediated disorder characterized by inflammation of the small intestine that occurs in genetically predisposed individuals after gluten ingestion.
  - Duodenal biopsy is still considered the gold standard for diagnosis of CD.
  - The Marsh classification (1992) was designed to characterize the spectrum of small intestinal mucosa architectural changes seen in CD.
  - Oberhuber published a modified scheme in 1999 termed the Marsh-Oberhuber classification (or Marsh modified).
  - This is widely used by some pathologists today.
    - Drawback
      - Does not correlate well with symptom response

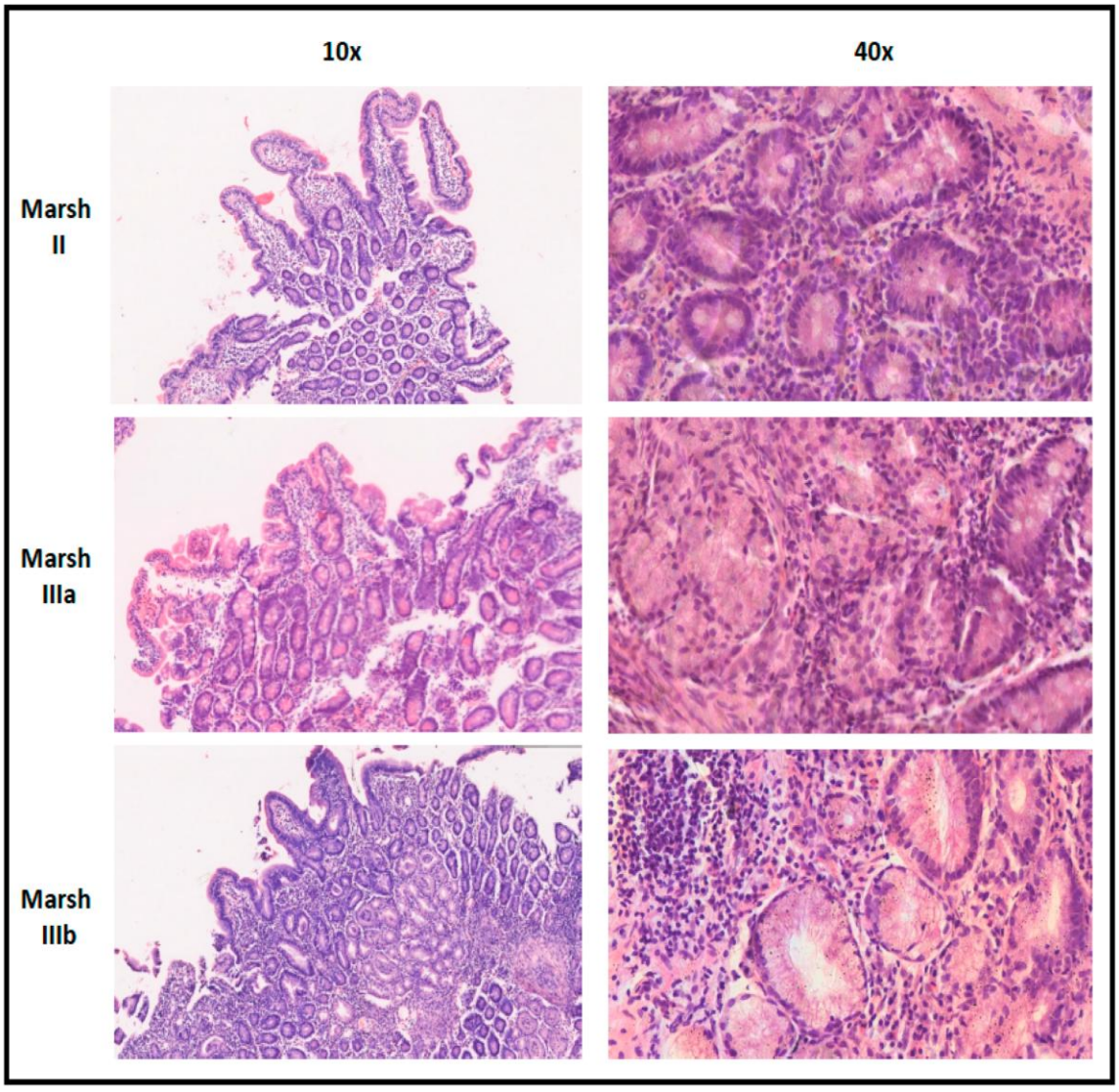
- Normal small intestine
  - Normal slender finger-like villi lined by epithelial cells and containing crypts in between
  - Villous length to crypt length ratio: 3–5:1
  - No increased intraepithelial lymphocytes (IELs)
  - Lymphocytes are higher in the base of villi than the tip (decrescendo pattern)

- Histopathology
  - Diagnosis of celiac disease involves confirmation of histopathologic findings
    - Duodenal biopsy is the “gold standard”
  - Histology findings include small intestinal mucosal lesions associated with gluten sensitivity
  - Marsh classification first published in 1992
    - 5 stages which were classified as:
      - Type 0: Pre-Infiltrative (Normal Mucosa)
      - Type 1: Infiltrative (Increased number of Intraepithelial lymphocytes (IEL)
      - Type 2: Hyperplastic (Crypt hyperplasia and increased number of IELs)
      - Type 3: Destructive *(most common change seen in CD)* (Villous atrophy and increased number of IEL)
      - Type 4: Hypoplastic (Hypoplasia of villous architecture)

Lesion category	Marsh classification
Marsh 0	Preinfiltrative – normal mucosal and villous architecture
Marsh 1	Infiltrative – normal mucosal and villous architecture, prominent intraepithelial lymphocytes
Marsh II	Hyperplastic – same as "infiltrative" but also with enlarged crypts and increased crypt mitoses

Lesion category	Marsh classification
Marsh III	Destructive lesion – flat mucosa, complete loss of villi, lymphocyte infiltration, enlarged hyperplastic crypts
Marsh IV	Hypoplastic – total villous atrophy, normal intraepithelial lymphocyte count, believed to reflect severe malnutrition and be nonspecific

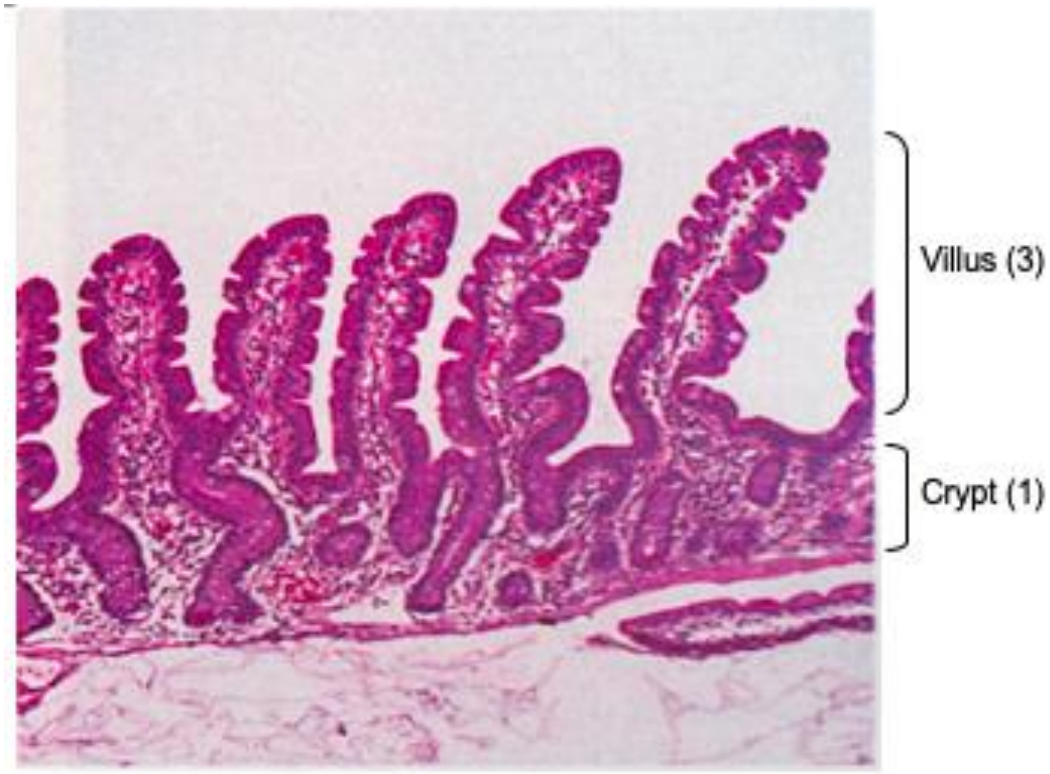
Marsh Classification of Celiac Disease



Courtesy of: Kamilova AT, et al. Diagnostics. 2023; 13(19):3066.

Pathology Slide Examples

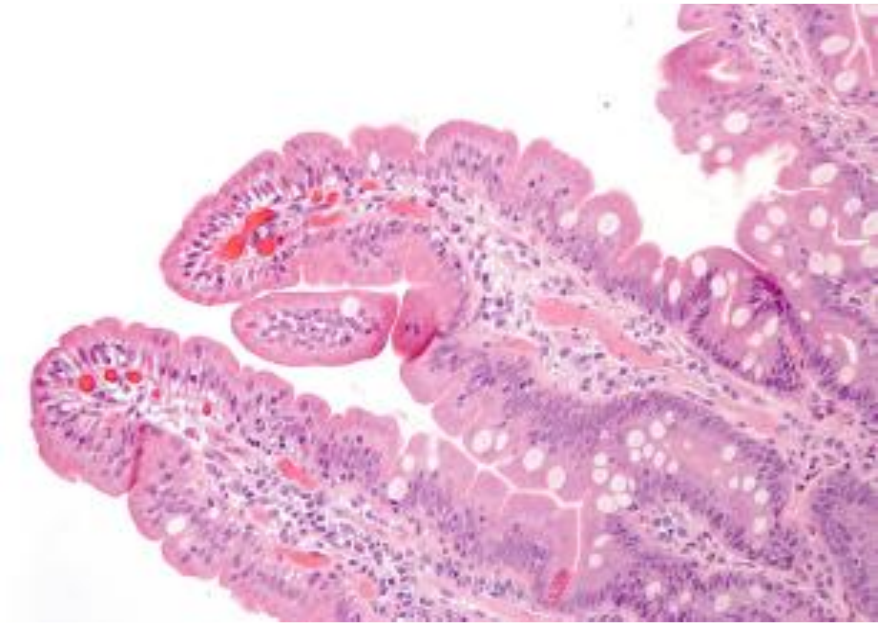
- Marsh stage 0: Normal mucosa



  - Long villi with villous:crypt ratio 3:1
  - Normal number of IELs

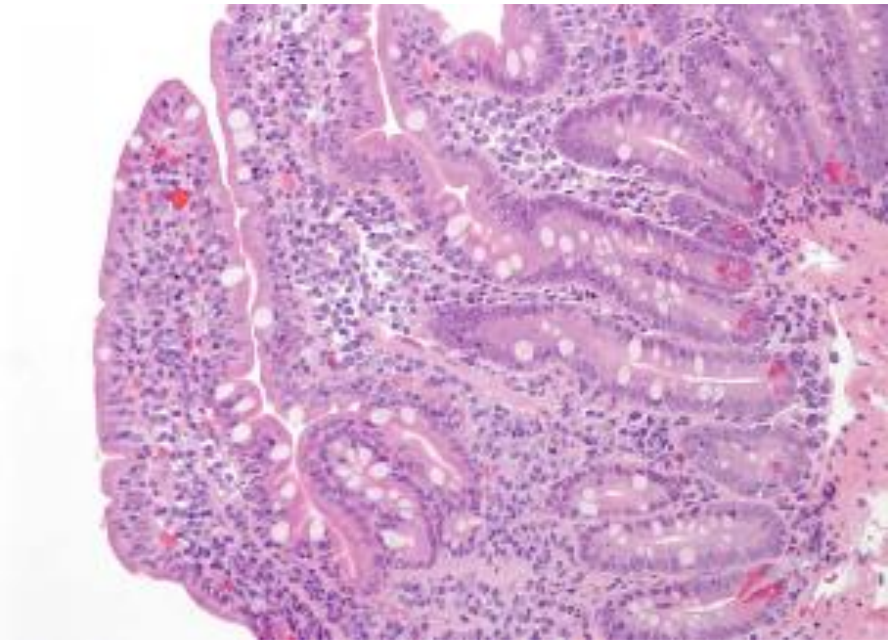
Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 1; 2021. ISBN: 9798719829074.

- Marsh Stage 1: Normal Architecture but Increased IELs



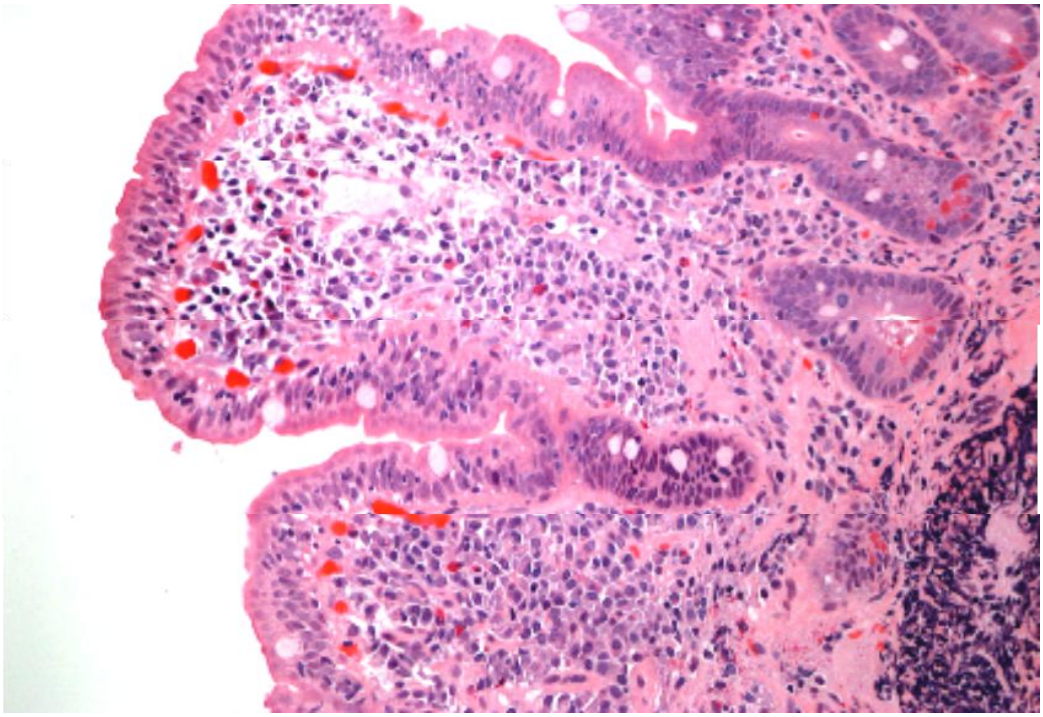
Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 1; 2021. ISBN: 9798719829074.

- Marsh Stage 2: Crypt Hyperplasia



Courtesy of: Dr. Aducio Thiesen, University of Alberta

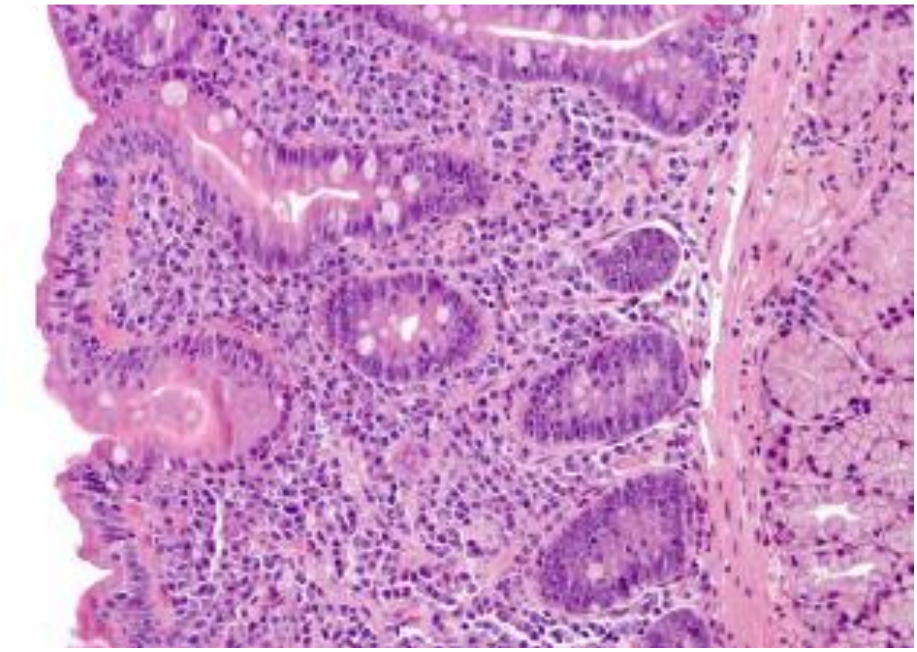
- Marsh Stage 3B: Subtotal Villous Atrophy



  - Villi markedly shortened, but not completely absent.
  - Crypts hyperplastic (elongated).
  - Intraepithelial lymphocytes (IELs) increased (>30 IELs per 100 enterocytes).

Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 1; 2021. ISBN: 9798719829074.

- Marsh Stage 3C: Total Villous Atrophy



  - Complete villous atrophy
  - Increased IELs
  - Crypt hyperplasia

Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 1; 2021. ISBN: 9798719829074.

  - Marsh-Oberhuber (modified Marsh) classification published in 1999

Marsh type	IEL/100 enterocytes: jejunum	IEL/100 enterocytes: duodenum	Crypt hyperplasia	Villi
0	<40	<30	Normal	Normal
1	≥40	>30		
2	≥40	>30	Increased	Mild atrophy
3a	≥40 (classical CD)			Marked atrophy
3b	≥40			Complete atrophy
3c	≥40		Atrophic	Severe (flat)
4	≥40			

  - Simplified classification systems proposed after 2005

- Clinical correlation
  - Type 0: Normal – celiac disease highly unlikely
  - Type 1: Not specific for celiac disease
    - Seen in patients on gluten-free diet
    - Seen in patients with dermatitis herpetiformis
    - Seen in family members of celiac disease patients
  - Type 2: Very rare
    - Occasionally seen in dermatitis herpetiformis (DH)
  - Type 3: Spectrum of changes seen in symptomatic celiac disease
  - Type 4: Extremely rare
    - Found in patients with
      - Refractory sprue
      - Ulcerative jejunoileitis
      - Enteropathy-associated T cell lymphoma (EATL)

- **Marsh-Oberhuber classification (Marsh modified)**

Made 2 major changes to the original Marsh criteria:

- Further categorization of Marsh type 3 into different subgroups based on degree of villous atrophy
  - Type 3a: Mild villous atrophy
  - Type 3b: Marked villous atrophy
  - Type 3c: Total villous atrophy with completely flat mucosa
- Addition of a numerical cut-off for intraepithelial lymphocytes (IEL)
  - >40 IEL/100 epithelial cells

- **Marsh-Oberhuber Classification**

5 stage classification similar to Marsh

- Type 0: Normal villous and crypt architecture with < 40 IEL/100 EC
- Type 1: Normal villous and crypt architecture with ≥40 IEL/100 EC
- Type 2: Normal villous architecture with Crypt hyperplasia and ≥40 IEL/100 EC
- Type 3 Subcategories
  - Type 3a: Mild villous atrophy with villous to crypt ratio of 3:1 or 2:1, and an increased number of IELs (≥40 IELs per 100 EC)
  - Type 3b: Marked villous atrophy with villous to crypt ratio of 1:1, and an increased number of IELs (≥40 IELs per 100 EC)
  - Type 3c: Total villous atrophy with completely flat mucosa and an increased number of IELs (≥40 IELs per 100 EC)

- Type 4: Flat mucosa with complete villous atrophy, few crypts visualized and near normal number of IEL

- **Corazza-Villanacci Classification**
  - Proposed in 2005 as simpler alternative with higher intra-observer reliability compared to both Marsh and Marsh-Oberhuber classifications
  - Mucosal lesions of celiac disease divided into 2 categories only:
    - Type A: Non-Atrophic lesion
      - Normal villous-crypt architecture
      - Increased IELs (>25/100 EC)
    - Type B: Atrophic lesion (Abnormal villous-crypt architecture)
      - B1: Atrophic with villi present but extremely distorted and increased IELs (>25/100 EC)
      - B2: Atrophic and flat, villi no longer detectable and increased IELs (>25/100 EC)
  - IEL cut off was lowered to >25 based on literature that it represents upper limit of normal in duodenum compared to both Marsh classifications which were based on jejunal samples

Comparative Classification Systems

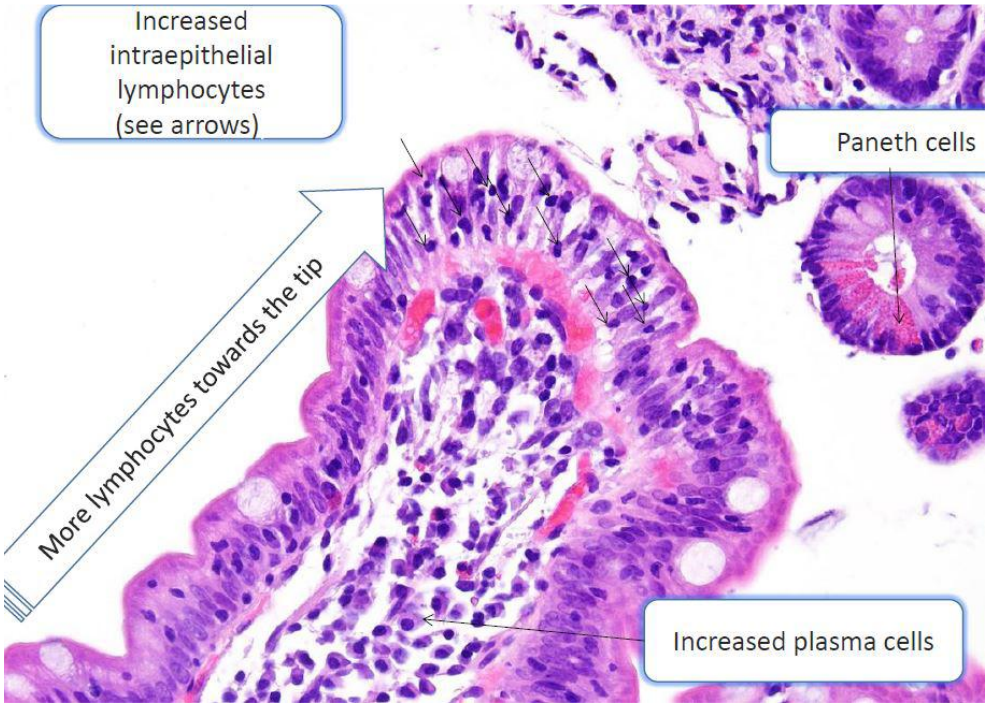
Marsh 1992	Oberhuber et al. 1999	Corazza & Villanacci 2005	Ensari 2010
Type 1	Type 1	Grade A	Type 1
Type 2	Type 2 Type 3a Type 3b	Grade B1	Type 2
Type 3	Type 3c	Grade B2	Type 3

- **Intraepithelial lymphocytes**

➢ **Definition**

- Intraepithelial lymphocytes (IELs) are CD3/CD8 positive T cell lymphocytes within the luminal gut mucosa
- ↑ IELs can follow local or systemic immune activation
- Measured in context of 100 epithelial cells for celiac disease and typically measured from tip of villi
  - Reported as number of IEL/100 epithelial cells (EC)
  - Normal small intestine mucosa has ≤ 40 IEL/100 EC

Celiac Disease: Marsh Classification



Marsh modified (Oberhuber)	Increased intraepithelial lymphocytes (IEL)	Crypt hyperplasia	Villous atrophy	Corazza
Type 0	No	No		None
Type 1			No	Grade A
Type 2				Grade A
Type 3a	Yes	Yes	Yes (partial)	Grade B1
Type 3b			Yes (subtotal)	Grade B1
Type 3c			Yes (total)	Grade B2

Thresholds:

- Marsh modified (Oberhuber): >40 IEL/100 enterocytes
- Corazza: >25 IEL/100 enterocytes

Type	Villous architecture	Crypt height	Intraepithelial lymphocytosis/EC	Diagnostic of CD
Type 0	Normal	Normal	<40 IEL/100 EC	No
Type 1				
Type 2		Crypt hyperplasia		—
Type 3A	Mild villous flattening	Increased height	>40 IEL/100 EC	Yes
Type 3B	Marked villous flattening			
Type 3C	Total villous flattening (flat mucosa)			

- Causes of Proximal Small Intestinal Intraepithelial Lymphocytosis With Normal Villus Architecture
  - Gluten sensitivity (most common associations: gluten sensitivity, infections, NSAIDs)
  - Nongluten food hypersensitivity (e.g., cereals, cow's milk, soy products, fish, rice, and chicken)
  - Infections (viral enteritis, Giardia, Cryptosporidia, Helicobacter pylori)
  - Bacterial overgrowth (small intestinal bacterial overgrowth – SIBO)
  - Iatrogenic
    - Drugs (e.g., NSAIDs)
  - Immune
    - Dysregulation (e.g., Hashimoto thyroiditis, rheumatoid arthritis, SLE, autoimmune enteropathy)
    - Deficiency (e.g., IgA deficiency, CVID)
    - Inflammatory bowel disease
    - Lymphocytic and collagenous colitis

Abbreviations: CVID, common variable immunodeficiency; IgA, immunoglobulin A; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus

- Biopsy collection
  - Important to collect adequate number of specimens from appropriate locations during upper endoscopy to increase yield of celiac disease diagnosis
  - False negative diagnosis rate as high as 30% due to issues with specimen retrieval
  - ACG guidelines (2013) recommend 1 to 2 biopsies from the duodenal bulb (since isolated CD changes are only seen at this site in 10% of patients) and at least 4 biopsies from D2

Abbreviations: ACG, American College of Gastroenterology; CD, celiac disease; CVID, common variable immunodeficiency; DH, dermatitis herpetiformis; EC, epithelial cells; EATL, enteropathy-associated T-cell lymphoma; IEL, intraepithelial lymphocyte; IgA, immunoglobulin A; NSAID, non-steroidal anti-inflammatory drug; SIBO, small intestinal bacterial overgrowth; SLE, systemic lupus erythematosus.

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EUROPEAN CROHN AND COLITIS GUIDELINES ON SEXUALITY, FERTILITY, PREGNANCY, AND LACTATION

Abdulaziz Alsihle

Background

- IBD often affects young adults during reproductive years.
- Diagnosis raises concerns about:
  - Fertility and pregnancy outcomes
  - Sexual health and heritability
  - Medication safety and disease activity
- These factors can influence family planning decisions.
- Effective management requires specialised counselling and multidisciplinary care.
- The ECCO Consensus provides updated guidance on preconception, pregnancy, and postpartum management in IBD.

Sections

- Sexuality, fertility, and counselling patients with IBD considering starting a family
  - Sexual dysfunction in patients with IBD
  - Contraception in IBD
  - The impact of paternal or maternal IBD on the risk of IBD in the offspring
  - Pre-conception counselling in patients with IBD who want to become pregnant
  - Voluntary childlessness in IBD
  - Fertility in IBD
- Management of IBD during pregnancy
- The impact of IBD on pregnancy and the baby's outcomes
- Management of IBD postpartum, including the lactation period

Sexuality, Contraception, Counselling, and Fertility in IBD

- **Sexual dysfunction in patients with IBD**

➢ Definition

- Disturbance of physical, emotional, or psychological sexual health
- More common in IBD due to:
  - Active disease and flares
  - Fatigue, pain, perianal disease
  - Psychosocial factors (depression, body image)
  - Medication side effects

Torres J, J Crohn and Colitis 2023; 17(1); 1–27

- Findings
  - ↓ erectile/sexual function, especially in active disease
  - ↓ sexual quality of life; depression is key predictor
  - IMPACT study: 40% reported negative effects on intimate relationships

- Systematic review & meta-analysis:
  - ↑ Risk vs controls
  - Men: RR 1.41 (95% CI 1.09–1.81)
  - Women: RR 1.76 (95% CI 1.28–2.42)
  - ↑ risk groups:
    - Males <50 years
    - Females <40 years
  - Gender differences: greater impact in females, mainly Crohn's disease (Danish study).

Statement 1

- In patients with IBD there is an ↑ risk of sexual dysfunction, particularly in females and in those with active disease or perianal disease [EL3].

- Treatment
  - Medications
    - Steroids: may ↓ sexual function (weight gain, acne, hypertrichosis)
    - Methotrexate & Sulphasalazine: linked to erectile dysfunction (case reports)
    - Immunosuppressants & Biologics: no clear evidence
  - Surgery
    - Conflicting data
    - Some report no change or improvement after proctocolectomy with J-pouch
    - Others note nerve injury–related erectile dysfunction in males

- **Contraception in IBD**
  - Oral contraceptive agent (OCA) absorption mainly in small bowel
  - Efficacy not affected in mild UC or after ileostomy
  - Systematic review identified two pharmacokinetic studies in women with UC.
    - Circulating hormone levels after oral contraceptive use were similar between healthy controls and UC patients with mild disease or ileostomy post-proctocolectomy.
    - Suggests no alteration in OCA absorption in mild UC or after surgery, so no need for dose escalation.

- Possible ↓ efficacy in Crohn's disease with extensive small bowel disease or large resections.
- No ↑ risk of IBD flare or UC progression with OCA use.
  - Systematic review (5 cohort studies): No ↑ risk of IBD relapse in current or past oral contraceptive users vs. never-users (low study strength).
  - Swedish registry (n=6104 UC patients): OC use not linked to disease progression, surgery, or need for steroids/anti-TNF.
- No added thromboembolic risk in remission; however, assess risk carefully as IBD (especially active) is prothrombotic.

Statement 2

- The efficacy of oral contraceptives does not seem to be ↓ in women with IBD [EL5].
- Oral contraceptives do not seem to be associated with ↑ probability of IBD flares [EL2].
- Oral contraceptives are generally low-risk in women with IBD; nevertheless, a careful assessment of thrombotic risk is recommended before prescription [EL5].

- **Impact of Parental IBD on Offspring Risk**
  - 12–20% of IBD patients report a family history (strongest known risk factor).
  - Risk patterns
    - ↑ Risk in White and Ashkenazi Jewish populations.
    - CD risk in first-degree relatives (FDRs): ~8× higher.
    - UC risk in FDRs: ~4× higher.
  - Prevalence
    - In FDRs ~5% (CD) and 3% (UC).
    - Maternal transmission may pose a higher risk than paternal.
    - Both parents affected: offspring risk ≈ 30%.
    - Multiplex families (≥2 FDRs): up to 57-fold increased incidence.

Statement 3

- Paternal or maternal IBD increases the risk of IBD development for the offspring [EL3].
- The risk is greater for Crohn's disease (CD) and is much greater when both parents are affected [EL3].

- **Pre-conception Counselling in IBD**
  - Purpose
    - Discuss parental concerns, disease heritability, optimize health, and minimize risks.

- Assessment & Preparation:
  - Achieve disease remission before conception.
  - Check anaemia, deficiencies, and nutritional status.
  - Stop teratogenic medications.
  - Update cervical screening and vaccinations.
  - Address smoking, alcohol, opiates, recreational drugs.
  - Folic acid supplementation: 0.4–0.8 mg/day; 2 mg/day if on sulphasalazine.
- Impact of Disease Activity:
  - Active IBD: ↑ risk of preterm birth, low birthweight, SGA.
  - Remission: Outcomes similar to general population.
- Monitoring: Clinical, biomarkers, endoscopy/cross-sectional imaging, and drug levels if available.
- Education: Improves knowledge and promotes medication adherence during pregnancy.
- Impact of Pre-Conception Care in IBD
- Study: Compared 155 patients referred to pre-conception IBD clinic vs. 162 referred after pregnancy.
- Benefits of Pre-Conception Counselling:
  - Improved medication adherence
  - Increased smoking cessation
  - Reduced flares during pregnancy
  - Lowered risk of low birthweight (LBW) infants

Statement 4

- Pre-conception counselling in IBD is associated with improved pregnancy outcomes [EL3].
- Individuals with IBD who are planning pregnancy should undergo pre-pregnancy counselling to address parental concerns, to aim for disease remission, and to discuss medication use during pregnancy [EL5].

- **Voluntary Childlessness in IBD**
  - Patients with voluntary childlessness have lower pregnancy-specific IBD knowledge
  - Counselling all patients of childbearing age helps informed family planning decisions
  - Higher rates of voluntary childlessness in IBD vs controls (17–38% prevalence)

Statement 5

- Patients with IBD, particularly with Crohn's disease (CD), are more likely to choose voluntary childlessness than healthy controls [EL2].
- Lack of pregnancy-specific IBD knowledge may impact voluntary childlessness.
- Therefore, appropriate education on pregnancy and family planning for all patients with IBD of childbearing age is recommended [EL5].

- **Fertility in IBD**

- Impact of Disease Activity
  - Women: ↓ likelihood of having biological children due to:
    - Voluntary childlessness
    - Psychosocial factors related to disease
    - ↓ fertility after abdominal or pelvic surgery
  - Men
    - Active disease → more difficulties conceiving (45%, OR 2.62)
    - Remission → fewer difficulties (21%, OR 0.93)
    - Sperm motility improves with disease remission (28.4% → 37.4%)

Key Point: Achieving disease remission supports fertility in both men and women.

Statement 6

- Active disease is associated with ↓ fertility in women with IBD [EL3].
- Achieving clinical remission may ↑ the probability of successful conception.
- Active disease is also associated with ↓ fertility in men with IBD [EL4].

- Impact of IBD Drugs on Fertility
  - Mesalazine
    - Avoid phthalate-containing tablets → may affect sperm quality and urogenital development.
  - Sulphasalazine
    - Strong evidence of lower sperm count, ↓ motility (asthenozoospermia), and oligospermia.
    - Switch to mesalazine recommended for men planning conception.
  - Thiopurines
    - Observational studies show **no** concerns for male fertility.

- Methotrexate (MTX)
  - Systematic review shows no direct impact on sperm integrity or fertility.
- Anti-TNF agents
  - **No** effect on sperm motility or vitality.
  - Negligible excretion in semen.
  - Minor reduction in sperm DNA fragmentation after treatment is clinically irrelevant.
- Tofacitinib
  - Supratherapeutic doses affect female fertility in rats.
  - Therapeutic doses: **no** impact on male or female fertility, sperm motility, or concentration.
- Ozanimod
  - No effect on male or female fertility.

Key Point: Medication choice can influence male fertility; sulphasalazine should be avoided in men planning conception.

Statement 7

- Most of the commonly used IBD drugs have **no** demonstrated impact on fertility, in particular sperm quality [EL4].
- Sulphasalazine is associated with reversible oligospermia and asthenozoospermia [EL2].

- Impact of IBD Drugs on Fertility
  - Ileal pouch-anal anastomosis (IPAA)
    - 2–5× increased infertility risk, especially in the first-year post-surgery.
    - Fertility reduction more pronounced in women than men.
  - Other surgeries
    - Impact on fertility is unknown.
  - Laparoscopic IPAA
    - Lower infertility rates than open surgery, likely due to fewer pelvic adhesions.
  - Colectomy
    - **No** risk associated.

Key Point: Female fertility can be significantly affected by pelvic surgery; laparoscopic approaches are preferred when possible.

Statement 8

- IBD-related pelvic surgeries lead to decreased fertility and fecundity rates in women [EL2]. Laparoscopic surgical approaches may lower the risk of infertility [EL2]

- Fertility in IBD: In Vitro Fertilisation Treatment
  - Overall: IVF pregnancy and live-birth rates in UC and CD are similar to controls.
  - National study findings
    - UC: ↓ live-birth odds per embryo transfer (OR 0.73)
    - CD: **No** significant difference overall (OR 0.77)
  - Prior CD surgery: lowers live-birth rate
  - Corticosteroid use before IVF: no effect
  - UC with IPAA: 3× higher IVF use; live-birth rates similar to general IVF population
  - Favorable predictors of IVF
    - Younger age
    - Lower BMI (~22.5 vs 24 kg/m²)
  - Disease activity
    - **No** linked to IVF success (most patients in remission)

Statement 9

- In women who have had restorative proctocolectomy with IPAA for UC, IVF procedures are three times more likely than in women without restorative proctocolectomy. However, both groups have a similar probability of having a live birth after IVF [EL3]

Management of IBD During Pregnancy

- **Multidisciplinary Care in Pregnancy with IBD**
  - Team approach: gastroenterologist, obstetrician, pediatrician, psychologist, dietitian, surgeon as needed.
  - Patient education: improves medication adherence and outcomes.
  - Disease monitoring: adjust therapy promptly for flares.
  - Nutrition: ensure adequate weight gain; malnutrition → ↑ risk of poor fetal outcomes.
  - Psychological support: high risk of postpartum psychiatric disorders; early intervention recommended.
  - Ostomy care: ↑ risk of preterm birth, low birth weight, stoma complications (prolapse, hernia, obstruction).

- Perianal fistulizing disease: early discussion on mode of delivery—balance sphincter injury risk vs C-section risk.

- **Impact of Pregnancy on IBD Course**
  - Crohn disease
    - Disease course similar during and after pregnancy.
  - Ulcerative colitis
    - ↑ relapse risk during pregnancy and postpartum.
  - Pregnancy & CD surgery
    - Retrospective data: pregnancy → ↑ risk of surgical disease (OR 2.9).
  - IPAA
    - No effect on pregnancy outcomes.
  - Predictors of relapse
    - Active disease at conception
    - Prior flare in previous pregnancy
  - Relapse outcomes
    - ↑ hospitalization (14.7% vs 0%)
    - ↑ preterm delivery (32.4% vs 5.7%)
    - ↓ birthweight (3039 g vs 3300 g)
  - Meta-analysis
    - Active disease at conception → more likely active during pregnancy.

Statement 10

- Pregnancy may ↑ risk of relapse or worsening disease in patients with UC and complications in patients with CD, especially if disease is active at conception [EL3]. IBD remission before conception is recommended [EL2].

- **Monitoring IBD During Pregnancy**
  - Physiological changes in pregnancy affect labs
    - ↓ Hemoglobin and albumin
    - ↑ CRP (may rise even in normal pregnancy)
  - Systematic review
    - Hemoglobin, albumin, CRP show poor correlation with IBD activity in pregnancy.
    - Useful mainly to monitor trends, not single values.
  - Fecal calprotectin (FC)
    - Unaffected by pregnancy in healthy women.
    - Correlates with disease activity in IBD across all trimesters.
    - Supported by multiple studies and systematic review (7 studies).

- Best practice
  - Use fecal calprotectin with clinical assessment for disease monitoring during pregnancy.

Statement 11

- Fecal calprotectin can reliably monitor disease activity during pregnancy [EL2]. Some blood parameters, such as haemoglobin and CRP, are affected by pregnancy and may not be reliable, although trends can be helpful [EL5].

- Endoscopy
  - Registry study (n=3052 vs 1.59M controls): ↑ preterm birth, SGA, LBW; no ↑ congenital malformations or stillbirth.
  - IBD subgroup: ↑ preterm birth and LBW; no ↑ SGA, neonatal death, malformations.
  - Uncontrolled study (n=48 IBD): no hospitalizations or complications.
  - Recommendation: perform only if strongly indicated; keep brief, minimal sedation, left lateral position.
- Capsule endoscopy
  - Limited data; 2 cases uneventful; relative contraindication due to unknown EM effects.
- Imaging
  - MRI preferred; avoid gadolinium.
  - CT ≤50 mGy acceptable only if essential.
  - Intestinal ultrasound (IUS): accurate (Sn 74%, Sp 83%); feasible up to early 3rd trimester.

Statement 12

- During pregnancy, endoscopy can be performed when needed to guide clinical decision making [EL3].
- Do **not** do capsule endoscopy during pregnancy (considered a contraindication) [EL5].
- Ultrasonography [EL4] and MRI without the use of gadolinium [EL4] are radiation-free and are recommended instead of a CT scan [EL5].
- Therapeutic drug monitoring
  - Adalimumab: stable through pregnancy.
  - Infliximab: ↓ clearance in 2nd–3rd trimester → ↑ trough levels.

- **Monitoring and Managing Thromboembolic Complications During Pregnancy**
  - IBD and pregnancy both ↑ risk of venous thromboembolism (VTE) — highest during active disease.
  - Pre-conception: screen for additional VTE risk factors (obesity, smoking, immobility, prior VTE).
  - High-risk patients → initiate thromboprophylaxis.
  - Meta-analysis (17,636 IBD vs 11.2M controls):
    - Overall ↑ VTE risk during pregnancy: RR 2.13 (95% CI 1.78–2.66)
    - ↑ DVT risk: RR 2.73 (95% CI 1.78–2.66)
    - UC: RR 2.24; CD: RR 1.87
    - During flares: RR 7.81 (trend, wide CI)
    - Postpartum: RR 2.61 (UC 2.85; CD 1.69)
  - Management
    - LMWH = safe and preferred anticoagulant.
    - Avoid DOACs, fondaparinux, danaparoid during pregnancy.
    - Continue therapy for 3 mon and ≥6 wk postpartum when indicated.

Statement 13

- Pregnancy and IBD ↑ risk of VTE events [EL2]. VTE risk assessment should be performed before conception and during pregnancy, especially in patients with active disease [EL5]. LMWH is recommended after C-section, during hospital admission for disease flares, or when other risk factors of VTE are present [EL5].

- **Managing IBD Flares During Pregnancy**
  - Manage flares similarly to non-pregnant patients (ECCO 2023).
  - Treatment individualized by severity and gestational age.
  - Multidisciplinary care essential (GI, obstetrician, pediatrician, surgeon)
  - Therapeutic approach:
    - Preferred: Anti-TNF agents → effective & safer than prolonged corticosteroids.
    - Mild disease: Budesonide may be used (low systemic exposure, limited data).
    - Avoid: Methotrexate, JAK inhibitors, S1P modulators (contraindicated).
    - Thiopurines: Avoid initiation (slow onset, idiosyncratic toxicity).
    - Vedolizumab: Can be considered (limited evidence, combine with fast-acting therapy).
    - Cyclosporin: May be used for severe UC if anti-TNF unsuitable.
  - Evidence summary
    - Anti-TNF (Infliximab/Adalimumab): ~67% remission (Czech study).
    - Vedolizumab: All 3 patients in CONCEIVE achieved remission.

Statement 14

- A multidisciplinary team that includes an experienced gastroenterologist, obstetrician, and surgeon may be valuable in helping to optimise outcomes in pregnant women with a disease flare [EL5]. The choice of therapy for a flare during pregnancy should consider the severity of disease activity and the gestational age [EL5].

Statement 15

- Pregnant women experiencing a flare should be managed according to current guidelines for non-pregnant patients, with 5-ASA, steroids, ciclosporin, anti-TNF agents [EL4], ustekinumab, or vedolizumab [EL5].
- Initiating monotherapy with a thiopurine is generally not recommended due to the slow onset of action and the potential risk of adverse events [EL5].
  Currently, JAK inhibitors and S1P receptor modulators should be avoided during pregnancy [EL5].

Statement 16

- In case of a flare beyond gestational week 37, early delivery could be considered prior to initiation of medical therapy [EL5].

- **Surgery in Pregnant Women with IBD**
  - Data limited; most evidence predates biologics/minimally invasive surgery.
  - Systematic review (1950–2015, 86 cases):
    - Common indications: refractory UC, perforated small bowel (CD).
  - Modern data (ECCO CONFER, 44 cases):
    - 55% operated in 2nd trimester.
    - 27% postoperative complications.
    - 4 fetal losses (2 intraoperative, 2 post-op).
    - 42% of newborns required hospitalization (25% NICU).
  - Key point: Surgical risk may reflect disease severity rather than surgery itself — multidisciplinary planning essential.

Statement 17

- Indications for surgery in pregnant women with IBD are the same as for non-pregnant patients [EL5].
- The indication for IBD-related surgery during pregnancy should be determined promptly, based on IBD severity and general maternal conditions.
- Urgent surgery should be performed if clinically indicated, regardless of the gestational age [EL5].

- The surgical management should be discussed in a multidisciplinary team involving gastroenterologists, colorectal surgeons, obstetricians, and neonatal specialists, as required [EL5].

- **Drug Discontinuation During Pregnancy: Thiopurines**
  - Stopping vs continuing:
    - Discontinuing before/early pregnancy ↑ risk of preterm birth (OR 6.56 vs 2.15).
  - Relapse risk:
    - Monotherapy withdrawal → higher relapse.
    - Combination therapy withdrawal (with biologic) → no significant relapse up to 2 years.
    - Discontinuation may ↓ anti-TNF trough levels — check before stopping.
  - Pharmacokinetic changes
    - Pregnancy causes ↓ 6-TGN and ↑ 6-MMP by 2nd trimester → potential hepatotoxicity.
    - Monitor thiopurine metabolites and LFTs each trimester.

Key takeaway: Continue thiopurines; monitor metabolites and anti-TNF levels to maintain remission and prevent adverse outcomes.

Statement 18

- Patients on thiopurine monotherapy can continue treatment throughout pregnancy [EL5]. When thiopurines are used as combination therapy with biologics, thiopurine discontinuation may be considered on an individual basis if the patient is in long-term remission [EL5]. Demonstration of adequate serum anti-TNF levels may be helpful in this setting [EL5].

- **Drug Discontinuation During Pregnancy: Biologics (Placental Transfer)**
  - Placental transfer
    - Starts ~week 13–17
    - Peaks in 3rd trimester
    - Mechanism
      - Active IgG1 transfer via Fc receptor.
  - Infant drug levels
    - Can persist for up to 12 mons (except certolizumab).
  - Clinical impact
    - Usually **no** short-term harm but avoid live vaccines for 6 months if exposed in 3rd trimester.

Drug	Transfer to Baby	Notes
Adalimumab	Moderate (≈ 1.5:1)	Still significant
Certolizumab pegol	Minimal / negligible	No Fc region → barely crosses placenta
Infliximab	High (baby: mother ratio ≈ 2.6:1)	Most crosses to fetus
Ustekinumab	Moderate to high	Cord levels often higher than maternal levels
Vedolizumab	Low (≈ 0.44:1)	Usually cleared by 6 months in baby

Statement 19

- For women with active disease just before or during pregnancy, or with disease that is difficult to control, continuation of anti-TNF [EL3] or non-TNF biologics [EL5] throughout pregnancy is recommended. The last dose of anti-TNF in the third trimester should be timed in accordance with the presumed due date to reduce foetal exposure [EL5].

Statement 20

- For women in remission, discontinuing anti-TNF prior to the third trimester is not recommended, as it may increase the risk of relapse [EL3] and lead to unfavourable pregnancy outcomes [EL3]. However, if a pregnant patient in long-term remission wishes to discontinue anti-TNF prior to the third trimester, resumption of anti-TNF shortly after delivery is recommended [EL5].

Statement 21

- For women in remission treated with non-TNF biologic agents (ustekinumab, vedolizumab), an individualised decision on discontinuing treatment should be made, considering the risk of relapse and the limited data on the consequences of fetal exposure [EL5].

- Continuation vs discontinuation:
  - Stopping early (<GW 30) → higher maternal relapse (RR ~2–6×).
  - Continuing throughout pregnancy does not ↑ risk of:
    - Preterm birth
    - Congenital malformations
    - Low birthweight
  - Early discontinuation → higher miscarriage and preterm delivery.

- Child outcomes:
  - No ↑ infections or developmental issues in infants exposed in utero.
  - Avoid live vaccines for 6 months if biologic exposure continued into 3rd trimester.
- Other biologics:
  - Vedolizumab/ustekinumab: limited data; stopping may ↑ relapse risk.
  - Decisions individualized, balancing disease control vs fetal exposure.

Impact of IBD and IBD Medications on Pregnancy and Neonatal Outcomes

Torres J, et al. J Crohns Colitis. 2023;17(1):1-27.

- **Impact of IBD on pregnancy outcome**
  - Adverse Pregnancy Outcomes in Women with IBD Meta-analysis (23 cohort studies; 15,007 IBD vs 4.6M controls)
    - ↑ Preterm birth: OR 1.85 (95% CI 1.67–2.05)
    - ↑ Stillbirth: OR 1.57 (95% CI 1.03–2.38)
    - ↑ Low birth weight (LBW): OR 1.36 (95% CI 1.16–1.60)
    - ↑ Small for gestational age (SGA): OR 1.96 (95% CI 1.01–3.81)
  - Other risks
    - Gestational diabetes: OR 2.96
    - Preterm PROM: OR 12.1
    - C-section: OR 1.79 (↑ in UC; not significant in CD)
      - UC: smoking, pancolitis, IPAA
      - CD: prior surgery, active perianal disease
  - No consistent increase
    - Abortion, miscarriage, placenta previa, abruption, preeclampsia, chorioamnionitis
  - Flare during pregnancy → worse outcomes
    - ↑ Preterm birth (OR 2.7)
    - ↑ LBW (OR ~2.0)
    - ↑ Stillbirth, SGA, low Apgar scores in active CD

Statement 22

- Pregnant women with IBD seem to have a higher risk of gestational diabetes, stillbirth, preterm pre-labour rupture of membranes, preterm delivery, small for gestational age, and low birthweight newborns [EL2].
- Disease activity during pregnancy is a risk factor, as it is associated with preterm pre-labour rupture of membranes, preterm birth, and low birthweight in IBD pregnant women. Disease activity during pregnancy also increases the risk of stillbirth and low Apgar score in Crohn's disease (CD) [EL3].

- **Risks of IBD Drugs During Pregnancy**
- 5-ASA & Sulphasalazine
  - Safety
    - Not linked to ↑ congenital malformations or adverse pregnancy outcomes.
    - Slight ↑ in preterm birth, stillbirth, LBW in some studies — likely due to active disease, not to drug.
  - Key points
    - No proven teratogenicity.
    - Sulphasalazine: may ↓ folate absorption → folate 2 mg/day recommended.
    - 5-ASA with dibutyl coating: rare reports of urogenital malformations → consider switching formulation during pregnancy.

Statement 23

  - Most drugs used for the treatment of IBD are considered low-risk during pregnancy [EL3].

Statement 24

  - ASA is regarded as low-risk during pregnancy [EL3].

- Corticosteroids
  - Short-term use: generally safe
    - No link to major birth defects.
  - First trimester: small studies suggested possible orofacial malformations, but large studies found
    - No ↑ risk
  - Late pregnancy: rare neonatal adrenal suppression reported; may depend on steroid type.
  - Budesonide / Budesonide MMX: no ↑ risk in reported cases.
  - Maternal risks:
    - Corticosteroids can increase risk of hypertension, diabetes, preeclampsia.
  - Pregnancy outcomes (PIANO registry, 432 mothers):
    - ↑ risk of preterm birth, LBW, IUGR, NICU admission.
    - Exposure in 2nd/3rd trimester linked to serious infant infections at 9–12 months.
  - Key point
    - Hard to separate effects of active disease vs steroids; emphasizes disease control and steroid-sparing strategies.

Statement 25

- Although short-term corticosteroids, including budesonide, can in general be regarded as low-risk during pregnancy for managing flares, the risk of maternal-fetal complications should be considered [EL3].

- Antibiotics
  - General role: limited; mainly for pouchitis, perianal, or abdominal sepsis in Crohn's disease.
  - Evidence in pregnancy: sparse; most data from non-IBD populations.
  - Metronidazole
    - Earlier case reports suggested cleft defects.
    - Larger studies/meta-analyses: no increased risk of preterm birth, LBW, or congenital anomalies.
    - Conclusion: considered safe in pregnancy when needed, but avoid in lactation.
  - Fluoroquinolones
    - Animal studies: bone/cartilage toxicity, concern in 1st trimester.
    - Human meta-analyses: no significant increase in birth defects/adverse outcomes.
    - Conclusion: avoid in 1st trimester of pregnancy (T1)
  - Key point
    - Use antibiotics only when indicated, prefer short courses, balance maternal benefit vs fetal risk.

Statement 26

- In case of perianal or abdominal sepsis or pouchitis, metronidazole and ciprofloxacin can be administered in patients with IBD during pregnancy. However, given the risk of arthropathies in children, ciprofloxacin should be avoided if possible during the first trimester of pregnancy [EL4].

- Thiopurines, Calcineurin Inhibitors, Methotrexate
  - Thiopurines
    - Safe overall: no ↑ risk of birth defects.
    - Preterm birth/LBW: rare, likely due to active disease.
    - Newborn effects: occasional transient anemia; no long-term issues.
    - Thiopurine + allopurinol: limited data, no clear safety concerns.
  - Calcineurin inhibitors (Cyclosporine, Tacrolimus)
    - Data mostly from transplant patients; limited IBD-specific data.
    - Cyclosporine: not linked to congenital malformations; small IBD series show use in severe relapses.

  - Tacrolimus: very limited data; one UC case reported, no malformations, but prematurity/LBW noted.
  - Key point: use only if necessary, careful risk-benefit assessment.
- Methotrexate
  - Teratogenic → strictly contraindicated.
  - Causes miscarriage, IUGR, fetal loss, craniofacial/limb/CNS defects.
  - Use barrier contraception; accidental conception may warrant termination discussion.

Statement 27

- Thiopurines not associated with significant neonatal adverse outcomes in pregnant patients with IBD [EL3]. Methotrexate [EL3], thalidomide [EL3], JAK inhibitors, and ozanimod are contraindicated during pregnancy [EL5]. Data for ciclosporin and tacrolimus in patients with IBD during pregnancy are limited.

- Biologics
  - Anti-TNF agents (Infliximab, Adalimumab, Certolizumab, Golimumab)
    - Low-risk: no increase in congenital malformations, preterm birth, LBW, infant infections.
    - PIANO registry: mono- or combination therapy with thiopurines safe; disease activity drives risk of spontaneous abortion.
    - Key point: generally considered safe, especially when controlling disease.
  - Vedolizumab & Ustekinumab
    - Animal studies: **no** adverse pre/postnatal effects.
    - Human data: small cohorts, mostly uneventful pregnancies.
    - Key point: safe but limited data → careful follow-up recommended.

Statement 28

- Anti-TNF antibodies are regarded as low-risk during pregnancy [EL3]. Data for vedolizumab and ustekinumab are limited, but **no** ↑ risk of adverse pregnancy outcomes has been identified [EL4].

- **Risks of IBD Drugs During Pregnancy: Small Molecules**
  - Tofacitinib
    - Teratogenic in animals at high doses; limited human data → contraindicated.
  - Filgotinib & other JAK inhibitors
    - May cause fetal harm → contraindicated.
  - Ozanimod
    - Insufficient human data (from MS/UC trials) → avoid in pregnancy.
  - Key point
    - JAK inhibitors and ozanimod are contraindicated during pregnancy.

- **Mode of Delivery**
  - Perianal Crohn's disease
    - Vaginal delivery does not increase relapse or new perianal disease if inactive.
    - No higher risk of fecal incontinence vs C-section.
  - Delivery mode decision
    - Individualized, multidisciplinary approach (GI, OB, IBD surgeon).
    - C-section preferred for:
      - Active perianal disease (can worsen).
      - History of rectovaginal fistula.
      - UC post-proctocolectomy or those likely to need colectomy.
  - VTE risk
    - Higher postpartum VTE risk in IBD (OR 6–8).
    - C-section adds further VTE risk (OR 1.7).
  - Key point
    - **No** universal recommendation — decide case-by-case, prioritizing disease activity and maternal safety.

Statement 29

- The mode of delivery does **not** influence outcome of patients with IBD regarding development or worsening of inactive perianal disease [EL2] and anal sphincter damage [EL2].

Statement 30

- Mode of delivery should be guided by obstetric considerations. In patients with active perianal disease, prior rectovaginal fistula, and after restorative proctocolectomy, C-section is recommended after multidisciplinary discussion involving gastroenterologists, obstetricians, and IBD surgeons [EL5].

- **Effect of In Utero Exposure of IBD Drugs on Offspring**
  - Anti-TNF & Thiopurines
    - Most studies: **no** increase in serious infections, growth issues, allergies, malignancy up to 5 years.
    - Combination therapy (anti-TNF + thiopurine) may slightly raise infection risk (aHR ~1.3).
    - **No** clear link between cord drug levels and infection/vaccine reactions.
    - Rare reports: one fatal BCG vaccine reaction; isolated neutropenia cases post-anti-TNF exposure.
  - Thiopurines
    - May cause transient neonatal anemia; long-term development appears normal.
  - Vedolizumab / Ustekinumab / Tofacitinib
    - Limited data; available evidence shows no increased infection risk in first year.

Statement 31

- The risk of serious infections requiring hospital admission in the first 5 years of life does **not** seem to be increased in children exposed to anti-TNF agents or thiopurines during pregnancy [EL4]. However, there are no data beyond 5 years of follow-up on the effect of in utero exposure of IBD drugs on the developing immune system and neurodevelopment [EL4]. Safety data on children exposed to vedolizumab, ustekinumab, and tofacitinib are limited [EL5].

Management of IBD in the Postpartum and During the Lactation Period

- **Risk of Postpartum Flare**
  - Relapse occurs in ~25–50% of patients; study results vary.
  - Crohn's disease: **no** consistent ↑ postpartum.
  - Ulcerative colitis: some studies show higher relapse rates during pregnancy/postpartum.
  - Predictors of relapse
    - Active disease in 3rd trimester or at conception.
    - Stopping biologic therapy during T3 or after delivery.
    - Stricturing/penetrating CD phenotype.
    - Longer disease duration.
  - Key point
    - Stable patients who maintain therapy through pregnancy → low postpartum flare risk.

Statement 32

- There is no ↑ risk of postpartum relapse in patients with Crohn's disease (CD) compared with non-pregnant patients with CD. In ulcerative colitis (UC), there may be an increased risk of relapse postpartum [EL3].

- **Restarting Biologics in the Postpartum Period**
  - Continuation: usually continued throughout pregnancy/postpartum unless complications (e.g., infection).
  - Breastfeeding: minimal transfer in breast milk → **no** harm; benefits outweigh risks.
  - Paused in late pregnancy: can be safely restarted postpartum, ideally soon after delivery.
  - Individualization**:** Re-induction/maintenance decisions depend on:
    - Duration of interruption
    - Disease activity
    - Concurrent immunomodulators
    - Biologic type

Statement 33

- For patients who continue biologics during the entire pregnancy, the treatment should be continued uninterrupted in the postpartum phase unless there is a contraindication to their use [EL5].
- For patients who interrupted treatment during pregnancy, the treatment should be resumed after delivery as soon as possible [EL5]. Re-induction or continuation of previous maintenance therapy is dependent on clinical circumstances [EL5].

- **Impact of In Utero Exposure to IBD Drugs on Infant Vaccinations**
  - Vaccine response
    - Mostly measured cross-sectionally; small studies → limited conclusions.
    - Some inadequate responses after primary series at 6 months; booster at 12 months generally effective.
    - No significant difference vs infants not exposed.
  - Safety
    - Inactivated vaccines: no adverse events reported.
    - Live vaccines: risk of severe reactions (e.g., BCG) if biologics detectable.
    - Minor adverse events rare (~3%).
  - Guidelines (EMA 2022)
    - Avoid live vaccines in first year for infliximab-exposed infants.
    - Consider live vaccines only if clear benefit and biologic undetectable.
  - Drug clearance
    - Vedolizumab: rapid neonatal clearance → live vaccines may be safe from 6 months of age baby.
    - Ustekinumab: median clearance 9 weeks (range 6–19 weeks).

Statement 34

- Inactivated vaccines are recommended according to national guidelines. In children exposed *in utero* to biologics, live attenuated vaccines should be withheld within the first year of life or until the biologic is no longer detectable in the infant's blood [EL3].

- **Breastfeeding with IBD**
  - Theoretical concern
    - Lactation ↑ prolactin → may upregulate TNF → potential ↑ disease activity.
  - Evidence
    - Limited, mostly retrospective.
    - Some studies: protective effect postpartum.
    - Others: possible ↑ relapse in Crohn's, but not significant after adjusting for medication changes.
    - Several studies: no association between breastfeeding and disease activity.

- Limitations
  - Small sample sizes, retrospective design, recall bias, differing disease activity assessments.
- Key point
  - Current evidence does not conclusively link breastfeeding with worsening IBD; benefits generally outweigh theoretical risks.

- Offspring IBD Risk
  - Some studies: breastfeeding may protect against IBD, especially if >3–12 months.
  - Other studies: no effect or conflicting results for Crohn disease.
  - Evidence limited; **no** clear recommendation can be made.

Statement 35

- Drugs that are considered low-risk during pregnancy are also considered low-risk during breastfeeding and thus can be continued [EL3].

Statement 36

- Breastfeeding does **not** influence disease activity of patients with IBD [EL4].

Pregnancy-Specific IBD Management Summary

- Monitoring & Relapse Risk
  - Women with IBD face higher risks of complications (gestational diabetes, preterm birth, low birthweight). Active disease increases these risks.
  - Relapse prevention is critical; monitoring tools include faecal calprotectin and intestinal ultrasound.
- Drug Safety During Pregnancy
  - Anti-TNF agents: generally low-risk.
  - Vedolizumab/ustekinumab: limited data, but no signal of increased adverse outcomes.
  - Thiopurines: not linked to major neonatal harm.
  - Corticosteroids (short-term, incl. budesonide): acceptable for flares, but maternal-foetal risks must be weighed.
  - Antibiotics: metronidazole acceptable; ciprofloxacin should be avoided in the first trimester.
  - Contraindicated: methotrexate, thalidomide, JAK inhibitors, ozanimod.
  - ASA: considered low-risk.
- Delivery Considerations
  - Mode of delivery usually guided by obstetric factors.
  - C-section recommended for active perianal disease, rectovaginal fistula, or after restorative proctocolectomy.
  - Delivery mode does not worsen inactive perianal disease or sphincter function.

- Postpartum & Breastfeeding
  - Crohn's disease: relapse risk similar to non-pregnant patients.
  - Ulcerative colitis: relapse risk may be higher postpartum.
  - Biologics: continue uninterrupted postpartum unless contraindicated; if stopped during pregnancy, restart promptly.
  - Breastfeeding: generally does not alter disease activity. Safety of drug continuation during lactation depends on updated evidence.
- Child Outcomes & Vaccination
  - No increased risk of serious infections in first 5 years for children exposed to anti-TNF or thiopurines.
  - Long-term immune/neurodevelopmental data are limited.
  - Inactivated vaccines: follow national schedules.
  - Live vaccines: defer for 6–12 months in infants exposed *in utero* to biologics, or until drug levels are undetectable.

Adapted from: Torres J, J Crohn and Colitis 2023; 17(1); 1–27 (Figure 1)

Abbreviations: 5-HIAA, 5-hydroxy indol acetic acid; 5-HT, 5-hydroxy tryptamine (serotonin); AIDS, acquired immunodeficiency syndrome; AMACR, alpha-methylacyl-CoA racemase; APC, adenomatous polyposis coli gene; bid, twice daily; BMI, body mass index; CDX2, caudal type homeobox 2; CK, cytokeratin; CTE, computed tomography enterography; D, duodenum; DLBCL, diffuse large B-cell lymphoma; EATLs, enteropathy-associated T-cell lymphomas; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; FAP, familial adenomatous polyposis; FL, follicular lymphoma; GIST, gastrointestinal stromal tumour; hpf, high-power field; HRT, hormone replacement therapy; IC, intracellular signaling; IPSID, immunoproliferative small intestinal disease; KIT, tyrosine kinase receptor CD117; LP, lamina propria; MALT, mucosa-associated lymphoid tissue lymphoma; MEN, multiple endocrine neoplasia; MLH1/2/6, mismatch repair genes; MMR, mismatch repair; mon, months; MRE, magnetic resonance enterography; NET, neuroendocrine tumour; NF, neurofibroma/neurofibromatosis; N/V, nausea/vomiting; OR, odds ratio; PDGFRA, platelet-derived growth factor receptor alpha; PPI, proton pump inhibitor; PSIL, primary small intestinal lymphoma; q, every (interval); RFA, radiofrequency ablation; RR, relative risk; SBA, small bowel adenocarcinoma; SATB2, special AT-rich sequence-binding protein 2; SI, small intestine; tid, three times daily; US, United States; VCE, video capsule endoscopy; yr, year.

TUMOURS OF THE SMALL INTESTINES

Ziad Hindi

- Introduction
  - Small intestinal (SI) tumours are located in the duodenum, jejunum and ileum
  - SI is ~6 m long
    - Represent only 5% of newly diagnosed cancers of the intraluminal digestive tract
  - Most common are
    - Adenocarcinomas
    - Carcinoids
    - Lymphomas, and
    - Sarcomas.

- Classification
  - Benign Epithelial Tumours/Polyps
    - Adenomas
    - Hamartomas
      - Bannayan-Riley-Ruvalcaba syndrome
      - Cowden disease
      - Cronkhite-Canada syndrome
      - Juvenile polyposis
      - Peutz-Jeghers syndrome
    - Brunner gland lesions
  - Malignant Epithelial Lesions
    - Carcinoid tumours (neuroendocrine tumours)
    - Primary adenocarcinomas
    - Secondary carcinomas (metastases)
  - Lymphoproliferative Disorders
    - B-cell
    - Diffuse large-cell lymphoma
    - Enteropathy-associated T-cell lymphoma
    - Follicular lymphoma
    - Immunoproliferative small intestinal disease
    - Mantle cell lymphoma (multiple lymphomatous polyposis)
    - Marginal B-cell lymphoma (MALT cell lymphoma)
    - T-cell
  - Mesenchymal Tumours*
    - Fatty tumours
      - Lipoma
      - Liposarcoma
    - Gastrointestinal stromal tumours (GIST; benign and malignant)

- Neural tumours
  - Ganglioneuromas
  - Granular cell tumours
  - Gut autonomic tumours
  - Neurofibromas
  - Schwannomas
- Paragangliomas
- Smooth muscle tumours
  - Leiomyoma
  - Leiomyosarcoma)
- Vascular tumours
  - Angiosarcoma
  - Hemangioma
  - Kaposi sarcoma
  - Lymphangioma
- Mucosa-associated lymphoid tissue (MALT)

➢ Demography

- Incidence of primary SI cancers (US) ~$2/10^5$
  - ↑ with age
  - Median age of diagnosis, aga 66 yr
  - Highest rates in North America, Northern Europe and Oceania
    - Lowest in Hispanics, Asian/Pacific Islanders
- In the US
  - Incidence of adenocarcinomas and malignant carcinoids are higher in African American (AA) compared to Caucasians, and
  - The converse is true for African Americans, as stromal tumours and lymphomas
- Incidence rises with age, with the median age of diagnosis is 66 years old
- Primary SI tumours
  - Adenocarcinoma, 24-52%
  - Malignant Carcinoid, 17-41%
  - Lymphoma, 12-29%
  - Sarcomas, 11-20%
- Location is dependent on subtype
  - Adenocarcinomas - 49% in duodenum
  - Crohn disease Adenocarcinoma - terminal ileum Hillary
  - Carcinoids/Primary Lymphoma, 52% and 30%, in ileum
- Theories why SI tumours are rare
- Rapid SI Transit time
  - ↓ mucosal contact with carcinogens

- Relatively low bacterial counts in SI
- Stem cells at the crypt base are deeper in the SI than in the colon → ↓ carcinogenic contact with these cells
- Apoptosis differs in the SI and colon lamina propria
- Lymphoid tissue in lamina propria (LP) and Peyer patches of the ileum → IgA rich secretions → ↑ provide immune surveillance against neoplastic cells

➢ Risk factors

❖ Genetics

- **Adenocarcinoma**
  - KRAS (encode guanine nucleotide-binding proteins → regulate intracellular signaling (IC) common in Crohn disease
  - SI adenocarcinomas may be associated with alteration in the p.53 gene and allelic loss of chromosome 17p (cell phase dysregulation)
  - APC gene on Chromosome 5 is mutated in familial adenomatous polyposis → may play a role of this gene in SI adenomas/ carcinomas
  - Microsatellite instability - 5-35% of SI adenocarcinomas
    - Defective mismatch repair (MMR)
    - MMR genes MLH1, 2, 6 identified in 81% of individuals with Lynch syndrome and SI tumours
  - Demography
    - Age > 65 – males
    - Smoking (OR, 1.24)
    - Alcohol (OR, 1.51)
    - Diet
      - Salt-cured foods
      - Heterocyclic amines (fried/BBQed foods)
      - High sugar intake
      - Bread
      - Pasta
      - Rice
    - ↑ BMI
    - Hormone replacement therapy (HRT) misuse
    - Diseases
      - Small intestine
        - Celiac disease
          - ↑ risk of SI adenocarcinoma and non-Hodgkin lymphoma
          - Lymphomas are usually of T-cell origin (enteropathy-associated T-cell lymphoma [EATLs])

- Crohn disease
  - Adenocarcinoma is the most common primary SI malignancy in Crohn disease 190 (2.2% cumulative risk after 20 yr of disease)
- Ileal loop conduits, ileal pouches, ileal cystoplasty
- Duplication cysts and Meckel diverticula

- Colon
  - Familial adenomatous polyposis (FAP)
    - 90-100% risk of lifetime adenomas
      - 70% lifetime risk of developing high-grade dysplasia in duodenal polyps
      - 0.9-6.1% lifetime risk of duodenal adenocarcinoma
    - Relative risk
      - For duodenal adenocarcinoma
      - For ampullary carcinoma
    - Periodic screening for proximal SI tumours is recommended
      - Start at age 25-30 years old
      - Spigelman Stage
        0 – q4 yr
        I – q4 yr
        II – q1 yr
        III – q12 mon
        IV – surgical evaluation (36% risk of duodenal cancer)
      - Classification
        - Most common primary malignant disease of SI (24-52%)
        - Adenomas and adenocarcinomas, especially of the duodenum and ampulla of Vater, are most frequently encountered in the setting of FAP
        - Used for classification of #, size, histology, and severity of dysplasia of polyps)
  - Long-standing ileostomy (especially with Crohn disease)
- Gallbladder
  - History of cholecystectomy
  - Juvenile polyposis syndrome (Autosome Dominant)
    - Hamartomas limited to the colon or stomach, or occur throughout GI tract -either
    - RR of SI cancer is unclear
  - Lynch syndrome (hereditary non-polyposis colorectal cancer)
    - 4% lifetime risk of SI adenocarcinoma development
    - May be distributed throughout the SI, but are most commonly found in the duodenum (47-65%)
    - Screen q3-5 yr

- Peutz-Jeghers syndrome (Autosomal Dominant - chromosome 19p13.3)
  - Extracolonic cancers are common - 50-90% of patients (RR of 15.2 of all cancer compare to the general population)
  - SI is the most frequent site of cancer development > RR of SI adenocarcinoma
- Neuroendocrine tumours
  - Epigenetic Dysregulation (methylation, chromatin modification)
- GIST
  - Gain of function mutations e.g.
    - Tyrosine kinase gene mutations
    - KIT
    - PDGFRA
- Non-Hodgkin B-Cell Lymphoma
  - Acquired immunodeficiency syndrome (AIDs)
  - Crohn disease
  - Infectious agents, e.g., Campylobacter jejuni (immunoproliferative small intestinal disease)
  - Nodular lymphoid hyperplasia (NLH)
- Enteropathy-Associated T-Cell Lymphoma
  - Celiac disease
- Gastrointestinal Stromal Cell Tumour
  - Germline mutations in succinyl dehydrogenase genes
  - Type 1 neurofibromatosis (von Recklinghausen neurofibromatosis)

➢ Clinical Features

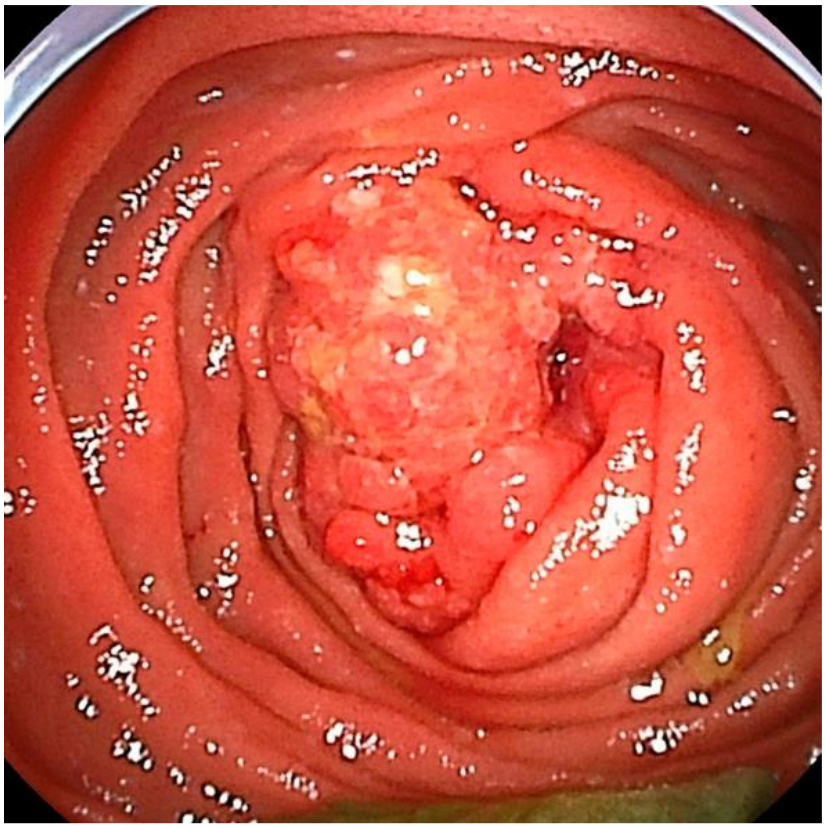
- Features to help to distinguish benign from malignant tumour
- Symptoms related to tumour size, location and blood supply
- Small tumours may present as anemia
- Late tumours may present with
  - Abdominal pain
  - Anemia
  - Nausea/vomiting
  - Weight loss
- Tumours located in the periampullary duodenum/ ampulla of Vater may present with
  - Jaundice and
  - Other signs of biliary obstruction

Clinical Features of Small Bowel Tumours

Symptom	Benign	Malignant
○ Abdominal pain	– Most frequent symptom	▪ Most frequent symptom ~1/3
○ Obstruction		
○ Intussusception	– Most common cause of intussusception in adults with a "virgin" abdomen – Lipomas are the leading cause	▪ Rare
○ Occult blood loss	– Rare	▪ Up to 50%
○ Frank bleeding	– Rare	▪ Rare (GIST is the most likely tumour)
○ Weight loss	– Very rare	▪ Up to 50% of cases ▪ Most severe with lymphoma
○ Palpable abdominal mass	– Rare	▪ 40%
○ Perforation	– Very rare	▪ ~10% of cases, ▪ Usually, lymphomas or GIST
○ Jaundice (periampullary tumours)	– Rare (benign)	▪ Malignant, ~80%
○ Flushing	– No	▪ Yes, occurs in few cases of metastatic carcinoid tumour
○ Diarrhea	– Very rare	▪ Common with lymphoma ▪ Can occur with carcinoid syndrome

- Endoscopy
  - Pedunculated or sessile

Small Bowel Tumour



Courtesy of: Yano T and Yamamoto H. Cancers. 2024; 16(9):1704.

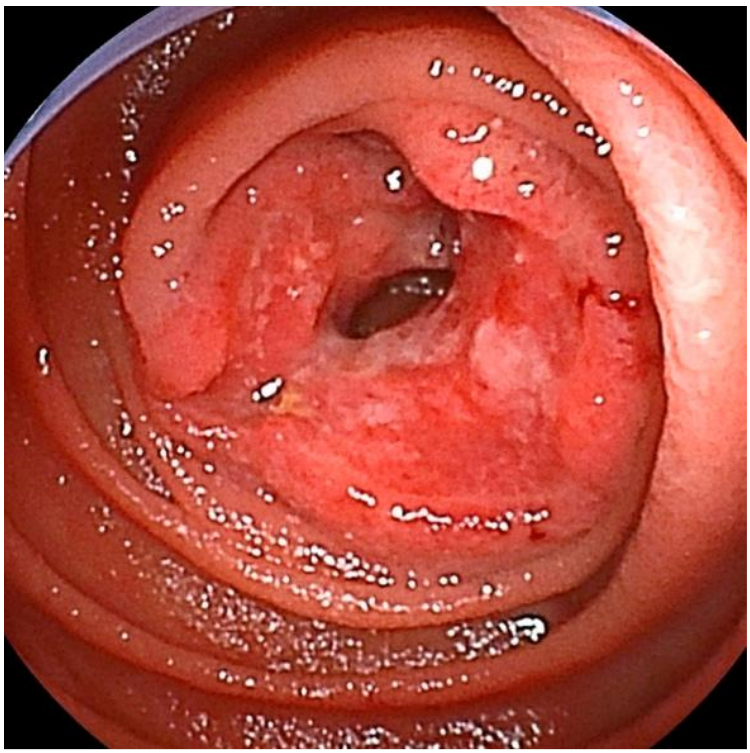
  - High-resolution endoscopy and chromoendoscopy
    - ↑ detection rates of adenomas in FAP biopsy,
    - Consider biopsy snare cautery or endoscopic mucosal resection (EMR)
  - Colonoscopy and intubation of terminal ileum (TI) in patients with Crohn disease
  - EUS is helpful in staging duodenal and ampullary lesions

- Video capsule endoscopy (VCE)
  - Obscure GI bleed
  - Diagnosis small jejunal or ileal polyps
    - Superior to MRE or small bowel follow through
    - MRE is better for other SI locations (more specific)
  - Inferior to upper endoscopy in the evaluation of duodenal adenomas and ampulla of Vater

➢ Histopathology

- Tubular-tend to be small
  - Tall, columnar, pseudostratified epithelial cells
- Villous-tend to be larger
  - Finger-like villous or papillary processes
- Dysplasia - a spectrum from mild, to intramucosal carcinoma and invasive carcinoma

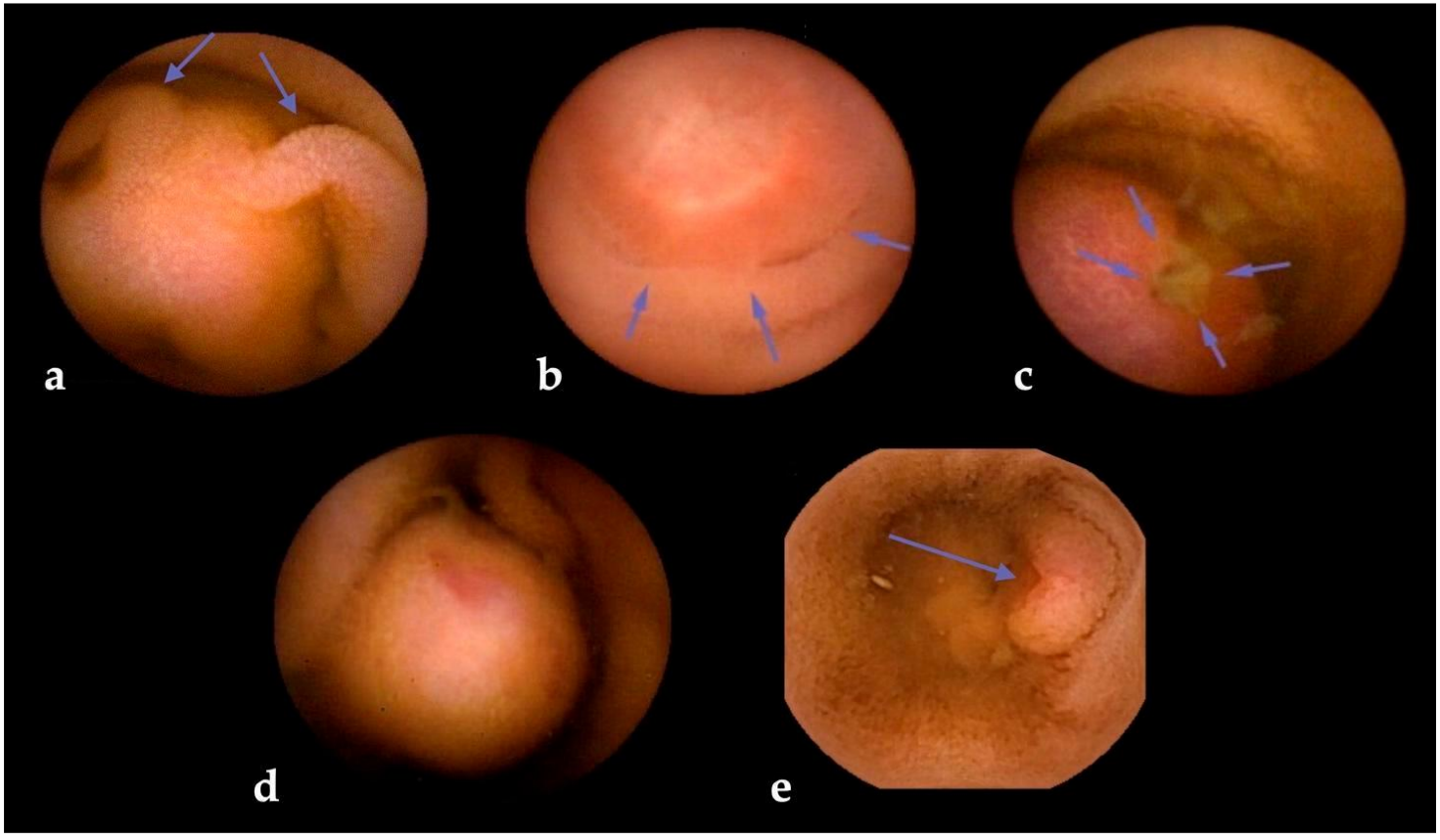
Small Bowel Tumour



Small bowel adenocarcinomas, which are often advanced at the time of diagnosis, and endoscopic findings often include ulceration and stenosis.

Courtesy of: Yano T and Yamamoto H. *Cancers*. 2024; 16(9):1704.

Visual Clues for Submucosal Tumours in Small Bowel Capsule Endoscopy

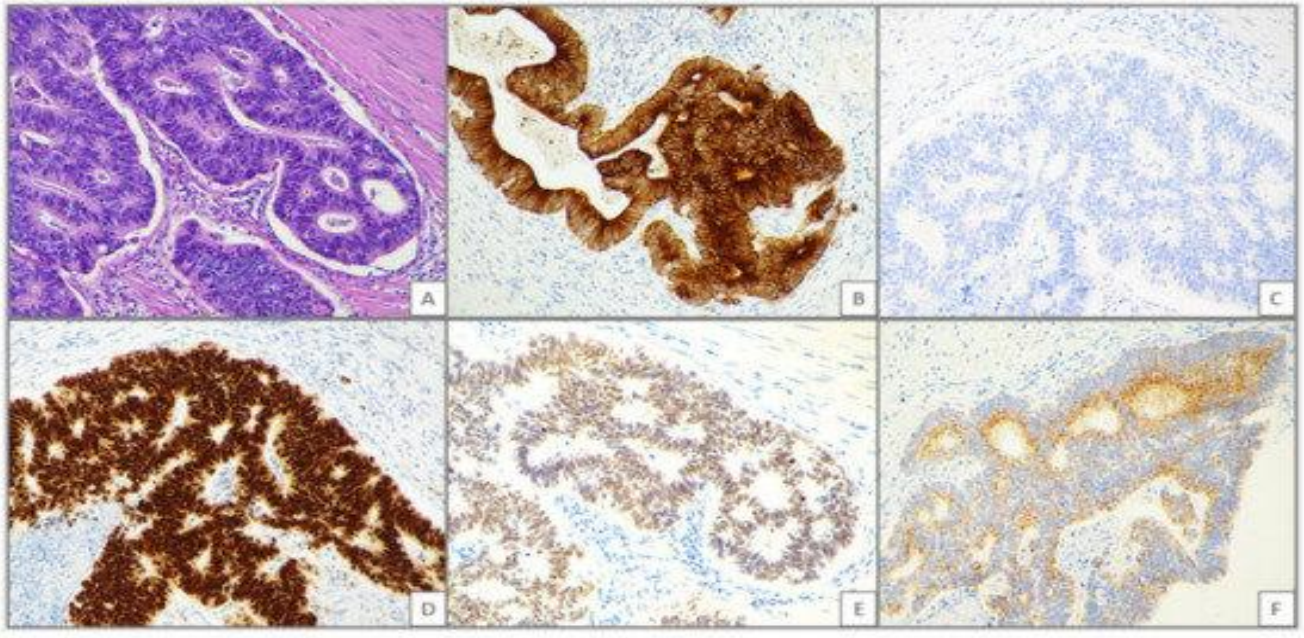


(**a**) bridging mucosal folds; (**b**) mucosal stretching; (**c**) surface ulceration; (**d**) altered villi on surface; and (**e**) central umbilication.

Courtesy of: Fantasia S, et al. Cancers. 2024; 16(2):262.

- Histopathology
  - Arise in discrete adenomatous polyps
  - May be flat, stenosing, ulcerative, infiltrating, or polypoid
  - Signet cells may be a feature (large vacuole of mucin displacing 22B nucleus to one side)

Tumours of the Small Intestine

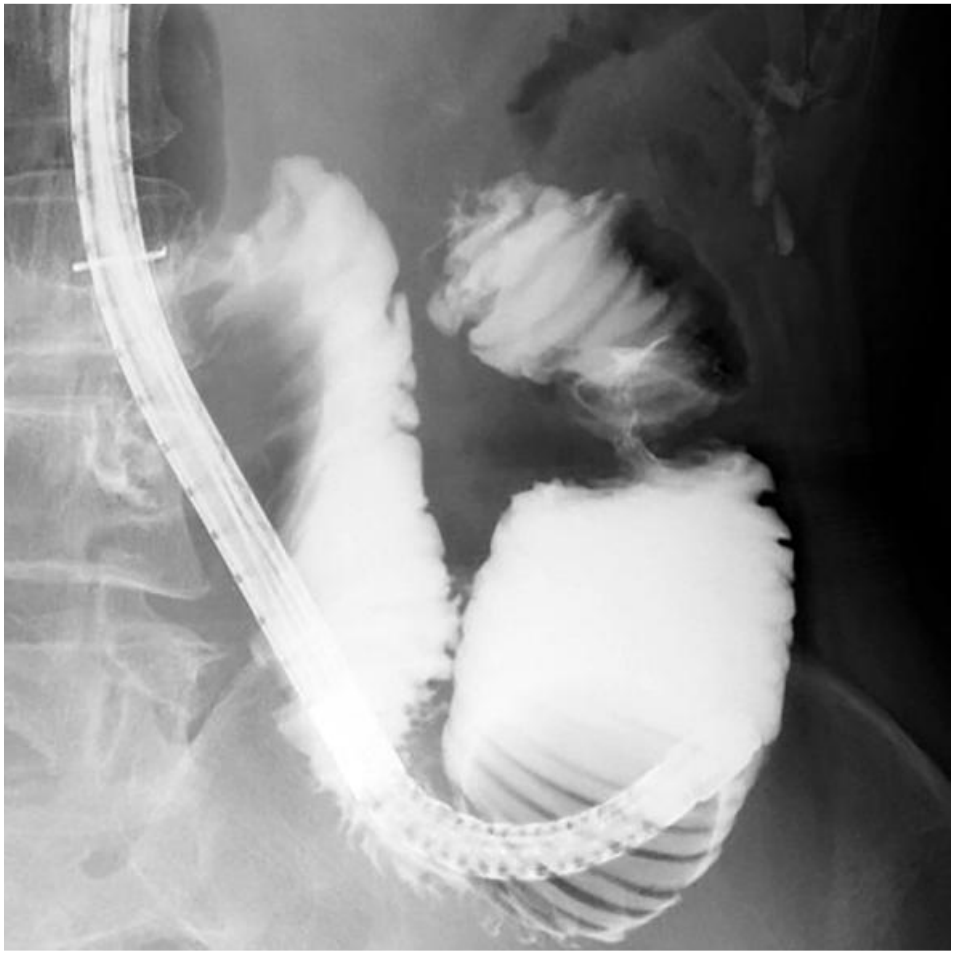


(**A**) hematoxylin and eosin staining, showing a glandular-type SBA with well-formed glandular structures; (**B**) Cytokeratin (CK)20 immunohistochemistry, showing a strong and diffuse cytoplasmic reactivity for CK20; (**C**) CK7 immunohistochemistry, showing negativity for CK7 (**D**) Caudal type homeobox 2 (CDX2) immunohistochemistry, showing positivity for CDX2; (**E**) Staining for special AT-rich sequence-binding protein 2 (SATB2), showing SATB2 positivity; (**F**) Alpha-methylacyl-CoA racemase (AMACR), immunohistochemistry, showing AMACR tumour cell positivity. Original magnification: 200X.

Courtesy of: Neri G, et al. Cancers. 2020; 12(11):3441.

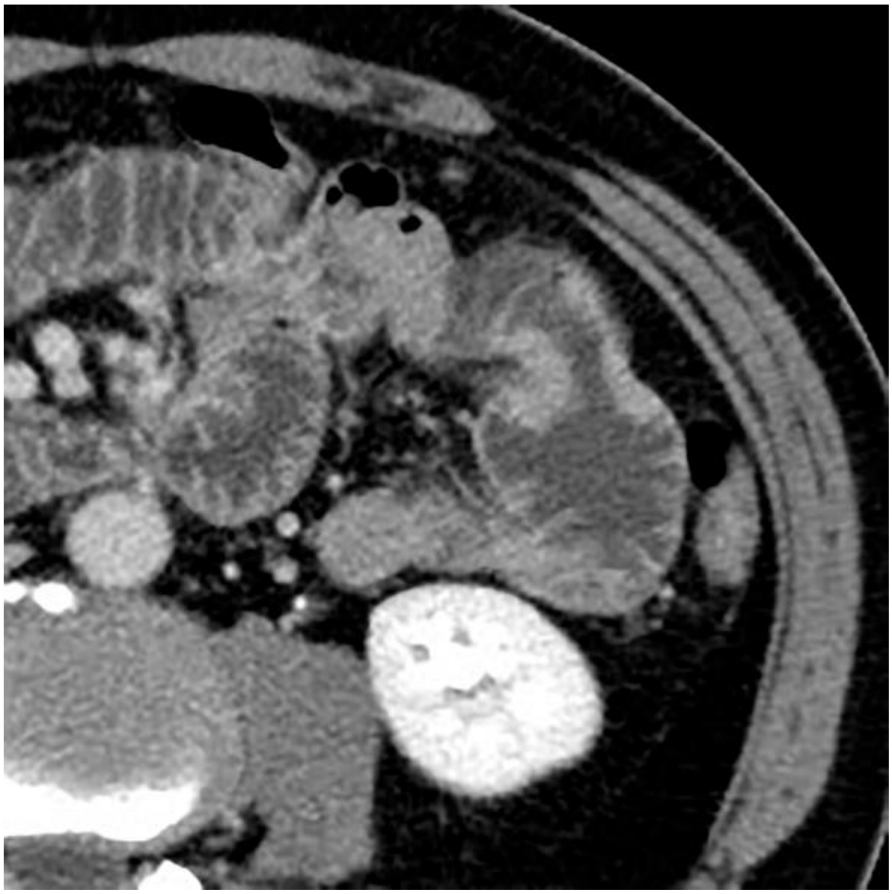
- Diagnostic Imaging
  - MR enterography (MRE)
  - Small bowel barium follow through
    - 60-80% accurate for detection of duodenal lesions
    - Annular narrowing/stricture formation
    - Filling defects may be polypod or ulcerated masses

MRI of Small Bowel



Courtesy of: Yano T and Yamamoto H. Cancers. 2024; 16(9):1704.

- CT enterography (CTE)



Courtesy of Yano T and Yamamoto H. Cancers. 2024; 16(9):1704.

- Prognosis
  - Poor
    - Median survival of 20 mon
    - 5-year survival of 26%
  - Factors associated with poor prognosis (adenocarcinomas in Lynch syndrome have a better prognosis than those in familial adenomatous polyposis [FAP])
    - Tumour stage
    - Age >75 yrs
    - Cancer-directed surgery
    - History of Crohn disease (poorer prognosis)

- Treatment
  - Chemoprevention
    - Sulindac with erlotinib reduced duodenal polyp burden
    - 71% after 6 mon of treatment
  - Endoscopic Submucosa Dissection (ESD) and Endoscopic Mucosal Resection (EMR)
    - Sporadic adenomas Complete resection in 98%, recurrence up to 37%
    - Overall complication rate, of 5-10%
  - Surgery
    - Treatment of choice
    - Location
      - D1/D2 (first and second part of duodenum)- Whipple Procedure resection
      - Distal duodenum, jejunum, proximal ileum - en bloc resection with 5 cm margins, plus resection of mesentery and regional lymph node dissection
      - Terminal ileal resection with right hemicolectomy
    - Spiegelman III/IV Stages
      - 63% present at stages III and IV
      - 25-59% are not surgical candidates
      - 16-23% who undergo resection do not achieve curative resection
      - Curative resection - 64-97%
      - Recurrence + 22-37%
  - Chemotherapy
    - No statistically significant survival benefit
      - Possible future role for EGDR inhibitors, VEGF-A inhibitors, and PD-1 pathway targeting

- **Neuroendocrine Tumours** (NETs)

- Demography
  - Most common malignancy of the SI (40% of SI tumours)
  - Most clinically significant carcinoids are found in SI
    - 90% found in distal ileum
  - Median age at diagnosis, 60 yr
    - 2 (median)-20 years from symptom-onset to time of diagnosis

- Clinical
  - Typical carcinoids
    - Secrete serotonin (5-HT)
  - Atypical ones
    - Do not (lack dopa decarboxylase)

- Carcinoid tumours
  - Usually malignant
  - Associated with locoregional spread at the time of diagnosis
  - Usually intramucosal (rarely extending into lumen)
- Small tumours are found incidentally, while most tumours are found when regional spread or metastasis has occurred
- Non-specific GI symptoms (ME)
- SI obstruction (50%)
- Intestinal ischemia
- Intussusception
- GI hemorrhage
- Hepatomegaly
- Symptoms of the carcinoid syndrome (presentation in 10% to 18% of SI carcinoids)
  - Diarrhea, 75% (explosive, watery)
  - Abdominal pain, 50%
  - Heart
    - Dyspnea
    - Carcinoid heart disease
  - Lung
    - Pulmonary fibrosis
    - Bronchoconstriction
  - Less common
    - Cyanosis
    - Edema
    - Arthritis
    - Pellagra (niacin used up in 5-HT (hydroxy tryptamine)

➢ Laboratory

- Urinary
  - 5-HIAA (hydroxy indol acetic acid)
  - Platelet 5-HT (hydroxy tryptamine)
  - Urinary 5-HT
- Chromogranin A - sensitivity of 80%
  - Used to monitor treatment response
  - Beware of intraassay variability and false positives
    - Renal/hepatic failure
    - PPI use
    - Chronic gastritis)

- Diagnostic Imaging
  - Helical CT-enteroclysis and CTE
    - Mass lesions
    - Calcifications
    - Fibrosis
    - Radiating strands of fibrosis
    - Spiculation
    - Mesenteric lymph node metastases, 91% of cases
    - MRI is more sensitive than CT to detect liver metastasis
  - Somatostatin receptor imaging and PET
- Endoscopy
  - Appearance
    - Nodular
    - Submucosal protuberances that are yellowish and shiny
    - Ulcerated lesions
    - Pedunculated lesions
  - Video capsule endoscopy (VCE) has been shown to have utility
- Histopathology
  - Endoscopic biopsy unrevealing
    - Lesions are subepithelial
  - Endoscopic ultrasound (EUS)
    - Snare polypectomy and EMR are more successful for histology
- Treatment

- Localized Tumours
  - Surgical resection is the only curative therapy
  - For duodenal lesions
    - EMR
    - Local transduodenal excision +/- lymph node sampling
    - Pancreatoduodenectomy
  - For ileal and jejunal carcinoids - bowel resection with regional lymphadenectomy is recommended
- Tumours with Regional Spread
  - 35% present with intestinal obstruction - emergent resection is acceptable
  - Consider vascular resection in the case of mesenteric ischemia

- Distant Metastases
  - Unresectable disease
    - Low tumour burden/absence of symptoms
      - Monitor q3-12 mon
    - High tumour burden +/- carcinoid syndrome
      - Long-acting SSAs
  - Consider everolimus (mTOR inhibitor) - 52% ↓ progression/death
  - Hepatic Metastases, consider
    - Surgical resection
    - Radiofrequency ablation (RFA)
    - Cryoablation

- Presurgical Management
  - Beware of carcinoid crises, even with minor procedures
  - Carcinoid Crises
    - Hypotension/hypertension
    - Flushing
    - Bradycardia/tachycardia
    - Bronchospasm
    - Complete vasomotor collapse
  - Premedicate with subcutaneous octreotide
    - Minor procedures: 100-200 mcg bid-tid during surgery bid-tid wk.
    - Elective intra-abdominal surgeries/er other major operations: 100 mcg tid for 2 wk prior to surgery

➢ Prognosis
  - Better than adenocarcinomas (5-yr survival rate, 60-82%)
  - Associated with location
    - The more distal, the worse the prognosis 36A

- **Mesenchymal Tumours** (aka Gastrointestinal Stromal Tumours, GIST)

➢ Demography
  - GISTs
    - 20-30% are in SI
    - Represent 11-20% of all SI tumours
  - Benign GISTs are 3-4x more abundant than malignant GISTs (M>F, 50-60 yr)

- Types
  - Most are sporadic
    - Some are associated with type I Neurofibromatosis (rarely metastasize)
  - Others
    - Ganglioneuromas (MEN-2)
    - Kaposi sarcoma
    - Schwannomas (NF)

- Pathology
  - GISTs arise from the muscularis propria
    - Often grow extramurally
    - Benign duodenal are more likely to grow intramurally/luminally GISTS
  - More cellularity and less cytoplasmic eosinophilia compared to leiomyomas/myosarcomas and schwannomas
    - Spindle-cell like appearance
  - GISTs types
    - Ganglionic
    - Myoid
    - Neural
  - 95% of GISTs express KIT or CD117
  - GISTs of the SI invade locally
    - Can presented with peritoneal seeing, or invasion of adjacent organs
  - Lymph node metastases are uncommon
  - Liver metastases occur in 40'% as presentation

- Clinical
  - Often asymptomatic / found incidentally
  - >50% of GISTs > 5cm will present with
    - Palpable mass
    - GI hemorrhage (may be brisk and acute)
  - 30-40% will present with
    - Abdominal pain
    - Nausea/Vomiting
    - Weight loss
  - 40% of ileal tumours will present with intussusception

- Diagnostic Imaging
  - CTE and MRE are useful
- Endoscopy
  - Endoscopic diagnosis
    - GISTs are submucosal, but ulcerations may be present
    - Biopsy is helpful in ulcerated submucosal lesions b
  - EUS Criteria to differentiate benign from malignant GISTs
    - Size >4 cm
    - Irregular extraluminal margins
    - Cystic spaces ≥ 2, PPI for malignant GISTs, 100%
- Treatment
  - Standard Treatment / Segmental surgical resection with complete resection of macroscopic tumour and documentation of negatives margins
    - Factors
      - Resectability
      - Surgery-Associated Mortality
    - Even if negative margins, 44-80% will suffer local/peritoneal recurrence 2-10 yr later
  - Neoadjuvant therapy (imatinib)
    - Consider in marginally resectable tumours or high-surgical mortality patients
  - Adjuvant therapy with Imatinib for
    - Completely resectable GISTs > 3cm (↑ survival)
    - Intermediate-to high risk of recurrence
    - Those who received neoadjuvant therapy with Imatinib
  - Unresectable tumours
    - Perform KIT and PDGFRA mutational analysis to predict response, and adjust dosing of Imatinib
  - If progresses on Imatinib → consider sunitinib (multi-kinase inhibitor)
    - 53% response rate
  - 3rd Line: Regorafenib
  - Chemotherapy and radiation therapy for advanced GIST
    - Ineffective for patients with recurrence or metastasis
- Prognosis
  - Median survival ~9.4 yr
  - Risk of actions for malignancy

GIST: Prognostic Factors

Factor	Low Risk of Malignancy	High Risk of Malignancy
○ Morphology		
− Anatomic site	Rectum	Jejunum
− Size	< 2 cm	> 5 cm
− Mitosis	0–1 per 30–50 hpf	> 5 per 10–50 hpf
− Cellularity	Low	High
− Necrosis	-	+
− Infiltration into lamina propria	-	+
− Cystic spaces	-	+
− Irregular borders†	-	+
○ Genetics		
− KIT exon 11 deletion	-	+

Abbreviation: hpf, high-power field.

- **Lymphomas**

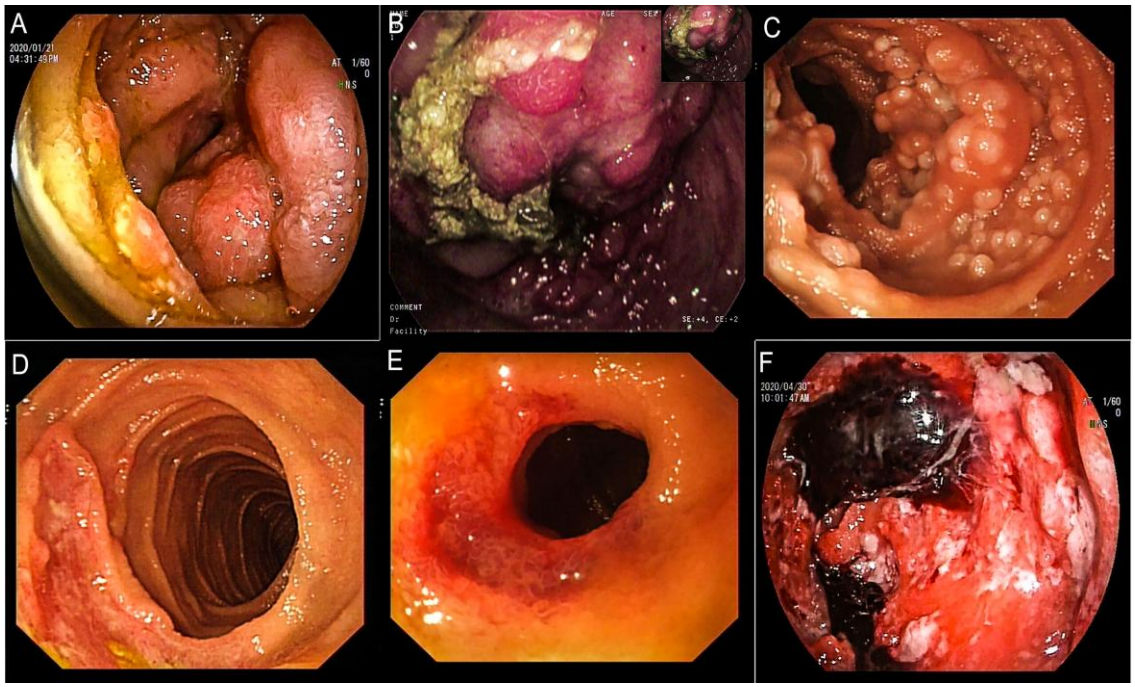
➢ Demography
  - SI represent 12-29% of all SI tumours

➢ Type
  - Primary SI Lymphoma (PSIL) – focal
    - Most are B-Cell Derived, with the exception of EATL
    - 54% are Diffuse Large B-Cell Lymphomas
  - Immunoproliferative Small Intestinal Disease (IPSID) - diffuse

- Primary SI Lymphoma (PSIL)
  - Involvement of only the organs of the GI tract and proximal regional lymph nodes
  - No mediastinal lymphadenopathy on chest X-ray
  - No palpable peripheral lymphadenopathy
  - Regional lymph nodes involved in ~50%, except in MALT, only 30%
  - A normal peripheral WBC / differential
  - No involvement of the liver or spleen

- Clinical
  - Abdominal Pain and Weight Loss - 59-87%
  - Others < 30%
    - Acute abdomen
    - Fatigue
    - GI Hemorrhage
    - Malaise
    - Night sweats
  - Diarrhea and Malabsorption - common in EATL
  - Most common physical finding; palpable abdominal mass, 30-50%
  - Exclude Celiac Disease
    - May be unresponsive to gluten-free diet with PHIL
- Endoscopy
  - Site
    - Ileum > Jejunum > Duodenum north
    - Usually localized to one area, but exception if Mantle cell lymphoma (multiple lymphoid polyposis)
  - Appearance
    - Large exophytic masses
    - Polyp-like
    - Ulcer-like
    - Nodular

Endoscopic Findings of Patients with Primary Small Intestinal Lymphoma (PSIL)



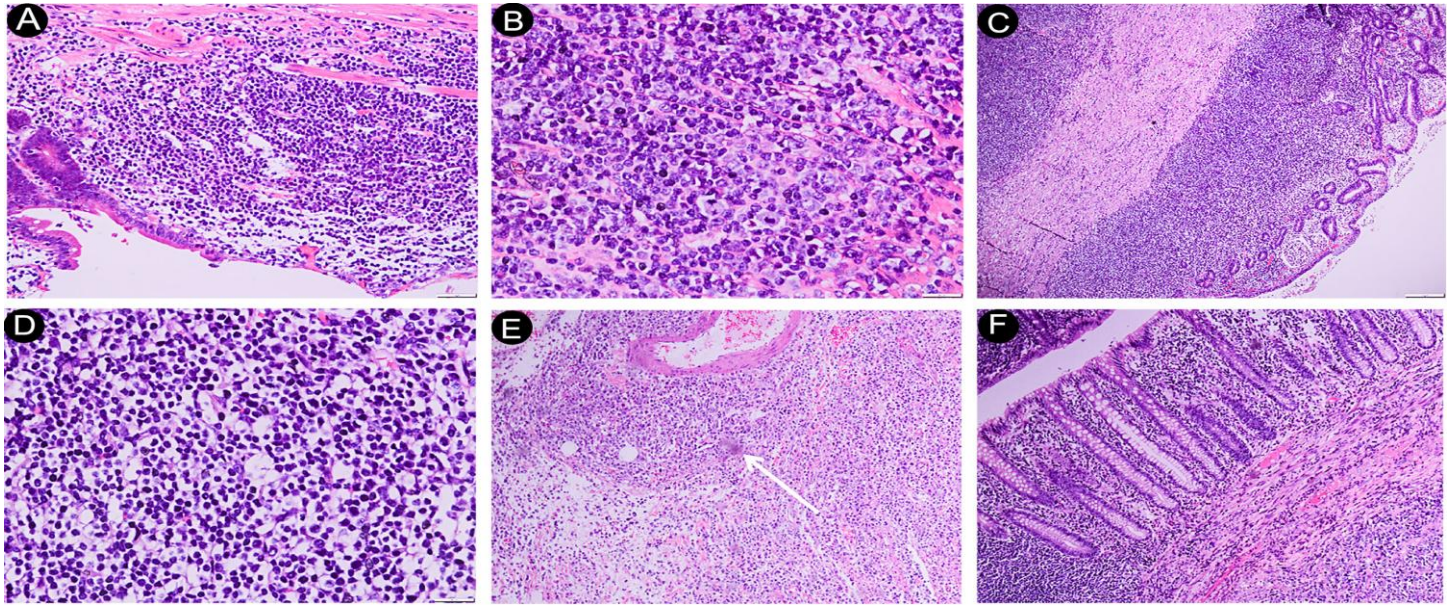
- Hypertrophic type, irregular mucosal eminence around the duodenum, pathologically confirmed as T-cell lymphoma (A).
- Exophytic type, ileocecum showed a huge protuberant lesion, surface hyperemia, edema and erosion, pathologically confirmed as MCL (B).
- Follicular/polypoid type, follicular mucosal eminence diffusely distributed in the proximal small intestine and pathologically confirmed as FL (C).
- Ulcerative type, irregular ulcer spots on the ileocecal area, pathologically confirmed as MALT lymphoma (D).
- Diffusion type, lower jejunum circumferential stenosis, surface ulceration, blood scab attachment, pathology confirmed as MALT (E).
- Diffusion type, diffuse mucosal hyperemia erosion in the middle part of jejunum, covered with mucus, old blood clots, a rigid wall, a narrow lumen, and DLBCL was confirmed by pathology (F).

Abbreviations: DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; PSIL, primary small intestinal lymphoma

Courtesy of: Tian FY, et al. Front Oncol 2023; 13:1142133 .

➢ Histopathology

Primary Small Intestinal Lymphoma



- DLBCL of the ileum, photomicrograph (original magnification ×200, 400; H-E stain) of the specimen shows diffuse large lymphocytes (> 2.5-times larger than normal cells) infiltrating into the intestinal epithelium; no germinal centers were observed; some lymphocytes had nucleoli; lymphoepithelial lesions; part of the muscular layer had been destroyed (A, B).
- MALT of the jejunum, photomicrograph (original magnification ×40, 400; H-E stain). Histologically, extensive infiltration of normal-sized lymphocytes was observed throughout the corresponding intestinal wall and, occasionally, into the subserosa (C, D).
- Follicular lymphoma of the duodenum. The photomicrograph (original magnification ×40; H-E stain) shows the presence of individual submucosal lymphoid follicles (arrow), and no apoptotic appearance was observed (E).
- Monomorphic epitheliotropic intestinal T-cell lymphoma of the jejunum. The photomicrograph (original magnification, ×40; H-E stain) shows small- to focally medium-sized lymphocytes diffusely infiltrating into the intestinal epithelium. The nuclei are oval-shaped or distorted (F).

Abbreviations: DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma.

Courtesy of: Tian FY, et al. Front Oncol 2023; 13:1142133 (Figure 2)

- **Secondary Tumours**

➢ Pathology
  - Submucosal nodules/plaques
    - Grow intramurally → cause obstruction, intussusception, or perforation.
  - May also simulate Crohn disease, presenting as stenotic lesions or infiltrative lesions.
  - Metastatic Melanoma - 1/3 of SI metastases
    - Others: carcinomas from
      - Lung
      - Testes
      - Adrenal
      - Ovary
      - Stomach
      - Large intestine
      - Uterus
      - Cervix
      - Liver/kidney

Abbreviations: 5- HIAA, 5-hydroxy indol acetic acid; 5-HT, 5- hydroxy tryptamine (serotonin); AIDS, acquired immunodeficiency syndrome; bid, twice-a-day; BMI, body mass index; CTE, computed tomography enteropathy; D, duodenum; EATLs, enteropathy-associated T-cell lymphomas; EMR, endoscopic mucosal reaction; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; FAP, familial adenomatous polyposis; GISTs, gastrointestinal tumours; hpf, high power field; HRT, hormone replacement therapy; IPSID, Immunoproliferative small intestinal disease; LP, lamina propria; MMR, defective mismatch; MALT, marginal B-cell lymphoma; MEN, multiple endocrine neoplasia; mon, months; MRE, magnetic resonance enterography; N/V, nausea/vomiting; NETs, neuroendocrine tumours; NF, neurofibroma; OR, odds ratio; PPI, proton pump inhibitor; PSIL, primary small intestinal cell lymphoma; RFA, radiofrequency ablation; RR, relative risk; SI, small Intestine; tid, three-times-a-day; US, United States of America; VCE, video capsule endoscopy; yr, year

FOOD ALLERGY, INTOLERANCE, AND ADVERSE REACTION

Zaki Alhashimalsayed

- Definitions
  - Adverse Food Reaction
    - Any untoward reaction following ingestion of food or food additive. May be toxic or non-toxic.
  - Food Allergy
    - Immune-mediated adverse reaction to food. May be IgE-mediated ("immediate") or non-IgE-mediated ("delayed").
  - Food Intolerance
    - Non-immune mediated adverse reaction. May be enzymatic, pharmacologic, or idiopathic.

Food Allergies

- Prevalence
  - Atopic Children, 35–40%
  - Non-atopic, 8%
  - Adults, 2–10%
- Common Food Allergens
  - Peanut (Most common)
  - Cow's Milk (Second most common)
  - Shellfish
  - Tree Nuts
  - Egg
  - Fish
  - Wheat
  - Soy
  - Sesame (least common)
- Pathophysiology
  - Normal barriers of the GI tract
  - Epithelial cells with tight junctions
  - Glycocalyx coating that traps particles
  - Intestinal peristalsis
  - Gastric acid and enzymes
  - Salivary amylases

- Immunologic Barriers
  - Secretory IgA in intestinal lumen
  - Serum antigen-specific IgA and IgG
  - Reticuloendothelial system
  - Regulatory T cells
  - Dendritic cells

- The Mucosal Immune System
  - Mucosal Immune Response
    - Constantly exposed to high antigen loads (food, microbes) but avoids overreaction. Balances tolerance, not protection.
  - Gut-Associated Lymphoid Tissue (GALT)
    - Differentiates harmful from harmless proteins.
      - The GI tract is the largest reservoir of immune cells in the body.

- Oral Tolerance Development
  - Antigen Exposure
    - Food proteins enter the GI tract
  - Dendritic Cell Processing
    - CD103+ cells take up and process antigens
  - Regulatory T Cell Induction
    - Suppresses immune reactivity to harmless proteins
  - Oral tolerance is an active regulatory response that prevents reactions to harmless food proteins.
  - Failure to develop oral tolerance results in food allergy.

- IgE-Mediated Food Allergies
  - Allergen Exposure: Food protein enters body
  - IgE Production: Antibodies bind to mast cells
  - Cell Activation: Re-exposure triggers mediator release
    - Histamine
    - Prostaglandins
    - Leukotrienes

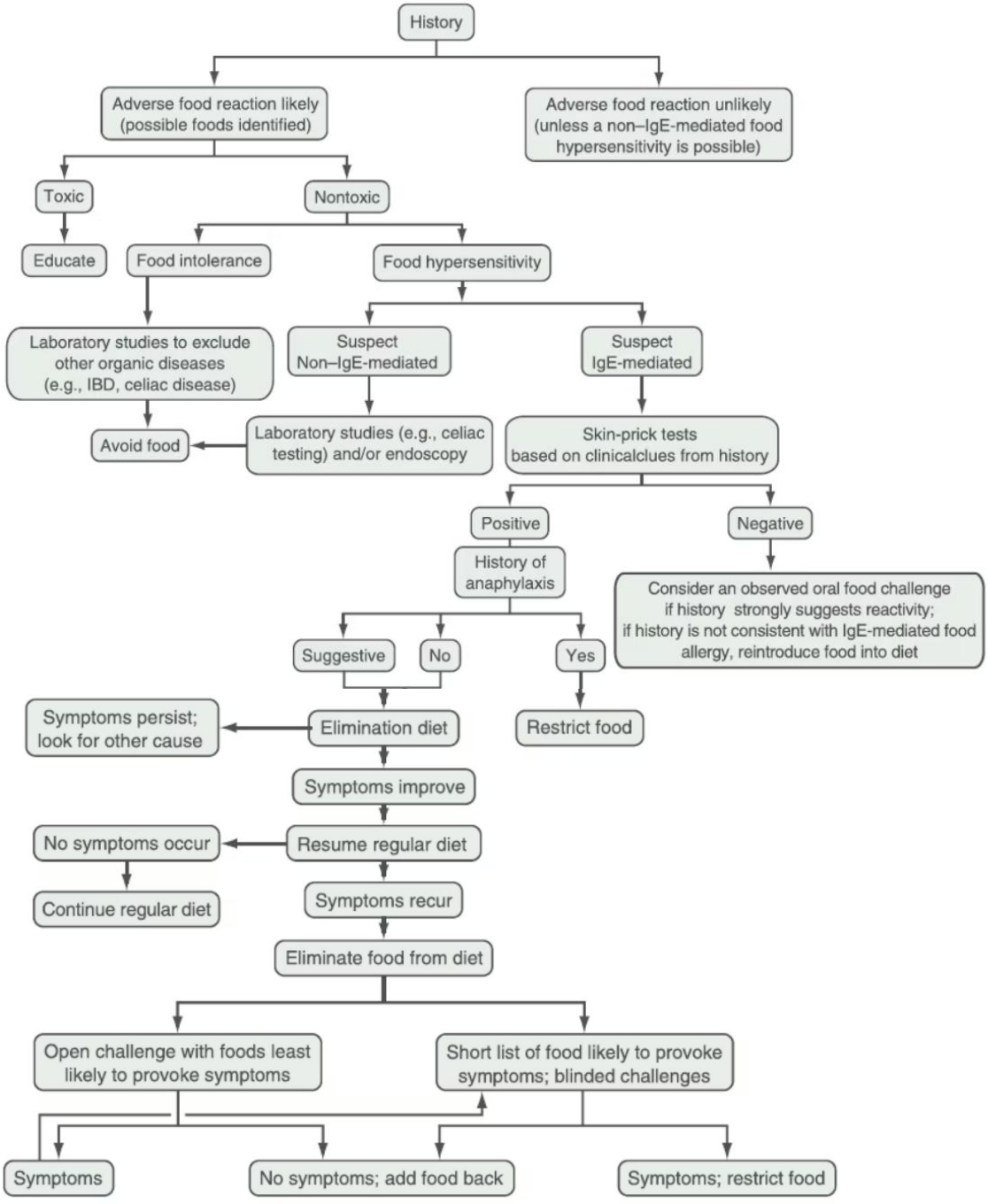
➢ Clinical
  - Symptoms: Rapid onset within minutes to 2 hours
    - Blood vessels → vasodilation
    - Smooth muscle → contraction
    - Mucus secretion

GI Food Hypersensitivities

- Classification
  - IgE-Mediated Hypersensitivities
    - Classic food allergies
    - Infantile colic (minor subset)
    - Pollen-food allergy syndrome (oral allergy syndrome)
  - Mixed IgE & Non-IgE-Mediated
    - Eosinophilic esophagitis
    - Eosinophilic gastritis
    - Eosinophilic gastroenteritis
    - Allergic eosinophilic proctocolitis
  - Non-IgE-Mediated Hypersensitivities
    - Dietary protein-induced enteropathy (e.g., Celiac disease, Dermatitis herpetiformis)
    - Food protein-induced enterocolitis syndrome (FPIES)
  - Mechanism Unknown
    - Cow's milk–induced occult GI blood loss (iron-deficiency anemia of infancy)
    - GERD
    - Infantile colic (subset)
    - Inflammatory Bowel Disease (IBD)

- Differential
  - Infectious Mimics
    - Enterotoxigenic bacteria: Vibrio cholerae, toxigenic E. coli, C. difficile
    - Post-infectious malabsorption: Shigella, Giardia, Rotavirus
  - Metabolic Disorders
    - Acrodermatitis enteropathica
    - Carbohydrate malabsorption: Lactase or sucrase deficiency
    - Fructose/sorbitol malabsorption
    - Hypo-/abetalipoproteinemia
  - Anatomic Abnormalities
    - Hirschsprung disease (esp. with enterocolitis)
    - Ileal stenosis
    - Intestinal lymphangiectasia
    - Short bowel syndrome
  - Other Mimicking Conditions
    - Chronic nonspecific diarrhea of infancy
    - Cystic fibrosis
    - Inflammatory Bowel Disease (IBD)
    - Tumours: Neuroblastoma, Zollinger-Ellison syndrome

- Diagnosis of Food Allergies
  - Medical History: Identify suspected foods and reaction patterns
  - Laboratory Testing: Skin prick tests or serum IgE for suspected foods
  - Elimination Diet: Remove suspected allergens for 1–12 weeks
  - Oral Food Challenge: Gold standard for confirming diagnosis
- Prevention of Food Allergies
  - Early Introduction: The LEAP trial showed 81% reduction in peanut allergy risk with early introduction in high-risk infants.
  - Allergenic Foods: Current guidelines recommend introducing allergenic foods in the first year of life, not delaying introduction.
  - Risk Assessment: Infants with severe eczema or egg allergy should be evaluated before peanut introduction at 4–6 months.
- Treatment Approaches
  - Allergen Avoidance
    - Strict elimination of offending allergens remains the primary management strategy. Patients must scrutinize food labels.
  - Emergency Medications
    - Epinephrine auto-injectors must be available at all times for those at risk of anaphylaxis. Antihistamines can
  - Allergen Avoidance
    - Strict elimination of offending allergens remains the primary management strategy. Patients must scrutinize food labels.
  - Emergency Medications
    - Epinephrine auto-injectors must be available at all times for those at risk of anaphylaxis.
    - Antihistamines can help with mild symptoms.
  - Immunotherapy
    - Emerging approaches include:
      - Oral immunotherapy (OIT)
      - Sublingual immunotherapy (SLIT)
      - Epicutaneous immunotherapy (EPIT)
  - Monitoring
    - Periodic rechallenges to determine if tolerance has developed, especially for milk, egg, wheat, and soy allergies.


History
Adverse food reaction likely (possible foods identified)
Adverse food reaction unlikely (unless a non–IgE-mediated food hypersensitivity is possible)
Toxic
Nontoxic
Educate
Food intolerance
Food hypersensitivity
Laboratory studies to exclude other organic diseases (e.g., IBD, celiac disease)
Suspect Non–IgE-mediated
Suspect IgE-mediated
Avoid food
Laboratory studies (e.g., celiac testing) and/or endoscopy
Skin-prick tests based on clinicalclues from history
Positive
Negative
History of anaphylaxis
Consider an observed oral food challenge if history strongly suggests reactivity; if history is not consistent with IgE-mediated food allergy, reintroduce food into diet
Suggestive
No
Yes
Symptoms persist; look for other cause
Elimination diet
Restrict food
Symptoms improve
No symptoms occur
Resume regular diet
Continue regular diet
Symptoms recur
Eliminate food from diet
Open challenge with foods least likely to provoke symptoms
Short list of food likely to provoke symptoms; blinded challenges
Symptoms
No symptoms; add food back
Symptoms; restrict food

Emerging Immunotherapies

Therapy Type	Method	Efficacy	Side Effects
○ Oral Immunotherapy (OIT)	− Ingesting gradually increasing doses of allergen	− 79% of subjects tolerated 443mg of peanut protein vs 19% placebo	▪ Common but generally mild
○ Sublingual Immunotherapy (SLIT)	− Small amounts of allergen under the tongue	− Desensitization in up to 70% of participants	▪ Well-tolerated, few systemic reactions
○ Epicutaneous Immunotherapy (EPIT)	− Allergen-containing patch on intact skin	− Modest changes in threshold, significant in children 6–11 years	▪ Mostly local skin reactions

- **IgE-Mediated GI Disorders**

➢ Clinical

- ○ Rapid onset (minutes to 1 hr after ingestion)
- ○ Involve IgE antibodies, confirmed via:
  - − Skin prick tests
  - − Serum food-specific IgE

➢ Classification

- ○ Pollen-Food Allergy Syndrome (PFAS)
  - − Also known as oral allergy syndrome
  - − Symptoms: itching/swelling of lips, tongue, palate
  - − Triggered by raw fruits/vegetables
  - − Linked to seasonal allergic rhinitis
- ○ Gastrointestinal Allergy
  - − Reaction involving GI tract + other organs
  - − Onset: within 2 hours of food ingestion
  - − Symptoms: nausea, pain, vomiting, diarrhea

- **Mixed IgE / Non-IgE Mediated GI Disorders**

➢ Clinical

- ○ Caused by both IgE and non-IgE mechanisms
- ○ Involve eosinophilic infiltration of the GI tract
- ○ Present with peripheral eosinophilia in up to 50%
- ○ Often overlap with atopic conditions (eczema, asthma)

- Eosinophilic Esophagitis (EoE)
  - Symptoms: dysphagia, food impaction, chest pain, vomiting, early satiety, failure to thrive
  - Common in young children; linked to food allergies
  - Diagnosis: ≥15 eos/hpf on biopsy, often requires multiple biopsies
  - Management: dietary elimination, topical steroids, PPIs
- Eosinophilic Gastritis (EG)
  - Symptoms: nausea, vomiting, diarrhea, pain, anemia, GI bleeding
  - Peripheral eosinophilia common
  - Diagnosis via gastric biopsy
  - Often associated with food antigens but mechanism unclear
- Eosinophilic Gastroenteritis
  - Involves multiple GI layers, from mucosa to serosa
  - May present with obstruction or protein-losing enteropathy
  - Biopsy confirms diagnosis; elimination diet or steroids used
- Allergic Eosinophilic Proctocolitis (AEP)
  - Typically seen in infants (esp. breastfed)
  - Painless rectal bleeding, often linked to cow's milk or soy protein
  - Biopsy: eosinophils in rectal lamina propria
  - Usually resolves within 6–24 mon of elimination

- **Non-IgE-Mediated GI Food Hypersensitivities**

➢ Pathogenesis

- No IgE-mediated reactions
- Cell-mediated immune responses

➢ Clinical

- Delayed symptoms

➢ Classification

- Food Protein-Induced Enterocolitis Syndrome (FPIES)
  - Triggers: cow's milk, soy, rice, oats, fish, egg
  - Acute: profuse vomiting (1–4 hrs after eating), lethargy
  - Chronic: diarrhea, failure to thrive, anemia
  - Diagnosis: clinical + food challenge

- Food Protein-Induced Enteropathy (FPE)
  - Presents with chronic diarrhea, poor weight gain
  - Cow's milk = most common cause
  - Biopsy: villous atrophy, crypt hyperplasia
  - Improves with allergen elimination
- Celiac Disease (CD)
  - Autoimmune enteropathy triggered by gluten
  - Associated with HLA-DQ2/8
  - Diagnosis: positive IgA TTG + biopsy
  - Treatment: strict gluten-free diet
- Other related conditions include
  - Dermatitis Herpetiformis (skin manifestation of CD)
  - Cow's milk-induced occult GI blood loss
  - Some cases of GERD in infants that respond to milk elimination

Abbreviations: AEP, allergic eosinophilic proctocolitis; CD, celiac disease; EoE, eosinophilic esophagitis; EG, eosinophilic gastritis; FPE, food protein-induced enteropathy; FPIES, food protein-induced enterocolitis syndrome; GALT, gut-associated lymphoid tissue; GERD, gastroesophageal reflux disease; GI, gastrointestinal; hpf, high-power field; IBD, inflammatory bowel disease; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; OIT, oral immunotherapy; PFAS, pollen-food allergy syndrome; PPI, proton pump inhibitor; SLIT, sublingual immunotherapy; EPIT, epicutaneous immunotherapy; TTG, tissue transglutaminase antibody.

COLON

BREAKING DOWN BLOATING

Khalid Alseiari

Bloating And Distention

- Background
  - Bloating and distention are among the most common GI complaints in outpatient practice, affecting >50% of patients with IBS and other DGBIs.
  - Impact
    - Impaired quality of life
    - Absenteeism
    - High healthcare utilization
  - Challenge
    - Limited high-quality evidence
    - Overlap with many DGBIs

Constipation

- Definitions
  - Belching
    - Audible escape of air from esophagus/stomach
    - Rome IV defines excessive belching when bothersome and >3 days/wk
    - Subtypes
      - Gastric vs supragastric.
  - Bloating
    - Subjective sensation of fullness/tightness.
  - Distention
    - Objective visible increase in girth.

- Differential Diagnosis
  - Distension
    - Fat
    - Feces
    - Flatus
    - Fetus
    - Fluid
    - (Fatal) Tumour
  - CIC
  - IBS-C
    - Subacute on chronic
      - Post-infectious

- IBS Symptoms
  - Abdominal pain and bloating commonly identified as worst IBS symptoms.
  - Patient-reported distress:
    - Abdominal pain/discomfort (58%)
    - Bloating (55%)
    - Gas (46%)
    - Constipation (46%)
    - Diarrhea (27%)

Bristol Stool Form Scale (BSFS)

- Type 1: Separate hard lumps, like nuts (hard to pass) → Severe constipation.
- Type 2: Sausage-shaped but lumpy → Mild constipation.
- Type 3: Sausage with cracks on surface → Normal.
- Type 4: Sausage or snake, smooth and soft → Normal.
- Type 5: Soft blobs with clear-cut edges → Lacking fibre.
- Type 6: Fluffy pieces with ragged edges, mushy stool → Mild diarrhea.
- Type 7: Watery, no solid pieces, entirely liquid → Severe diarrhea.

- Causes/Associations
  - Gas and liquid in gut
  - Central nervous system
  - Enteric nervous system.
  - Poorly absorbed carbohydrates (innate or disease-related)
  - Microbiome (species/location)
  - Visceral hypersensitivity.

- Diagnostic Approach
  - History/physical usually sufficient for functional bloating.
  - Tests when indicated
    - Celiac serology ± biopsy for diarrhea/iron deficiency.
    - SIBO testing only in high-risk patients (CF, scleroderma, post-surgical, severe malnutrition).
    - Imaging/endoscopy only if alarm features (weight loss, bleeding, abnormal exam, family history of cancer/IBD).
    - Anorectal testing if constipation/evacuation disorder suspected.

- Treatment
  - Belching
    - Supragastric
      - First line
        - Brain–gut behavioral therapies (CBT, diaphragmatic breathing, speech therapy)
      - Adjunct
        - Neuromodulators
      - Gastric
        - Related to GERD
          - Treat GERD ± baclofen
  - Bloating/Distention
    - Dietary
      - Trial of low-FODMAP diet with dietitian guidance
      - Address carbohydrate enzyme deficiencies (lactose, fructose)
      - Gluten-free diet only if celiac confirmed
  - Pharmacologic
    - Avoid probiotics (not recommended).
    - Use constipation-targeted drugs if present (PEG, linaclotide, prucalopride).
    - Central neuromodulators for visceral hypersensitivity.
  - Behavioral
    - Cognitive behaviour therapy (CBT)
    - Gut-directed hypnotherapy
    - Biofeedback if pelvic floor dysfunction
  - Abdominophrenic Dyssynergia (APD)
    - Pathophysiology
      - Paradoxical diaphragm contraction with abdominal wall relaxation.
    - Treatment
      - Diaphragmatic breathing
      - Biofeedback
      - Neuromodulators.

Best Practice Advice

- Clinical history and physical examination findings and impedance pH monitoring can help to differentiate between gastric and supragastric belching.
- Treatment options for supragastric belching may include brain–gut behavioral therapies, either separately or in combination, such as cognitive behavioral therapy, diaphragmatic breathing, speech therapy, and central neuromodulators.
- Rome IV criteria should be used to diagnose primary abdominal bloating and distention.

- Carbohydrate enzyme deficiencies may be ruled out with dietary restriction and/or breath testing. In a small subset of at-risk patients, small bowel aspiration and glucose- or lactulose-based hydrogen breath testing may be used to evaluate for small intestinal bacterial overgrowth.
- Serologic testing may rule out celiac disease in patients with bloating and, if serologies are positive, a small bowel biopsy should be done to confirm the diagnosis. A gastroenterology dietitian should be part of the multidisciplinary approach to care for patients with celiac disease and nonceliac gluten sensitivity.
- Abdominal imaging and upper endoscopy should be ordered in patients with alarm features, recent worsening symptoms, or an abdominal physical examination only.
- Gastric emptying studies should not be ordered routinely for bloating and distention, but may be considered if nausea and vomiting are present. Whole gut motility and radiopaque transit studies should not be ordered unless other additional and treatment-refractory lower gastrointestinal symptoms exist to warrant testing for neuromyopathic disorders.
- In patients with abdominal bloating and distention thought to be related to constipation or difficult evacuation, anorectal physiology testing is suggested to rule out a pelvic floor disorder.
- When dietary modifications are needed (e.g., low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet), a gastroenterology dietitian should preferably monitor treatment.
- Probiotics should not be used to treat abdominal bloating and distention.
- Biofeedback therapy may be effective for bloating and distention when a pelvic floor disorder is identified.
- Central neuromodulators (e.g., antidepressants) are used to treat bloating and abdominal distention by reducing visceral hypersensitivity, raising sensation threshold, and improving psychological comorbidities.
- Medications used to treat constipation should be considered for treating bloating if constipation symptoms are present.
- Psychological therapies, such as hypnotherapy, cognitive behavioral therapy, and other brain–gut behavior therapies may be used to treat patients with bloating and distention.
- Diaphragmatic breathing and central neuromodulators are used for patients with bloating and distention related to abnormal dyssynergia.

- Take-home messages
  - Bloating is very common and important in primary and tertiary care.
  - History and physical are very accurate in excluding sinister pathology.
  - Always consider celiac disease in the differential, but non-celiac gluten sensitivity is more common.
  - Be aware of pitfalls of SIBO diagnosis.
  - Use diet-microbiome-neural hypersensitivity model to guide treatment and patient-physician relationship.

MISCELLANEOUS (please see later chapters for further detail)

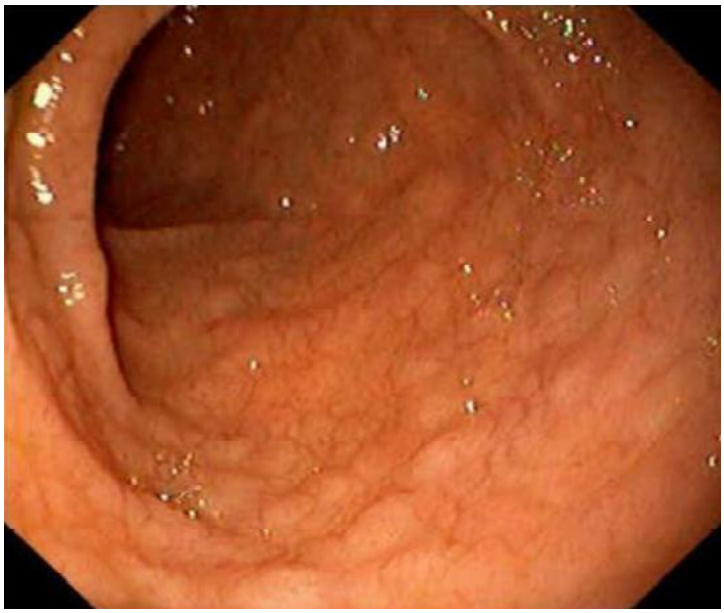
Celiac Disease

- Whole Grain Kernel
  - Gluten = gliadin + glutelin
  - Starch = amylose + amylopectin.
  - Slice of bread = 2 g gluten.
  - Average daily consumption = 12 g.

- Pathogenesis
  - Allergic reaction to toxic alcohol-soluble protein components in grains (prolamins) = antigens
    - Gliadins - wheat gluten
    - Secalins - rye
    - Hordeins - barley
  - Immune complexes form in mucosa triggering activation of killer T-lymphocytes
  - Specific HLA class II DQ haplotypes
  - DQ gene (ch 6) products preferentially present gluten-derived peptides to mucosal T-cells
  - Amino acid sequence homology between gliadin and a protein in adenovirus type 12; infection sensitizes T-cells to antigenic determinant shared with gliadin

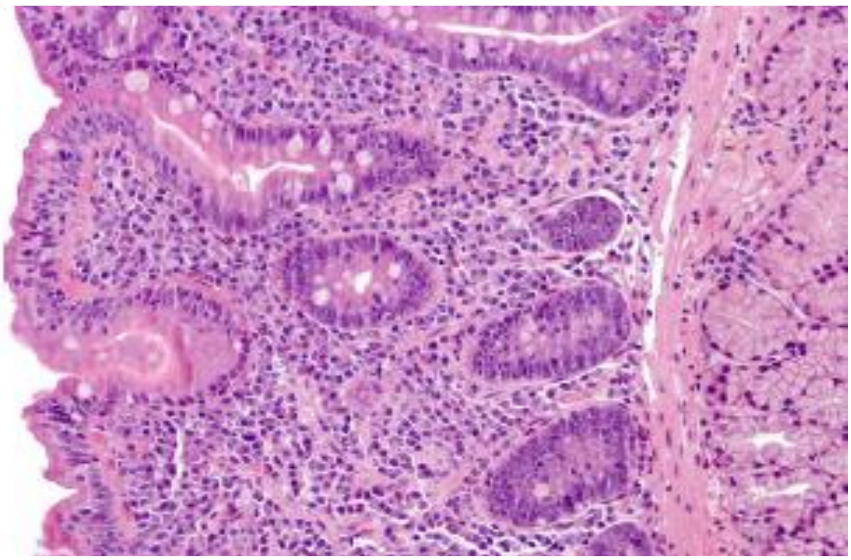
- Diagnosis

Endoscopy, Celiac Disease



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

Histopathology, Celiac Disease



- Complete villous atrophy
- ↑ intraepithelia cells (IELs)
- Crypt hyperplasia

Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 1; 2021. ISBN: 9798719829074.

- Serology testing
  - All screening and diagnostic tests need to be done with the patient on a gluten-containing diet *
  - Old serology – outdated
    - IgG/IgA anti-gliadin antibodies, antireticulin antibodies
  - IgA EMA – qualitative immunofluoresence technique
    - Monkey esophagus or human umbilical cord
  - IgA anti-tTG – quantitative immunosorbant assay
    - Guinea pig (GP) or human recombinant (HU)

*NIH Consensus Document 2004; AGA technical review: Gastroenterology 2006;131:1977-1980

  - Sensitivity & Specificity of Serology for Diagnosis of Celiac Disease

Test	Sensitivity (95% CI)	Specificity (95% CI)
- IgA EMA	0.974 (0.957-0.985)	0.996 (0.988-0.999)
- IgA EMA HU	0.902 (0.863-0.925)	0.996 (0.984-0.999)
- IgA tTG-GP	0.90 (Heterogeneity)	0.953 (0.925-0.981)
- IgA tTG-HR	0.951 (0.918-0.981)	0.983 (0.971-0.996)

- IgA Deficiency
  - Up to 1/50 CD patients IgA deficient
    - results in false negative serology
  - IgG antibodies can be ordered
    - IgG anti-tTG
    - Role for IgG anti-deamidated gliadin peptide (anti-DGP)?

- Diagnostic strategies when on GFD
  - Gluten challenge then serology +/- biopsy
    - 2-4 pieces of bread (8 g of gluten) for 4-8 weeks
  - Endoscopy/biopsy to look for subtle change
    - Over 50% of patients with severe disease can have residual changes for up to two years
    - Ensure six biopsies proximal duodenum
  - HLA typing to exclude
    - Over 95% of patients DQ2 and/or DQ8 positive

Small Intestinal Bacterial Overgrowth (SIBO)

- Up to 20% of IBS patients have abnormal breath hydrogen test.
- Trial of antibiotics reasonable if abnormal test result.

Irritable Bowel Syndrome (IBS)

- IBS is a chronic functional bowel disease (FBD) with no structural organic cause characterized by abdominal pain, cramps, bloating, and altered bowel habits
- The Rome IV Criteria specifically defines IBS as recurrent abdominal pain at least 1 day/week (on average) in the last 3 months 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
- Criteria should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Lacy BE, Mearin FC, et al. Gastroenterology 2016; 150: 1393-1407.

➢ **IBS Symptoms Relief**

Low FODMAP diet

Category	FODMAPs	Absorption	Potential GI Effects	Foods High in FODMAPs
○ Polysaccharides and Oligosaccharides	Fructans, Galactans (prebiotics)	Malabsorbed by all people (lack digestive enzymes)	Rapidly fermented in large intestine → gas, bloating	Legumes (beans), onion, cabbage, chicory root
○ Disaccharides	Lactose	Malabsorbed in people with lactase deficiency	Fermented in large intestine → gas, bloating; attracts water → laxation	Dairy products (amount varies by type)
○ Monosaccharides	Fructose	Slowly absorbed in small intestine; faster when consumed with more glucose	Fermented in large intestine; attracts water → laxation	Apples, pears, artichoke, asparagus, honey, fruit juices

Category	FODMAPs	Absorption	Potential GI Effects	Foods High in FODMAPs
○ Polyols (Sugar Alcohols)	Mannitol, Sorbitol	Malabsorbed by all people (lack digestive enzymes); small portion absorbed via passive diffusion	Fermented in large intestine; attracts water → laxation	Apples, pears, pitted fruits, mushrooms, cauliflower, many diet foods/beverages

- **Rifaximin**
  - Minimally absorbed oral antibiotic
  - Rifaximin mode of action mediated by the microbiome

- **Tenapanor** (Transport inhibitor NHE3)

PHASE III Clinical Trials in IBS-C: Tenapanor (Transport inhibitor NHE3)

- TENAPANOR
  - 629 patients, Rome III IBS-c, 12-wk RCT phase, ITT analysis
  - Mean age 45 (81.4 % female)
  - 4-wk randomized withdrawal period
  - Tenapanor 50 mg bid vs placebo
  - Colonoscopy if over 50 or “red flags”
- The Primary Outcome: A Composite Endpoint
  - 30% decrease in IBS related pain
  - ≥ 1 increase CSBM* in same week

  } For at least 6 of the 12 weeks

Rome II definition3: At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features: Relieved with defecation; and/or onset associated with change in frequency of stool; and/or onset associated with change in form (appearance) of stool.
Rao S, et al. Am J Gastroenterol. 2012;107(11):1714–24; 2.
Chey WD, et al. Am J Gastroenterol. 2012;107(11):1702–12.

- Results (Tenapanor vs placebo)
  - 12 WEEK RANDOMIZED PHASE
    - Completed therapy: 87.7% vs 81.8%
    - Combined outcome: 27.0% vs 18.7% (p= 0.02)
    - Abdominal pain: 44.0% vs 33.1% (p= 0.008)
    - CSBM responder: 33.9% vs 29.4% (p= 0.27)

- 4 WEEK RANDOMIZED WITHDRAWAL
  - Placebo/tenapanor
    - 40% improvement in pain
    - 1.5 more CSBMs per week
    - (p< 0.05)

Rao S, et al. Am J Gastroenterol. 2012;107(11):1714–24.
Chey WD, et al. Am J Gastroenterol. 2012;107(11):1702–12.
CONSTELLA, Canadian Product Monograph, Allergan In., August 28, 2018

- **Linaclotide** (Agonist of Guanylate Cyclase)

  - PHASE II Clinical Trials in IBS-C: Linaclotide (peptide guanylate cyclase-C agonist)

Rome II definition3: At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features: Relieved with defecation; and/or onset associated with change in frequency of stool; and/or onset associated with change in form (appearance) of stool.

- TRIAL 31[1] & 302[2]
  - Two similar, Phase III, double-blind, randomized, multicenter, placebo-controlled trials
  - 1,604 IBS patients (Rome II criteria*), with constipation.
  - 12-wk (Trial 31) and 26-wk (Trial 302) Tx phase (linaclotide 290 µg OD or placebo)
- The Primary Outcome: A Composite Endpoint
  - 30% decrease in IBS related pain
  - ≥ 1 increase CSBM* in same week

  } For at least 6 of the 12 weeks

1. Rao S, et al. Am J Gastroenterol. 2012;107(11):1714–24
2. Chey WD, et al. Am J Gastroenterol. 2012;107(11):1702–12.

  - PHASE III Clinical Trials in IBS-C & Practical CONSIDERATIONS
    - Primary Endpoint: Composite response = improvement in both abdominal pain and complete spontaneous bowel movements (CSBM).
    - Trial 301
      - Linaclotide (290 µg once daily): 33.6% of patients responded
      - Placebo: 21.0% responded
      - Statistical significance: P < 0.0001
    - Trial 302
      - Linaclotide (290 µg once daily): 33.7% of patients responded
      - Placebo: 13.9% responded
      - Statistical significance: P < 0.0001
    - Practical considerations
      - Indication is for the treatment of IBS-C in adults.
      - The recommended dose for IBS-C is oral 290 µg OD on an empty stomach, at least 30 minutes prior to the first meal of the day

- Counsel patients that improvement of bowel symptoms should occur within the first week of treatment, but improvement of abdominal symptoms may take longer
- Periodically assess the need for continued treatment
- Patients who experience severe diarrhea should stop treatment

Rao S, et al. Am J Gastroenterol. 2012;107(11):1714–24.
Chey WD, et al. Am J Gastroenterol. 2012;107(11):1702–12.
CONSTELLA, Canadian Product Monograph, Allergan In., August 28, 2018

Chronic Idiopathic Constipation (CIC)

- Regularity
  - Regular meals, exercise, time to have BM (especially in am)
- Diet
  - More water, high fiber food that are soluble in water (e.g., oatmeal)
- Stool bulking
  - Metamucil, Benefiber
    - ½ tbsp to 2 tbsp each morning (increase over two months)
- Stool hydration
  - MOM, Lactulose or PEG 3350
    - 17 g (one capful) in 250 mL of water each evening
    - Increase to 34 g in 500 mL after 2 weeks if < one BM/day
    - Decrease to 8.5 g in 250 mL after if loose or urgent BMs
- Secretory agents
  - Linaclotide (Constella) 145 micrograms before breakfast
- Motility agents
  - Prucalopride (Resotran) 2 mg each morning for 4 weeks, continue at least three months if effective

Abbreviations: AEP, allergic eosinophilic proctocolitis; APD, abdominophrenic dyssynergia; BSFS, Bristol Stool Form Scale; CBT, cognitive behavioural therapy; CD, celiac disease; CIC, chronic idiopathic constipation; CI, confidence interval; CSBM, complete spontaneous bowel movement; DGBI, disorder of gut–brain interaction; DGP, deamidated gliadin peptide; EMA, endomysial antibody; FBD, functional bowel disease; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; FPIES, food protein-induced enterocolitis syndrome; GP, guinea pig; GFD, gluten-free diet; GI, gastrointestinal; hpf, high-power field; HU, human recombinant; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IEL, intraepithelial lymphocyte; ITT, intention-to-treat; MOM, milk of magnesia; NHE3, sodium/hydrogen exchanger isoform 3; OD, once daily; OIT, oral immunotherapy; PEG, polyethylene glycol; PFAS, pollen-food allergy syndrome; PPI, proton pump inhibitor; RCT, randomized controlled trial; SIBO, small intestinal bacterial overgrowth; SLIT, sublingual immunotherapy; SSA, somatostatin analogue; tTG, tissue transglutaminase antibody.

COLORECTAL CANCER (CRC)

Hasan Bualbanat

- Demography
  - The 3rd most common cancer in males and females in the US
  - The 4th most common cause of cancer related deaths in the US.
  - Around 90% of CRC cases occur in patients >50 yr old
  - Lifetime risk of CRC6%
  - Younger patients are being diagnosed with CRC, their CRC often advanced histopathology and recommendation for onset of screening for CRC is now age 45

- Types
  - 95% of CRCs are adenocarcinomas
  - Other subtypes
    - Lymphoma
    - Leiomyosarcoma
    - Carcinoid
  - Metastasis-to the colon may occur from
    - Adenocarcinoma from breast, ovary, prostate, lung, and stomach.
    - Lymphoma
    - Leiomyosarcoma
    - Malignant melanoma
    - From colon to
      - Liver
      - Peritoneal cavity
      - Lungs
      - Less common: adrenal glands, ovaries, and bones

- Clinical
  - Related to tumour size and location
    - Proximal tumour (cecal to splenic flexure)
      - Vague abdominal pain, weight loss, anemia and occult bleeding
      - Sometimes a palpable mass
    - Distal tumours (descending colon to rectum)
      - Altered bowel movement, ↓ stool caliber, Hematochezia/anemia
      - Bowel obstruction
    - Other presentations!
      - Abscess formation
      - Perforation
      - Jaundice (a hepatic mutation)

- Risk factors of CRC
  - Age
  - Gender
  - Race
  - First degree relatives with CRC
  - Smoking
  - Alcohol consumption
  - Lack of physical activity
  - Diet
  - Hereditary colon syndromes
  - Inflammatory Bowel Disease (IBD)
    - IBD plus primary sclerosing cholangitis
  - Prior Surgery e.g., cholecystectomy

- Genetic Pathways
  - Chromosomal Instability pathway:
    - Hereditary
      - FAP- and MutHY-associated polyposis
    - Acquired due to mutations of APC, KRAS, DCC, SMAD, and TP53 genes
  - Mutator Phenotype (Hereditary pathway):
    - Cancer pathway of Lynch syndrome.
    - Germline mutation on one of the mismatch repair gene (MMR gene)
    - Mutations in
      - BAX
      - Caspase5
      - Insulin growth factor one (IGF-1) and
      - TGF-B II Receptors
  - Serrated neoplasia pathway
    - Sessile serrated lesions (develop through BRAF mutation)
      - CpG island hypermethylation phenotype (CIMP) → DNA hypermethylation → MLH1 methylation → dysplasia → MMR deficient CRC
      - TP53 mutation → dysplasia → MMR proficient CRC
    - Sessile serrated lesions developed through KRAS mutation → TP53 mutation → dysplasia → Proficient CRC

❖ Adenomatous CRC Syndrome

- **Familial Adenomatous Polyposis** (FAP)
  - Autosomal dominant condition
    - Genetic occurring for first degree relatives
    - Due to mutation in the APC gene
  - Risk of CRC by age 451, 100%
  - Screen with flexible sigmoidoscopy yearly starting at age 10-12 yr
  - Treatment prophylactic colectomy starting at ~20 yr
  - Duodenal carcinoma → screen with EGD/side viewing duodenoscope, starting at age 25 yr
    - Use Spigelman Score to determine when surgery is required

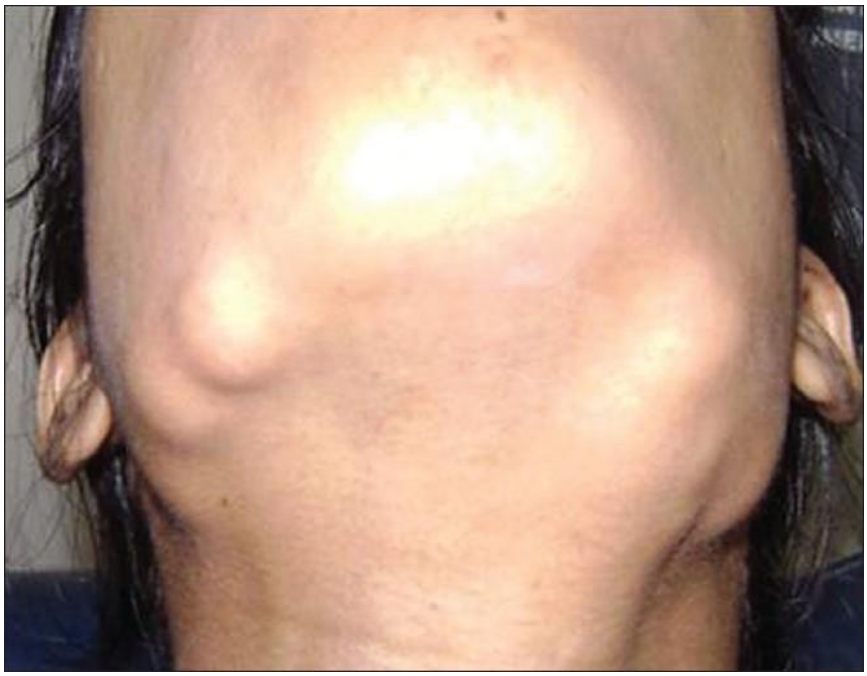
- Spigelman Score (FAP polyps in duodenum to direct decision about surgical duodenectomy)

		Points	
Factor	1	2	3
Polyp			
− Number	< 4	5–20	> 20
− Size (mm)	1–4	5–10	> 10
− Histology	Tubular	Tubulovillous	Villous
Dysplasia	Low-grade	— (not applicable)	High-grade

- **Gardner Syndrome**
  - Variant of FAP (APC mutation)
    - Same phenotypic features of FAP, plus
      - Eyes
        - Congenital hypertrophy of the retinal pigmented epithelium
      - Teeth
        - Supernumerary teeth
      - Skull / long bones
        - Osteomas of the skull and long bones.
      - Pancreas
        - Ampullary adenocarcinoma
      - Tumours
        - Desmoid tumours
        - Epidermoid cyst
        - Fibromas/lipomas

- Genetic screening
  - First degree relatives
  - Once polyposis occurs → refer patient for prophylactic colectomy

Extraoral Osteomas in Patients with FAP



- Diffuse bilateral swellings on the lower third of face along the mandibular border.

Courtesy of: Panjwani S, et al. J Clin Imaging Sci 2011;1:65.

- **Attenuated FAP**
  - Adenomas typically < 100 (less than FAP)
    - Onset of polyps, at age 45 yr
    - Carcinoma at age 55 ye
  - Life-time cumulative risk of CRC,70%
  - Surveillance starts at age of 20 yr
    - Colonoscopy q2-3 yr
    - EGD q1-3 yr

- **MutYH Associated Polyposis** (MAP)
  - Autosomal recessive
    - Wide-range phenotype
  - Colorectal adenoma burden
    - May be similar to attenuated FAP.
  - Other sites for adenoma
    - Duodenal
    - Periampullary
  - Risk of CRC
    - One MYH allele affected
      - No risk of CRC
    - Both MYH alleles affected
      - 80% risk of CRC by age 70 yr
  - Surveillance starts at age 20 yr, then
    - Colonoscopy q2-3 yr
    - EGD start age 25-30 yr then q1-3 yr

- **Lynch Syndrome** (Hereditary Non-polyposis Colon Cancer [HNPCC])
  - Accounts as 6% of all CRC
  - Autosomal dominant
  - CRC affect mainly the right side of the colon
  - Peak incidence
    - 40-46 yr
    - Development of CRC ~80%
  - Defect in MMR genes → microsatellite instability (MSI) → Promote DNA mutation → tumour development
  - Types
    - Type 1: cancers involve only the colon
    - Type 2: cancers involve colon (CRC) female genital tract (ovary, uterus) and other sites

➢ Models to Predict Presence of Lynch Syndrome

- PREMM Model
  - Proband Information (*Proband" refers to the individual being evaluated. Ideally, this individual should have a cancer or adenoma diagnosis.)

– How many separate colorectal cancers has the proband had?	☐ None ☐ One ☐ Two or more
▪ If one, what was the age at diagnosis?	_____ (if unknown, estimate)
▪ If two or more, what was the youngest age at diagnosis?	_____ (if unknown, estimate)
– Has the proband had colonic adenoma(s)?	☐ Yes ☐ No
▪ What was the youngest age at diagnosis?	_____ (if unknown, estimate)
– Has the proband had endometrial cancer?	☐ Yes ☐ No
▪ What was the youngest age at diagnosis?	_____ (if unknown, estimate)
– Has the proband had another HNPCC-associated cancer?	☐ Yes ☐ No

(Other HNPCC-associated cancers include ovary, stomach, small intestine, urinary tract/kidney, bile ducts, glioblastoma multiforme, sebaceous gland tumours, and pancreas.)

  - Relatives' Information-First Degree (Only from affected side of family)

– How many first-degree relatives have had colorectal cancer?	☐ None ☐ One ☐ Two or more
▪ If one, what was his/her age at diagnosis?	_____ (if unknown, estimate)
▪ If two or more, what was the youngest age at diagnosis?	_____ (if unknown, estimate)
– How many first-degree relatives have had endometrial cancer?	☐ None ☐ One ☐ Two or more
▪ If one, what was her age at diagnosis?	_____ (if unknown, estimate)
▪ If two or more, what was the youngest age at diagnosis?	_____ (if unknown, estimate)
– Have any first-degree relatives had another HNPCC-associated cancer?	☐ Yes ☐ No

- Relatives' Information-Second Degree (Only from affected side of family)

– How many second-degree relatives have had colorectal cancer?	☐ None ☐ One ☐ Two or more
▪ If one, what was his/her age at diagnosis?	_____ (if unknown, estimate)
▪ If two or more, what was the youngest age at diagnosis?	_____ (if unknown, estimate)
– How many second-degree relatives have had endometrial cancer?	☐ None ☐ One ☐ Two or more
▪ If one, what was her age at diagnosis?	_____ (if unknown, estimate)
▪ If two or more, what was the youngest age at diagnosis?	_____ (if unknown, estimate)
– Have any second-degree relatives had another HNPCC-associated cancer?	☐ Yes ☐ No
Probability of MLH1, MSH2 Mutation	**CALCULATE** _____

- Amsterdam
  - Amsterdam 1 Criteria
    - ≥ 3 relatives with CRC (one must be first degree relative)
    - CRC involves in ≥2 generations
    - ≥1 CRC cases diagnosed in a patient < 50 yr
  - Amsterdam 2 Criteria
    - ≥3 relatives with histologically proven HNPCC-associated cancer (renal pelvis, ureter, small bowel, endometrium, colon) and one of them should be first degree relative
    - CRC involves ≥2 generations
    - ≥ 1 relative diagnosed at age < 50 yr

➢ Treatment

- Endoscopic Resection
  - If CRC is not endoscopically respectables total colectomy (panproctocolectomy), ileorectal anastomosis (IRA)

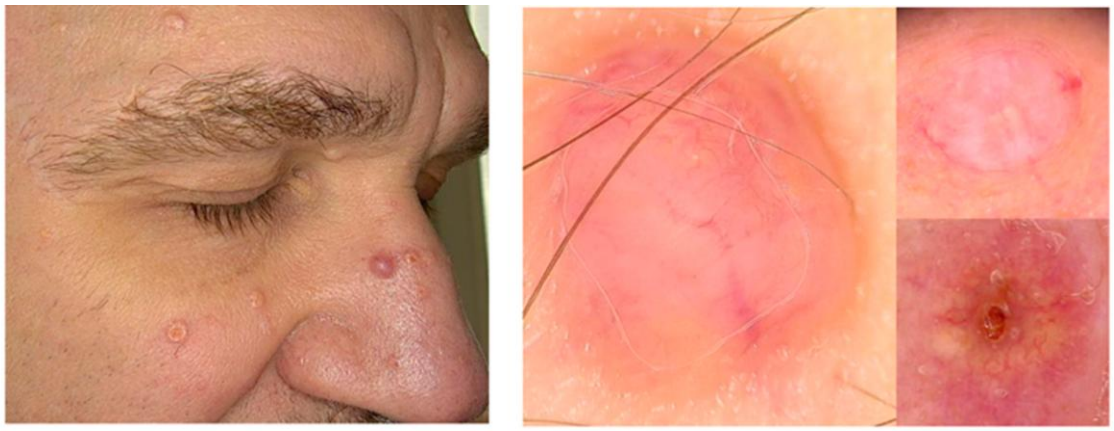
➢ Prevention and Surveillance!

- Offer ASA for CRC prevention
- Colonoscopy q1-2 yr, starting at 20-25 yr, or 10 yr younger than the youngest relative diagnosed with CRC in the family.
- Annual colonoscopy when ≥ 40 yr

- **Muir-Torre Syndrome** (MTS)
  - Due to DNA mismatch repair
    - Variant of Lynch syndrome
  - Male to female affected, 2:1
  - Associated with sebaceous neoplasm, urogenital malignancy, and GI including colon carcinoma

Muir-Torre Syndrome

Photograph Hair Follicle Opening Sebaceous Adenoma



(a) (b)

  - The case of Muir–Torre syndrome:
    - (a) clinical presentation of the face with numerous small yellowish nodules with umbilical centres and larger pink nodules with visible telangiectasias on the surface.
    - (b) the videodermoscopic examination enabled the differential diagnosis of the lesions—pink nodule with thin and large arborising vessels and yellowish blotches located peripherally, corresponding to larger sebaceous adenoma (on left), pink and white in colour nodule with visible withe strands, yellow micro-blotches, and irregular short vessels at the walls of the nodule corresponding to small sebaceous adenoma (upper right), yellow clods with crown vessels and central hair follicle opening—corresponding to the sebaceous hyperplasia (on lower right) (Fotofinder Medicam HD 1000 Systems GmbH, Bad Birnbach, Germany).

Courtesy of: Płatkowska A, et al. J Clin Med 2024; 13(15):4377.

- **Turcot Syndrome** (TS)
  - Associated with colonic and CNS malignancy.
  - Can be a variant of both FAP or Lynch Syndrome
    - FAP variant: might have medulloblastoma
    - Lynch variant glioblastoma multiforme

❖ **Hamartomatous Polyposis Syndrome**

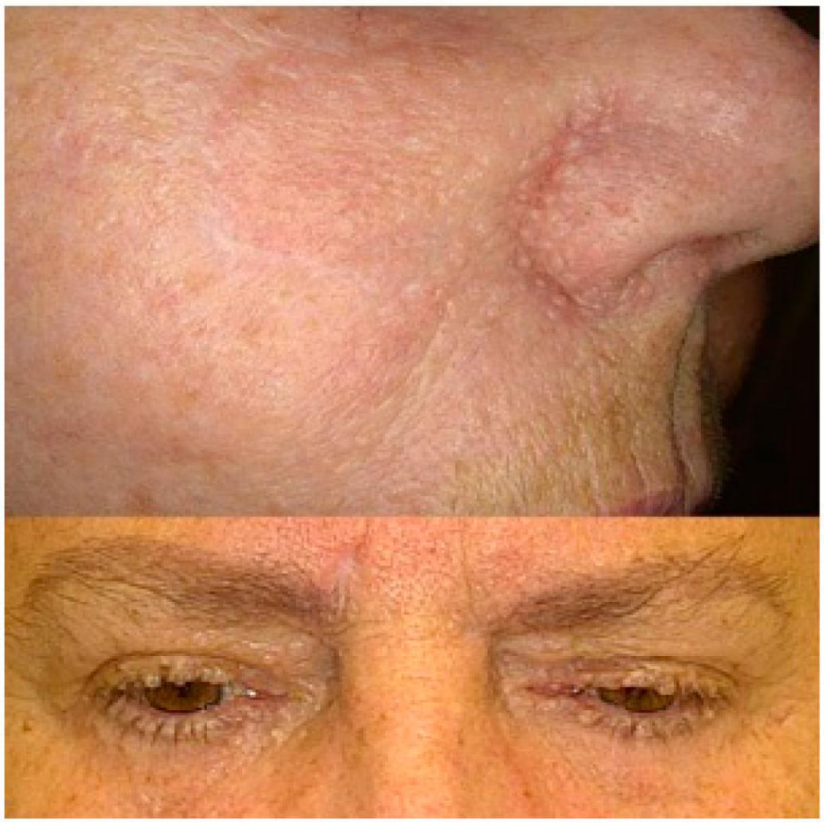
- **Peutz-Jeghers Syndrome** (PJS)
  - Autosomal dominant condition
  - Multiple Hamartomatous polyps scattered in the GI tract > enlarged > GI bleeding, intestinal obstruction, Intussusception
  - Due to germline mutations in the LKB1 (STK11) gene on chromosome 9
  - Often has
    - Pigmentation of mucus membranes/skin
    - CRC
    - Extracolonic cancer

- **Tuberous Sclerosis**
  - Autosomal dominant
    - Hamartomas
    - Mental retardation / epilepsy, and
    - Adenoma sebaceum
    - CRC, distal colon

- **Juvenile Polyposis**
  - Autosomal dominant
  - Juvenile retention polyps in the colon, stomach, or elsewhere in the GI tract.
  - Due to mutations in the growth factor B pathways
  - Usually presents during childhood with
    - Bleeding, or
    - Bowel obstruction
    - There is a risk of CRC.
  - Treatment
    - Prophylactic / therapeutic colonic resection, with ileorectal anastomosis, or
    - Total proctocolectomy.

- **Cowden Disease**
  - Autosomal dominant
    - Involve PTEN Mutation
  - Clinical
    - Hamartomatous polyps throughout the GI
      - ↑ risk of CRC
    - Trichilemmomas/ skin lesions
    - Polyps are histologically similar to polyps of juvenile polyposis syndrome.
    - ↑ risk of
      - Bilateral breast cancer
      - Papillary thyroid cancer
      - Endometrial cancer

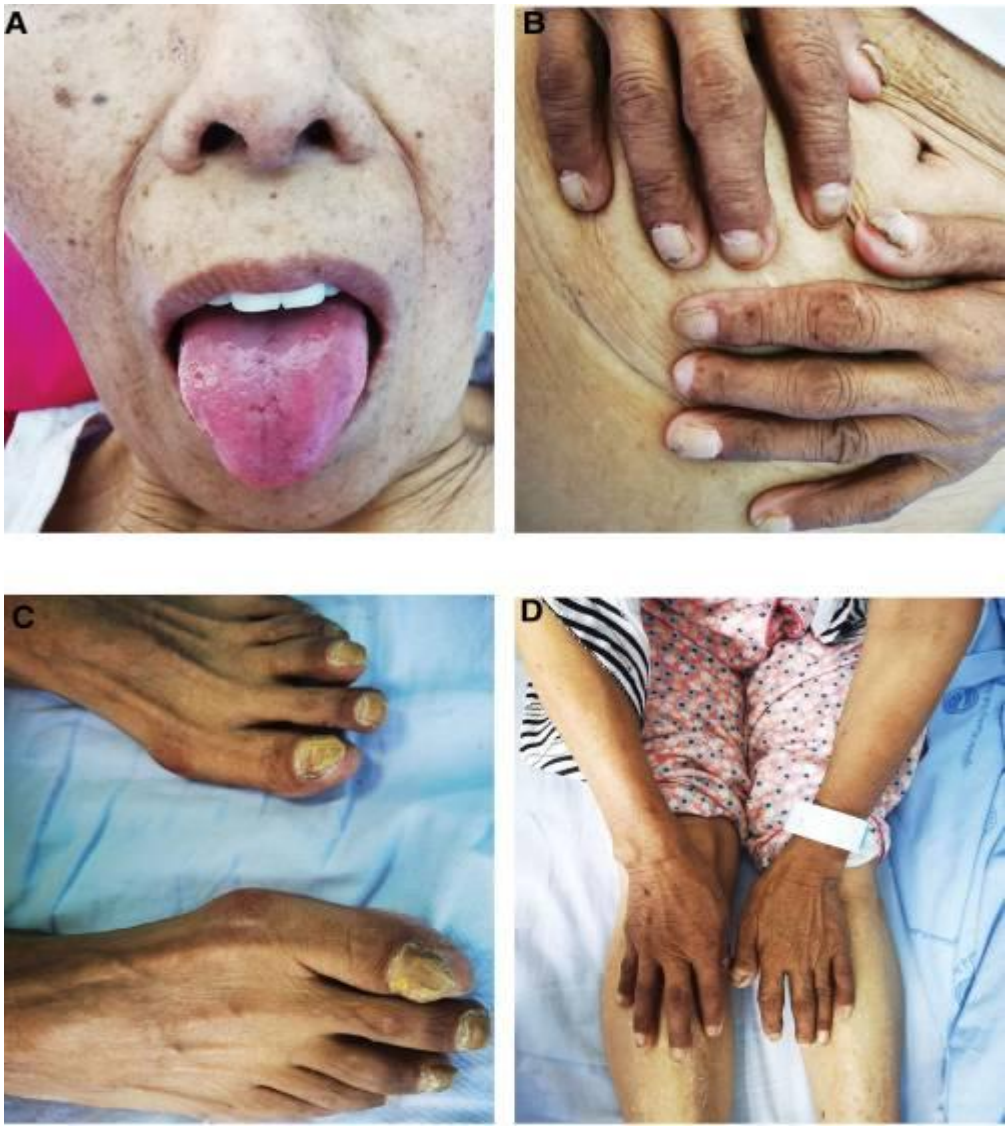
Cowden Disease



Clinical presentation of multiple tumours originated from the hair follicles (trichoblastomas, trichoepitheliomas) on the face and the eyelids

Courtesy of: Płatkowska A, et al. J Clin Med 2024; 13(15):4377.

- **Cronkhite-Canada Syndrome** (CCS)
  - Not inherited.
  - Clinical
    - Malnutrition or malabsorption
    - Alopecia
    - Hyperkeratosis of toenail and fingernails.
  - Hamartomatous polyps in the colon, stomach and small bowel
    - Neoplastic potential unknown



Courtesy of: Wang N, et al. Medicine (Baltimore) 2024;103(43): e40242.

Table of Buzzwords to Help Identify Type of Polyposis Syndrome on multiple Choice Questions (MCQs)

Buzzwords	Associated Condition(s)
○ CNS	
– Epilepsy	▪ Tuberous sclerosis
– Gliomas	▪ Turcot syndrome
– Intellectual disability	▪ Tuberous sclerosis
– Medulloblastoma	▪ Turcot syndrome
– Ganglioneuromas	▪ Tuberous sclerosis
○ Eyes	
– Congenital hypertrophy of the retinal pigment epithelium	▪ Gardner syndrome
○ Teeth	
– Supernumerary teeth	▪ Gardner syndrome
○ Heart	
– Cardiac rhabdomyomas	▪ Tuberous sclerosis
○ Skin	
– Epidermoid cysts	▪ Gardner syndrome
– Sebaceous cysts	▪ Gardner syndrome
– Trichilemmomas	▪ Cowden syndrome
○ Bone	
– Bone cysts	▪ Tuberous sclerosis
– Osteoma	▪ Gardner syndrome
○ GI/BT/P	
– Ampullary cancer	▪ FAP
– Biliary tract malignancy	▪ HNPCC (Muir-Torre variant)
– Duodenal cancer	▪ FAP
– Gastric cancer	▪ HNPCC (Muir-Torre variant)
– Hyperpigmentation of lips	▪ Peutz-Jeghers syndrome
– Mesenteric fibromatosis	▪ Gardner's syndrome
– Small intestinal cancer	▪ HNPCC (Muir-Torre variant)
○ GU	

Buzzwords	Associated Condition(s)
− Ovarian cancer	▪ HNPCC; Peutz-Jeghers syndrome (sex-cord tumour)
− Renal cysts	▪ Tuberous sclerosis
− Sertoli cell testicular tumour	▪ Peutz-Jeghers syndrome
○ Miscellaneous	
− Angiofibromas	▪ Tuberous sclerosis
− Desmoid tumours	▪ Gardner syndrome
− Fibromas	▪ Gardner syndrome
− Hamartomas	▪ Peutz-Jeghers syndrome; Cowden syndrome; juvenile polyposis; tuberous sclerosis
− Lipoma	▪ Gardner syndrome
− Ureteral cancer	▪ HNPCC (Muir-Torre variant)

➢ Diagnosis

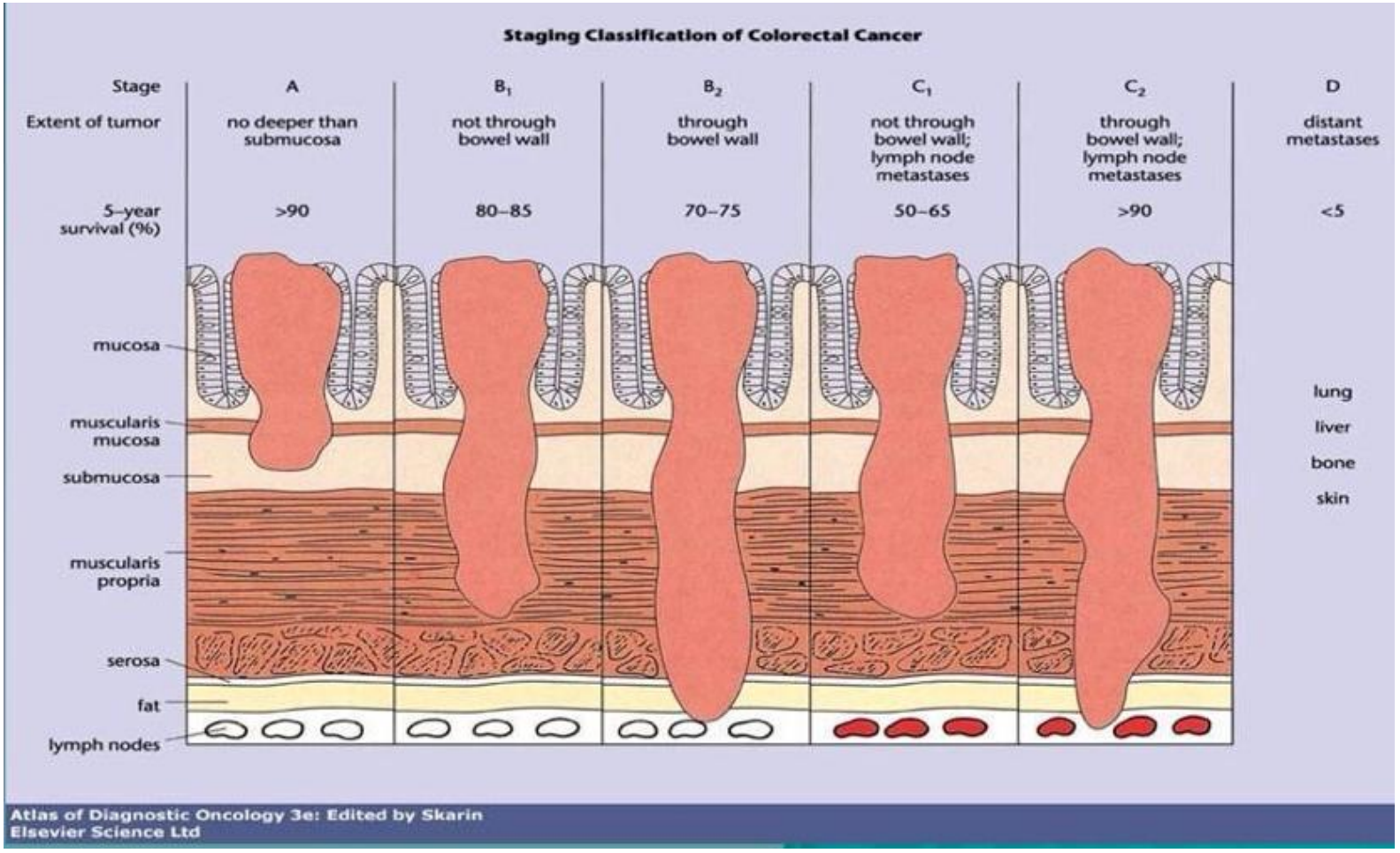
- ○ Laboratory
  - − Blood
    - ▪ Complete blood counts (CBC)
    - ▪ Liver enzymes (LEs)
    - ▪ Carcinogenic antigen (CEA, not initial screening diagnosis, but useful for surveillance post surgical reaction)
    - ▪ Iron / ferritin
  - − Stool
    - ▪ Fecal immune testing (FIT)
- ○ Diagnostic Imaging
  - − Barium enema +/- flexible sigmoidoscopy
  - − CT colonography
  - − Liver ultrasound
  - − CT chest/Abdomen/Pelvis.
- ○ Endoscopy
  - − Colonoscopy

➢ Histopathology

- ○ Variable amount of mucin
- ○ Appearance of Signet ring cell
- ○ Histopathology suggestive for Lynch Syndrome Adenocarcinoma

- Classification and Staging

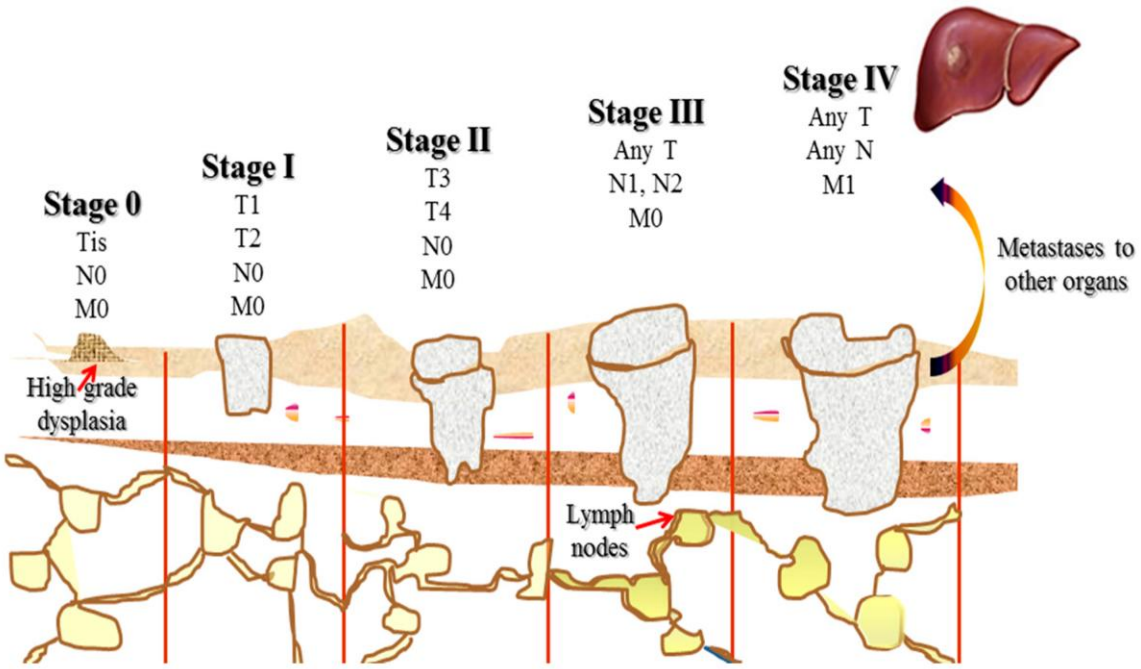
Modified Dukes' Staging Classification of Colorectal Cancer



Courtesy of: https://mindthebleep.com/colorectal-cancer-and-polyps/

- TNM Staging

Classification of Colorectal Cancers (American Joint Commission on Cancer)



  - Tis—carcinoma *in situ*: intraepithelial or invasion of lamina propria;
    - T1—tumour invades submucosa;
    - T2—tumour invades muscularis propria;
    - T3—tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues;
    - T4—tumour penetrates the surface of the visceral peritoneum or tumour directly invades or is histologically adherent to other organs or structures;
    - N0—no regional lymph node metastasis;
    - N1—metastasis in one to three regional lymph nodes;
    - N2—metastasis in four or more regional lymph nodes;
    - M0—no distant metastasis;
    - M1—distant metastasis.

Courtesy of: Lin C, et al. Int J Mol Sci 2015; 16(11):26936-26952.

TNM Stage	Description
Tumour	
T1	− Tumour invades submucosa
T2	− Tumour involves muscularis propria but does not cross it
T3	− Tumour extends beyond muscularis propria into mesorectal or pericolic fat
T4	− Tumour invades adjacent organs or perforates the visceral peritoneum
Node	
N0	− No nodal metastasis
N1	− 1–3 perirectal or pericolic nodes
N2	− 4 or more perirectal or pericolic nodes
Metastasis	
MX	− Cannot be assessed
M0	− No metastasis
M1	− Distant metastasis

Colorectal Cancer Staging and 5-Year Survival Rates

Stage	TNM Classification	5-Year Survival (%)
0, I	Tis, T_1, N_0, M_0	>90
I	T_2, N_0, M_0	80–85
II	T_3–T_4, N_0, M_0	70–75
III	T_2, N_1–N_3, M_0	70–75
III	T_3, N_1–N_3, M_0	50–65
III	T_4, N_1–N_2, M_0	25–45
IV	M_1	<3

Abbreviations: CRC, colorectal cancer; N_0–N_3: number of affected lymph nodes; M_0 / M_1: absence or presence of distant metastasis; TNM, tumour-node-metastasis; T_{IS}, carcinoma in situ intraepithelia or invasion of lamina propria; T1, tumour invasion of submucosa; T2, tumour invasion of muscularis propria; T3, tumour invasion through the muscularis propria into pericolorectal tissues; T4, penetration of tumour through the surface of the visceral peritoneum and further directly invading other organs

➢ Treatment

- Surgery
  - CRC is mainly treated with involved colonic segment resection and lymph node removal (can be done laparoscopically or via an open surgical approach)
    - Surgery can also be done for patients with isolated lung/liver metastasis surgery could be done too
  - Types of surgery
    - Right hemi-colectomy
    - Left hemi-colectomy
    - Sub-total colectomy
    - Pan proctocolectomy
    - High anterior resection
    - Low anterior resection
    - Abdomino-perineal resection
  - For surgically incurable patients, -resection of primary tumour is only indicated for:
    - Refractory bleeding
    - Perforation
    - Impending obstruction or obstruction 420
  - Surveillance of CRC post- resection
    - Colonoscopy q1 yr post surgery for 4 yr, then q5 yr
    - CEA level q3 mon for 2 yr, then q6 mon, or
    - CT scan
    - Combining CT and CEA showed no additional benefit

- Chemotherapy
  - Indications for post-op (Adjuvant chemotherapy)
    - Stage III CRC
    - Stage II CRC with poor prognostic factors based on histopathology review.
  - Palliative chemotherapy for metastasis
    - Preferred Regimen is
      - FOLFOX (5-fluorouracil leucovorin, and Oxaliplatin) for 6 mon, or
      - FOLFIRI (contain Irinotecan instead of Oxaliplatin)
  - For rectal cancer
    - Indications
      - For T3 and higher or N1 and higher staged via CT or EUS.
      - For stage II and III rectal cancer
  - Metastatic CRC
    - Bevacizumab (commonly used)
    - Cetuximab and Panitumumab → might benefit from KRAS tumour gene testing

- Radiotherapy
  - Neoadjuvant chemoradiotherapy
    - Indication
      - T3-T4, rectal cancer
      - N1, lymph node involvement

➢ Protective Factors / Chemoprevention

- Aspirin
  - ↓ risk of CRC
  - ↓ recurrence of adenoma
  - Assess patient risk for complications of ASA
    - Consider gastroprotection with proton pump inhibitors (PPI)
    - Do **not** use COXIB in place of ASA/NSAIDs for protection (↑ cardio-/neurovascular complications)
- NSAIDs
  - ↓ proliferation
  - Slow cell cycle progression
  - Stimulate Apoptosis
- Dietary protective factors
  - Calcium/
  - Vitamin D
  - Low fat / High fiber diet

➢ Total Patient Care

- Compassionate approach by all members if healthcare team.
- Assessment for
  - Patient education
  - Mental/emotional state
  - Financial consideration
  - Diet, exercise, smoking assessment
  - Family history

Abbreviations: APC, adenomatous polyposis coli gene; ASA, acetylsalicylic acid (aspirin); CBC, complete blood count; CCS, Cronkhite-Canada syndrome; CEA, carcinoembryonic antigen; CI, confidence interval; CIMP, CpG island methylator phenotype; CNS, central nervous system; CRC, colorectal cancer; DCC, deleted in colorectal carcinoma gene; EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasound; FAP, familial adenomatous polyposis; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; GI, gastrointestinal; HNPCC, hereditary non-polyposis colorectal cancer (Lynch syndrome); IGF-1, insulin-like growth factor 1; IRA, ileorectal anastomosis; KRAS, Kirsten rat sarcoma viral oncogene homolog; LE, liver enzyme; LKB1/STK11, serine/threonine kinase 11 gene; MAP, MUTYH-associated polyposis; MLH1, MutL homolog 1; MMR, mismatch repair; MSI, microsatellite instability; MTS, Muir-Torre syndrome; MYH, mutY homolog gene; NSAID, non-steroidal anti-inflammatory drug; PJS, Peutz-Jeghers syndrome; PREMM, prediction model for Lynch syndrome mutations; PTEN, phosphatase and tensin homolog; q, every (interval); TNM, tumour-node-metastasis staging; TP53, tumour protein p53; TS, Turcot syndrome.

HEREDITARY COLORECTAL CANCERS

Ziad Hindi

❖ **CRC with a Family History, Otherwise Undefined**

- ~15-20%, of CRC occurs in an individual with a first-degree relative with CRC, but considered to be sporadic
- This ↑ 2-3x risk of CRC compared to the rest of the population, and
  - The RR is even higher when the family member is younger than 50 years old
- The role of genetic and environmental factors at play remains to be defined

❖ **Hereditary Colorectal Cancer**

- Account for 3-5% of all CRCs overall
- Mostly composed of familial adenomatous polyposis (FAP)

- **Non-Neoplastic Polyps**
  - Peutz-Jeghers Polyps - Hamartomatous polyps characterized by glandular epithelium and well-developed smooth muscle

Cancer Type	Risk (%) or Age Range	Screening Method	Screening Interval	Start Age
– Colon cancer	39%	Colonoscopy	q2–3 yr	-
– Gastric cancer	29%	Upper endoscopy	q2–3 yr	-
– Small intestine	13%	CT/MR enterography or VCE	q2 yr	10 yr
– Pancreatic cancer	11–36%	MRI/MRCP or Endoscopic US	q1–2 yr	30 yrs
– Breast cancer	45–50%	Breast exam, mammogram, and MRI	Annually	-
– Uterine/ovarian cancer	9%; 18–21%	Pelvic exam, Pap smear, pelvic US	Annually	20 yrs
– Sertoli cell tumour	Uncommon	Testicular exam; testis US if feminizing features	Annually	10 yrs

  - Inflammatory Polyps/Pseudopolyps
  - Mucosal Prolapse Polyps
  - Colitis Cystica Profunda and Superficialis
  - Pneumatosis Cystoides Coli - gas filled cysts within mucosa, submucosa, and subserosa

- **Non-Inherited Polyposis Syndromes**
  - Cronkite-Canada Syndrome
    - Associated with being middle aged, presenting with protein losing enteropathy, chronic diarrhea
    - Polyps are hamartomas - like Juvenile Polyposis, but the mucosa is abnormal with edema and inflammation
  - Lymphomatous Polyposis
    - Immunoproliferative small intestinal disease - multiple lymphomatous polyps in the GI tract
  - Nodular Lymphoid Hyperplasia
    - Nonspecific bet can be seen in
      - Gardner Syndrome
      - Immunodeficiency syndrome (CVID/IgA deficiency)
    - More common in small intestine

❖ **Inherited Polyposis Syndrome**

- **Adenomatous Polyposis Syndromes**
  - Classic familial adenomatous polyposis (FAP) – please see next section
    - Gene Mutation: APC (usually truncated protein)
    - Inheritance: Autosomal dominant
    - Polyps: Colonic adenomas (thousands), duodenal, periampullary adenomas, gastric fundic gland polyps, jejunal and ileal adenomas
    - Extraintestinal Abnormalities: Osteomas (mandible, skull, long bones), CHRPE, desmoid tumours, epidermoid and sebaceous cysts, thyroid/adrenal tumours, medulloblastoma
  - FAP plus extraintestinal manifestations - Gardner Syndrome
  - Attenuated FAP
    - Gene Mutation: APC (5’ and 3’ regions)
    - Inheritance: Autosomal dominant
    - Polyps: Colonic adenomas (~100, proximal colon), duodenal, periampullary adenomas, gastric fundic gland polyps
    - Extraintestinal Abnormalities: Mandibular osteomas (rare)
  - MUTYH-associated polyposis (MAP)
    - Gene Mutation: MUTYH (MYH)
    - Inheritance: Autosomal recessive
    - Polyps: Colonic adenomas (≤100%), duodenal polyposis
    - Extraintestinal Abnormalities: CHRPE, osteomas
  - Polymerase proofreading-associated polyposis
    - Gene Mutation: POLD1, POLE
    - Inheritance: Autosomal dominant
    - Polyps: Colonic adenomas, duodenal adenomas
    - Extraintestinal Abnormalities: Endometrial cancer

- Familial tooth agenesis
  - Gene Mutation: AXIN2
  - Inheritance: Autosomal dominant
  - Polyps: Colonic adenomas, hyperplastic polyps
  - Extraintestinal Abnormalities: Agenesis of teeth
- NTHL1 Polyposis
  - Gene Mutation: NTHL1
  - Inheritance: Autosomal recessive
  - Polyps: Colonic adenomas
  - Extraintestinal Abnormalities: —

Cancer Type	Risk (%) or Age Range	Screening Recommendation
MUTYH-Associated Polyposis		
– Colon cancer	43–100	▪ Colonoscopy every 1–2 yrs, starting age 25 yrs
– Duodenal cancer	5	▪ Upper endoscopy with exam of ampulla, starting age 30 yrs
Juvenile Polyposis		
– Colon cancer	40–50	▪ Colonoscopy every 2–3 yrs; annually if multiple polyps are identified
– Gastric cancer	21% (if multiple polyps)	▪ Upper GI endoscopy every 2–3 yrs; more frequently if multiple polyps; start in early teens
Cowden Syndrome		
– Colon cancer	9	▪ Colonoscopy every 5 yrs; start at age 35 yrs
– Thyroid cancer	35	▪ Annual thyroid ultrasound; start in teens
– Breast cancer	85	▪ Annual breast examination at age 25 yrs; annual mammogram at age 30 yrs
– Uterine cancer	28	▪ Consider endometrial biopsy or pelvic ultrasound
Serrated Polyposis		
– Colon cancer	SIR = 18.72	▪ Colonoscopy every 1–2 yrs

Abbreviation: FAP, Familial Adenomatous Polyposis; FGP, Fundic Gland Polyp; HGD, High Grade Dysplasia; LGD; Low Grade Dysplasia; MUTYH, mutY Homolog (Escherichia coli); Pap, Papanicolaou; SIR, Standardized Incidence Ratio

- **Familial Adenomatous Polyposis** (FAP)

➢ Genetics

- APC gene encoded at 5q21-22
  - The APC protein is a multifaceted regulator of colonic epithelial cell homeostasis
    - Regulates cell proliferation
    - Migration
    - Differentiation
    - Apoptosis, and
    - Chromosomal segregation
  - Most APC mutations truncate the protein
    - Disrupts the constitutive breakdown of 3-catenin → activation of cancer-associated genes
    - Creating abnormal chromosomal segregation with resultant CIN
- Autosomal dominant mutation - Chromosome 5 (tumour suppressor gene)
  - 80-100% penetrance
  - Prevalence of 1 in 5000-7500
- Hundreds to thousands of colonic adenomas ± extracolonic tumours
  - Adenomas appear approximately I decade before cancer

➢ Clinical Presentation

- Non-specific symptoms
  - Hematochezia
  - Diarrhea
  - Abdominal pain
- Optimal period for diagnosis is the pre-symptomatic phase
  - Pursue diagnosis in relatives of affected patients
- Diagnosis can be made with Flexible Sigmoidoscopy
  - Colonoscopy is preferred to evaluate the entire colon and exclude malignancy

➢ Diagnosis

- Phenotypic
  - 100 polyps and histologic diagnosis
- Definitive
  - APC gene test positive
- Perform genetic testing as early as age 10 yr

➢ Malignant Transformation

- ~10 years elapse between the first appearance of a polyp and appearance of malignancy
- Perform total colectomy even if pre-symptomatic
  - Exception
    - Only time to delay is with allowing for completion of puberty

- Endoscopy
  - Colonoscopy
    - Progressive development of hundreds to thousands of colonic polyps
      - All varieties of polyps can be seen - villous, tubular, TV - typically < 1 cm in size
    - These typically develop at age 10-12, but rarely can develop earlier
      - 50% of FAP gene carriers will have polyps at age 15
      - 90% of FAP cases will be diagnosed by age 50
      - Averages:
        - Age at polyp onset (25)
        - Age at diagnosis (33)
        - Age at adenoma onset (36)
        - Age at Cancer (39)
        - Age at Death from Cancer (42)
      - Average number of polyps at colectomy is 1000.
  - Esophagogastroduodenoscopy (EGD)
    - Polyps can also be present in the stomach and small intestine
    - These are mostly non-neoplastic fundic gland polyps, 1-5 mm sessile growths
    - Unlike FGP associated with PPIs, these can be neoplastic (25-41%) – resulting from APC gene mutation)
    - Duodenal adenomas occur in 60-90% of FAP patients
      - Develop at or near peri-ampullar system and may obstruction the pancreatic or biliary ductal system
      - 4-12% lifetime incidence of duodenal cancer, usually peri-ampullary (RR 124-331)
  - Screen at age of diagnosis of FAP, or at least by age 25 years
    - Use CT or MR-E, VCE or balloon enteroscopy

Cancer Type	Lifetime Risk (%)	Screening Recommendation
○ Colon cancer	Near 100	− Sigmoidoscopy annually; start at age 10–12 yrs. If polyps are detected, colonoscopy is performed to exclude proximal neoplasia. − Colonoscopy annually starting at age 25 yrs for attenuated FAP.

- **Spigelman Classification** (duodenal polyps in FAP)
  - The Spigelman Classification is historical, and underestimates correct methods to determine number of polyps and grade of dysplasia

Number of points	1	2	3
Polyp number	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Polyp histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Spigelman Stage:
0 = 0 points
I = 1-4 points
II = 5-6 points
III = 7-8 points
IV = 9-12 points

Cancer Type	Lifetime Risk (%)	Screening Recommendation
Gastric cancer	≈0.5	EGD every 1–2 yrs if numerous FGPs (with or without LGD); every 6–9 mon if HGD.
Duodenal or peri-ampullary	5–12	EGD with side-viewing endoscope; start at age 25–30 yrs. Spigelman stages: 0–1: every 5 yrs; II: every 3 yrs; III: every 1–2 yrs; IV: consider surgery.

- Extraintestinal Findings of FAP
  - Congenital Hypertrophy of the Retinal pigmented epithelium
  - Diffuse mesenteric fibromatosis / desmoid tumours
  - Epidermoid Cysts / Inclusion Cysts
  - Fibromas
  - Lipomas
  - Osteomas

Cancer Type	Lifetime Risk (%)	Screening Recommendation
Thyroid cancer	≈2	Thyroid examination or thyroid ultrasound; start at age 10–12 yrs.
Hepatoblastoma	1.6	Annual physical examination, hepatic US, serum AFP for first decade of life.

- Treatment
  - Surgery is definitive treatment
  - Annual colonoscopic examination should be undertaken until surgery
  - Total proctocolectomy with either ileostomy or with ileal pouch anastomosis but
    - Risk of ↓ fecundity in women
    - ↑ risk of adenoma (45% at 10 yr) or carcinoma (1%)

- **Categories of Risk for Developing Colorectal Cancer**
  - Average Risk
    - Family history of sporadic adenoma / CRC
    - Individuals ≥50 years of age with no
    - Personal history of adenoma, CRC or IBD

- High Risk
  - Polyposis syndromes
    - FAP
      - Attenuated FAP
      - MYH-associated polyposis
    - Peutz-Jeghers syndrome,
      - Turcot syndrome
      - Gardner
      - Muir-Torre syndrome
    - Juvenile polyposis syndrome
    - Hyperplastic polyposis syndrome
    - IBD (UC, Crohn disease)
  - Non-polyposis syndromes:
    - Lynch syndrome
    - Family colon cancer syndrome X
    - Biallelic mismatch repair deficiency syndrome (BMMRD)

❖ **Non-polyposis Inherited Syndromes**

- **Lynch Syndrome** (formerly HNPCC)
  - Inherited disease where colon cancer arises in discrete adenomas
  - Autosomal dominant disorder, germline mutation in genes that are responsible for repair of DNA errors
  - MMR genes (Mismatch Repair – repair errors in microsatellite DNA sequences) in Lynch syndrome have been associated with
    - hMSH2 gene (Chromosome 2), and
    - hMLH1 gene (Chromosome 3)
  - Adenomas are often Right-sided, flat or slightly raised, and may be multiple with a higher incidence of mucosal carcinomas
  - CRC comes 2 decades earlier than the regular population – at age 40-50
  - Associated with endometrial or ovarian cancers
  - Previously classified using the Amsterdam Criteria, but this did not include extracolonic malignancies
    - Revised Bethesda Guidelines then created by the National Cancer Institute

- **Revised Bethesda Guidelines for Lynch Syndrome**
  - Person with CRC and
    - A first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed at <50 years of age
    - CRC in person <50 years of age
    - 2 or more first-degree or second-degree relatives with a Lynch syndrome-related tumour, regardless of age
  - Presence of synchronous or metachronous CRCs or other Lynch syndrome-associated extracolonic tumours, regardless of age
  - CRC with MSI-H phenotype diagnosed in an individual <60 years of age

- **Comparison of Clinical Features in Lynch Syndrome and Sporadic Colorectal Cancer**

Clinical Feature	Lynch Syndrome	Sporadic CRC
Mean age at diagnosis (yr)	45	67
Multiple colon cancers	35%	4–11%
Synchronous colon cancers	18%	3–6%
Metachronous colon cancers	24%	1–5%
Proximal location of the initial cancer	72%	35%
↑ risk of malignant tumours at other sites	Yes	No
Mucinous / poorly differentiated	Common	Infrequent
Prognosis	Favorable	Variable

- **Biallelic Mismatch Repair Deficiency Syndrome** (BMMRD)
  - Also known as Constitutional MMR deficiency (MMR deficiency at birth)
  - Highest risk of all genetic CRCs
    - Tumours are often diagnosed in the first decade of life
  - Features in
    - Colon
      - Polyps
      - CRC
    - Small bowel
      - Cancer
      - Lymphoma
    - Brain tumours
    - Leukemia

Abbreviations: APC, adenomatous polyposis coli gene; AXIN2, axis inhibition protein 2 gene; BMMRD, biallelic mismatch repair deficiency; CBC, complete blood count; CHRPE, congenital hypertrophy of the retinal pigmented epithelium; CI, confidence interval; CIN, chromosomal instability; CRC, colorectal cancer; CT, computed tomography; CVID, common variable immunodeficiency; EGD, esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; FGP, fundic gland polyp; GI, gastrointestinal; HGD, high-grade dysplasia; HNPCC, hereditary non-polyposis colorectal cancer (Lynch syndrome); HU, human umbilical cord (substrate for EMA testing); IgA, immunoglobulin A; IgG, immunoglobulin G; LKB1/STK11, serine/threonine kinase 11 gene; LGD, low-grade dysplasia; MAP, MUTYH-associated polyposis; MMR, mismatch repair; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; MUTYH/MYH, mutY homolog gene; NTHL1, endonuclease III-like protein 1 gene; Pap, Papanicolaou smear; PJS, Peutz-Jeghers syndrome; POLE, DNA polymerase epsilon gene; POLD1, DNA polymerase delta 1 gene; PPI, proton pump inhibitor; q, every (interval); RR, relative risk; SIR, standardized incidence ratio; US, ultrasound; VCE, video capsule endoscopy.

HEPATOBILIARY

TUMOURS OF BILE DUCT, GALLBLADDER AND AMPULLA

Pavithra Parthasarathy

❖ Cholangiocarcinoma (CCA)

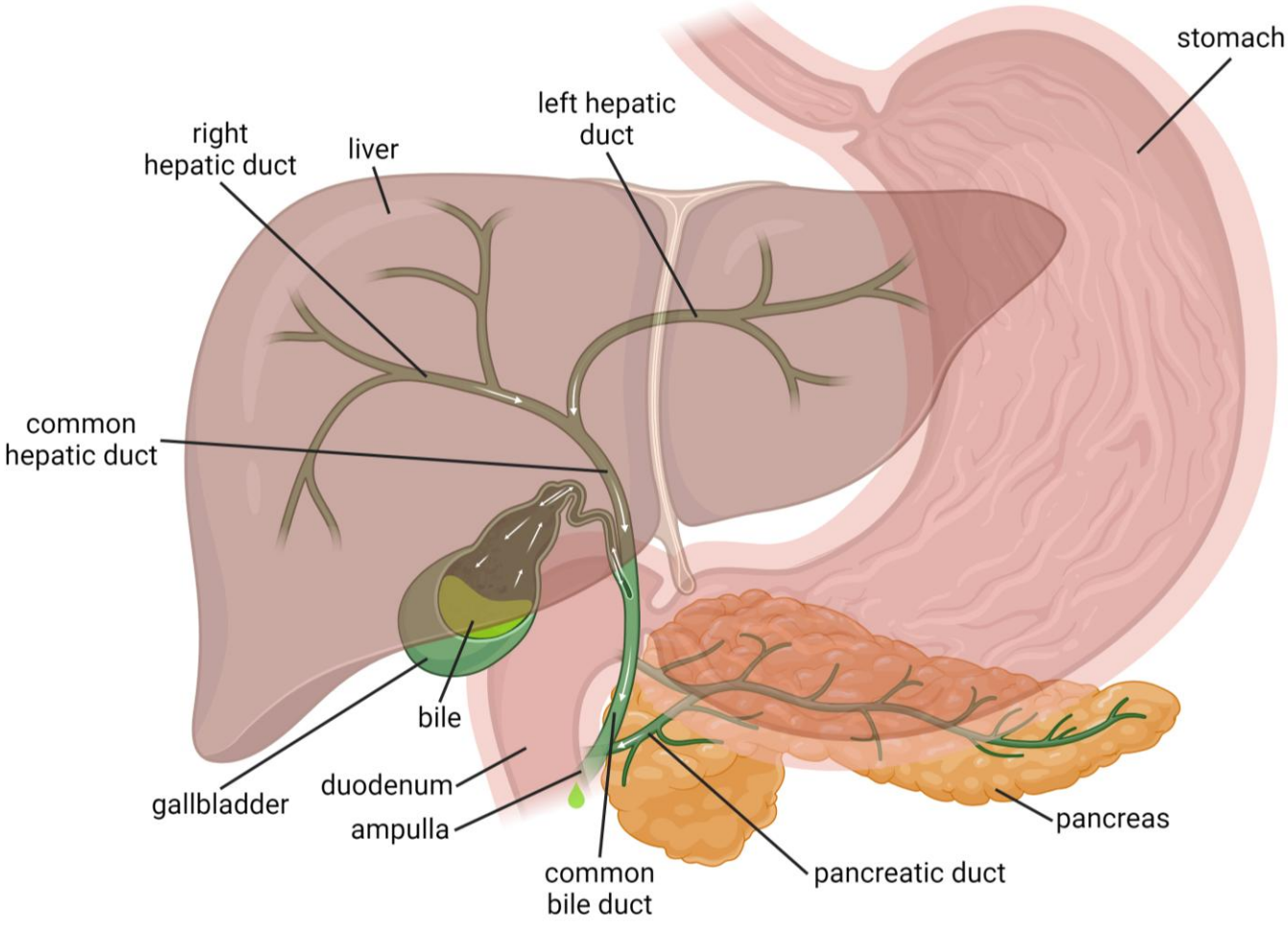
- Definition
  - Epithelial carcinoma
    - Desmoplastic
    - Paucicellular tumour
    - Multiple subtypes of pathologic characteristics

- Demography
  - Subdivided by location
    - Intrahepatic
    - Extrahepatic
    - Perihilar
    - Distal
  - Variations in risk factors, pathogenesis, management

- Types
  - Intrahepatic
    - Within liver parenchyma
    - Above 2nd-order bile ducts
  - Perihilar/hilar (Klatskin tumours)
    - Between 2nd-order bile ducts, and
    - Insertion of cystic duct
    - Represent 50% to 60% of CCAs
  - Distal
    - Below cystic duct
    - Represent 20% of CCAs
  - Most common biliary malignancy
  - Median survival <24 mon from diagnosis

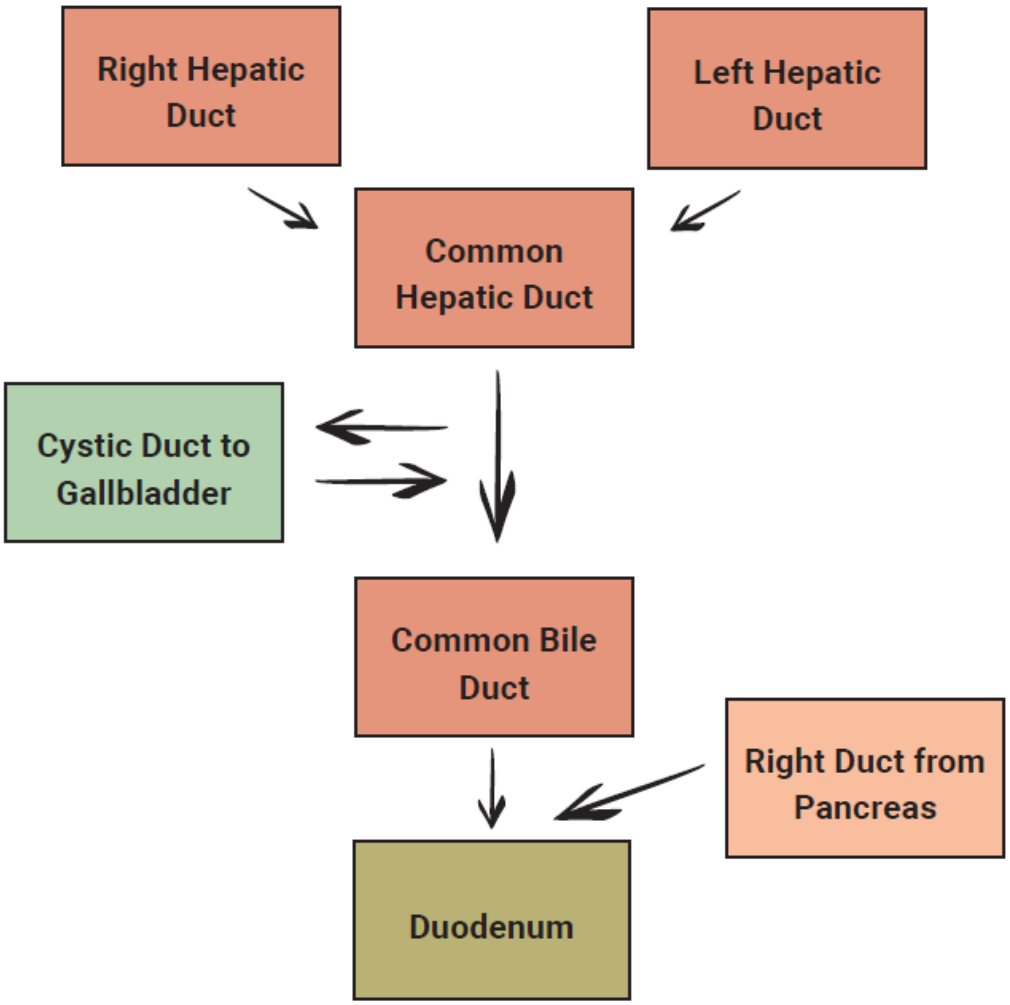
- Anatomy

Anatomy of Biliary Tree



Courtesy of: https://uen.pressbooks.pub/anatomyphysiology2/chapter/liver-gallbladder/

Anatomy of Biliary Tree

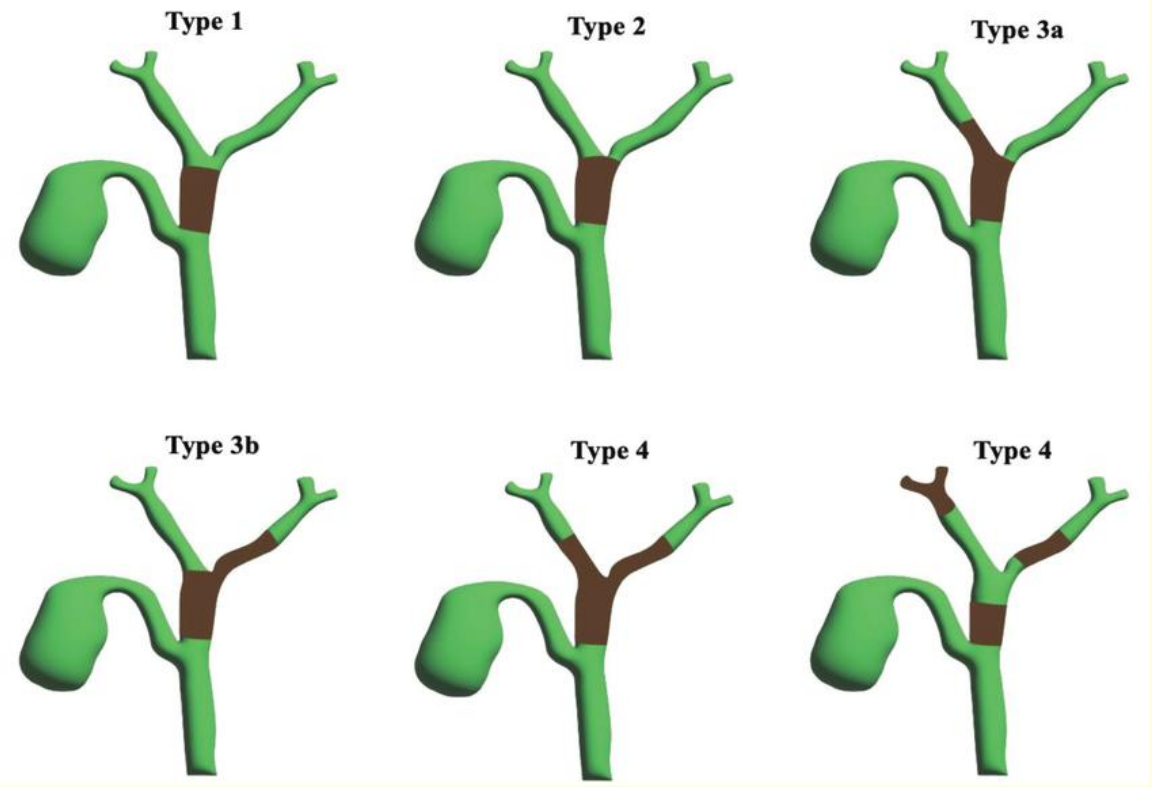


Courtesy of: https://uen.pressbooks.pub/anatomyphysiology2/chapter/liver-gallbladder/

➢ Classification

- Klatskin Tumour
  - Bismuth-Corlette classification system:
    Type I: Tumour below the confluence of left and right hepatic ducts
    Type II: Tumour reaching the confluence
    Type IIIa: Tumour occluding common hepatic and right hepatic ducts
    Type IIIb: Tumour occluding common hepatic and left hepatic ducts
    Type IV: Tumour involves confluence and both right/left hepatic ducts or is multicentric

The Bismuth-Corlette Classification of Perihilar Tumours



Type 1 is tumour below the confluence of the right and left hepatic ducts. Type 2 is tumour involving the confluence of the right and left hepatic ducts. Type 3a is tumour involving the confluence and right hepatic duct. Type 3b is tumour involving the confluence and left hepatic duct. Type 4 is tumour involving the confluence and both right and left hepatic ducts or multicentric tumours.

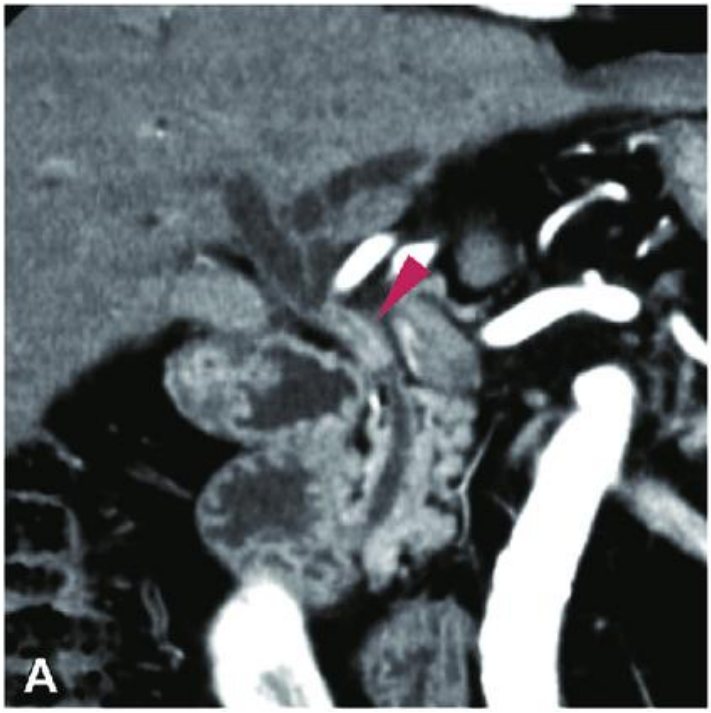
Courtesy of: Lee L and Rajesh A. J Gastrointestinal Abdominal Radiol ISGAR 2023; 6: 212–226.

- Risk Factors
  - Most cases are sporadic
  - Risk factors related to inflammation and cholestasis
  - Definite
    - Primary sclerosing cholangitis (PSC): 10% of cholangiocarcinoma attributed; 30-year cumulative incidence ~20%
    - Choledochal cysts (Types I & IV): 50x ↑ risk, even post-excision
    - Caroli disease
    - Hepatolithiasis
    - Liver fluke infections (e.g., Opisthorchis viverrini)
    - Lynch syndrome
  - Probable
    - Alcohol use, heavy
    - Biliary-enteric drainage procedures
    - Cirrhosis
    - Hepatitis C viral infection
    - Toxins (dioxins, polyvinyl chloride)

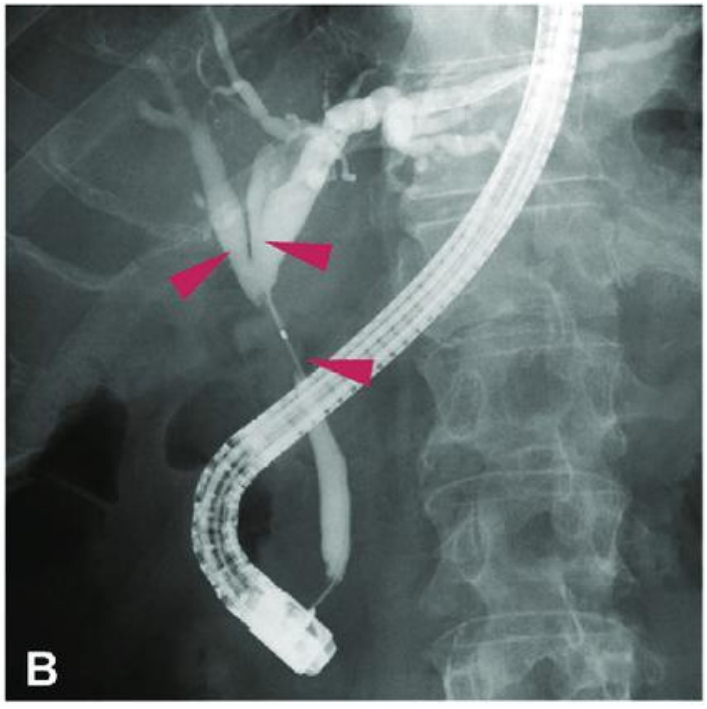
- Pathology & Pathogenesis
  - Inflammation
  - Environmental factors
  - Multiple genetic mutations
    - ↓ Tumour suppressor gene inhibition such as
      - ARID1A
      - ARID1B
      - BAP1
      - PTEN
      - TP53
    - ↑ gain-of-function mutations, such as
      - BRAF
      - KRAS

- Clinical
  - Presentation
    - Abdominal pain
    - Asymptomatic / insidious
    - Fever
    - Itching
    - Jaundice
    - Weight loss
  - Intrahepatic: abdominal pain, cachexia, malaise
  - Extrahepatic: painless jaundice due to obstruction
  - ~10% present with bacterial cholangitis
- Laboratory
  - CA 19-9
    - Moderate specificity
    - Low sensitivity (53%)
    - Outside PSC but higher in PSC, 98%
    - False negative
      - RBC antigen issues
    - False positive
      - Bacterial cholangitis or choledocholithiasis
- Diagnostic Imaging
  - CT, MRI, EUS
    - Mass
    - Biliary stricture
    - Ductal dilation CCA from HCC

Perihilar Cholangiocarcinoma on Contrast-Enhanced CT Scan



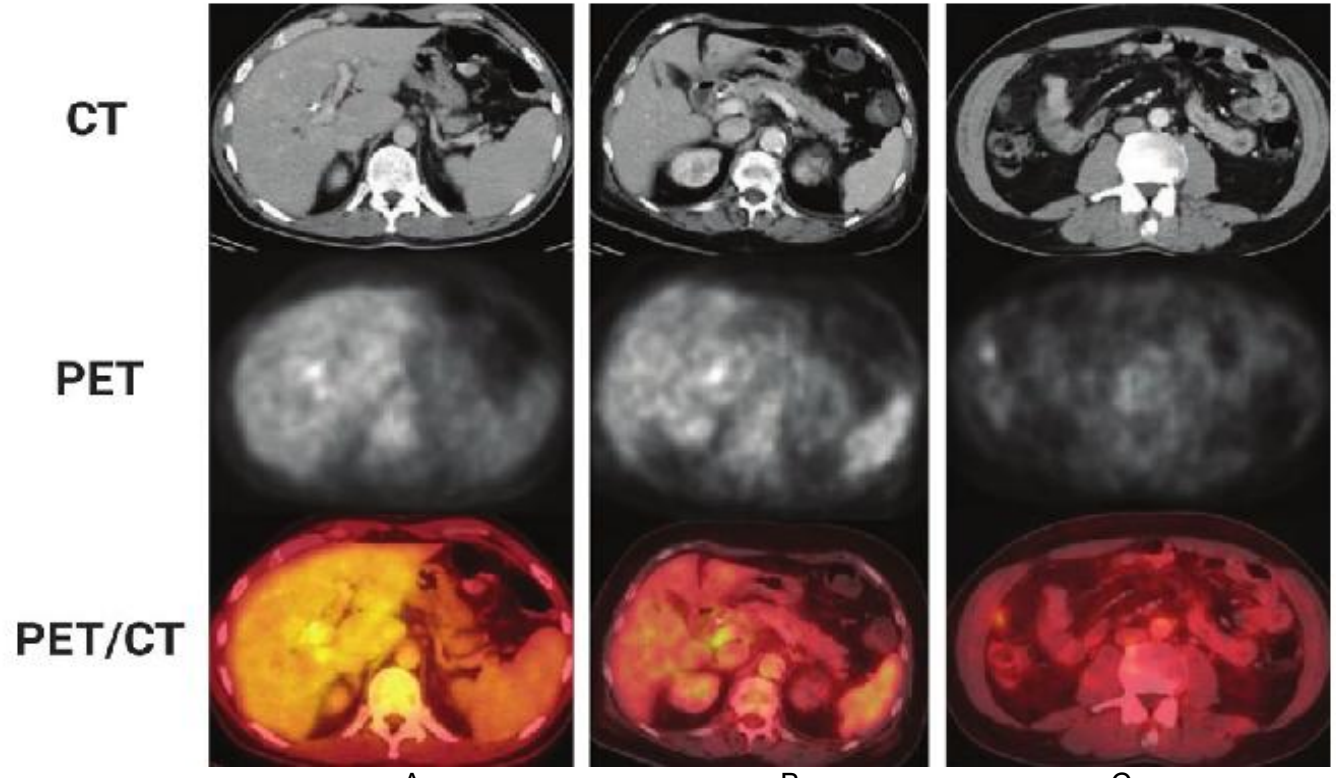
- A, Contrast-enhanced CT showing a 20-mm-long wall thickening in the hilar region (red arrow), suggestive of perihilar cholangiocarcinoma.



- B, Endoscopic retrograde cholangiography finding of a 20-mm-long stenosis in the hilar region. Red arrows indicate the biopsy sites.

Courtesy of: Mitchell DG, et al. RadioGraphics. 2022;42(1):125–142 .

Perihilar Cholangiocarcinoma



A B C

- A. CT scan also showed an increase in glucose metabolism on the PET scan.
- B. CT analysis revealed that a lymph node along the head of the pancreas was enlarged. PET analysis showed that this region had high glucose metabolism.
- C. CT analysis revealed a small nodule near the right abdominal wall with no obvious malignant features. However, PET/CT analysis showed that the nodule was a peritoneal metastasis, which was further verified by histopathology after surgical excision

Courtesy of: Liu J, et al. Insights Imaging 2022; 13(10)

Suggested Diagnostic Algorithm for Malignant-Appearing Intrahepatic Mass (CT/MRI)

Malignant-appearing intrahepatic mass on CT or MRI

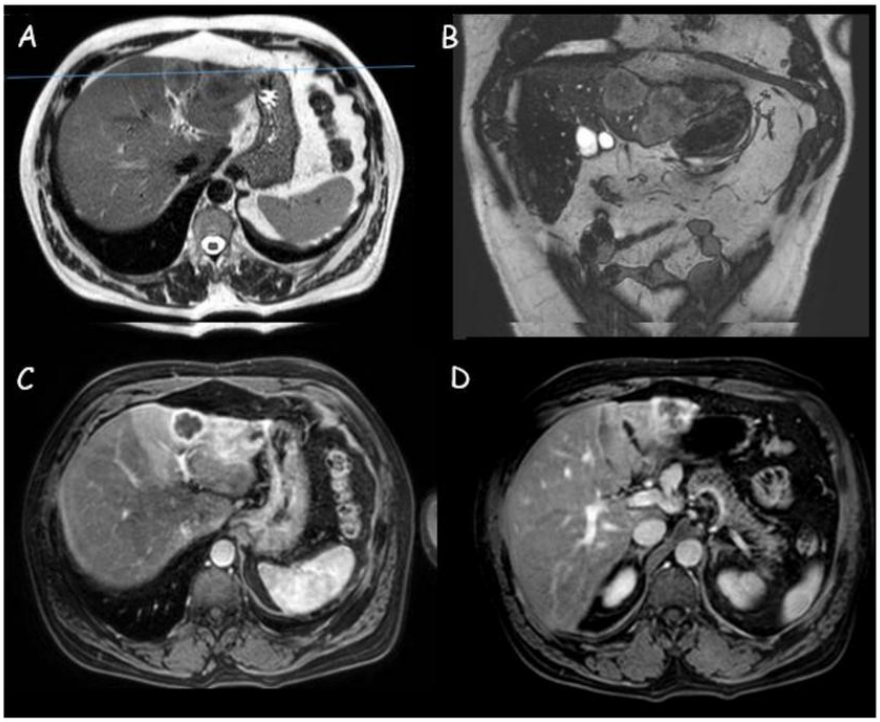
↓

Obvious history of extrahepatic primary malignancy?

- Yes → Evaluate for metastatic disease
- No → proceed to imaging features
  - Arterial phase rim enhancement + delayed venous phase enhancement → Suspicion of intrahepatic cholangiocarcinoma
    - Resectable?
      - Yes → Surgery
      - No → Biopsy
  - Arterial phase enhancement + venous phase washout → Hepatocellular carcinoma (HCC)

Adapted from: https://clinicalpub.com/tumors-of-the-bile-ducts-gallbladder-and-ampulla/

Magnetic Resonance Imaging of A 3 cm Intrahepatic Cholangiocarcinoma in Segment III:



(A,B) Moderately hyperintense lesion in T2 weighted sequences with weak restriction in diffusion-weighted imaging; (C,D) Peripheral contrast enhancement with perfusional alterations.

Courtesy of: Cerrito L, et al. Cancers 2023; 15(13):3393.

Diagnostic Algorithm for Suspected Cholangiocarcinoma

Clinical suspicion of cholangiocarcinoma

↓

Initial evaluation

- Serum CA 19-9 level
- ERCP with brush cytology, FISH, DIA

↓

Stratify findings

Diagnostic Findings	Next Step
Dominant stricture + (CA 19-9 ≥ 129 U/mL or positive biopsy/cytology/FISH polysomy)	→ Proceed to management of cholangiocarcinoma
Indeterminate results	→ MRI
CA 19-9 < 129 U/mL and no dominant stricture and negative biopsy/cytology/FISH	→ Observation

↓

MRI interpretation (if indeterminate)

- Mass vascular encasement / significant concern → PET
  - PET "hot spot" → Management of cholangiocarcinoma
  - PET negative → Observation
- Negative / minimal concern → Observation

Abbreviations: CA 19-9, carbohydrate antigen 19-9; DIA, digital image analysis; ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence in situ hybridization

Adapted from: https://clinicalpub.com/tumors-of-the-bile-ducts-gallbladder-and-ampulla/

- ERCP, EUS, transhepatic cholangiogram, MRI, CT – all provide different benefits (e.g. non-invasive, LN sampling (not tissue!), vascular assessment)
- Note that use of PET is further down in the cascade – low sens/spec for perihilar cholangio, and can have false-positive PET in inflammation – use for indeterminate lesions, after other studies

➢ Staging and Prognostic Factors

- Intrahepatic
  - Number of tumours
  - Vascular invasion
  - Lymph node metastasis
  - Only TNM staging correlates with survival (some stages need tissue confirmation)
- Perihilar
  - Tumour differentiation
  - Lymph node (LN) metastases
  - Negative (R0) surgical margins
  - Mayo Clinic non-operative staging system shows better prognostic performance compared to others
- Distal
  - Depth of tumour invasion
  - LN metastases
  - Perineural
  - Microscopic vascular
  - Pancreatic invasion
  - R0 resection status
  - TNM staging

- **Mayo Clinic Staging System for Perihilar Cholangiocarcinoma** (Table 69.4)

Stage	Criteria
I–II	− Unicentric mass ≤3 cm − ECOG performance status 0 − Serum CA 19-9 <1000 U/mL − No vascular encasement − No metastasis
I–II	− Unicentric mass ≤3 cm − ECOG performance status 1–2 − Serum CA 19-9 <1000 U/mL − Vascular encasement present − No metastasis
III	− Unicentric mass >3 cm or multicentric − ECOG performance status 0–2 − Serum CA 19-9 ≥1000 U/mL − Lymph node metastasis present
IV	− ECOG performance status 3–4 − Peritoneal or other organ metastasis present

Abbreviation: ECOG, Eastern Cooperative Oncology Group

- Intrahepatic

TNM and AJCC/UICC Staging Systems for **Intrahepatic Cholangiocarcinoma**

TNM Stage	Criteria
Tx	− Primary tumour cannot be assessed
T0	− No evidence of primary tumour
Tis	− Carcinoma in situ (intraductal tumour)
T1a	− Solitary tumour ≤5 cm without vascular invasion
T1b	− Solitary tumour >5 cm without vascular invasion
T2	− Solitary tumour with vascular invasion OR multiple tumours (± vascular invasion)
T3	− Tumour perforating visceral peritoneum
T4	− Tumour involving local extrahepatic structures by direct invasion
Nx	− Regional lymph nodes cannot be assessed
N0	− No regional lymph node metastases
N1	− Regional lymph node metastases present
M0	− No distant metastases
M1	− Distant metastases

Stage Table

AJCC/UICC Stage	Tumour	Node	Metastasis
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
III	Any T	N1	M0
IV	Any T	Any N	M1

Abbreviation: AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control

- Distal

TNM and AJCC/UICC Staging Systems for **Distal Cholangiocarcinoma**

TNM Stage	Criteria
Tx	− Primary tumour cannot be assessed
Tis	− Carcinoma in situ (intraductal tumour)
T1	− Tumour invades bile duct wall, depth <5 mm
T2	− Tumour invades bile duct wall, depth 5–12 mm
T3	− Tumour invades bile duct wall, depth >12 mm
T4	− Tumour involves celiac axis, SMA, or common hepatic artery
Nx	− Regional lymph nodes cannot be assessed
N0	− No regional lymph node metastases
N1	− Regional lymph node metastases (≤3 nodes)
N2	− Regional lymph node metastases (≥4 nodes)
M0	− No distant metastases
M1	− Distant metastases

AJCC/UICC Stage	Tumour	Node	Metastasis
0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIA	T2	N0	M0
IIB	T2	N1	M0
IIB	T3	N0–1	M0
IIIA	T1	N2	M0
IIIA	T2–3	N2	M0
IIIB	T4	N0–2	M0
IV	Any T	Any N	M1

Abbreviation: AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control

➢ Treatment

- **Intrahepatic Cholangiocarcinoma**
  - Curative options
    - Surgical resection
    - Liver transplant
  - Many cases are unresectable:
    - ~54% unresectable at presentation
    - Additional ~30% unresectable at time of attempted resection
    - Solitary masses can be resected by
      - Hepatic segmentectomy, or
      - Lobectomy
  - High recurrence rates, ~62%
  - Rule out (R0) resection
    - Achieved in ~63% of patients
    - 5-year survival after R0 resection is 40–63%
  - Liver transplant offered only in very early disease; rarely used
  - No statistically significant benefit from
    - Neoadjuvant, or
    - Adjuvant therapy
  - Unresectable/advanced disease
    - Transarterial chemoembolization (TACE): median overall survival 12–15 mon
    - Transarterial radioembolization (TARE): comparable outcomes

- Extrahepatic Cholangiocarcinoma
  - Surgical resection is treatment of choice (when no PSC present)
  - Perihilar
    - Lobar or extended lobar hepatic + biliary duct resection
    - With regional lymphadenectomy, Roux-en-Y hepaticojejunostomy
  - Pre-operative portal vein embolization: induces compensatory hyperplasia of contralateral lobe → increases remnant liver volume → makes resection more achievable

- Distal: Whipple resection
  - R0 resection difficult to achieve (<50%)
    - Post-R0 survival:
      - Perihilar, 20–67%
      - Distal, 27–37%
      - Adjuvant or neoadjuvant therapies: no proven benefit
- PSC patients: considered non-resectable → liver transplant ± neoadjuvant chemo/radiation
  - Resection complications: liver failure, second lesion at biliary-enteric anastomosis

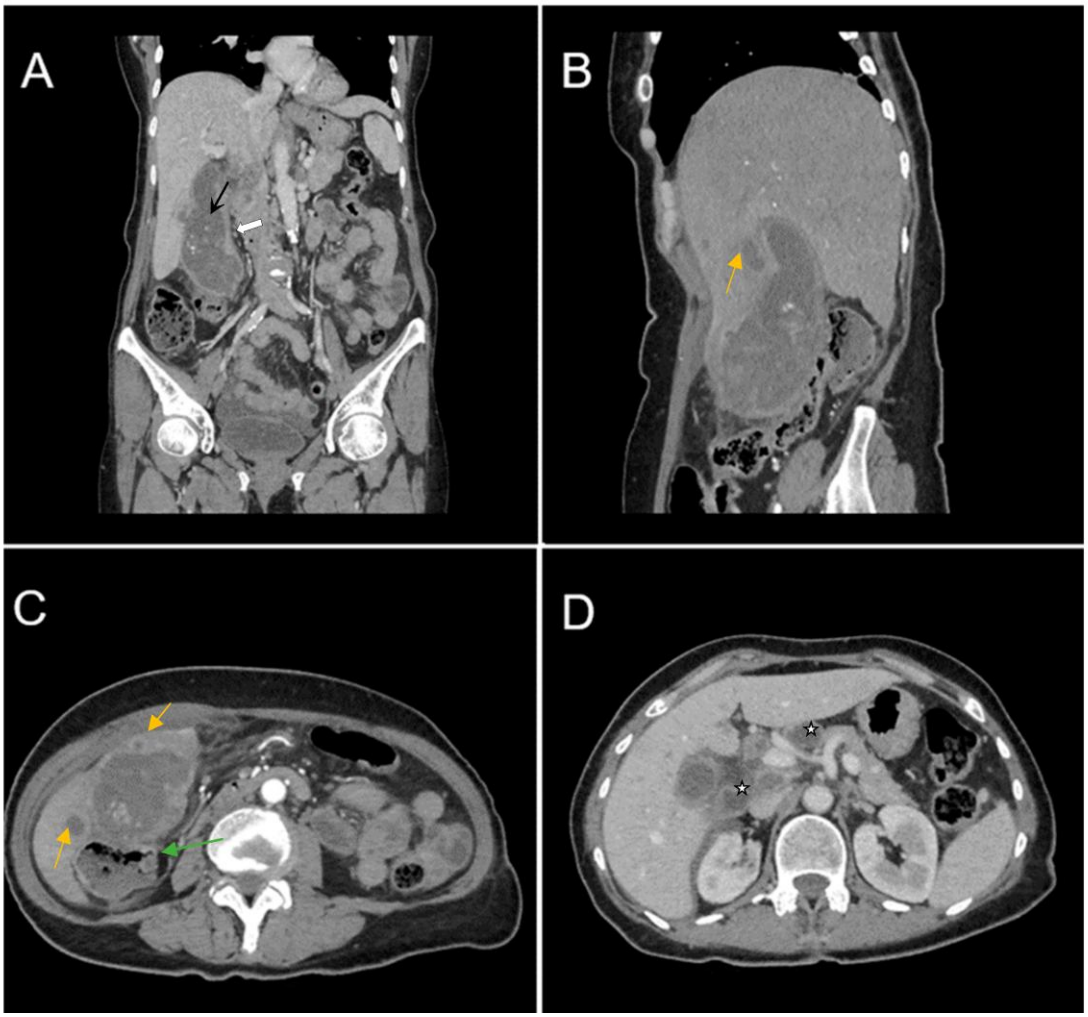
- General Treatment Principles
  - Gemcitabine
    - Approved for cholangiocarcinoma (no survival benefit from other chemo agents)
  - Palliative therapy essential for symptom management
  - Restore biliary drainage
    - Early intervention provides faster results
    - Bilateral drainage may increase survival

❖ Gallbladder Adenocarcinoma

➢ Demography

- Often diagnosed at advanced stage
- Faster growth profile than cholangiocarcinoma
- Surgical resection is the only possible curative approach (few candidates eligible)
- Average diagnosis age, 65 yr
- Female-to-male ratio: 2–3:1
- Survival
  - 5-year, 0–10%
  - Median: <6 mon

Multiplanar Sections of Contrast-Enhanced CT Acquisitions Richly Illustrating A Low Differentiated Gallbladder Adenocarcinoma.



- Gallbladder hydrops (>40 mm transverse measurement, 142 mm longitudinal measurement) with asymmetric gallbladder mural thickening, 7 mm (white arrow), and multiple intraluminal mixed stones, 5–8 mm (black arrow).
- (B,C) Liver metastases—hypodense nodular hepatic lesions with rim contrast enhancement (yellow arrow).
  - (C) Tumoural extension into IV, V segments of the right hepatic lobe and contact with the ascending colon (green arrow).
  - (D) Lymphatic metastases (white stars).

Courtesy of: Neculoiu D, et al. Diagnostics 2024; 14(5):475 (Figure 1)

- Pathophysiology
  - 80–95% of gallbladder carcinomas are adenocarcinomas
    - Moderately to well-differentiated
  - Papillary carcinoma
    - Least aggressive
    - Nodular and tubular variants also exist
  - Direct Invasion pathways
    - Lymphatic
    - Hematogenous
    - Perineural
    - Intraperitoneal
    - Intraductal
    - Often involves liver segments IVb and V (due to venous drainage and proximity)
  - Progression from dysplasia to carcinoma: ~10–15 yr
  - Genetic mutations:
    - ErbB protein mutations → worse outcomes
    - EGFR activation
    - TP53 mutations

- Risk Factors
  - Aflatoxin exposure
  - Carcinogen exposure
  - Cholangiocarcinoma
  - Cholelithiasis >1 cm
  - Chronic Salmonella Typhi or Paratyphi carrier status
  - First-degree relative with gallbladder carcinoma
  - Inflammatory bowel disease (IBD)
  - Intrahepatic biliary dysplasia
  - Lynch syndrome
  - Pancreaticobiliary malunion
  - Porcelain gallbladder
  - Primary sclerosing cholangitis (PSC)
  - Segmental adenomyomatosis in those >59 yr

- Laboratory
  - CEA >4.0 ng/mL (50% sensitivity, 93% specificity)
  - CA 19-9
- Diagnostic Imaging
  - Abdominal ultrasound (85% sensitivity, 80% specificity)
    - Focal/diffuse mural thickening of gallbladder wall
    - Intraluminal mass >2 cm from gallbladder wall
    - Concerning features
      - Irregular/asymmetric mural thickening >1 cm in depth
      - Nodular/smooth mass >1 cm with wall fixation
  - CT/MRI for indeterminate cases
- Staging and Treatment
  - TNM staging: 0 / I / II / IIIA / IIIB / IVA / IVB
    - 5-year survival rates
      - Stage 0: ~80%
      - Stage IVB: ~2%
  - Surgery is the only curative option
  - Typical contraindications for contraindications
    - Extensive metastases
    - Vascular invasion
    - Malignant ascites
    - Poor functional status
  - Direct colon/duodenum/liver invasion
    - Not absolute contraindication
  - Various levels of resection from
    - Simple cholecystectomy to extended cholecystectomy with pancreaticoduodenectomy, etc.
  - Use of surgery in advanced disease remains controversial
  - Unresectable disease
    - Gemcitabine and cisplatin per ABC-02 trial (↑ survival of 3.6 mon)
    - Gallbladder cancer is radioresistant

➢ Suggested Approach

Algorithm for Management of Gallbladder Carcinoma Discovered Intra- or Postoperatively during Laparoscopic Cholecystectomy

Diagnosis of Gallbladder Cancer

↓

Staging:

- T1a with negative surgical margins → No further treatment if margins are negative
- T1b or positive margins → Re-exploration for further resection
- T2, T3, T4 tumours → Re-exploration
  - If resectable → Radical cholecystectomy
  - If unresectable → Palliative treatment
- M1 → Palliative treatment

Abbreviations: M, metastasis stage; T, tumour stage

Adapted from: Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol 2003; 4: 167–76.

❖ **Ampullary Adenocarcinoma**

➢ Demography

- Rare, <1% of all GI cancers
- Etiology often unknown

➢ Pathology

- Ampulla of Vater anatomy: papilla + common pancreaticobiliary channel + distal bile duct + distal main pancreatic duct → Several histologic cell types
- Ampullary carcinoma subtypes
  - Intramural
  - Protruding (intra-ampullary)
  - Extramural protruding (periampullary)
  - Ulcerating ampullary
- Common sites for atypia
  - Common pancreaticobiliary channel followed by pancreatic duct, duodenal epithelium, and Brunner glands
- Most are adenocarcinomas (90% of ampullary malignancies)
  - Adenoma-to-carcinoma sequence is typical

- Clinical
  - Obstructive jaundice in 70–82%
  - Cholestasis occurs earlier in certain anatomic subtypes
  - Other clinical findings
    - Bacterial cholangitis in anicteric patients
    - Silver stools (acholic stools + bleeding from tumour)

- Risk Factors
  - Familial adenomatous polyposis (2nd most common cause of death in these patients)
  - Gardner syndrome
  - Neurofibromatosis type 1
  - Muir-Torre syndrome
  - Chronic liver fluke infection

- Laboratory
  - Bloodwork
    - CEA
    - CA 19-9

- Diagnostic Imaging
  - Diagnosed by endoscopy followed by imaging (CT, MRI, MRCP)
  - Hypodense mass on T2-weighted MRI
  - Double-duct sign (dilation of bile + pancreatic ducts)

- Staging
  - TNM staging system used
    - 5-yr survival rates
      - Stage 0, 40%
      - Stage IV, 4%

- Treatment
  - Surgical resection is the only curative option
    - But better rates of resection at time of diagnosis (77-93%)
    - Pancreaticoduodenectomy
      - If no LN involvement (5-yr survival is 59–78%

- Poor prognostic factors
  - LN involvement
  - Extracapsular LN involvement
  - Node microinvolvement
- Some RCT data suggesting
  - Chemoradiation may provide survival benefit, but meta-analyses are conflicting
- Consider palliative treatment
  - Obstructive cholestasis is a major morbidity (biliary stent or bypass)

❖ **Indeterminate Biliary Strictures**

➢ Differential Diagnosis

- Malignant
  - Cholangiocarcinoma
  - Gallbladder carcinoma
  - Hepatocellular carcinoma
  - Lymphoma
  - Metastatic disease
- Benign
  - IgG4 cholangiopathy (rule out by serology and biliary samples)
  - Ischemic stricture
  - Mirizzi syndrome
  - Post-operative stricture
  - Primary sclerosing cholangitis (PSC)
  - Radiation-induced strictures

Tumours of the Biliary Tract Other than Adenocarcinoma

➢ Classification

- Gallbladder
  - Benign
    - Adenoma
    - Granular cell tumour
    - Mesenchymal tumours (lipoma, leiomyoma, hemangioma, lymphangioma)
    - Paraganglioma
  - Malignant
    - Adenosquamous carcinoma
    - Neuroendocrine tumour (carcinoid)
    - Small cell carcinoma
    - Spindle cell sarcomatoid carcinoma

        - Others: angiosarcoma, carcinosarcoma, Kaposi sarcoma, leiomyosarcoma, malignant fibrous histiocytoma, melanoma, metastatic tumours, non-Hodgkin lymphoma, rhabdomyosarcoma
    - Tumour-like lesions:
        - Adenomyoma / adenomyomatosis
        - Cholesterol polyp
        - Heterotopia (gastric, pancreatic, liver, adrenal, thyroid)
        - Inflammatory polyp
- Bile Ducts
    - Benign
        - Adenofibroma
        - Adenoma
        - Adenomyoma
        - Ciliated hepatic foregut cyst
        - Cystadenoma and cystadenocarcinoma
        - Granular cell tumour
        - Hamartoma
        - Neuroma
        - Serous cystadenoma
        - Solitary or multiple cysts
    - Malignant
        - Embryonal (botryoid) rhabdosarcoma
        - Leukemia
        - Lymphoma
        - Melanoma
        - Metastatic tumour
        - Neuroendocrine tumour (carcinoid)
        - Paraganglioma
    - Precursor Lesions
        - Dysplasia (intraepithelial neoplasia / atypical hyperplasia)
        - Intraductal papillary mucinous tumour of the bile duct (biliary papillomatosis)

Abbreviations: AJCC, American Joint Committee on Cancer; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; DIA, digital image analysis; ECOG, Eastern Cooperative Oncology Group; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FISH, fluorescence in situ hybridization; HCC, hepatocellular carcinoma; LN, lymph node; MRI, magnetic resonance imaging; PET, positron emission tomography; PSC, primary sclerosing cholangitis; R0, negative surgical margin; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TNM, tumour-node-metastasis; UICC, Union for International Cancer Control.

Suggested Reading:

Turriff AE, Annunziata CM, Malayeri AA, et al. Prenatal cfDNA sequencing and incidental detection of maternal cancer. N Engl J Med. 2024;391(22):2123-2132. doi:10.1056/NEJMoa2405123

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

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

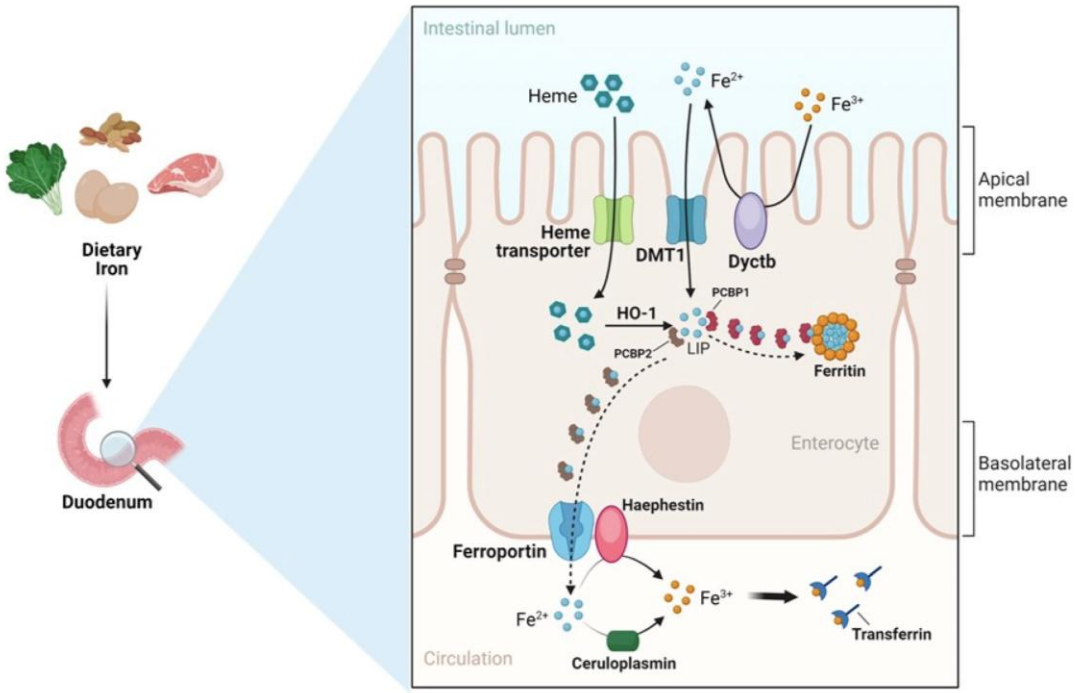
IRON METABOLISM AND HEREDITARY HEMOCHROMATOSIS

Alvi Islam

➢ Physiology

- **Dietary Iron Absorption**

Duodenal Absorption of Iron



- Dietary iron is mainly composed of poorly absorbed inorganic iron, which is found in food derived from both plants and animals and is mostly in the ferric (Fe^{3+}) form.
  - Heme iron, primarily present in animal food sources like meat, though less abundant is more bioavailable.
  - The first step of duodenal iron absorption is the transport of ferrous (Fe^{2+}) iron by DMT1 at the apical surface of enterocytes.
  - Previous reduction of the predominant Fe^{3+} by Dcytb is necessary. Iron bound to heme is internalized by a still unknown importer and iron is then released in the cytoplasm by the degradative action of heme oxygenase (HO-1).
  - Following the brush border transit, both the iron imported by DMT1 and that liberated from heme enter the labile iron pool (LIP) and are either utilized, incorporated in ferritin shells or exported by ferroportin.
  - PCBP1 and PCBP2 function as chaperones that deliver iron to client proteins. At the basolateral surface, following the efflux of Fe^{2+} into the bloodstream by ferroportin, the oxidative action of hephaestin and ceruloplasmin is required for the binding of Fe^{3+} to circulating transferrin.

Courtesy of: Correnti M, et al. Metabolites. 2024; 14(4):228.

- **Iron Transport and Storage**
  - In plasma, iron binds to transferrin for safe delivery.
  - Transferrin delivers iron mainly to the bone marrow for erythropoiesis.
  - Excess iron is stored intracellularly in ferritin.
  - Hemosiderin accumulates in states of iron overload.
    - Major storage sites include liver, spleen, and macrophages.

- **Regulation by Hepcidin**
  - Hepcidin is made by the liver in response to iron load and inflammation.
  - High hepcidin > Ferroportin degradation > Reduced iron absorption and release.
  - Low hepcidin > Increased iron absorption.
  - IL-6 during inflammation stimulates hepcidin ("anemia of chronic disease").
  - Mutations in regulation pathways cause iron overload syndromes.

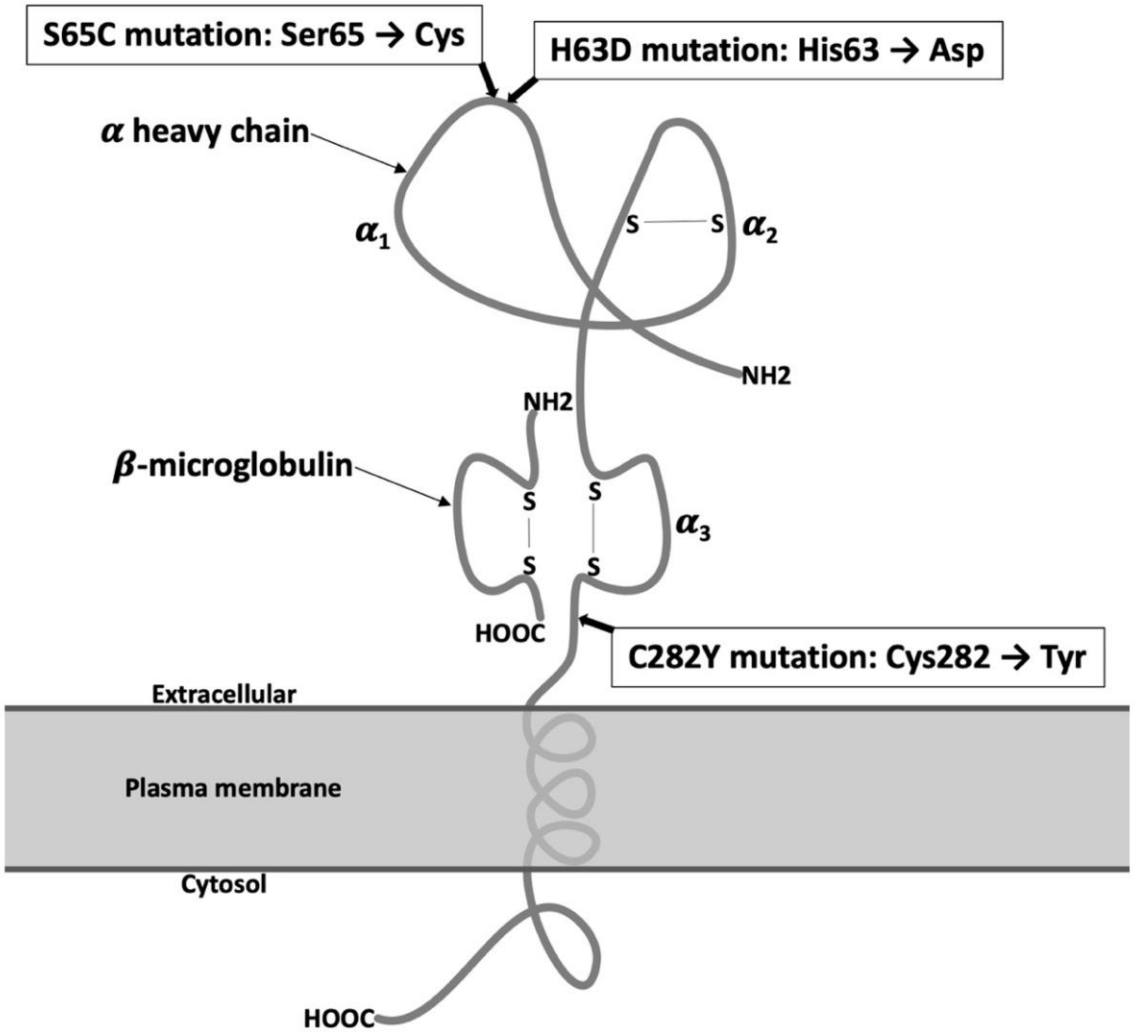
- **HEREDITARY HEMOCHROMATOSIS (HH)**

➢ Definition
  - HH is a genetic disorder of systemic iron overload.
  - Caused by increased intestinal absorption of iron.
  - Iron progressively deposits in multiple organs.

➢ Demography
  - Predominantly affects individuals of Northern European descent.
  - Early detection prevents irreversible organ damage.

➢ Genetics
  - Caused by mutations in the HFE gene.
  - C282Y homozygosity accounts for most clinical cases.
  - H63D and S65C are less penetrant variants.
  - Inheritance is autosomal recessive.
  - Genetic testing confirms diagnosis of HH, but only testing iron status determines if the HH phenotype is present
    - It is the storage of excess body iron which leads to the clinical disease and complications.

Genetics of Hereditary Hemochromatosis Leading to HFA Mutation



- The HFE protein scheme presented with β2-microglobulin.
  - This complex is located on the surface of the cell.
  - The HFE protein consists of three domains: α1, α2, and α3. β2-microglobulin binds to a protein through an α3 domain.
  - Positions of the three HFE mutations, C282Y, H63D, and S65C, are shown.

Courtesy of: Daniłowicz-Szymanowicz L, et al. Diagnostics 2021; 11(7):1279.

- Pathophysiology
  - Deficient hepcidin production is the central defect.
  - Persistent ferroportin activity = unregulated iron export.
    - Also indirectly increases DMT1 activity --> leads to increased intestinal absorption of iron.
  - Net effect: Plasma iron levels rise despite iron overload.
    - Excess iron deposits in parenchymal tissues.
  - Oxidative stress drives organ injury.

- Clinical
  - Symptoms usually appear in middle adulthood.
  - Bronze skin pigmentation may develop ("bronze diabetes").
  - Cardiac involvement leads to cardiomyopathy and arrhythmias.
  - CNS
    - Chronic fatigue
    - Hypopituitarism
  - Heart
    - Cardiac rhythm disorders
    - Cardiac failure
    - Cardiomyopathy
  - Liver
    - Chronic iron deposition → bridging fibrosis and cirrhosis.
    - Cirrhosis → ↑ risk of HCC
    - Early stages show hepatomegaly without fibrosis.
  - Pancreas
    - Diabetes mellitus (from pancreatic iron deposition)
  - Skin
    - Bronze skin pigmentation ("bronze diabetes").
    - Flat nails
    - Koilonychia
    - Melanoderma
    - Skin dryness
    - White nails
  - MSK
    - Joint pain
    - Osteoporosis
    - 2nd/3rd MCP, hooked osteophytes)

- Diagnosis
  - First-line tests: serum transferrin saturation and ferritin.
  - Transferrin saturation >45% suggests iron overload.
  - Elevated ferritin supports diagnosis but is nonspecific.
    - Screen when Ferritin >300 ng/ml in men; >200 ng/ml in women.
  - Exclude inflammatory or infectious causes of hyperferritinemia.
  - Genetic testing confirms HFE mutations (C282Y, H63D).
  - MRI can quantify liver iron concentration noninvasively.
  - Fibrosis assessment may be needed using elastography or biopsy.
  - Liver biopsy
    - Indicated if ferritin >1000, or liver enzymes elevated in a patient with confirmed HH
    - Differentiate between classic HH and ferroportin disease
    - Assess degree of fibrosis
    - Assess hepatic iron concentration

- Differential Diagnosis
  - Secondary iron overload from transfusions, hemolysis, or ineffective erythropoiesis.
  - Non-HFE genetic hemochromatosis (hemojuvelin, hepcidin, ferroportin mutations).
  - Chronic liver disease can elevate ferritin without true iron overload.
  - Dysmetabolic iron overload syndrome linked to obesity and metabolic syndrome.
  - Clinical context and testing differentiate these entities.

- Treatment
  - Therapeutic phlebotomy is first-line treatment.
  - Weekly removal of 1 unit of blood (500 mL) during induction phase.
  - Each session removes approximately 250 mg of iron.
  - Goal: ferritin 50–100 ng/ml, transferrin saturation <50%, hematocrit (HCT) <35%.
  - Maintenance phlebotomy every 2–4 mon.
  - Other management
    - Chelation therapy reserved for patients who cannot undergo phlebotomy.
      - Desferoxamine, Deferiprone
    - Avoid vitamin C supplementation, which increases iron absorption.

- Limit alcohol to reduce additional liver injury.
- Genetic counselling: Screen first-degree relatives with transferrin saturation and genetic testing.
- Immunize against hepatitis A and B if not already immuned.

➢ **HH Variants and Special Populations**

- Juvenile hemochromatosis presents earlier and progresses rapidly.
- Non-HFE hemochromatosis caused by mutations in hemojuvelin, hepcidin, or ferroportin (please see below).
- African iron overload linked to dietary factors (iron-rich beer) and genetic predisposition.
- Atypical cases require specialized genetic panels for diagnosis.
- Management principles remain similar to classic HH: reduce iron burden early.

- **Iron Overload Syndromes and Hereditary Hemochromatosis Types.**

Category	Subtype	Gene / Defect	Inheritance	Key Features
Primary Iron Overload (Hereditary Hemo-chromatosis)	Type 1A (Classic HH)	HFE (C282Y homozygote)	Autosomal recessive	Adult onset; common in Northern Europeans; liver, heart, pancreas iron overload
	Type 1B	HFE (C282Y/H63D compound heterozygote)	Autosomal recessive	Similar to Type 1A, variable penetrance
	Type 1C	HFE (S65C mutation)	Autosomal recessive	Rare variant
	Type 2A (Juvenile HH)	HJV (Hemojuvelin)	Autosomal recessive	Severe hepcidin deficiency; early onset (teens–20s); cardiomyopathy, hypogonadism
	Type 2B (Juvenile HH)	HAMP (Hepcidin)	Autosomal recessive	Absent/nonfunctional hepcidin; very early and severe
	Type 3	TFR2 (Transferrin receptor 2)	Autosomal recessive	Impaired iron sensing; intermediate severity; presents earlier than Type 1
	Type 4A (Ferroportin disease, classic)	SLC40A1 (loss of function)	Autosomal dominant	High ferritin, low/normal transferrin saturation; iron trapped in macrophages
	Type 4B (Ferroportin disease, hepcidin-resistant)	SLC40A1 (gain of function)	Autosomal dominant	High ferritin and high transferrin saturation; resembles Type 1

Category	Subtype	Gene / Defect	Inheritance	Key Features
Secondary Iron Overload	Dyserythro-poiesis	—	—	Thalassemia, chronic hemolytic anemia
	Chronic transfusions	—	—	Iatrogenic iron overload
	Chronic liver disease	—	—	Viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH/MASH)

Adapted from: MSD Manual Professional Edition. Hematology: Hereditary Hemochromatosis. Kenilworth, NJ: Merck & Co., Inc.; reviewed 2023. Available at: https://www.msdmanuals.com/professional/hematology-and-oncology/iron-overload/hereditary-hemochromatosis

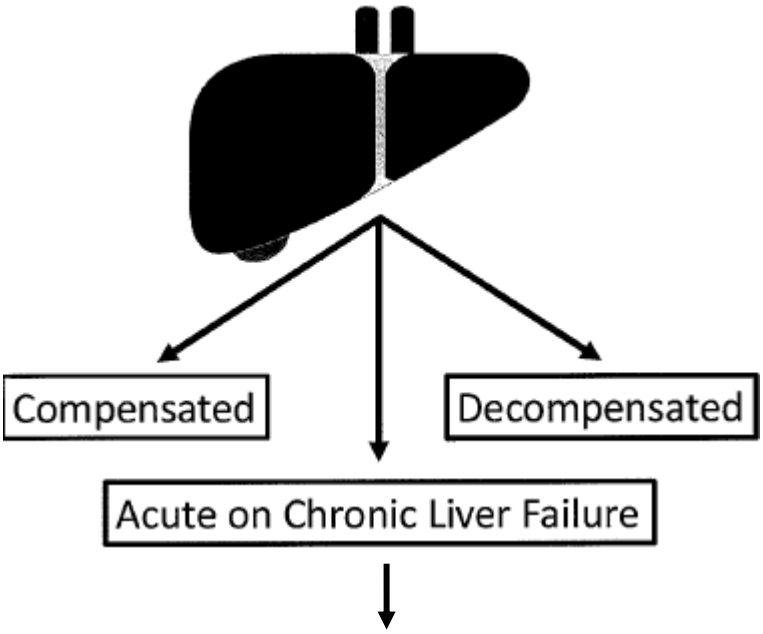
- **Summary Take Away**
  - Hereditary hemochromatosis causes systemic iron overload.
  - Early symptoms are subtle; proactive screening is essential.
  - Diagnosis relies on transferrin saturation, ferritin, and HFE genetic testing.
  - Phlebotomy is safe, effective, and life-saving.
  - Early treatment prevents cirrhosis, diabetes, and cardiomyopathy.
  - Awareness and family screening improve patient outcomes.

Abbreviations: DMT1, Divalent Metal Transporter 1; Dcytb, Duodenal Cytochrome b; HO-1, Heme Oxygenase-1; LIP, Labile Iron Pool; PCBP1, Poly(rC) Binding Protein 1; PCBP2, Poly(rC) Binding Protein 2; FPN, Ferroportin; IL-6, Interleukin-6; HFE, High Iron Fe gene; HJV, Hemojuvelin; HAMP, Hepcidin gene; TFR2, Transferrin Receptor 2; HH, Hereditary Hemochromatosis; HCC, Hepatocellular Carcinoma; MRI, Magnetic Resonance Imaging; MCP, Metacarpophalangeal joint; HCT, Hematocrit; NASH, Non-Alcoholic Steatohepatitis; MASH, Metabolism-Associated Steatohepatitis; DFO, Desferoxamine; DFP, Deferiprone

ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

Tamoor Afzaal

➢ Clinical Stages of Chronic Liver Disease



Triggers:
- Hepatic
  - 1 – Alcoholic Hepatitis
  - 2 – Drug-Induced Liver Injury (DILI)
  - 3 – Variceal Bleed
  - 4 – Viral Hepatitis
- Non-Hepatic
  - Infection
  - Surgery

Acute-on-Chronic Liver Failure (ACLF)

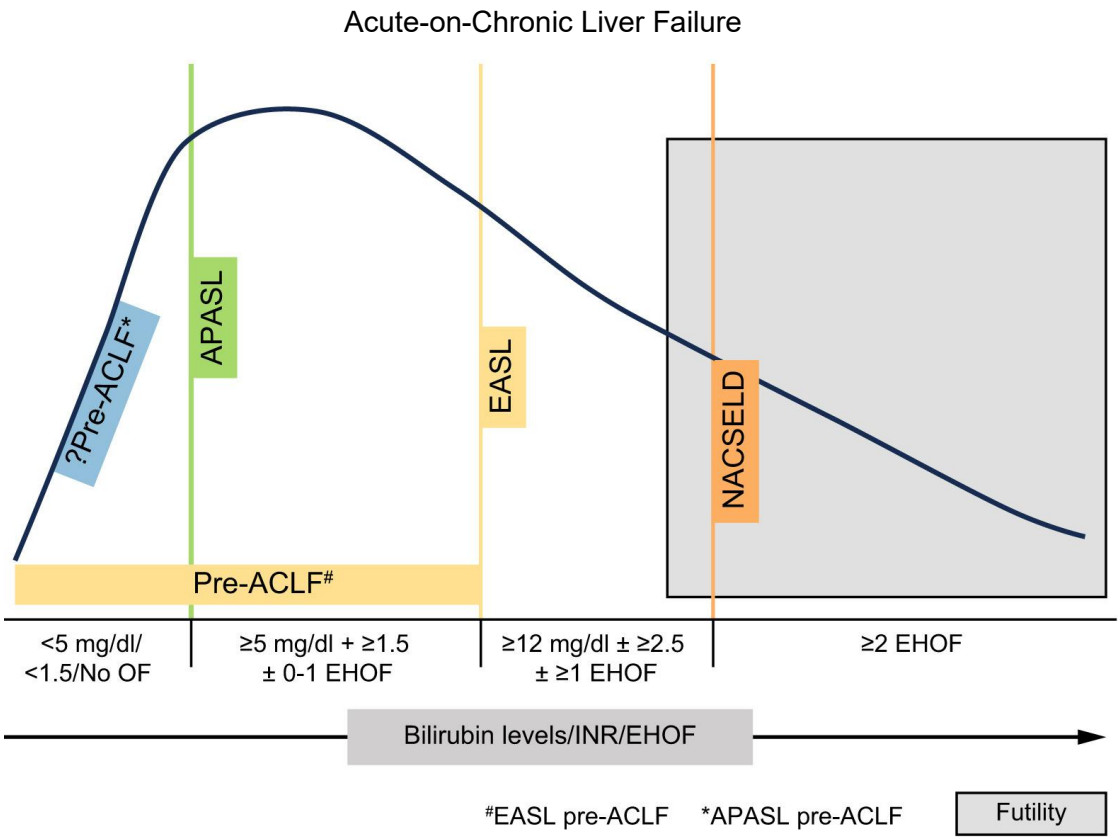
- Life-threatening syndrome, associated with systemic inflammation, causing hepatic and extra-hepatic organ failure.
- ↑ short-term mortality – up to 80% for ACLF Grade 3.
  - Often affects younger patients
- Very few treatment options
  - Liver transplant can be lifesaving (1-year survival, >80%).

- Definitions
  - There are 3 major definitions of ACLF
    - APASL – Asian Pacific Association for the Study of the Liver
      - Liver failure (bilirubin >85 µmol/L or INR >1.5), followed by ascites and/or hepatic encephalopathy within 4 weeks, in a patient with known or unknown liver disease (if cirrhosis, has to be compensated).
    - EASL – European Association for the Study of the Liver
      - Patient with cirrhosis with failure of >1 organ and systemic inflammation that may have been induced by an acute precipitant.
    - NACSELD – North American Consortium for the Study of End-Stage Liver Disease
      - Patient with cirrhosis who has >2 organ failures precipitated by intra- or extrahepatic trigger.
  - World Gastroenterology Organization (WGO) combined elements of the three regional definitions of ACLF (not frequently used definition)
  - Choice of Guideline
    - Depends upon laboratory values (bilirubin, INR)

- Differences amongst organizations of characteristics of ACLF
  - Stage of underlying liver disease (cirrhosis +/-)
  - Previous episodes of decompensation
  - Requirement of specific magnitudes (bilirubin/INR) of liver failure

	APASL	EASL	NACSELD
Stage of Liver Disease	Any chronic liver disease (if cirrhosis – compensated)	Cirrhosis	Cirrhosis
First episode of decompensation	Yes	No	No
Precipitating factor	Intrahepatic	Intra- or extrahepatic	Intra- or extrahepatic
# organ systems considered	Two	Six	Four
Definition of liver failure	Bilirubin > 85 µmol/L or INR > 2.5	Bilirubin > 204 µmol/L, no INR cut-off	Not defined
Minimum organ system failure	N/A	≥1	≥2

Adapted from: Artru F et al. Lancet Gastroenterol Hepatol 2024; 9(6): 564-576.

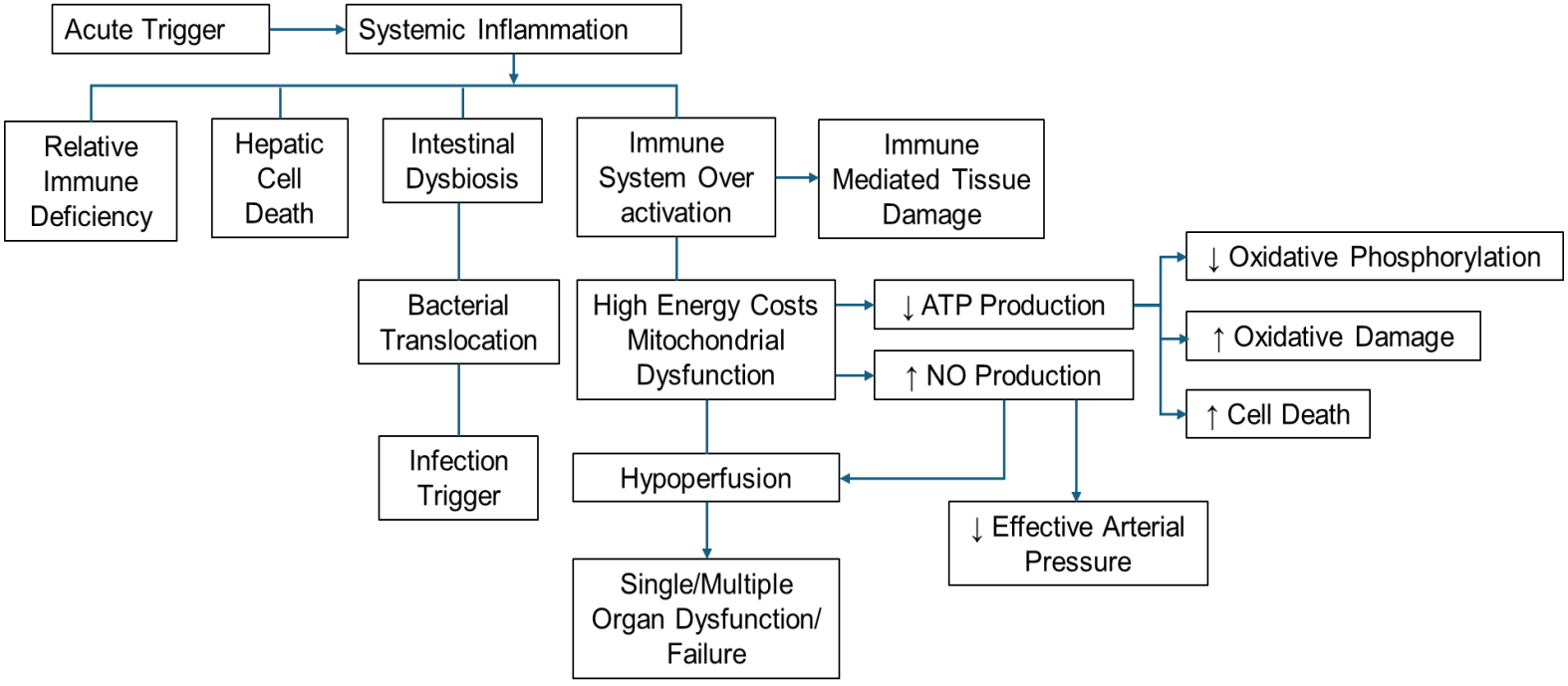


- Pathophysiology
  - Triggers/Precipitants
    - Hepatic
      - Alcohol
      - Drugs
      - GI Bleeding
      - Viral
    - Non-Hepatic
      - Surgery
      - Infection

    ↓
  - Release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) into blood.

    ↓
  - PAMPs/DAMPs bind to pattern-recognition receptors (PRRs) → release of pro-inflammatory cytokines.

➢ **Pathophysiology of Acute-on-Chronic Liver Failure** (ACLF)



Adapted from: Artru F et al. Liver transplantation for ACLF. Lancet Gastroenterol Hepatol 2024; 9(6): 564-576.

- Grades (of ACLF)
  - Cirrhosis + Liver dysfunction + ≥ 1 organ failure (red)*
    plus
  - Intra- or extrahepatic trigger

- Organ Dysfunction/Failure
  - Brain
    - HE grade I–II (West-Haven criteria)
    - HE grade III–IV (West-Haven criteria)
  - Lung
    - PaO_2/FiO_2 ≤200
    - SpO_2/FiO_2 ≤214
  - Heart
    - Need for vasopressor
    - Cirrhotic cardiomyopathy
  - Liver
    - Bilirubin ≥12.0 mg/dL
  - Gut
    - ↓ barrier function
    - ↑ bacterial translocation
  - Blood/Immune
    - INR ≥2.5
    - Immune deficiency
    - Systemic inflammation
  - Kidney
    - Creatinine 1.5-1.9 mg/dL
    - Creatinine ≥2 mg/dL
    - Need for renal replacement therapy
  - Adrenal Glands
    - Adrenal insufficiency
  - MSK
    - Sarcopenia
    - Frailty

EASL. J. Hepatol 2023; 79(2): 461-491.

	Age	Yrs	
○	WBC count	Norm: 3.7 – 10.7 ×10³ cells/μL	
○	Liver		
	− Bilirubin	<6 mg/dL (<102.6 μmol/L)	+1
		6 to 12 mg/dL (102.6 to <205.2 μmol/L)	+2
		≥12 mg/dL (≥205.2 μmol/L)	+3
○	Kidney		
	− Creatinine	<2 mg/dL (<176.8 μmol/L)	+1
		2 to <3.5 mg/dL (176.8 to <309.4 μmol/L)	+2
		≥3.5 mg/dL (≥309.4 μmol/L) / renal replacement therapy	+3
○	Coagulation		
	− INR	<2.0	+1
		2.0 to <2.5	+2
		≥2.5	+3
○	Circulatory		
	− MAP (mmHg)	≥70	+1
		<70	+2
		Any MAP with vasopressors	+3
○	Respiratory		
	− Information available	PaO_2/FiO_2 ratio	
		SpO_2/FiO_2 ratio	
○	PaO_2/FiO_2 ratio	>300	+1
		≥200 to 300	+2
		≤200 (if patient intubated for respiratory failure)	+3

- **SALT-M Score** – Sundaram ACLF Liver Transplantation Mortality
  - Predicts 1-year survival post-LT for ACLF grades 2 and 3.
  - Variables:
    - Age
    - BMI
    - Inotrope use
    - Respiratory failure
    - Diabetes

- **TAM Score** – Transplantation for ACLF Grade 3 patients
  - Components
    - Recipient age ≥53 years
    - Pre-LT lactate ≥4
    - Intubated with PaO_2/FiO_2 ratio <200
    - Pre-LT leukocyte count ≤10
  - Predicts 1-year survival post-LT for ACLF-3 patients
    - 2 points = 8% survival
    - ≤2 points = 84% survival
  - Recently evaluated with external cohort, multicentre French cohort
    - Did nit effectively identify patients at risk of death at 1 yr

Courtesy of: Kulkarni AV, et al. Clin Liver Dis 2023;27(3):735–762; Artru F, et al. Lancet Gastroenterol Hepatol 2024;9(6):564–576.

➢ Mortality

- Inflamed by
  - Grade of ACLF on day of diagnosis
  - Time span (duration) from diagnosis (e.g., day 28 or 90)
- Short term mortality is very high

28-day mortality rates:

- Grade

Grade	EASL	APSAL
1	22%	13%
2	32%	45%
3	77%	86%

  - ACLF is dynamic syndrome:
    - Its severity can undergo rapid changes daily
    - >80% of patients reach final ACLF grade by day 7 from diagnosis of ACLF (day 3-7 assessment is the best prognosticate)**

Adapted from: Artru F et al. Lancet Gastroenterol Hepatol 2024; 9(6): 564-576; EASL. J. Hepatol 2023; 79(2): 461-491.

Sankey Plots – 90-day Mortality in ACLF

Baseline ACLF Grade (D1)	Condition at D3–7	% of Patients	90-Day Survival (%)	90-Day Mortality (%)
ACLF-1	No ACLF	50%	85%	15%
	ACLF-1	28%	70%	30%
	ACLF-2	11%	43%	57%
	ACLF-3	11%	6%	94%
ACLF-2	No ACLF	28%	86%	14%
	ACLF-1	17%	78%	22%
	ACLF-2	32%	56%	44%
	ACLF-3	23%	15%	85%
ACLF-3	No ACLF	9%	90%	10%
	ACLF-1	7%	69%	31%
	ACLF-2	20%	43%	57%
	ACLF-3	64%	20%	80%

Adapted from: Artru F, et al. Lancet Gastroenterol Hepatol 2024; 9(6): 564-576 (Figure 1)

- Reversibility of ACLF
  - Grade 1: ~55% may resolve
  - Grade 2: ~35% may resolve
  - Grade 3: ~15% may resolve
  - Short-term mortality remains very high, but reversibility is possible depending on grade.
  - Patients with ACLF-3 at the time of listening have greater 14-day mortality than those listed as status 1a (acute liver failure), independent of MELD-Na Score
- Treatment

❖ Principles

- Diagnosis, early and accurate
- Precipitant, identify and treat
- Organ-specific, monitor and treat complications
- Liver transplant, assessment and consideration

Schulz MS, et al. Transpl Int 2022; 35: 10108.

❖ Organ-Specific Failure

- Brain (Hepatic Encephalopathy [HE])
  - West Haven Grade 3–4 HE.
  - Principles in managing brain failure
    - Care of airway to prevent aspiration
      - Consider ICU in Grade 3–4 HE).
    - Determine cause of altered mental status (DIMS work-up).
    - Determine and treat precipitating factors of HE.
    - Consider CT/MR head.
    - Empiric therapy for suspected HE:
      - Lactulose (PO/PR) or PEG (if ileus or concern for abdominal compartment syndrome).
      - Role of rifaximin not well studied in ACLF.
- Heart
  - Volume assessment
    - Exam, POCUS TTE, central venous pressure (CVP), inferior vena cava (IVC), urine output, lactate.
    - If hypovolemia → resuscitate with IV fluids/albumin, then pressors
      - If not hypovolemia, early intervention with pressors + inotropes (if low cardiac index)
    - Dynamic measurements/assessments recommended.
  - Fluid resuscitation
    - Balanced (Ringers/ normal saline [NS]) for first-line volume replacement.
    - Albumin can be used for resuscitation fluids in
      - Hepatorenal syndrome (HRS)
      - Spontaneous bacterial peritonitis (SBP)
      - SBP, HRS.
  - Vasopressors
    - No ACLF/Cirrhosis specific evidence
    - Target mean arterial pressure (MAP) >65 mmHg.
    - First-line: norepinephrine.
    - Second-line: vasopressin.
- Lung (Acute Lung Injury [ALI])
  - Hypoxemia plus bilateral infiltrates → progression to acute respiratory distress syndrome (ARDS).
  - Ventilated patients
    - Low PEEP
    - Low tidal volume (ARDSNET).

- Hepatic hydrothorax
  - Intermittent thoracentesis.
  - Can lead to hypoxemic + ventilatory insufficiency
- Respiratory failure
  - Assess degree of based on P/F (PaO_2/FiO_2) ratio

- Kidney (Renal Failure)
  - Most common extrahepatic organ failure in ACLF
    - Often precipitated by infection.
  - HRS-AKI
    - ↑ serum creatinine ≥26.4 µmol/L within 48 h, or
    - ≥50% from baseline (while fulfilling all diagnostic criteria for HRS type 1)
    - 50% of injuries are pre-renal AKI, 35% ATN AKI.

Abbreviations: AKI, acute kidney injury; ATN, acute tubular necrosis; sCr, serum creatinine concentration; HRS, hepatorenal syndrome

  - Management**:**
    - Identify cause of AKI (septic work-up).
      - Every hour delay in antibiotics increases mortality ~1.86x.
    - Remove/treat precipitating factor.
    - Trial of fluid challenges.
      - Use 25% albumin (oncotic + anti-inflammatory properties).
      - 1 g/kg body weight, max 100 g/day for 48h.
    - Hold nephrotoxic medications (diuretics).
    - HRS therapy
      - Vasoconstrictor therapy + albumin (20–40 g/day).
    - Renal replacement therapy (RRT)
      - Consider in LT ACLF candidates.
      - For non-transplant candidates: case-by-case basis.

Adapted from: Karvelas CJ, et al. AASLD Practice Guidance on Acute-on-chronic liver failure. Hepatology 2024; 79(6): 1463–1502.

➢ Liver Transplantation in ACLF

- Survival post liver transplant
  - 1 yr, > 80%
  - 5 yr, ~70%

  - Variable
  - Golden window: first opportunity before superimposed complications.

- Predictors of reduced survival post-LT:
  - Patient related
    - Prior to admission
      - ↑ Age
      - Complications
        - Diabetes
        - Cardiac risk factors
        - Frailty
        - Malnutrition
    - During hospitalization/ICU
      - Organ failure
        - Number of organ failure
        - Long duration of admission in ICU
      - Lung
        - Respiratory failure (P/F ratio < 200)
        - Intubation and mechanical ventilation
      - Heart
        - Requirement of vasopressors
          - Norepinephrine >1 mcg/kg/min or
          - Need for >2 vasopressors
      - Metabolic
        - Lactate > 4
      - CLIF-C Score > 64 (AASLD guidelines)*
  - Donor variable
    - Donor Risk Index (Donor age, race, CIT, etc.)
    - DRI ≥ 1.7*

*predictors of fertility

Courtesy of: Artru F, et al. *Liver transplantation for acute-on-chronic liver failure.* Lancet Gastroenterol Hepatol 2024;9(6):564–576.

- Scoring Systems
  - Further external validation required
  - Single score does not give clear answer

- **CLIF-C ACLF Scores** – Chronic Liver Failure Consortium
  - Predicts 1-month, 3-month, 6-month, and 1-year mortality.
  - Score >64 suggests futility for transplantation.
  - Score >70 at admission or day 3 associated with ~90% mortality at 90 days.

- Summary Points
  - ACLF is generally defined as a patient with chronic liver disease who has hepatic decompensation with associated extrahepatic organ failure, often due to a trigger.
  - Short-term mortality in ACLF is very high.
  - Most common triggers: infection, GI bleeding, alcohol.
  - Organ-specific management is important in achieving reversibility.
  - Liver transplantation is life-saving / effective short/long-term treatment for carefully selected patients.

Abbreviations: ACLF, Acute-on-Chronic Liver Failure; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; WGO, World Gastroenterology Organization; PAMPs, Pathogen-Associated Molecular Patterns; DAMPs, Damage-Associated Molecular Patterns; PRRs, Pattern-Recognition Receptors; HE, Hepatic Encephalopathy; PaO_2/FiO_2, Arterial Oxygen Partial Pressure/Fraction of Inspired Oxygen ratio; SpO_2/FiO_2, Oxygen Saturation/Fraction of Inspired Oxygen ratio; MAP, Mean Arterial Pressure; SALT-M, Sundaram ACLF Liver Transplantation Mortality score; TAM, Transplantation for ACLF Mortality score; LT, Liver Transplant; WBC, White Blood Cell; BMI, Body Mass Index; CLIF-C, Chronic Liver Failure Consortium score; MELD-Na, Model for End-Stage Liver Disease with Sodium; ICU, Intensive Care Unit; AKI, Acute Kidney Injury; ATN, Acute Tubular Necrosis; sCr, Serum Creatinine; HRS, Hepatorenal Syndrome; RRT, Renal Replacement Therapy; SBP, Spontaneous Bacterial Peritonitis; NS, Normal Saline; POCUS TTE, Point-of-Care Ultrasound Transthoracic Echocardiography; CVP, Central Venous Pressure; IVC, Inferior Vena Cava; ALI, Acute Lung Injury; ARDS, Acute Respiratory Distress Syndrome; ARDSNET, ARDS Network ventilation protocol; CT, Computed Tomography; MR, Magnetic Resonance; DIMS, Differential for Impaired Mental Status; DRI, Donor Risk Index; CIT, Cold Ischemia Time.

AASLD PRACTICE GUIDANCE (2024): RISK STRATIFICATION AND MANAGEMENT OF PORTAL HYPERTENSION AND VARICES IN CIRRHOSIS

Yifan Han

Kaplan DE, et al. Hepatology 2024; 79: 1180-1211

- **Portal Hypertension** (PH) **in Cirrhosis**

➢ Definition (PH)

- Portal venous pressure (PVP) is the product of splanchnic inflow and resistance opposing flow
  - PV pressure aka portocaval pressure gradient (PPG)
- Normal value is 1 - 5 mm Hg
  - PH in cirrhosis >5 mm Hg
- Mechanistically, in all causes of PH, the first physiologic change is the increase in resistance to portal flow.
- Thus, classified by the area of increased resistance.

➢ Classification

Classification	Level	Examples
○ Prehepatic	− Portal vein and branches	▪ Portal vein thrombosis
○ Intrahepatic	− Presinusoidal (portal triads)	▪ Schistosomiasis ▪ Primary biliary cholangitis (PBC) ▪ Sarcoidosis ▪ Portosinusoidal vascular disorder
	− Sinusoidal	▪ Cirrhosis (all causes) ▪ Alcohol-associated hepatitis
	− Postsinusoidal (central veins)	▪ Sinusoidal obstruction syndrome
○ Post-hepatic	− Hepatic veins, inferior vena cava (IVC)	▪ Budd-Chiari syndrome (BCS) ▪ Congestive hepatopathy (multiple causes including pulmonary hypertension, heart failure, constrictive pericarditis)

Kaplan DE, et al. Hepatology 2024; 79: 1180-1211

- Stages of cirrhosis
  - Pathologic
    - FO-F4
  - Clinical
    - Compensated
      - Divided into those without and those with clinically significant portal hypertension (CSPH)
      - Decompensation occurs with pressure gradients of ≥10 mm Hg.
      - CSPH is the term clinically significant portal hypertension.
    - Decompensated
      - Clinically overt complications of PH (ascites, variceal bleed, overt hepatic encephalopathy)

Stages of Chronic Liver Disease	No Cirrhosis	Compensated Cirrhosis	Decompensated Cirrhosis
○ Clinical features (ascites, variceal hemorrhage [VH] or hepatic encephalopathy [HE])	None	None	>1 event or complication
○ Histological diagnosis	F0-F2	F3/F4 (thin septa)	Clinical
○ Hemodynamic features (HVPG mmHg)	3-5	5-10	>20 worse outcomes in VH
○ Endoscopic features:	None	No varices	± Varices

Stages of chronic liver disease (non-invasive):	No CACLD	Possible CACLD	Highly suggestive of CACLD	CACLD
○ Liver stiffness (kPa)	<10	10–15	15–20	≥20
○ Platelet count (K/mm³)	NR	NR	If <110 = CSPH	–

  - Liver stiffness and platelets (non-invasive method)
    - Identifies advanced chronic liver disease (ACLD).
      - Probably patient is close to having or has cirrhosis.

Abbreviations: CACLD, compensated advanced chronic liver disease; CSPN, clinically significant portal hypertension; F, fibrosis stage; HE, hepatic encephalopathy; HVPG, hepatovenous pressure gradient; NR, not relevant; VH, variceal encephalopathy

- Diagnosis and monitoring

- Invasive methods
  - Use hepatic vein wedge pressure (HVPG) measurements
    - Transjugular catheter inserted into the hepatic vein
    - Balloon inflated to measure pressure of static column (approximates PV pressure)
    - Then measured without balloon (caval pressure)
    - The difference of these two measurements is the hepatic vein pressure gradient (HVPG), which roughly is the portacaval pressure gradient (PPG).

- **Caveats of HVPG**
  - Useful only in patients with cirrhotic liver (cirrhotic liver loses sinusoidal communication which has collaterals)
  - Does not accurately estimate portal pressure in presinusoidal disease and some pre-hepatic disease
    - Non-cirrhotic primary biliary cholangitis (PBC)
    - Granulomatous disease
    - Porto-sinusoidal vascular disorder
    - Perhaps metabolism associated steatotic liver disease (MASLD) as well as (under estimation), pre-sinusoidal vs. abdominal obesity
  - Risks
    - Local injury at puncture site
    - Bleeding/hematoma
    - Arrhythmia
    - Radiation

➢ Guidance statements
  - HVPG measurement is the gold-standard method to assess portal pressure in patients with cirrhosis.
  - Clinically significant portal hypertension (CSPH) is defined as HVPG ≥10 mm Hg.
  - HVPG may underestimate portal pressure in some patients with obesity and non-alcoholic steatohepatitis (NASH)-related cirrhosis.

- **Non-invasive modalities**
  - Ultrasound, CT, MRI have fairly good performance compared to HVPG to detect elevated portal pressures and thus CSPH.
  - Esophageal varices on endoscopy correlate with elevated HVPG.
  - Guidance Statements:
    - The presence of clinical decompensation, gastroesophageal varices (GEV) on endoscopy, or portosystemic collaterals/hepatofugal flow on imaging is sufficient to diagnose CSPH.
    - Transient elastography and platelet count
      - "Rule of 5's")
    - Stiffness values >25 kPa had >90% portal protective value (PPV) for CSPH.
      - Obese MASLD patients had lower PPV of 62.8%.
      - MRE, SWE not well validated at time of guideline.
    - CSPH can be noninvasively identified by LSM by vibration-controlled TE (or non-TE approaches when validated cutoffs exist) and platelet count.
    - CSPH diagnosed at:
      - LSM ≥25 kPa irrespective of platelet count
      - LSM 20–24.9 kPa with platelet count <150 K/mm³
      - LSM 15–19.9 kPa with platelet count <110 K/mm³
    - Monitoring the development of CSPH and varices
      - Multiple longitudinal studies for various liver disease etiologies showed relevance of serial liver stiffness measurements on disease outcomes.
      - Can be used to decide on timing of NSBB initiation or endoscopic screening for gastroesophageal varices (GEV).
    - Annual LSM by TE (or non-TE approaches when validated cutoffs exist) and serum platelet counts.
      - Provide prognostic information in patients with cACLD without baseline CSPH in whom the underlying etiologies of cirrhosis remain active/uncontrolled.

Abbreviations: CSPH, clinically significant portal hypertension; GEV, gastroesophageal varices; LSM, liver stiffness measurement

- **Nonselective beta-blockers** (NSBBs)
  - Choices
    - First
      - Carvedilol (6.25 mg po od to 6.25 mg bid – aiming for SBP ≥90 or above)
    - Second
      - Propranolol
      - Nadolol

- Pharmacology
  - ↓cardiac output and
  - Induce splanchnic arterial vasoconstriction.
  - Carvedilol also has
    - Alpha-1 blocking effects → NO release → intrahepatic vasodilation → greater lowering of the HVPG than do other NSBB (nadolol, propranolol)
    - Mortality benefit and less decompensation

- Guidance statements (NSBBs)
  - Carvedilol is the preferred NSBB for the treatment of PH in patients with cirrhosis.
  - Dose
    - 6.25–12.5 mg/day, as a single daily dose or divided twice daily
    - May be ↑ further to address non-hepatic indications (e.g., patients with concomitant arterial hypertension or cardiac disease)

➢ Stage-specific management of PH

- Compensated cirrhosis without CSPH but PH
  - During regular HCC screening with Doppler abdominal ultrasound, look for evidence of
    - Collateral veins
    - Recanalization of the umbilical vein, or
    - Portal vein flow reversal (evidence of patient developing CSPH).
  - Do **not** give NSBBs (no ↓ in liver outcomes)
  - If LSM <20 kPa and PLT >150
    - ↓ risk of high-risk varices is low
    - Do not do screening EGD
    - Reevaluate q1yr
  - If TE not available, perform endoscopic surveillance.
  - Treat underlying cause.

Portal Hypertension and Varices in Cirrhosis

Stage of Disease	LSM Range (kPa)	cACLD Interpretation	CSPH Interpretation (with Platelets)	Endoscopy Guidance	Monitoring Frequency
○ No cACLD / Possible fibrosis	5–9.9	Rules out cACLD	Rules out CSPH	Not indicated	Every 3–5 years if suspecting progression
○ Possible cACLD, no CSPH	10–14.9	Possible cACLD		Not indicated	Annually if risk factors present
○ Certain cACLD, probable CSPH	15–19.9	≥15 → rules in cACLD	15–20 & Plt <110 → probable CSPH	Consider endoscopy	Annually
○ Certain cACLD, highly probable CSPH	≥20	Rules in cACLD	20–25 & Plt <150 → highly probable CSPH		Annually
○ Decompensated stage	—	No role for LSM	CSPH assumed	Endoscopy per decompensation	Only if recompensation

Alternatives to TE (Transient Elastography):

- MRE: <3.0 kPa rules out cACLD; ≥3–4 kPa rules in cACLD; ≥4–5 kPa predicts varices/decompensation
- pSWE/ARFI: <1.3–1.7 m/s rules out; ≥1.7–2.1 m/s rules in; ≥2.4 m/s predicts varices/decompensation
- 2D-SWE: <7.8 kPa rules out; 13–16 kPa rules in; ≥17–20 kPa predicts varices/decompensation
- ELF: <7.7 rules out; ≥9.8 rules in; ≥10.5–11.3 predicts varices/decompensation

Adapted from: EASL Clinical Practice Guidelines. J Hepatol 2023; 79(2):461–491; AASLD Practice Guidance. Hepatology 2024; 79(6):1463–1502.

- Guidance statements
  - Do **not** use NSBBs to prevent decompensation in patients with cirrhosis without CSPH.
  - Use lifestyle modification and treatment of underlying liver disease to prevent progression to CSPH / decompensation.

- Compensated cirrhosis with/with likely CSPH
  - NSBBs
    - Propranolol / carvedilol
    - ↓ risk of decompensation (HR 0.51) after 2 years in PREDESCI trial 201 patients.
    - ↓ mortality with carvedilol (HR 0.491).
  - If transient elastography not available
    - Perform surveillance EGD establish CSPH
      - Ongoing, q2 yr
      - Stable, q3 hr
    - 25% of compensated cirrhotic patient have varices on index endoscopy
    - New varices detected at 5% per year for compensated cirrhotic without varices initially.
  - Guidance statements
    - In patients with compensated cirrhosis and CSPH
      - The goal of therapy is to prevent the development of clinical decompensation.
    - Give NSBBs (preferably carvedilol 12.5 mg/day) to prevent decompensation
    - In patients with cACLD and CSPH.
    - Do **not** give NSBBs to patients with cACLD and evidence of CSPH if they have with
      - Asthma
      - Heart block (advanced)
      - Bradyarrhythmia
      - Give with caution in patients with relative contraindications
      - Patients with cACLD and evidence of CSPH (by endoscopy, TE, HVPG or imaging)
        - Treat with NSBB unless they are contraindications to prevent hepatic decompensation
        - If NSBB given, no further screening endoscopy
        - Not considered due to prior intolerance, endoscopic surveillance of all patients with cirrhosis is recommended.
  - In patients with cirrhosis, and where TE is not available to diagnose CSPH, and when empiric NSBB are contraindicated or not considered due to prior intolerance
    - Do EGD surveillance

- Patients with cACLD without varices on screening endoscopy should have endoscopy q2 yr
  - With ongoing liver injury or associated conditions (such as obesity and alcohol use) or do q3 yr
  - If liver injury is quiescent (e.g., after viral elimination, alcohol abstinence), EGD q3 yr
- cACLD without varices who develop decompensation should have a repeat endoscopy when this occurs.
  - The presence of varices of any size should prompt initiation of NSBB (in absence of contraindication).
- Where TE is not available screening EGD is not necessary in patients
  - On NSBB therapy
  - Patients on a selective beta-blocker may be switched to a non-selective beta-blocker (after discussion with the prescribing clinician)

- Compensated cirrhosis but can't take beta-blockers
  - Surveillance EGD with goal of performing EVL on high-risk varices.
    - Uncontrolled disease q2 yr
    - Controlled, q3 yr
  - If varices found
    - Uncontrolled, q1 yr
    - Controlled, q2 yr
    - 10–20% of patients had their small varices grow within 1–2 years
  - EVL performed repeat q2–4 wk until obliteration of EV achieved, then relook EGD at 6 mon, then q1yr
    - Do more EVL, repeat EVL q2 wk
  - Do **not** do TIPS as primary prophylaxis (↑ mortality)

Abbreviations: EGD, esophagogastroduodenoscopy; EVL, endoscopic variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt

- Guidance statements:
  - Patients with compensated cirrhosis and CSPH without varices who have contraindications or intolerance to beta-blockers
    - Screen for EV needing treatment with surveillance EGD q2 yr when the underlying disease remains uncontrolled and q3 yr when controlled.
  - Patients with compensated cirrhosis and CSPH with varices that have not bled who have contraindications or intolerance to beta-blockers
    - Screen for EV needing treatment with surveillance EGD q1 yr when the underlying disease remains uncontrolled and q2 yr when controlled.
  - Primary prophylaxis with EVL should be performed in patients with cACLD and CSPH and high-risk varices that cannot receive NSBBs.

- Esophageal band ligation (EBL) q2–4 wk until obliteration
  - Then repeat EGD at 6 mon, and then q12 mon to assess for reappearance of varices requiring additional treatment.
- TIPS contraindications
  - Prevention of decompensation of cirrhosis
  - Primary prophylaxis for variceal hemorrhage.

- Preventing variceal hemorrhage in decompensated liver disease
  - Small varices
    - Give NSBBs
  - Large varices
    - NSBBs or EVL (preference for NSBBs)
      - Carvedilol for high-risk varices and ascites
        - ↑ survival (HR 0.41–0.61).
      - Carvedilol has a median survival benefit of ~8 yr vs 4 yr compared to EVL in patients undergoing primary prophylaxis (half had ascites).
  - ↓ stop NSBBs in patients with low SBP <90 mmHg
    - Then proceed with EGD pathway.
    - ↓ SBP → ↓ renal perfusion and ↑ HRS

- Decompensated Cirrhosis
  - Guidance statements:
    - Patients with decompensated cirrhosis not taking NSBBs, no previous EVH
      - Do EGD q1 yr
    - If high-risk varices are detected
      - Use NSBBs or EVL (preference given to NSBBs, including carvedilol, because of benefits beyond prevention of variceal hemorrhage.
    - NSBBs should be dose reduced or discontinued in patients who develop
      - Persistently ↓ systolic arterial pressure <90 mm Hg, or
      - Severe adverse effects
        - NSBB discontinuation should prompt endoscopic evaluation for presence of high-risk varices requiring EVL

➢ Acute variceal hemorrhage (AVH) – initial treatment

- ABCs
  - Airway intubation for ↓ GCS/airway compromise
  - Restrictive transfusion threshold when Hgb <70 g/dL
    - Unless higher targets refined because of comorbid conditions of ischemic heart disease
- Coagulation parameters poorly predict hemostatic function in cirrhosis.
  - Aggressive administration of fresh frozen plasma may be harmful.
  - Consider consultation with hematologist

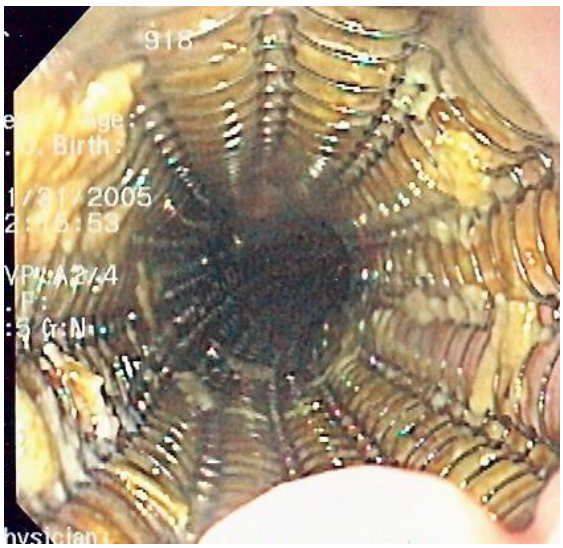
- Vasoactive therapy
  - Terlipressin
  - Somatostatin/octreotide.
- Antibiotic prophylaxis against infection, tailored to local resistance patterns (often ceftriaxone 1 g/d IV) including spontaneous bacterial peritonitis (SBP)
  - Stop antibiotic when
    - Bleeding controlled
    - No active infection
- Endoscopy
  - Consider uses erythromycin pre-procedure per UGIB guidelines within 12 hr
    - Perform EVL if variceal bleeding source is confirmed (varix with white nipple, or red wale sign).

Abbreviations: AVH, acute variceal hemorrhage; EVL, esophageal variceal ligation; GCS, Glasgow Coma Scale; UGIB, upper gastrointestinal bleeding;

- Guidance statements
  - Suspected cirrhosis plus acute UGIB
    - Give vasoactive therapy (somatostatin, octreotide, or terlipressin if available) and intravenous antibacterial therapy as soon as possible.
  - If portal hypertensive bleeding confirmed at EGD
    - Continue vasoactive therapy for 2–5 days.
- Tailor IV antibacterial treatment
  - Local resistance patterns, and patient allergies
  - The most commonly used agent is ceftriaxone 1 g/24 hours up to 5 days
  - Stop antimicrobial therapy
  - Once bleeding is controlled, and
  - In absence of an active infection
- Target packed red blood cell (PRBC) transfusions to hemoglobin ~7 g/dL
  - Unless higher targets required.
- Do **not** give fresh frozen plasma (FFP) and platelet transfusions based on INR or platelet count targets because
  - No evidence of benefit of such transfusion in AVH
  - Evidence of potential harm with FFP
- Upper endoscopy should be performed within 12 hr of presentation with AVH.
- If esophageal variceal bleeding is confirmed, EVL should be performed.

Abbreviations: EGV, esophagogastric varices

- If EVL fails
  - Use balloon tamponade
    - Sengstaken-Blakemore tube (3 ports)
    - Minnesota tube (+ esophageal suction port, 4 ports)
    - Linton-Nachlas tube (esophageal balloon)
  - Esophageal stent (SX-ELLA Danis most commonly used)



*Not the SX-ELLA-Danis, most commonly used stent for variceal bleeding.

Courtesy of: https://commons.wikimedia.org/wiki/File:SEMS_endo.jpg

- If all the above fail, consider
  - TIPS
  - Liver transplantation

- Guidance statements:
  - In patients with CTP class B score >7 and active bleeding on endoscopy or CTP class C score 10–13, use preemptive TIPS creation (within 72 hr and ideally within 24 hr of initial EGD) (unless absolute contraindications to TIPS)
    - If TIPS is not locally available
      - Transfer patient to a center with the TIPS available
  - In patients presenting with AVH who do not undergo
    - Start NSBB at discontinuation of vasoactive therapy
  - Covered expandable esophageal stents (where available) or
    - Balloon tamponade should be considered as a bridge to TIPS, use in patients with uncontrolled AVH.

- Use salvage TIPS in patients
  - With uncontrolled AVH ("salvage" TIPS) or
  - Who rebleed despite vasoactive therapy and EVL ("rescue" TIPS).
- Start, enteral feeding AVH has been controlled
  - The presence of variceal bands does not contraindicate placement of a feeding tube if indicated.
- Stop proton pump inhibitors (PPIs) once AVH has been confirmed as the bleeding source, unless there are other specific indications.

Abbreviation: CTP, Child Turcotte Pugh

➢ Prevention of recurrent hemorrhage after initial bleed

- Risk of rebleeding ↑ within 6 wk after index AVH
  - Start preventive therapies within 7 days of admission.
- EVL + NSBB
  - ↓ rebleeding risk compared with monotherapy with either
  - Possibly has mortality benefit in CP-B/C patients
- TIPS if
  - Another indication, or
  - Rebleeds despite EVL + NSBB.
  - For all patients, TIPS had ↓ rebleeding but
    - No differences in mortality and ↑ hepatic encephalopathy

Abbreviations: EVL, esophageal variceal ligation; HE, hepatic encephalopathy; NSBB, non-specific beta blockers

- Guidance statements:
  - In patients with AVH who do not
    - Fulfill criteria for preemptive TIPS and/or do not undergo TIPS during admission
    - Use secondary prophylaxis with NSBB and EBL
  - Use TIPS for secondary prophylaxis in patients with additional indications for TIPS (e.g., refractory ascites).

- Gastric and ectopic varices

➢ **Sarin classification**

- GOV1, GOV2, IGV1, IGV2
- Presence of gastric/ectopic varices predicts
  - Liver dysfunction
  - Bleeding, and
  - Other portal hypertensive events.

- There may be similar or different upstream vascular formations compared to esophageal varices.
- Guidance statements:
  - Patients with gastric or ectopic varices have CSPH
    - Use NSBBs for prevention of rebleeding and decompensation.
    - Investigate for the presence of portal vein thrombosis (PVT)

➢ Prevention of bleeding for gastric varices

- Cyanoacrylate injection of high-risk cardiofundal varices ↓ risk of bleeding (compared to beta-blockers or no treatment) after median follow-up of 26 mon.
- Balloon-occluded retrograde transvenous obliteration (BRTO) beneficial effect on non-bleeding and survival from 1 to 5 years in study of 34 patients.
  - BUT, BRTO ↑ portal hypertension
- Guidance statements:
  - Patients with high-risk cardiofundal (GOV2 or IGV1) varices (≥10 mm, red wale signs, CTP class B/C) who have contraindications or intolerance to NSBBs
    - Use primary prophylaxis with endoscopic cyanoacrylate injection (ECI).
  - Neither TIPS nor BRTO (or related obliterative techniques) are recommended to prevent first hemorrhage in patients with fundal varices that have not bled.
    - However, new evidence shows that prophylactic TIPS ↑ bleeding-free survival in 21 patients with 40-mon follow-up

Abbreviations: BRTO, balloon-occluded retrograde transvenous obliteration; CTP, Child-Turcott-Pugh; ECA, endoscopic cyanoacrylate injection

- Initial and recurrent bleeding: gastric / ectopic varices (G/EV)
  - Treat G/EV like any cirrhosis patient.
  - EGD administered, cyanoacrylate is superior to EVL.
  - TIPS and BRTO may also be effective
  - NSBBs for secondary prophylaxis for GV.
  - Repeat EGD until obliteration G/EV
  - For G/EV due to isolated splenic vein thrombosis shown efficacy for splenic vein stenting/embolization/splenectomy
    - Prepare patient for possible
      - Splenic vein stenting / embolization, or
      - Splenectomy
  - Guidance statements:
    - Initial treatment of bleeding gastric or ectopic varices is similar to the management of EVH, including
      - Vasoactive therapy

        - Antimicrobials
        - Conservative transfusion strategy, and
        - EGD evaluation within 12 hours.
    - The patients with bleeding G/EV bleeding should have contrast-enhanced cross-sectional imaging (to define anatomy of portosystemic collaterals or presence of venous thrombosis that would guide therapy).
    - In patients with acute hemorrhage from gastric (GOV2/IGV1) or ectopic varices, use as first-line options
        - Endoscopic cyanoacrylate therapy
        - TIPS, or
        - Retrograde transvenous variceal embolization/obliteration
        - Retrograde obliteration is preferred when TIPS is contraindicated.
    - In patients who underwent ECI as the main therapy, the addition of NSBBs is recommended to prevent rebleeding, in absence of contraindications.
        - Repeat EGD treatment at intervals q2–4 wk until obliteration and long-term surveillance should be performed.
    - Evaluate patients with bleeding gastric varices caused by isolated splenic vein thrombosis for
        - Splenectomy
        - Splenic vein stenting, or
        - Splenic artery embolization

➢ Miscellaneous / Additional topics

- Portal Hypertensive Gastropathy (PHG)
    - Multiple ways to describe severity (e.g., Baveno III, New Italian Endoscopic Club)
    - Endoscopic pattern is red/brown/black then PG is “severe”
    - Guidance statements
        - Highly correlates with HVPG >12 mm Hg
        - Bleeding is usually chronic bleeding than acute.
            - >50% of acute bleeding stops without treatment.

➢ Treatment

- Acute bleeding
    - Fluid/PRBC replacement
    - Propranolol bleeding stops within 3 d in 93%
    - Somatostatin
    - Octreotide to vasopressin/omeprazole
- Chronic
    - Propranolol maintenance ↓ rebleeding at 30 mon
    - TIPS → EGD improved PHG
        - Mild, 89%
        - Severe, 75%

- Guidance statements
  - Patients with moderate/severe PHG are presumed to have CSPH
    - Give prophylactic NSBBs ↓ risk of to
      - Decompensation
      - Hemorrhagic complications
      - Iron deficiency anemia
  - Acute bleeding: vasoactive therapy
    - Somatostatin
    - Somatostatin analogs, such as octreotide, terlipressin (if available) for 2–5 days at doses used for variceal bleeding
  - Use NSBBs to ↓ risk of rebleeding from
    - PHG, and
    - PH-related polyps
  - If bleeding from PHG becomes transfusion-dependent despite NSBB, use TIPS placement

- Varices in Cirrhotic Patients with Hepatocellular Cancer (HCC)
  - Recommendation:
    - Prevention/treatment of AVH and hepatic decompensation in patients with HCC should follow the same principles are those for patients with HCC
    - In the absence of contraindications use NSBB
      - Primary prophylaxis for VH
      - Prevention of decompensation in patients with HCC with CSPH (including varices)
    - In the presence of occlusive bland or malignant PVT, do EGD to investigate the presence of gastroesophageal varices (GEV). If GEV are detected, use NSBB/EBL.
      - Give preference to NSBB (including carvedilol) because of benefits beyond prevention of variceal hemorrhage

- Pregnancy in patients with cirrhosis
  - Limited data
  - Variceal bleeding
    - High mortality event in pregnancy
  - Baveno criteria miss 30% of small varices
    - Clinical necessity to detect varices of any size
  - Unscreened pregnant patients → EGD early in second trimester.
  - Guidance statement:
    - All patients with cirrhosis or non-cirrhotic PH planning pregnancy do EGD within 1 yr conception.
    - Previously unscreened pregnant patients with cirrhosis or non-cirrhotic PH
      - Do EGD early in the second trimester (T2)

- Insertion of Tubes into Esophagus of Person with Possible Varices
  - Esophageal varices are relative contraindication to transesophageal echo (TEE), but
    - Retrospective analysis of 191 cirrhotic patients undergoing TEE showed no post-EGD GI bleeding in persons with or without varices.
  - Routine endoscopy before TEE not recommended.
  - Guidance statement:
    - Do **not** do EGD prior to TEE in patients with cirrhosis.

- TIPS before surgery
  - 2022 retrospective study on 90 patients with cirrhosis undergoing surgery
    - Patients who have TIPS before surgery had ↓ AoCLF at 28 and 90 d post-surgery (9%) vs 29%, and 13% vs. 33%
    - Matched for age, sex, cause of cirrhosis, ASA score, MELD, CP score, surgery type / urgency
  - Guidance statement
    - Preoperative TIPS can be considered on a case-by-case basis after careful consideration of potential surgical benefits relative to potential harms related to the procedure (encephalopathy, worsening of liver failure)
    - 2024 retrospective study on 64 patients with TIPS vs. 131 patients without TIPS in patients with cirrhosis undergoing surgery.
      - Preoperative TIPS cohort had ↓ rate of post-operative in house mortality (HR 0.44) and ↓ blood transfusion, ↓ RRT, ↓ ICU stays, ↓ bleeding, and HE

Abbreviations: ACLD, advanced chronic liver disease; AoCLF, acute-on-chronic liver failure; ASA, American Society of Anesthesiologists; AVH, acute variceal hemorrhage; BCS, Budd-Chiari syndrome; BRTO, balloon-occluded retrograde transvenous obliteration; CACLD, compensated advanced chronic liver disease; CP, Child-Pugh; CSPH, clinically significant portal hypertension; CT, computed tomography; CTP, Child-Turcotte-Pugh; EGD, esophagogastroduodenoscopy; EGV, esophagogastric varices; EV, esophageal varices; EVH, esophageal variceal hemorrhage; EVL, endoscopic variceal ligation; FFP, fresh frozen plasma; GEV, gastroesophageal varices; GOV, gastroesophageal varices (types 1 and 2); GCS, Glasgow Coma Scale; GV, gastric varices; HBV, hepatitis B virus; HE, hepatic encephalopathy; HR, hazard ratio; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; IGV, isolated gastric varices (types 1 and 2); IVC, inferior vena cava; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NSBBs, non-selective beta blockers; PH, portal hypertension; PHG, portal hypertensive gastropathy; PPG, portocaval pressure gradient; PRBC, packed red blood cells; PSC, primary sclerosing cholangitis; PVP, portal venous pressure; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; SWE, shear wave elastography; TIPS, transjugular intrahepatic portosystemic shunt; UGIB, upper gastrointestinal bleeding; US, ultrasound; VH, variceal hemorrhage; VTE, venothrombotic embolization.

AASLD PRACTICE GUIDANCE ON PRIMARY SCLEROSING CHOLANGITIS (PSC) AND CHOLANGIOCARCINOMA (CCA)

Zaki Alhashimalsayed

❖ **Primary Sclerosis Cholangitis** (PBC)

➢ Definition

- Chronic fibroinflammatory damage of the biliary tree, often linked to inflammatory bowel disease (IBD).

➢ Phenotypes

- Fibrotic biliary strictures on cholangiogram (majority).
- Small-duct PSC (normal cholangiogram, PSC histology on biopsy).
- PSC-AIH overlap (autoimmune hepatitis features).

➢ Complications

- ↑ risks of
  - Cholangiocarcinoma (CCA), and
  - Colorectal cancer (CRC) in patients with UC

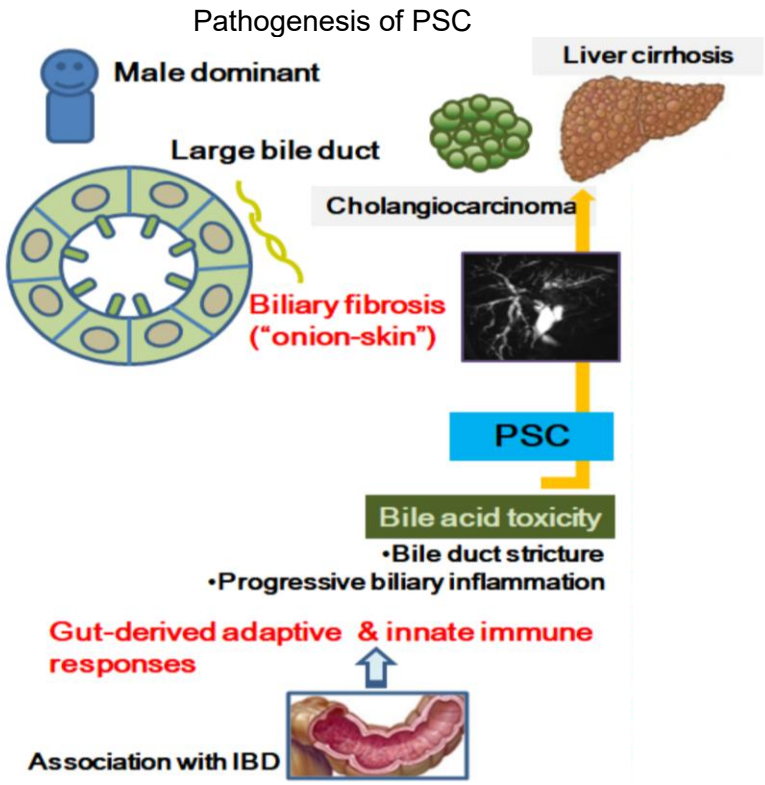
➢ Demography

- Incidence
  - North America / Western Europe, ~1.5/10^5 person-years
  - Prevalence, 6–16 per 100,000.
  - Peak incidence: Ages 25–45, median diagnosis age 36–39 years.
  - Male > female, 2:1
  - Other regions, ↓ prevalence.
- IBD Association
  - 70%–80% of PSC patients have IBD.
  - Prevalence of PSC in IBD: 0.6%–4.3%.
- Overlap Syndromes
  - PSC-AIH overlap
    - 3–5% in adults
    - 35% in children.

➢ Pathogenesis

- Underlying Factors:
  - Genetic predisposition (HLA), and environmental triggers (non-smoker).

- Key Mechanisms:
  - Intestinal Alterations
    - Altered microbiome
    - Inflamed mucosa
    - Impaired barrier function (“leaky gut”).
  - Immune Activation
    - Translocation of intestinal lymphocytes
    - Microbial products, or
    - Metabolites to the liver via the portal vein → activate innate and adaptive immune responses.
  - Biliary Activation
    - Microbial components/metabolites
    - Directly stimulate biliary epithelial cells → perpetuating inflammation
  - Fibrosis Formation
    - Peribiliary glands expand
    - Mesenchymal cells adopt a myofibroblast phenotype through the Hedgehog pathway → large-duct fibrosis.



Courtesy of: Park J-W, et al. Biomedicines 2022; 10(6):1288.

- Diagnosis
  - Key Diagnostic Tools
    - Cholangiography: Identifies characteristic biliary strictures.
      · Histology: Used to diagnose small-duct PSC when cholangiogram is normal.
  - Exclusions to Consider
    - Rule out secondary sclerosing cholangitis (critical in patients without IBD).
  - Overlap Syndromes
    - PSC-AIH Overlap:
      - Suspect in patients with features of both PSC and autoimmune hepatitis (AIH).
      - Common in AIH patients with IBD, unexplained cholestasis, or poor response to glucocorticoids.

Diagnostic Approach to Suspected Primary Sclerosing Cholangitis (PSC)

Step	Evaluation	Possible Findings	Next Action
1	Clinical suspicion (history, physical exam, serum liver tests)	Cholestatic pattern (↑ ALP, ↑ GGT)	Proceed to imaging
2	MRI/MRCP	Biliary strictures present	Compatible with PSC → confirm diagnosis
	MRI/MRCP	No strictures	Consider small-duct PSC if biopsy compatible
	MRI/MRCP	Equivocal findings	Consider repeat imaging or biopsy
3	Liver biopsy (if needed)	Histology compatible with PSC	Diagnose PSC or small-duct PSC
	Liver biopsy	Not compatible	Exclude PSC, consider alternative diagnosis
4	Exclude secondary sclerosing cholangitis	History of surgery, ischemia, infection, toxins	Diagnose secondary sclerosing cholangitis
5	Final outcome	PSC, small-duct PSC, or alternative diagnosis	Guide management accordingly

Adapted from: AASLD Practice Guidance. Hepatology 2022; 76(3):1010–1034; EASL Clinical Practice Guidelines. J Hepatol 2022; 77(3):761–806.

- **Secondary Sclerosing Cholangitis** (SSC)
  - Infectious
    - Ascariasis
    - Cholangitis lenta
    - Clonorchiasis
    - Echinococcosis
    - Fascioliasis
    - HIV-related cholangiopathy
    - Hydatid cyst
    - Opisthorchiasis
    - Parasitic cholangiopathy
    - Recurrent pyogenic cholangitis
    - Schistosomiasis
    - Subacute nonsuppurative cholangitis
  - Ischemic
    - Critically ill patients
    - Hereditary hemorrhagic telangiectasis
    - Intra-arterial chemotherapy
    - Hepatic artery thrombosis
  - Infiltration
    - Cholangiocarcinoma
    - Diffuse intrahepatic metastasis
    - Langerhans cell histiocytosis
    - Lymphoma
  - Immune
    - Eosinophilic cholangitis
    - Hepatic inflammatory pseudotumour
    - IgG4-associated cholangitis
    - Mast cell cholangiopathy
    - Sarcoidosis
  - Anatomic
    - Biliary tree
      - Anastomotic stricture
      - Choledochal cyst
      - Choledocholithiasis
    - Liver
      - Cystic fibrosis liver disease
      - Intrahepatic lithiasis
      - Portal hypertensive biliopathy
    - Pancreas
      - Recurrent pancreatitis
    - Blood
      - Sickle cell cholangiopathy
  - Injury
    - Surgical biliary trauma

- Iatrogenic – Immunotherapy with checkpoint inhibitors
  - Atezolizumab
  - Nivolumab
  - Pembrolizumab

➢ Clinical

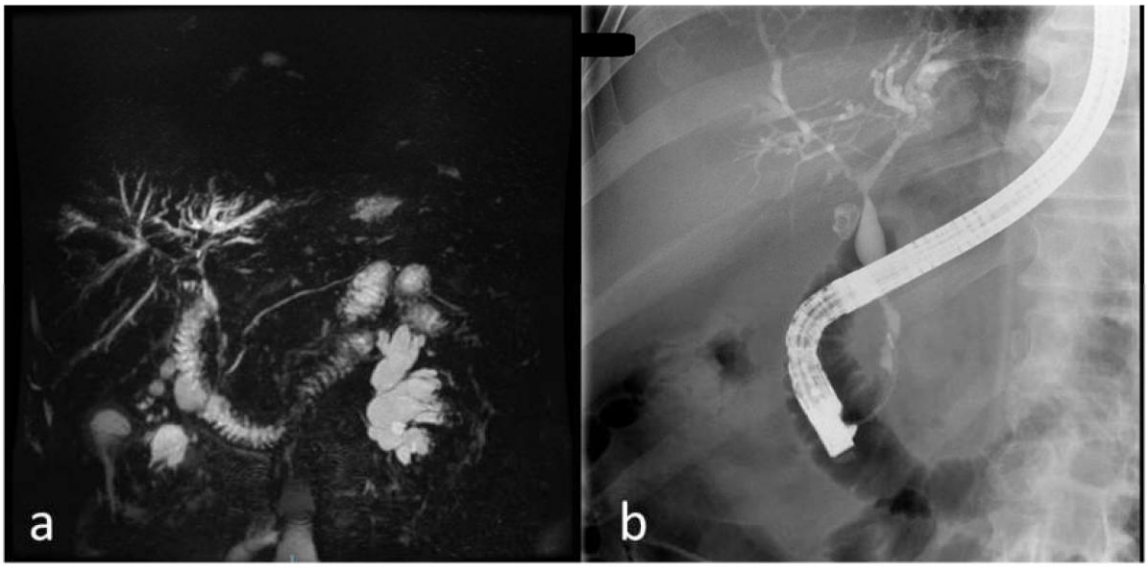
- Fatigue
- Abdominal pain
- Fever
- Pruritus (can fluctuate with biliary obstruction or cholangitis).
- Anxiety and depression linked to disease uncertainty, and cancer risks.

➢ Natural History of PSC

- Variable course with complications
  - Cirrhosis
  - Bacterial cholangitis
  - Cholangiocarcinoma (CCA)
  - Colorectal cancer (CRC)
- Good prognosis
  - Young age (<20)
  - Female
  - PSC-AIH (↓ risk of need for liver transplant (LT) / Death)
  - Small-duct PSC
- Small duct → large duct PSC within 5–14 yr
  - Perform MRI/MRCP recommended q3–5 years to detect PSC progression.
- Cholangiocarcinoma (CCA)
  - 160–400× higher than general population.
- Colorectal cancer (CRC)
  - 5–12× higher than general population (6% of population in Canada)
  - Often right-sided
  - Younger onset.
- Gallbladder cancer
  - 9–78× higher than general population
  - Influenced by polyps.

- Laboratory
  - Liver Enzymes
    - ↑ ALP / ↑ GGT in ~75% of cases, cholestatic profile).
    - ↑ aminotransferases
      - But don't always indicate overlap with AIH, unless
      - Markedly high (>5x ULN).
  - Autoantibodies
    - Variable presence of
      - ANA
      - ASMA, and
      - ANCA (limited diagnostic value).
  - Serum IgG4
    - ↑ in ~15% of patients.
    - High titers (>5.6 g/L) suggest IgG4-sclerosing cholangitis, while
      - Low IgG4/IgG1 ratio (<0.24) excludes it when IgG4 is 1.4–2.8 g/L.

- Diagnostic Imaging
  - Preferred Imaging Modality
    - MRI with cholangiopancreatography (MRCP)
      - Recommended for suspected PSC.
  - Comparison with ERCP
    - ERCP reserved for
      - Therapeutic intervention or
      - Tissue sampling (due to higher complication risks)
    - MRI/MRCP have similar diagnostic accuracy.
  - Limitations and Follow-ups
    - A negative MRCP in high-pretest probability PSC
      - False negative in 30%
      - Repeat imaging at an expert center if results are suboptimal.
  - Stricture Definitions
    - Dominant Stricture
      - ERCP ≤1.5 mm in common bile duct (CBD) or ≤1 mm in hepatic duct
    - Relevant Stricture
      - Proposed term for clinically significant strictures (even if criteria for dominant/high-grade stricture are not met)



- Cholangiography of a patient with PSC from our clinical practice:
  - (a) magnetic resonance cholangiography (MRCP) images;
  - (b) endoscopic retrograde cholangiopancreatography (ERCP) images.

Courtesy of: Vlăduţ C, et al. *J Clin Med* 2020; 9(3):754 (Figure 2)

- Histopathology
  - ↓ need
    - Modern imaging (MRI/MRCP) has minimized requirement for liver biopsy in diagnosing PSC.
  - Indications
    - Suspected small-duct PSC.
    - Possible overlap with autoimmune hepatitis (AIH).
- Histological Features
  - Typical for PSC
    - Periductal fibrosis (“onion skin” appearance – rare)
    - Fibro-obliterative duct lesions.
  - Compatible with PSC
    - ↑ bile duct loss / ↑ ductular proliferation
    - Biliary interface activity
      - Chronic cholestatic changes
  - AIH Overlap
    - Lymphoplasmacytic interface hepatitis.

- **IBD in PSC**

➢ Demography

- Prevalence
  - > 70% of PSC patients have IBD.
  - Distribution
    - Ulcerative colitis, ~66%
    - Crohn disease (CD) or indeterminate colitis (IC), ~33%
- Localized in right colon, often with backwash ileitis.
- Histological evidence of IBD can occur without endoscopic changes.

➢ Screening

- At PSC diagnosis
  - Perform ileocolonoscopy with biopsies to screen for asymptomatic colitis
- Follow-up
  - q5 yr, or
  - If IBD symptoms develop

➢ Diagnostic Imaging

- In patients suspected PSC
  - Obtain 3D MRI/MRCP with T1w and T2w axial images and contrast enhancement
  - To evaluate for cholangiographic features intra/extrahepatic strictures alternating with normal or slightly dilated segments.
- In patients with suspected PSC and a normal, high-quality MRI/MRCP
  - Perform liver biopsy to rule out small-duct PSC.
- Patients with an equivocal MRI/MRC refer to experienced center for consideration of a repeat high-quality MRI/MRCP or liver biopsy
- Repeat MRI/MRCP in 1 year if the diagnosis remains unclear
- Do not do ERCP for diagnosis of PSC.
- Measure serum IgG4 levels in all patients with positive PSC to exclude IgG4-sclerosing cholangitis.
- Perform ileocolonoscopy with biopsies in patients with new diagnosis of PSC and no previous diagnosis of IBD.
- In patients with IBD repeat ileocolonoscopy q5 yr, or whenever symptoms suggestive of IBD occur.

- Simplified Guidance Statements
  - Use 3D MRI/MRCP with contrast to evaluate PSC-specific cholangiographic features.
  - Perform liver biopsy if MRI/MRCP is normal or equivocal
    - Repeating in 1 yr
  - Do not do ERCP for PSC diagnosis.
  - Measure serum IgG4 levels to exclude IgG4-sclerosing cholangitis.
  - Perform liver biopsy only if MRI/MRCP suggests AIH overlap.
  - Conduct ileocolonoscopy with biopsies at diagnosis and every 5 years if no IBD is present.

Liver Biopsy in PSC

- Advanced fibrosis correlates with poorer outcomes.
- Liver biopsy is suitable for
  - Fibrosis staging, or
  - Prognostication in PSC
- Nakanuma, Ishak, and Batts-Ludwig systems
  - Provide similar prognostic ability.
- Baseline Ishak fibrosis stage
  - Strongly predicts 2-year outcomes (Simtuzumab trial).
- Limitations (sampling variability) of Liver Biopsy
  - Unequal fibrosis distribution due to high-grade strictures and cholestasis
  - Variability in fibrosis staging
    - 16% differ by one stage
    - 11% differ by two stages (Batt-Ludwig system)

➢ ↑ Liver Stiffness (LS) in PSC (Page 14)

- Measurement Methods
  - Transient Elastography (TE)
    - F3 (extensive fibrosis), cutoff 9.6 kPa
    - F4 (cirrhosis), cutoff 14.4 kPa.
  - Magnetic Resonance Elastography (MRE): Cirrhosis, cutoff 4.6 kPa (AUC 0.82).
  - Clinical Relevance
    - Higher LS correlates with
      - ↑ risk of decompensation and
      - Worse outcomes.
    - LS increases slowly in early fibrosis stages, but in later stages accelerates toward cirrhosis.

- Monitoring
  - Optimal frequency of monitoring LS is unclear.
  - ↑ LS (>0.34 kPa/yr)
    - Predict worse prognosis

➢ Scoring Systems (Clinical Prediction Tools)

- Non-invasive risk assessment
  - Utilize biochemistry and imaging for stratification.
  - Hels predict
    - Progression
    - Complications, or
    - Guide follow-up frequency
- For End-Stage Disease
  - Use MELD adults score
- Limitations
  - Does not predict CCA risk
  - Patient-specific probabilities should be interpreted cautiously
  - Primary validated at PSC diagnosis
    For end-stage disease: MELD or Pediatric MELD scores.

	Models			
	Amsterdam-Oxford (2017)	UK-PSC (2019)	PRESTO (2020)	SCOPE (2020)
Variables	Age, bilirubin, albumin, AST, ALP, platelets, PSC subtype (large-duct or small-duct)	Age, bilirubin, albumin, ALP, platelets, extrahepatic disease, history of variceal hemorrhage	Age, bilirubin, albumin, AST, ALP, platelets, hemoglobin, sodium, years since PSC diagnosis	Bilirubin, albumin, platelets, GGT, cholangiography (large-duct or small-duct involvement)
Risk threshold	Lower risk, < 1.58 Higher risk, ≥ 1.58	Lower risk, < 1.46 Higher risk, ≥ 1.46	Lower risk, < 20% Higher risk, ≥ 20%	Lower risk, 0-5 Higher risk, 6-11
Major use in PSC	AIH overlay	Small duct PSC	Large duct PSC	Childhood < 18 yr diagnosed
Website	https://sorted.co/psc-calculator/	http://www.uk-psc.com/resources/the-uk-psc-risk-scores/	rtools.mayo.edu/PRESTO_calculator/	Scopeindex.net

Clinical Model Selection Framework

Patient Group	Subtype / Condition	Recommended Model
No portal hypertensive complications	Child (<18 years)	SCOPE
No portal hypertensive complications	Adult (≥18 years) – AIH overlap	Amsterdam–Oxford
No portal hypertensive complications	Adult (≥18 years) – Small duct PSC	UK-PSC-LT
No portal hypertensive complications	Adult (≥18 years) – Large duct PSC	PREsTO
Decompensated cirrhosis	Any	MELD / PELD

Notes

- Cross-links: In adults, AIH overlap, small duct, and large duct PSC may also be evaluated with UK-PSC-LT or PREsTO depending on context.
- Model choice: Driven by age, disease subtype, and presence of portal hypertensive complications.
- Decompensated cirrhosis: MELD/PELD remains the standard prognostic tool.

Adapted from: AASLD Practice Guidance. Hepatology 2022; 76(3):1010–1034; EASL Clinical Practice Guidelines. J Hepatol 2022; 77(3):761–806.

- Guidance Statements
  - Small-duct PSC monitoring
    - MRI/MRCP q3–5 yr to check for large-duct disease.
  - Risk stratification: Assess and stage fibrosis at diagnosis and during follow-up
    - Using risk tools cautiously.
  - Preferred liver stiffness (LS; fibrosis assessment)
    - TE, or
    - MRE.
  - Liver biopsy
    - Do **not** perform routinely to assess fibrosis

➢ Treatment

- No approved treatments
  - No medication has been proven
    - To halt PSC progression, or
    - To offer clinical benefit
  - Management focuses on treating complications.

- Numerous agents tested with no proven efficacy
  - Azathioprine
  - Budesonide.
  - Colchicine
  - Methotrexate
  - Pentoxifylline
  - Prednisone
  - Tacrolimus
- Liver transplantation
  - Recommended for
    - Refractory cholangitis or
    - Decompensated cirrhosis.
- Challenges
  - Unclear pathogenesis
  - Slow progression
  - Patient heterogeneity
  - Lack of clinical trial endpoints
  - Low disease prevalence complicates design

- Ursodeoxycholic Acid (UDCA)
  - Potential benefits
    - ↑ bile flow
    - Anti-inflammatory
    - Cytoprotection
    - Dilution of hydrophobic bile acids
    - Down-regulated apoptosis
    - Immunomodulation,
    - Prevents cellular senescence
    - Stabilizes cell membranes
  - Low-dose (13–15 mg/kg/day)
    - Alkaline phosphatase (ALP) in 12 mon, but no effect on histology or transplant-free survival.
  - Intermediate-dose (17–23 mg/kg/day)
    - Largest study showed no significant impact on LT, CCA or mortality
    - Limitations
      - Study underpowered only (63% of predicted enrollment)
  - High-dose (28–30 mg/kg/day)
    - Associated with ↑ risk of serious adverse event, and colorectal cancer in PSC + UC patients
    - Not recommended (AASLD Guidelines, 2010)

- Recent Data
  - ↓/normalization of ALP/GGT linked to better outcomes
    - ALP < 1.5x ULN, or a 40% ↓ normalization
  - UDCA withdrawal may worsen
    - Fatigue
    - Liver biochemistry
    - Pruritus
    - Risk score
- Suggested treatment approach
  - For patients with persistent ↑ALP / ↑GGT
    - Observe for 6 mon before starting UDCA
    - Continue UDCA 13-23 mg/kg/day if:
      - ALP/GGT ↓/normalize within 12 mon
      - Symptoms ↓ improve, and UDCA is well tolerated
- Do **not** use high-dose UDCA (>28 mg/kg/day)

- Antibiotics in PSC

➢ Rationale

- Gut dysbiosis
  - Linked to biliary injury (to achive microbiome modulation)
- Antibiotics studied
  - Minocycline
  - Metronidazole
  - Rifaximin
  - Vancomycin (oral)
- Oral Vancomycin: Key Studies
  - Small RCTs
    - Trial 1: 15 adults (8 on 125 mg qid, 7 on 250 mg qid; higher dose showed improvement in 12 wk
    - Trial 2: 29 adults; 18 treated with 125 mg qid, ↓ PSC Mayo risk score
  - Open-label studies: enzyme improvements but inconsistent results.
- Largest retrospective study
  - Pediatric PSC Consortium (264 patients)
    - Compared UDCA, vancomycin, and observation
    - **No** significant improvements in biochemistry, fibrosis, or outcomes.

➢ Current Position

- Evidence insufficient
  - Lack of robust randomized trials and concerns over antibiotics resistance
- Oral vancomycin **not** recommended.
  - Clinical trial underway (NCT03710122)

• Emerging Therapies

- Cilofexor
  - Non-steroidal FXR agonist)
  - Phase 2 RCT, 100 mg daily ↓ALP by 21% after 12 wk
- Obeticholic Acid (OCA)
  - FXR agonist, approved for primary biliary cholangitis (PBC)
  - Phase 2 RCT in PSC
  - ↓ ALP by 14–25%, depending on dose (1.5-3 mg or 5-10 mg daily), plus UDCA use
- Bexotegrast (Bexo)
  - UDCA + OCA integrin-mediated inhibition of TGF-β
  - Bexo 320 mg po for up to 40 wk
    - ↓ symptoms
    - ↑ ALP
    - Stabilize TE
- Nor-UDCA
  - Side chain-shorten homolog of UDCA
  - Phase 2 RCT, 1500 mg daily ↓ALP by 26% after 12 wk
- Bezafibrate
  - Pan-PPAR agonist with efficacy in PBC, not available in US
- Fenofibrate
  - Encouraging results in PSC, but no RCTs
- Simvastatin
  - Nationwide Swedish case-control study
    - ↓ all cause mortality (HR 0.68), and
    - ↓ death/LT (HR 0.50)
    - RCT ongoing (NCT04133792)

❖ PSC–AIH Overlap and IgG4 Sclerosing Cholangitis

➢ Definition

- Patients with predominant manifestations of autoimmune hepatitis (AIH) or IgG4 sclerosing cholangitis as per AASLD guidelines.

❖ Bacterial Cholangitis

- Common in PSC
  - Presenting as the first symptom in ~6% of cases.
- May occur post-ERCP.

➢ Treatment

- Antibiotics
  - Rotating courses may be needed for recurrence
- MRCP after first episode
- ERCP if
  - Poor response to antibiotics

• Progression to End-Stage Liver Disease

- Many patients develop end-stage liver disease.
- Unique associations
  - Non-cirrhotic portal hypertension
  - Rare TIPS infections in chronically infected bile ducts

➢ Treatment

- Portal Hypertension
  - Management is similar to other chronic liver diseases.
  - Use Baveno-VI criteria to predict absence of varices needing treatment:
    - LS ≤20 kPa and platelet count >150 × 10^9/L
    - Accurate in avoiding unnecessary EGDs, 0% false-negative rate for varices needing treatment (as per one study)
    - Avoids 30% of EGDs
- Cirrhosis Management:
  - Vaccination
    - Hepatitis A and B if not immune.
    - Lifestyle counseling
      - Strict abstinence from alcohol
- Guidance Statements
  - Clinical Trials
    - Consider all PSC patients for clinical trials.
  - UDCA Treatment
    - Consider UDCA (13–23 mg/kg/day) for patients not eligible/interested in trials
      - ↓ ALP/GGT ↓ symptoms within 12 mon

- Oral Vancomycin
  - Evidence is not insufficient to recommend oral vancomycin for PSC treatment
- Concurrent AIH Management
  - PSC patients with AIH should follow AASLD AIH guidelines
- Bacterial Cholangitis
  - Treat with antibiotics; consider MRCP to rule out strictures
- ERCP Indications
  - Perform ERCP if bacterial cholangitis does not respond to antibiotics.
- Varices Screening
  - Conduct upper endoscopy (EGD) for varices if LS >20 kPa or platelets ≤150,000/mm³.

➢ Surveillance

- Cholangiocarcinoma (CCA)
  - Surveillance for PSC-associated hepatobiliary cancer
    - Essential due to its significant long-term risk, but
    - Strong evidence supporting its impact on outcomes is limited
    - Early detection can lead to curative surgical intervention
  - Surveillance Methods
    - Abdominal ultrasound
      - Specificity, 94%
      - Sensitivity, 57%.
    - MRI/MRCP
      - Sensitivity, 89%
      - Specificity, 75%
      - Preferred for asymptomatic PSC patients.
    - CA 19-9: serum marker for CCA, but sensitivity/specificity depend on cut-off
      - 129 U/mL
        - Sensitivity, 78%
        - Specificity, 98%.
      - 20 U/mL
        - Sensitivity, 78%
        - Specificity, 67%.
    - Fluorescence in situ hybridization (FISH) for Improved Diagnosis
      - FISH can ↑ diagnostic accuracy of CCA in PSC patients by detecting chromosomal abnormalities.
      - FISH polysomy (≥5 cells with gains in ≥2 probes), strong predictor of CCA, especially in combination with CA19-9 or dominant stricture
      - FISH polysomy with CA 19-9 ≥129 U/mL suggests a high likelihood of CCA even in the absence of a mass lesion.
      - Serial FISH polysomy and suspicious cytology should prompt follow-up ERCP with brushings in 3 mon.

Diagnostic Algorithm for PSC Patients with Relevant Stricture (No Mass)

Step	Test / Result	Next Action	Outcome
1	MRI/MRCP shows relevant stricture without mass	Proceed to ERCP with biliary biopsy + brushings (cytology, FISH)	—
2	Biopsy negative, cytology negative, FISH negative	MRI/MRCP in 6–12 months	Surveillance
3	Cytology suspicious, FISH negative	Repeat ERCP in 3 months	Surveillance
4	Cytology suspicious, FISH polysomy	Probable cholangiocarcinoma (CCA)	Diagnosis
5	Cytology positive	Confirmed CCA	Diagnosis
6	Cytology negative/suspicious, FISH polysomy	Repeat ERCP in 3 months	Surveillance
7	Biopsy positive and/or cytology positive	Confirmed CCA	Diagnosis

Notes

- FISH polysomy increases suspicion for CCA even if cytology is negative.
- Surveillance intervals vary: 3 months for suspicious findings, 6–12 months for negative results.
- Definitive diagnosis requires positive cytology or biopsy.

Adapted from: AASLD Practice Guidance. *Hepatology* 2022; 76(3):1010–1034; EASL Clinical Practice Guidelines. *J Hepatol* 2022; 77(3):761–806.

- Hepatocellular Carcinoma (HCC)
  - Rare in PSC unless cirrhosis is present.
  - Surveillance
    - Perform in PSC patients with cirrhosis (similar to patients with cirrhosis unrelated to PSC)
  - Guidance Statements
    - Perform CCA and gallbladder carcinoma surveillance: q1 yr using MRI/MRCP ± serum CA 19-9
      - In patients >18
      - Large-duct PSC
    - Sample intraductal tissue sampling for cytology and FISH routine during ERCP for relevant strictures.

- Gallbladder Cancer/Polyps

➢ Imaging

  - The best imaging for detecting gallbladder polyps is unclear
    - US has high
      - Sensitivity, 84%
      - Specificity, 96%
    - CT (sensitivity, 79%)
    - MRI (limited data)

➢ Management of Gallbladder Polyps

  - Polyps
    - <8 mm: monitor with US every 6 mon (Sensitivity, 96%; Specificity, 53%)
    - >8 mm: consider cholecystectomy (preferably at experienced center) or continued monitoring depending on liver function/perioperative risk.
  - Perform cholecystectomy for patients with gallbladder polyps >8 mm
    - Preferably at an experienced center
      - Polyps ≤8 mm may be monitored with US q6 mon
  - Patients with PSC plus cirrhosis should have HCC surveillance per AASLD guidelines.

- Colon Cancer
  - Surveillance guidelines for CRC in PSC-IBD linked to lower CRC rates
    - High-definition colonoscopy plus biopsies q1–2 yr, starting at time of PSC-IBD diagnosis.
    - Surveillance begins at age 15 (CRC rare before 15).
  - Guidance Statement
    - For PSC patients with IBD begin high-definition colonoscopy with biopsies at age 15, repeated q1–2 yr.

- Endoscopic and Percutaneous Therapy in PSC
  - Indications for ERCP
    - New-onset/ ↑ pruritus
    - Unexplained weight loss
    - ↑ liver tests
    - ↑ CA 19-9
    - Stricture / CCA on imaging.
    - MRI/MRCP should clarify need for intervention and guide approach
      - Weigh risks before proceeding.

- Antimicrobial Prophylaxis
  - Administer peri-procedure for 1–3 days (unless already on therapy) to prevent bacterial cholangitis (2%–8% risk).
- Balloon Dilation and Stenting
  - Multidisciplinary team decision
  - Remove plastic stents within 4 wk to ↓risks of infection

- Post-ERCP Complications:
  - Pancreatitis, 1%–9%
  - Prophylaxis
    - Rectal indomethacin
    - Lactated Ringer's IV
    - Pancreatic duct stent (if needed)

- Guidance Statements
  - Use MRI/MRCP prior to ERCP to assess need for ERCP.
  - ERCP indication for evaluating
    - Strictures
    - New/worsening pruritus
    - Liver test abnormalities
    - ↑ CA 19-9
    - Recurrent cholangitis, or
  - Antimicrobial Prophylaxis
    - Administer during peri-procedure period in PSC patients undergoing ERCP.
  - Biliary Balloon Dilation
    - Endpoint chosen between
      - Dilation +/- stenting
      - Remove plastic stents within 4 wk

- Pruritus

➢ Prevalence and Impact

- Pruritus affects 30%–60% of PSC patients
- Worsens at night and with heat
- Impacts quality of life → social isolation and depression.

➢ Treatment

- Initial Measures
  - Rule out biliary obstruction (MRI/MRCP)
  - Avoid heat/hot baths; use emollients and antihistamines.

- First-line Therapy
  - Bile acid sequestrants (e.g., cholestyramine 4–16 mg/day before meals)
  - Ask pharmacist to check patients' medication list exclude drug-drug interactions with cholestyramine
- Second-line Therapies (for refractory cases):
  - Naltrexone 50–100 mg/day.
  - Rifampin 150–300 mg/day (monitor hepatotoxicity).
  - Sertraline 100 mg/day.
- Alternative and Emerging Options
  - Bezafibrate
    - Randomization trial, 45% of PSC patients had ≥ 50% ↓ itch (not approved in the US)
  - Severe/Refractory Cases
    - Phenobarbital (60-100 mg/day)
    - Phototherapy, plasmapheresis
    - Liver transplantation (LT) as a last resort for pruritus

Management of Pruritus in PSC

Condition / Result	Recommended Action
○ PSC patient with pruritus	− Assess for dominant or relevant stricture/obstruction
○ Stricture/obstruction present	− ERCP management
○ No stricture/obstruction	− Supportive measures: avoid heat, use emollients, consider antihistamines
○ No improvement	− First-line therapy: Cholestyramine (4–16 g/day) − Second-line therapy: Sertraline (100 mg/day) OR Rifampin (150–300 mg/day) OR Naltrexone (50–100 mg/day) − Third-line therapy: Phenobarbital (60–100 mg/day), plasmapheresis, or phototherapy
○ Persistent pruritus despite therapy	− Consider liver transplantation

Adapted from: AASLD Practice Guidance. Hepatology 2022; 76(3):1010–1034; EASL Clinical Practice Guidelines. J Hepatol 2022; 77(3):761–806.

- IBD management in PSC

➢ Complications

- Pouchitis
  - Common after ileoanal anastomosis for ulcerative colitis (UC)
- Peristomal/Stomal Varices
  - ↑ risk with portal hypertension
  - Refractory bleeding may require interventions like
    - TIPS
    - Surgical shunts
    - Embolization, or
    - Liver transplantation (LT)

➢ Treatment

- Similar Management:
  - IBD treatment in PSC follows standard protocols for IBD without PSC.
- IBD Management in PSC
  - Aligns with standard IBD care, with
  - Continued focus on colon cancer surveillance (even after liver transplantation)
- Therapeutic Options:
  - Anti-TNF-α Antibodies
    - Safe but limited effect on liver biochemistry.
  - Vedolizumab: Effectively treats IBD; no liver enzyme improvement.

- Post-Transplant IBD Management
  - Disease Activity:
    - Variable post-LT, often uncoupled from clinical symptoms.
    - ↑ colorectal cancer (CRC) risk
      - 23% develop CRC/dysplasia post-LT (10x higher risk compared to non-PSC transplants.)
  - Proactive Management
    - Continue colonoscopic CRC surveillance.
    - Control IBD to ↓ risk of recurrent PSC (rPSC) risk
    - Emerging data supports the safety and efficacy of anti-TNF and anti-Integrins post-LT.

- Nutrition and Mineral Bone Disease in PSC
  - Nutritional Risks
    - ↑ risk of
      - Protein-energy malnutrition and
      - Frailty in advanced liver disease.
    - Fat-soluble vitamin deficiencies
      - Common due to ↓ intestinal absorption:
      - Early PSC
        - Vitamin A (40%)
        - Vitamin D (14%)
        - Vitamin E (2%)
      - Advanced PSC
        - Vitamin A (82%)
        - Vitamin D (57%)
        - Vitamin E (43%)
    - Management
      - Regular monitoring and supplementation of vitamins A, D, and E as needed.

- Bone Health in PSC
  - Osteoporosis Risk
    - ↑ prevalence in PSC,15% (a 23.8-fold ↑ risk compared to the general population
    - Risk factors include
      - Age > 54
      - BMI ≤ 24 kg/m^2
      - IBD duration ≥19 yr
  - Complications
    - Nontraumatic fractures
    - ↑ morbidity before / after LTI → quality of life (QoL)
  - Screening
    - Bone density testing at diagnosis
      - q2-3 yr (if normal bone mineral density is maintained)
  - Bone Health in PSC
    - Assess bone density for osteopenia or osteoporosis at diagnosis, then q2 to 3 yr, based on individual risk factors.
  - Nutritional Monitoring
    - Do nutritional assessments, (including lipid-soluble vitamin levels, at diagnosis and then q1 yr
    - Provide interventions and supplements as needed.

- Guidance statements
  - Pruritus Management
    - Use conservative measures
    - If these fail, use bile acid sequestrants for first-line treatment
    - Alternatives for refractory cases include
      - Sertraline
      - Naltrexone, or
      - Rifampin

- Liver Transplantation
  - PSC accounts for ~5% of LTs annually (in the US)

➢ Indications
  - Life-threatening cirrhosis complications of portal hypertension
  - Intractable pruritus, recurrent bacterial cholangitis,
  - Early-stage cholangiocarcinoma (CCA.)

➢ Post-transplant Complications in PSC
  - ↑ risk of steroid-refractory allograft rejection.
  - Questionable benefit of modified immunosuppression protocols
  - Use
    - Prolonged dual/triple therapy
    - Slow steroid withdrawal, or
    - IBD induction treatment

- Recurrence of PSC (rPSC) Post-Liver Transplantation

➢ Incidence (rPSC)
  - Occurs in 10%-37% of transplant recipients with PSC
  - High recurrence of PSC than PBC post-LT → ↓ graft function

➢ Diagnosis
  - Confirmed diagnosis of PSC before LT
  - Laboratory
    - ↑ ALP, ↑ GGT
    - Cholestatic pattern

- Diagnostic imaging
  - Cholangiography showing multifocal non-anastomotic biliary strictures.
  - Exclusion of other causes
    - Chronic ductopenic rejection
    - Hepatic Ischemia, or
    - Blood type Incompatibility (after 90 days).

➢ Risk Factors

- Male sex
- Extended criteria
- Grafts
- Steroid-free antithymocyte globulin Induction
- Tacrolimus as primary immunosuppression
- Pretransplant colectomy may be protective
- Living donor transplants ↑ rPSC risk
- Impact on Graft and Patient Survival
  - Retransplantation rate for rPSC: 12% at 10 yr (> PBC, which is 9%)
  - Higher recurrence rate than PBC, impacting graft function.

- Guidance statements
  - Do liver transplantation (LT) in PSC for patients with
    - PSC who develops end-stage liver disease
    - Recurrent cholangitis
    - Intractable pruritus, or
    - Early-stage hepatobiliary cancers
  - Post-Transplant Monitoring)
    - ↑ AP GGT → do MRCP plus liver biopsy to differentiate recurrent PSC (rPSC) from
      - Allograft rejection or
      - Biliary complications.
    - Elevated liver enzymes post-LT require histological and cholangiographic assessments

❖ **Cholangiocarcinoma** (CCA)

The following guidance is applicable for the diagnosis and management of CCA in patients with or without underlying PSC

➢ Definition

- Heterogeneous cancers with cholangiocyte differentiation along the intrahepatic or extrahepatic biliary tree.

- Subtypes (Based on Anatomic Location):
  - Intrahepatic (ICCA)
    - Proximal to second-order bile ducts in the hepatic parenchyma.
  - Perihilar (pCCA)
    - Between second-order bile ducts and the cystic duct insertion.
  - Distal (dCCA):)
    - Common bile duct below the cystic duct insertion.

- Demography
  - Geographic Variations
    - ↑ rates in Southeast Asia (e.g., Thailand: ASIR ~100 in men)
    - Due to liver fluke infection
    - Rare in the Western world (ASIR: 0.3-3.4)
  - Trends:
    - ICCA
      - ↑ incidence
      - ↑ mortality globally ~$2/10^5$ in men
    - pCCA/dCCA
      - Stable incidence mortality <1/100,000 in most countries.

- Risk Factors

- Genetic
  - Southeast Asians
    - Liver fluke infections.
  - Western Countries
    - Primary sclerosing cholangitis (PSC)
    - 50% of Western CCA cases are sporadic.

Potential Actionable Mutations

Mutation	iCCA	pCCA/dCCA
FGFR2 Fusion	√	–
ROS Kinase	√	–
BRCA1/2	√	√
BRAF	√	√
MSI	√	√
TMB	√	√
IDH1	√	–

Mutation	iCCA	pCCA/dCCA
IDH2	√	–
NRTK	√	–
ERBB2	–	√
HER2	–	√

Risk Factor	iCCA	pCCCA/dCCA
Type II Diabetes Mellitus	1.5–7.1	–
Hemochromatosis	2.0	–
NAFLD	2.9	–
Alcohol Consumption	3.3–3.7	2.0–6.5
Hepatitis C	4.5–4.7	3.2
Hepatitis B	3.1–5.0	2.1–2.4
Cholangitis	3.5	5.5
Liver Fluke Infection	6.1	14.0–16.5
Cirrhosis	10.5	3.6
Choledocholithiasis	21.5	–
Choledochal Cysts	15.6–27.6	27.1–34.9
Caroli's Disease	38.1	96.8
Cigarette Smoking	–	1.7–1.8
Chronic Pancreatitis	–	5.2–19.9
Primary Sclerosing Cholangitis	–	50.8

- Clinical Features
  - Often incidental or diagnosed during cirrhosis surveillance
  - Symptoms (e.g., jaundice, abdominal pain) suggest advanced disease
- Diagnostic Tests
  - Serology
    - CA 19-9 (↑ >1000 U/mL indicates possible metastasis)
    - Limited specificity for diagnosis.

- Imaging Modalities
  - Multiphase CT
    - Vascular assessment and resectability.
  - MRI
    - Tumour characterization.
  - Contrast-enhanced US
    - For inconclusive CT/MRI.
  - PET
    - Lymph node
    - Metastasis detection (not primary diagnosis).

➢ Histopathological

- Assessment of core needle biopsy.
- Guidance statement
  - CA 19-9
    - Elevated levels alone should not be used to diagnose CCA.
  - Histopathological Confirmation
    - Required for a definitive diagnosis of iCCA.
  - Multiphasic CT or MRI
    - Necessary for assessing the primary tumour, vascular invasion, metastasis, and resectability.
  - Cross-sectional Imaging
    - Needed for disease staging of the chest and abdomen.
  - PET Scan
    - Should not be used to diagnose the primary tumour in CCA.

➢ Treatment

- Only consider LT for unrespectable liver-limited iCCA under research protocols.
- Locoregional therapy (LRT)
  - No sufficient data to recommend LRT as a standard treatment for locally advanced unresectable iCCA.

• Locoregional therapy (LRT) for iCCA

- TACE, debTACE, TAE, TARE (yttrium-90)
  - External beam radiation therapy.
- Median OS with LRT
  - 9-22 mon (no significant difference between CCA types
- Impact of ECOG Performance Status
  - ECOG 0
  - Better survival than ECOG ≥1. ☒

- Combination with Chemotherapy: plus ☒
  - Hepatic arterial infusion (floxuridine) + systemic gem/cis:
    - year OS, 89%, median OS- 25 months.
  - Ongoing trials combining systemic chemotherapy + SBRT.
- Advances in Radiation Therapy
  - SBRT
    - Median OS: 30 mon (higher doses improve OS).
    - Multi-institutional study
      - 2-yr local control rate, 94%
  - Proton Beam Therapy
    - Precision delivery
    - Sparing healthy tissue

- Liver Transplantation (LT) for iCCA
  - Historical Outcomes
    - Early studies: 5-year OS 18%–25%, poor recurrence-free survival (RFS).
  - Emerging Evidence for Select Patients
    - Small solitary ICCA (≤2 cm)
      - 5-yr OS, 62%–65%
      - Recurrence risk, 19.7%
    - Tumours 2–5 cm with pretransplant locoregional therapy (LRT)
      - 5-yr RFS, 74%.
    - Key risk factors: Larger tumours, absence of pretransplant LRT
  - Neoadjuvant Therapy + LT
    - Promising for unresectable, locally advanced ICCA
      - 5-yr OS, 83.3%
      - RFS: 60% (median tumour size: 14.3 cm)
    - Highlights importance of multimodal pretransplant strategies
  - Future Directions
    - Referral to transplant centres with research protocol
    - Prospective trials for neoadjuvant and LT therapies to ↑ therapeutic options
  - Guidance statements
    - Surgical Resection
      - Preferred treatment for patients with a single iCCA nodule, resectable location, no metastatic disease, and sufficient liver function.
    - Specialized Referral
      - Patients with iCCA should be referred to centres with hepatobiliary surgical expertise.
    - Adjuvant Capecitabine
      - Recommended as part of treatment for all patients with CCA.

- pCCA and dCCA

➢ Clinical

- Painless jaundice

➢ Diagnostic Imaging

- MR/MRCP for biliary invasion and distinguishing malignancy
  - Sensitivity, 87%
  - Specificity, 85%
- CT & PET
  - Role in staging and detecting LN/distant metastasis.

➢ Laboratory

- CA 19-9 (caution in interpretation of patients with biliary obstruction)
- IgG4 to exclude sclerosing cholangiopathy).

➢ Endoscopy

- ERCP
  - Biliary anatomy
  - Brushings for cytology/FISH (specificity, ~97%; sensitivity, 43%)
- EUS-FNA
  - pCCA
    - Avoid tissue acquisition if LT is considered (risk of tumour spread)
  - dCCA
    - ↑ sensitivity than for pCCA
- Guidance statements
  - Perform imaging and cholangiography for suspected pCCA/dCCA
    - Evaluate tumour extent, vascular encasement, and contrast enhancement.
  - Perform ERCP with cytology
    - Obtain biliary brushings and FISH analysis for patients with suspected pCCA/dCCA.
  - Do **not** do EUS-Guided FNA for diagnosing pCCA
    - If LT is an option due to tumour dissemination risk
    - If LT is not considered, EUS-guided FNA can be diagnostic

➢ Treatment

- Surgical Resection
  - Indications
    - Early-stage perihilar cholangiocarcinoma (pCCA)
    - Normal liver function and sufficient functional liver volume
    - Transplantation is preferred over resection in PSC

- Preoperative Recommendations
  - Biliary drainage of future remnant lobes for jaundiced patients improves outcomes.
- Referral
  - Patients should be assessed at experienced centers.
- Contraindications
  - Intrahepatic/extrahepatic metastases
  - Extraregional lymph nodes
- Guidance statements
  - Perform preoperative biliary drainage for patients with pCCA/dCCA undergoing resection if biliary obstruction is present.
  - Use surgical resection for early-stage pCCA/dCCA without metastatic disease.
  - Refer patients with pCCA/dCCA to centers with hepatobiliary surgical expertise.

- Neoadjuvant Chemoradiation and LT for pCCA

➢ Overview

- Historical Context
  - Historically poor OS and RFS with LT alone
  - pCCA was a contraindication for LT
- Modern Approach
  - Neoadjuvant chemoradiation combined with LT is now widely accepted
  - Indications
    - Recognized by OPTN for early-stage pCCA (<3 cm) without metastasis

➢ Patient Selection Criteria

- Confirmed Diagnosis: Positive biliary biopsy or cytology
- Definitive Diagnosis (if no positive biopsy)
  - Malignant stricture + CA 19-9 >100 U/mL (without cholangitis/obstructed obstruction)
  - Malignant stricture + suspicious cytology / FISH polysomy
  - Imaging show perihilar mass with CCA features.

➢ Contraindications

- Lymph node metastasis
- Peritoneal tumour biopsy
- EUS-FNA or surgical violation due to risk of seeding
- Tumour radial diameter >3 cm
- CA 19-9 >500 U/mL, MELD ≥20

- Neoadjuvant Therapy
  - Radiation
    - External beam + brachytherapy.
  - Chemotherapy
    - 5-FU and capecitabine maintenance
  - Staging laparoscopy
    - Required before LT.
  - Guidance statements
    - Perform liver transplantation post-neoadjuvant therapy for patients with pCCA (≤3 cm) that is
      - Unresectable, or
      - Arising in PSC
    - Perform EUS-FNA for regional LNs in patients with pCCA being evaluated for LT to exclude metastases before initiating neoadjuvant therapy.
    - After neoadjuvant therapy, perform operative staging
      - Assess regional hepatic LN involvement, and
      - Peritoneal metastases before LT

- Systemic Therapy for CCA
  - Current Standard of Care
    - Surgery is definitive, but
    - Often not feasible due to advanced disease at presentation
    - Chemotherapy remains the cornerstone for unresectable/metastatic CCA and is largely palliative
  - First-Line Therapy
    - Gemcitabine + Cisplatin (GemCis)
    - Standard based on the ABC-02 trial
    - Outcomes: Median OS = 12 mon, PFS = 8 mon
  - Second-Line Therapy
    - FOLFOX (5-FU + Oxaliplatin)
      - ABC-06 trial: Marginal OS benefit (6 mon vs. 5 mon with active symptom control)
      - Currently the gold standard
      - Better therapies are urgently needed
  - Advances in Targeted Therapy
    - Molecular profiling identifies targetable alterations in ~40% of CCAs
    - ICCA
      - FGFR2 Fusions (10–15%)
        - Pemigatinib, FDA-approved, ORR = 36%, PFS = 7 mon (FIGHT-202 study)
        - Infigratinib and Futibatinib also show promise.

        - IDH1 mutations (15–20%)
            - Ivosidenib FDA-approved for IDH1-mutant advanced/metastatic CCA.
        - BRAF mutations (5–7%)
            - Dabrafenib + Trametinib, biomarker-driven-targeted therapy.
    - pCCA/dCCA
        - Higher prevalence of EGFR alterations (10–15%).

- Immunotherapy
    - Limited efficacy, except in a rare MSI-high tumours
    - Pembrolizumab (PD-L1 inhibitor): KEYNOTE-158 study: ORR = 5.8%.
    - Nivolumab
        - Investigator-initiated study: ORR, 22%; central review, 11%
    - Combination Strategies
        - Early promise with Durvalumab + GemCis in ongoing trials

- Guidance statements
    - Systemic chemotherapy (Gemcitabine/cisplatin) is first-line treatment for advanced CCA in newly diagnosed patients.
    - FOLFOX is second-line therapy after progression on gemcitabine and platinum chemotherapy.
    - Consider, next-generation sequencing at diagnosis to guide second-line treatment options.
    - Refer patients with advanced CCA to centres with hepatobiliary malignancies expertise and available clinical trials.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; CCA, cholangiocarcinoma; CBD, common bile duct; CD, Crohn disease; CRC, colorectal cancer; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence in situ hybridization; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; HR, hazard ratio; IBD, inflammatory bowel disease; IC, indeterminate colitis; IgG4, immunoglobulin G4; IV, intravenous; kPa, kilopascal; LT, liver transplant; LS, liver stiffness; MELD, Model for End-stage Liver Disease; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; NASH, non-alcoholic steatohepatitis; NSBBs, non-selective beta blockers; OCA, obeticholic acid; PBC, primary biliary cholangitis; PELD, Pediatric End-stage Liver Disease; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis; QoL, quality of life; RCT, randomized controlled trial; rPSC, recurrent primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis; SSC, secondary sclerosing cholangitis; TE, transient elastography; TGF-β, transforming growth factor beta; TIPS, transjugular intrahepatic portosystemic shunt; UC, ulcerative colitis; UDCA, ursodeoxycholic acid; US, ultrasound.

NON-INVASIVE TESTING/SCORES FOR LIVER FIBROSIS

Hasan Bualbanat

➢ Introduction

- Several scores and non-invasive tests are used to assess liver fibrosis
- There are
  - Easy to use
  - Inexpensive
  - Non-invasive / no complications
  - Accessible for most internists and gastroenterologists
  - Appropriate to follow-up the progression of the liver disease

➢ Examples

- AST to Platelet Ratio Index (APRI Score)
  - Calculation
    - APRI = (AST / ULN for AST) / Platelet count × 100
  - Interpretation

	Sensitivity	Specificity
APRI > 1	76%	72%
APRI > 2	41%	91%
APRI < 0.5	91%*	-

*ruling out cirrhosis

- FIB-4 Score
  - Variables
    - Age
    - AST
    - ALT
    - Platelet count
  - Calculation
    - FIB-4 = (Age × AST) / (Platelet × √ALT)
  - Retrospective Analysis 2006
    - Score analysis (based on Ishak staging system)
      -

FIB-4 Score	Fibrosis Stage	For Advanced Fibrosis
< 1.45	0-1	NPV 90%
1.45 – 3.25	2-3	
> 3.25	4-6	Specificity 97%, PPV 67%)

- Cohort Study 2017
  - If age < 35 yr
    - Use other modality score to assess fibrosis
  - Age 36–65 yr
    - Score < 1.3 → Advanced fibrosis excluded (METAVIR stage F3-F4)
    - Score 1.3–2.67 → Further investigation needed
    - Score 2.67 → Advanced fibrosis likely
  - Age > 65 (sensitivity, 65-77%, specificity, 80%)
    - Score < 2 → Advanced fibrosis excluded
    - Score 2–2.67 → will need further investigation
    - Score 2.67 → Advanced fibrosis likely
- If FIB-4 combined with APRI score → excellent NPV to exclude advanced fibrosis
- If APRI < 0.5 and FIB-4 > 1.5 → perform Fibroscan to assess degree of fibrosis
- Specific conditions
  - Hepatitis
    - HCV
      - With caution with patients < 35 or > 65
      - No value in following up patients who are being treated with direct antiviral medication (AST/ALT level tend to normalize after achieving sustained virological response [SVR])
  - Alcoholic liver disease
    - Caution: high alcohol intake → ↑ AST → falsely ↑ FIB-4 (overestimate presence of fibrosis)

- Fibrosure Test
  - Variables
    - ALT
    - Bilirubin
    - GGT
    - Haptoglobin
    - Apoprotein A1
    - α2-Macroglobulin
    - Patient Age and gender
  - No fasting required
  - Use proprietary algorithm to estimate the degree of liver fibrosis (in the US results uploaded to Biopredecitive server where they will exam the data for outliers, false positive, and false negative prior to releasing the results (take a week)

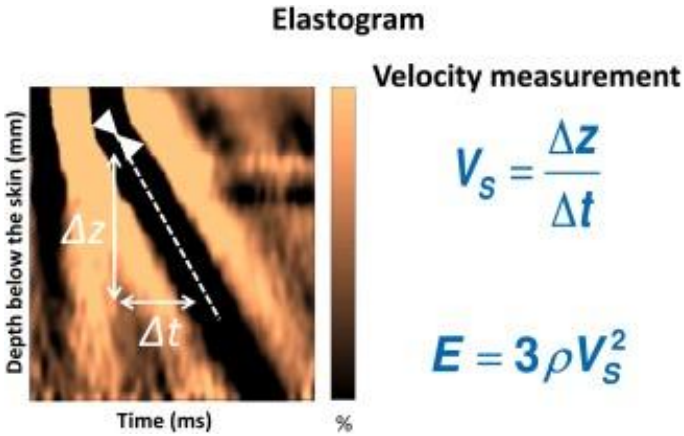
- Factors Affecting Results
  - Alcohol
  - Liver
    - Acute hepatitis
    - Gilbert syndrome
    - Extra-hepatic cholestasis
  - Kidney
    - Nephrotic syndrome
    - CKD
  - Inflammation
    - Acute inflammatory response
  - Blood
    - Hemolysis
- Result
  - Cut-off values
    - < 0.31 → NPV 91% to rule out cirrhosis
    - 0.72 → PPV 76% for predicting cirrhosis

- Vibration Controlled Transient Elastography (VCTE; Fibroscan)

➢ Background

- Uses small transducer / small ultrasound probe
- Position
  - Right intercostal space, mid-axillary line (to be close to the right hepatic lobe)
- Measures the shear wave velocity of an impulse emitted by the transducer and which goes through the liver (4.5-6.5 cm through the liver)
  - The speed of the shear wave will pass through the liver correlates liver stiffness (degree of fibrosis), measured in kilopascals (kPa)

Vibration Controlled Transit Elastography (VCTE; Fibroscan)



Comparison between successive ultrasound signals to calculate local strains as a function of time and space. Adapted from Echosens.

Courtesy of: Patel K and Wilder J. Clin Liver Dis (Hoboken). 2014; 4(5):97-101.

- Outcomes

Category	Guidelines / Notes
○ Examination Quality	− Use ≥10 shots − Success rate ≥ 60% − IQR ≤ 25% of median value
○ Liver Disease	− Not used in ▪ Acute hepatitis ▪ Acute exacerbation ▪ Ascites & extrahepatic cholestasis
○ Choice of Cutoff Point	− Cutoffs different for each chronic liver disease (CLD) − Use range of values rather than fixed cutoff

- Transient Elastography
  - Inflammation
  - Solid tumours
    - Leukemic cells
    - Mast cells
    - Inflammatory cells (neutrophils lymphocytes)
  - Edema (osmotic, toxic, apoptotic inflammation)
  - Venous pressure (Liver congestion, RBCs)
  - Ductular pressure (mechanical cholestasis)
  - Other deposits e.g., amyloidosis

Liver Stiffness Measurement (LSM) Cut-offs in Chronic Liver Disease

LSM (kPa)	METAVIR Stage	Fibrosis Interpretation
2.5 – 7	F0–F1	Mild or absent fibrosis likely
>7 – 9.5	F2	Significant fibrosis likely
>9.5 – 12.5	F3	Severe fibrosis likely
>12.5	F4	Cirrhosis likely
Up to 75	—	Advanced cirrhosis range

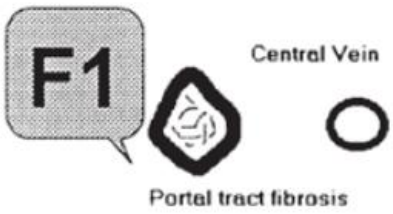
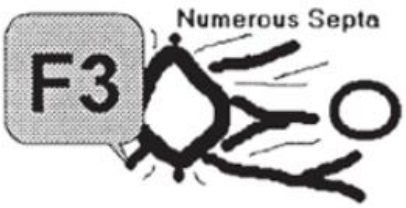
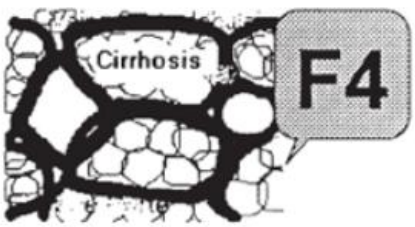
Adapted from: EASL Clinical Practice Guidelines. J Hepatol 2023; 79(2):461–491; AASLD Practice Guidance. Hepatology 2024; 79(6):1463–1502.

Correlation Between Liver Stiffness Measurement (LSM) and Fibrosis Stage Across Diseases

Condition	LSM Range (kPa)	Typical Fibrosis Stage (METAVIR)
○ Hepatitis B	0–75	F0–F4 (progression from mild to cirrhosis)
○ HCV–HIV co-infection	0–75	F0–F4, often accelerated progression
○ Hepatitis C recurrence post-transplant	0–75	F0–F4, rapid fibrosis progression
○ Hepatitis C	0–75	F0–F4, standard progression
○ Chronic cholestatic diseases	0–75	F0–F4, variable progression
○ Alcohol-related liver disease	0–75	F0–F4, often advanced fibrosis
○ NAFLD	0–75	F0–F4, progression slower but possible to cirrhosis

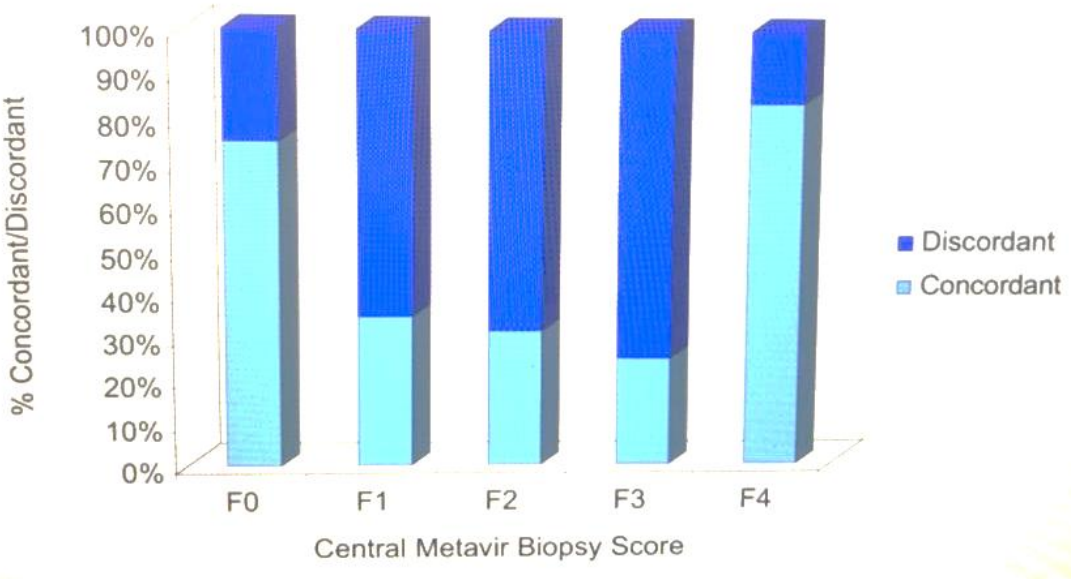
- As the shear wave speed increases, it indicates ↑ liver stiffness and fibrosis (range of stiffness 0-75)
  - Liver stiffness of > 9.5 kilopascal indicates advanced fibrosis, 95% sensitivity
- Other Applications of Fibroscan
  - CAP score (controlled attenuation parameter) measures how fast U/S wave attenuates as it travels through the liver
    - High CAP → high steatosis. Range (0-400)
  - Fibroscan AST (FAST score): combine elastography score, CAP score, and AST to predict fibrosis.

- Limitations of liver biopsy
  - Invasive Procedure
  - Serious complications might occur (rare)
  - Poor patient acceptance
  - Samples small portion of the liver parenchyma → ↑ risk of sampling variation (needs at least 2 cm sample and contain > 10 portal triads)
  - Expensive
  - Significant inter-observer variability for interpretation.

	Ishak (1995) Fibrosis 0–6	METAVIR Fibrosis F0–F4
Normal Liver (No Fibrosis)	0	0 (F0)
	1–2	1 (F1)
	3	2 (F2)
	4–5	3 (F3)
	6	4 (F4)

Adapted from: Shiha G and Zalat K. Ishak versus METAVIR: Terminology, Convertibility and Correlation with Laboratory Changes in Chronic Hepatitis C. Liver Biopsy. InTech; 2011.

Proportion of Concordant and Discordant Results between 3 pathologists; n=234



- AUROC for FS, FT, and APRI and Their Combinations, According to METAVIR Fibrosis Stages

Fibrosis Stage	FS	FT	APRI	FS+APRI	FS+FT	FS+FT+APRI
≥F2	0.83	0.85	0.78	0.84	0.88	0.88
≥F3	0.90	0.90	0.84	0.91	0.95	0.95
F4	0.95	0.87	0.83	0.95	0.95	0.95

Adapted from: Castera L, et al. Gastroenterology. 2005;128(2):343–350.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; CKD, chronic kidney disease; CLD, chronic liver disease; FS, FibroScan; FT, FibroTest; GGT, gamma-glutamyl transferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; kPa, kilopascal; LSM, liver stiffness measurement; METAVIR, meta-analysis of histological data in viral hepatitis; MM, mid-axillary line; NPV, negative predictive value; PPV, positive predictive value; RBCs, red blood cells; SVR, sustained virological response; ULN, upper limit of normal; US, ultrasound; VCTE, vibration-controlled transient elastography.

AUTOIMMUNE HEPATITIS

Amindeep Sandhu and Alan BR Thomson

- Definitions
  - Acute liver failure (ALF) – INR ≥ 2; hepatic encephalopathy within 26 weeks of onset of illness; no previously recognized liver disease
  - Acute severe AIH – Jaundice, INR > 1.5 but < 2, no encephalopathy, no previously recognized liver disease
  - AIH – Characteristic histologic abnormalities (lymphoplasmacytic interface hepatitis), elevated AST, ALT, and total IgG, and presence of one or more characteristic autoantibodies
  - Biochemical remission – Normalization of serum AST, ALT, and IgG* levels
  - Histological remission – Absence of inflammation in liver tissue after treatment
  - Inactive cirrhosis – Absence of inflammatory infiltrates in both portal tracts and fibrous bands in cirrhosis
  - Incomplete response – Improvement of laboratory and histological findings that are insufficient to satisfy criteria for remission
  - Relapse – Exacerbation of disease activity after induction of remission and drug withdrawal (or nonadherence)
  - Treatment failure – Worsening laboratory or histological findings despite compliance with standard therapy

*Patients with cirrhosis in biochemical remission may have persistent elevation of IgG.

- Demography
  - Incidence is ~1–2/10^5 persons per yr
  - Prevalence ~11–17/10^5 persons per yr
  - Female > male 3.6:1
  - Seen in
    - All ethnic groups, and
    - At all ages (most common in 40s–50s)

Manns MP, et al. Hepatology 2010; 51: 1–28

- Ethnic effects
  - African American
    - Presentation
      - Younger
      - ↑ risk of
        - Cirrhosis
        - Liver failure
        - ↑ hospitalization
        - Liver transplantation
    - ↑ mortality
  - Asian American
    - ↑ mortality
  - Hispanic
    - ↑ hospitalizations

➢ Pathogenesis

- Overview
  - A complex genetic disease that requires interplay among genetic, epigenetic, immunological, and environmental factors *
  - ↓ self-tolerance to autoantigens in persons who are genetically susceptible to AIH as a result of extent triggers such as infections.
- Histocompatibility complex loci
  - Linkage disequilibrium in HLA class I, II, and III loci
- Genetics
  - HLA
    - AIH-1 (90%) HLA DR3, DR4, DR13
    - AIH-2 (10%) HLA DR3, DR7
    - AIH-3 (rare, same as AIH-1, but SLA/LP positive and Ro52 antibody positive)
  - Non-HLA
    - Genetic polymorphisms
      - CTLA-4 (cytotoxic T lymphocyte antigen 4)
      - TNF-α (Tumour Necrosis Factor-alpha)
      - FAS (cluster of differentiation 95 {CD95}), or apoptosis antigen-1
      - Vitamin D receptor
      - Signal transduction/activation of transcription
      - Transforming growth factor-beta
      - Macrophage migration inhibitory factor
      - SA2B adapter protein
      - Caspase recruitment domain family member
      - IL-23 receptor

- Genetic variants & gene products:
  - Homeostatic, proliferation/survival & autoreactive T/B cells
  - Proliferation/survival autoreactive T/B cells
  - Cytokine production
  - Immune responses

*Exception: A rare form of AIH-associated with autoimmune polyendocrine syndrome type I (APS-1) due to an autosomal recessive mutation in the autoimmune regulator gene on Chromosome 21q22.3

- Immunological features
  - Environmental Triggers
    - ↓ ability of thymic autoantigens-specific in Tregs
      - Indicated Treg cells to ↓ immune response to hepatic autoantigens. found from exposure to environmental triggers to prevent autoreactivity
      - ↓ B regulatory cells (Bregs) → ↑ autoreactivity B cells production ↑ autoantibodies
      - Autoantigen binds to class II HLA alleles
        - Autoantigen binds not reactive T-cell receptors on
          - CD4 T helper (TH) cells
          - CD8 cytotoxic T lymphocytes (CTLs)

          } Activation of mast cells → production of autoantibodies (mucosal invariant T)
      - Expression of T-cell genes → autoantigen-specific CD4 Th subset of CD8+ CTLs / CD8+ Treg cells
      - T-cell stimulation of Breg → cytokine-activated macrophages
      - CD4+ Th17 cell cytotoxicity CD4+ iTreg → pathogenic CD4+ Th cells
      - Cytotoxicity of hepatocytes (periportal lobular → inflammation/necrosis → activation of stellate cells → fibrosis
- Autoantibodies
  - Presence of ANA (anti-nuclear antibodies), SMA (smooth muscle antibodies), and anti-LKM (liver, kidney, muscle in Caucasian adults in US/Canada with AIH)
    - ANA, 80%
    - SMA, 60%
    - Anti-LKM, 3%
- AIH with one of these, 49%
  → ≥2 of these, 51%
- Autoantigens
  - ASGPR
  - Anti-CYP2D6
  - SLA/LP
  - Antigen-specific regulatory T cell
  - Antigen-presenting cell

- Recruitment of non-antigen-specific effectors
  - Monocytes
  - NK cells
  - CD4
  - CD8
  - Th17
  - γδ T cells

- Immune Regulation
  - T cell function
  - B cell function

Adapted from: Liberal R, et al. J Autoimmun 2013; 41:126–139; Heneghan MA, et al. Lancet 2013; 382:1433–1444

- Natural History
  - No treatment
    - Survival rates
      - 5 yr, 10%
      - 10 yr, 50%
  - Survival benefit with corticosteroids
    - Overall ~85% in 10 yr

- Clinical
  - Signs and Symptoms
    - Fatigue/lethargy/malaise
    - Nausea/anorexia
    - Pruritus
    - Weight loss
    - Abdominal pain
    - Amenorrhea
    - Arthralgias
    - Hepatomegaly
    - Splenomegaly
  - Asymptomatic
    - Cirrhosis on imaging
    - Cirrhosis upon surgery
  - Mild
    - Non-specific symptoms
      - Fatigue
      - Lethargy
      - Malaise
      - Anorexia
      - Nausea
      - Arthralgias

- Presentation
  - Acute (< 30 days) hepatitis, 25% to 75%
    - Jaundice / ↑INR
    - ↑ ALT > 1000
    - ALT >10× ULN / ALT 5× ULN + IgG >2× ULN → predictive of early mortality if untreated
  - Acute liver failure, 3% to 6%
  - Chronic liver disease (CLD)
  - Extrahepatic immune-associated conditions
  - Overlap syndrome (AIH-PBC, AIH-PSC)
  - Hepatocellular cancer (HCC)
  - AIH-negative hepatitis
    - ANA/SMA may become positive later in the clinical cause
    - Maybe positive for SLA/pANCA, rather than AN/SMA
  - Concurrent immune disease
- Acute severe
  - HE within 8 wk of any symptoms
- Extrahepatic manifestation
  - Extra liver GI luminal disease
    - F > M
    - Positive family history
    - Positive HLA DRB1*04:01
    - Age
      - > 60 yr: Autoimmune thyroid, MSK disease
      - ≤ 30 yr, IBD, hemolytic anemia
  - Common
    - Thyroiditis (10-23%)
    - Diabetes (7–9%)
  - Uncommon
    - Inflammatory Bowel Disease (2–8%)
    - Mixed Connective Tissue Disease (2.5%)
    - Rheumatoid Arthritis (2–5%)
    - Psoriasis (3%)
    - Sjögren Syndrome (1–4%)
    - Systemic Lupus Erythematosus (1–2%)
    - Celiac Disease (1–2%)
    - Glomerulonephritis (1%)
    - Multiple Sclerosis (1%)
- Extrahepatic complications (EHCs)
  - Present in ~30% of AIH patients
  - Occur before, during, or after diagnosis/treatment of AIH
  - Family history in 48%

- Skin diseases
  - Can occur at any time
  - 14% have rashes at presentation
  - Often maculopapular on face/trunk/arms)
- Types
  - Acne
  - Erythema nodosa
  - Impetigo
  - Lichen planus
  - Psoriasis
  - Pyoderma
  - Urticaria
  - Vitiligo
- Hepatocellular cancer (HCC)
  - AIH plus HCC
    - Incidence, ~1% to 2%
      - Standardized incidence ratio, 23.3 (95%CI, 7.5 – 54.3)
    - Prevalence, 1% to 9%
    - Standardize mortality ratio, 42.3 (95%CI, 20.3-77.9)
  - Risk factors for HCC in AIH
    - Cirrhosis, ≥ 10 yr
    - Portal hypertension
    - Continued inflammation
    - Immunotherapy ≥ 3 yr
- Celiac disease
  - 1-2% affects patients with AIH, or
  - 10x higher prevalence in IgA deficiency
- Other rare associations
  - Antiphospholipid syndrome
  - Autoimmune pancreatitis (AIP)
  - Felty syndrome
  - Fibrosing alveolitis
  - Hemolytic anemia
  - ITP
  - Mononeuritis multiplex
  - Myasthenia gravis
  - Panniculitis
  - Polyglandular autoimmune syndrome type 1
  - Polymyositis
  - Uveitis

- Guidance Statements
  - The diagnosis of AIH should be suspected when patients have one of these presentations.
  - Test all patients with AIH for
    - Autoimmune thyroid disease
    - Celiac disease
  - Test patients for clinically suspected other extrahepatic immune conditions
  - AIH
    - Age-appropriate screening guidelines
  - AIH plus cirrhosis
    - Abdominal ultrasound +/- α-fetoprotein q6 mon

➢ Diagnosis (AIH)

- Guidance statements
  - Compatible histopathology on liver biopsy, plus
    - ↑ ALT / ↑ AST plus ↑ IgG
    - Abnormal compatible serology e.g., ANA, SMA
  - Exclusion of other liver diseases which may look like AIH
    - Inherited
    - Infection, viral
    - Iatrogenic
    - Metabolic
    - Cholestatic
  - If diagnosis of AIH uncertain
    - Expert multi-disciplinary

Alert

- The above histopathological changes in the patient with AIH-cirrhosis suggest active disease.
- Please see below for histopathological features of AAIH presenting with active liver failure

➢ Diagnostic Tests

- Laboratory
  - Liver enzymes, synthetic function
  - Serology (autoantibodies)
  - Immunoglobulins

Type 1	Type 2
ANA	LC1
SMA	LKM1
pANCA	LKM3

Autoantibodies

Antibody	Target Antigen(s)	Liver Disease	Value in AIH
− ANA	Chromatin, ribonucleoproteins	AIH, PBC, PSC, drug-induced, viral hepatitis, NAFLD	Diagnosis of type 1 AIH
− ASGPR	Asialoglycoprotein receptor	AIH, PBC, drug-induced hepatitis, viral hepatitis	Prognostic implications, relapse
− LC1	FTCD	Type 2 AIH, chronic hepatitis C	Prognostic implications, severe disease
− LKM1	CYP2D6	Type 2 AIH, chronic hepatitis C	Diagnosis of type 2 AIH
− LKM2	CYP2C9	Ticrynafen-induced hepatitis	None (resolves after withdrawal)
− LKM3	UGT1A	Type 2 AIH, chronic hepatitis D	Diagnosis of type 2 AIH
− LM	CYP1A2	Dihydralazine-induced hepatitis	Diagnosis of APECED hepatitis
− pANCA	Nuclear lamina proteins	AIH, PSC	Diagnosis of type 1 AIH
− SLA	RNP/SEC	AIH, chronic hepatitis C	Diagnosis, prognosis, relapse risk
− SMA	Actin, vimentin, desmin	Same as ANA	Diagnosis of type 1 AIH

		AIH	PBC	PSC	DIW	Chronic			MASH
						HBV	HCV	HDV	
−	ANA/SMA	T1	+	+	+	+	+	+	+
−	pANCA	T1					+		
−	LKM1	T2	+						
−	SLA	T1/T2					+		
							Severity relapse		
−	LKM3	T2						+	
−	ASGPR	T1/T2	+		+	+	+	+	
			Severity						
−	LC1	T2				↑ risk, relapse + severity			

- Diagnostic Criteria / Scoring Systems
  - May ↑ likelihood of diagnosis
- **International Autoimmune Hepatitis Group** (iAIHG)

Scoring System	Sensitivity	Specificity	Accuracy	Best for Patient Group
○ Original	100%	73%	82%	Typical
○ Simplified/Revised	95%	90%	92%	Complex

  - Suggestion:
    - If the score of the simplified is low, perform the revised system
    - Use scoring system for complex patients

- **iAIHG Revised Scoring System**

Parameter	Feature	Score
○ Patient		
− Sex	Female	+2
− Hepatotoxic drug history	Yes	-4
	No	+2
− Alcohol intake	<25 g/day	+2
	>60 g/day	-2
− Immune diseases	Thyroiditis, colitis, other	+2
− Response to therapy	Remission	+2
	No response	0
○ Laboratory		
− ALP:AST (or ALT) ratio	>3	-2
	1.5–3	0
	<1.5	+2
− Serum globulins/IgG	>2× ULN	+3
	1.5–2× ULN	+2
	1–1.5× ULN	+1
	<1× ULN	0
− ANA, SMA, or anti-LKM1 titres	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
− AMA	Positive	-4
− Viral markers	Positive	-3
	Negative	+3
− HLA	DR3 or DR4	+1
− Other autoantibodies	Anti-SLA/LP, actin, ASGPR	+2
○ Histology	Interface hepatitis	+3
	Plasma cells	+1
	Rosettes	+1
	None	0
	Biliary changes	-3
	Atypical changes	-3

○ Scoring
- − Definite AIH
  - ▪ Pretreatment >15
  - ▪ Post-treatment >17
- − Probable AIH
  - ▪ Pretreatment 10–15
  - ▪ Post-treatment 12–17

Adapted from: Heneghan MA et al. Lancet 2013; 382: 1433-44.

- **Simplified criteria for the diagnosis of AIH** (Hennes et al., Hepatology 2008)

Variable	Cut-off	Points
○ ANA or SMA	≥1:40	1
○ ANA or SMA	≥1:80	2
○ Anti-LKM1 or SLA	Positive	2
○ IgG	>ULN >1.1× ULN	1 2
○ Liver histology	Compatible with AIH Typical of AIH	1 2
○ Absence of viral hepatitis	Yes	2

  - Interpretation

	Sensitivity	Specificity
▪ Probable: ≥6	88%	97%
▪ Definite: ≥7 points	88%	99%

➢ Classification

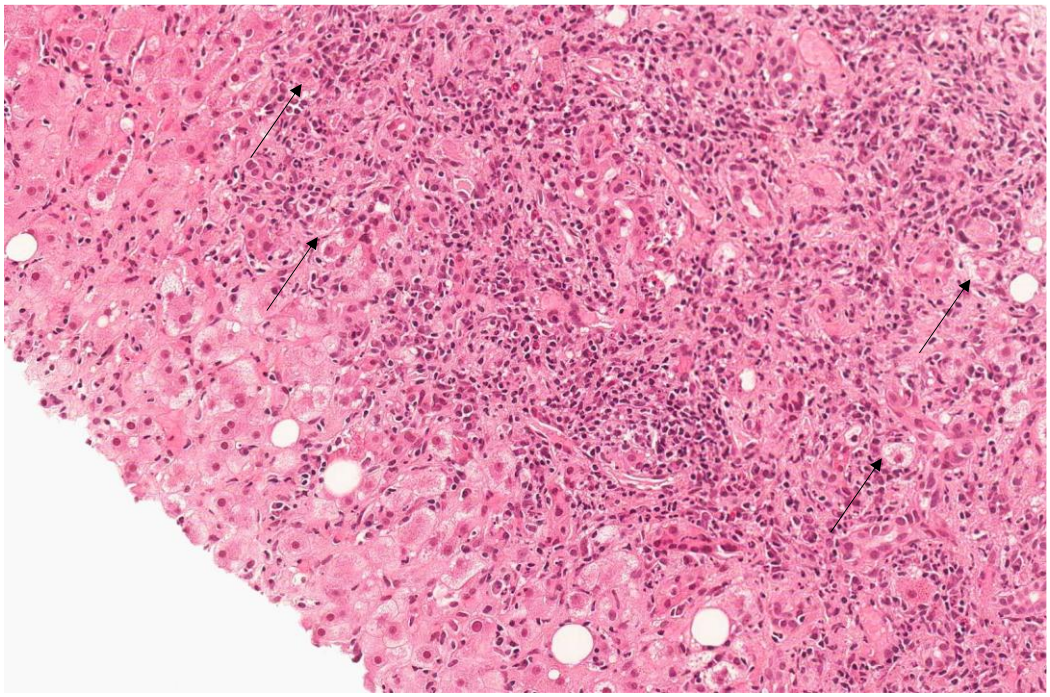
Feature	Type 1 (90%, Classical)	Type 2 (10%)
○ Laboratory		
− Characteristic autoantibodies	▪ Antinuclear antibody (20% may be negative) ▪ Anti-smooth muscle antibody ▪ Anti-actin antibody ▪ Anti-SLA/LP ▪ Anti-liver-pancreas antigen	▪ Anti-liver-kidney microsomal antibody type 1 (rare in North America) ▪ Anti-liver-cytosol antibody type 1 antibody ▪ Anti- liver-kidney microsomal antibody type 3
− HLA	▪ HLA-DR-3/4/13	▪ HLA-DR-3/7
○ Demography		
− Geographical variation	▪ Worldwide	▪ Worldwide
− Age at presentation	▪ All ages	▪ Usually childhood/young adulthood
− Female-to-male ratio	▪ 4:1	▪ 10:1
○ Clinical		

Feature	Type 1 (90%, Classical)	Type 2 (10%)
− Phenotype	▪ Variable	▪ Generally severe
− Presentation	▪ Thyroiditis ▪ Graves disease ▪ UC even with absence of cholangitis ▪ Celiac disease	▪ Diabetes mellitus (often type 1) ▪ Autoimmune thyroid disease ▪ Vitiligo ▪ Alopecia
○ Histopathology (features at presentation)	▪ Mild disease to cirrhosis	▪ Generally advanced (inflammation and cirrhosis common)
○ Treatment		
− Treatment failure	▪ Rare	▪ Common
− Relapse after drug withdrawal	▪ Variable	▪ Common
− Need for long-term maintenance	▪ Variable	▪ ~100%

- AIH Type 3
  - HLA DR3, DR7
  - Serology positive for
    - SMA
    - Anti-SLA/LP
    - Ro 52 antibody positive

➢ Histopathology
  - Exclude other causes of chronic liver disease (CLD)
  - Interface hepatitis (hallmark)
    - Interface between liver parenchyma and portal triads
  - Plasma cell infiltrate in periportal distribution
  - Lobular inflammation in rosette pattern
  - Bile duct sparing
  - Bridging fibrosis

Autoimmune Hepatitis



Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 2; 2021. ISBN: 979-8743669325

- Differential Diagnosis
  - Autoimmune
    - Other autoimmune liver diseases
      - Primary biliary cholangitis (PBC)
      - Primary sclerosing cholangitis (PSC, including small duct PSC)
    - Non-autoimmune liver diseases
      - IgG4-associated cholangitis
      - Systemic lupus erythematosus
      - Celiac disease
  - Infection
    - Chronic hepatitis: HBV ± Chronic hepatitis HCV
    - Human immunodeficiency virus infection (HIV)
  - Infiltration
    - Cholangiopathy
    - Non-alcoholic steatohepatitis (NASH)

- Iatrogenic
  - Drug-induced liver injury
- Alcoholic liver disease
- Idiopathic
  - Granulomatous hepatitis
- Inherited
  - Hemochromatosis
  - α1-antitrypsin deficiency
  - Wilson disease

Category	Criteria
Absolute	– AST >10× ULN – AST ≥5× ULN + globulin ≥2× ULN – Bridging/multiacinar necrosis – Incapacitating symptoms
Relative	– Symptoms (fatigue, arthralgia, jaundice) – AST/globulin less than absolute criteria – Interface hepatitis – Osteopenia – Emotional instability – Hypertension – Diabetes – Cytopenia (WBC ≤2.5×10⁹/L or platelets ≤50×10⁹/L)
None	– Asymptomatic with normal/near-normal AST and globulin – Inactive cirrhosis or mild portal inflammation – Severe cytopenia (white blood cell counts ≤2.5×10⁹/L or platelets ≤50×10⁹/L) or known complete deficiency of TPMT activity precludes treatment with azathioprine – Miscellaneous ▪ Vertebral compression ▪ Psychosis ▪ Brittle diabetes ▪ Uncontrolled hypertension ▪ Known intolerances to prednisone or azathioprine

- AIH versus drug-induced liver disease (DILI)
  - DILI may appear histopathologically similar to but not in identical to immune based AIH (Adapted from: Sugiura R, et al. Hepatology 2014; 54: 921–931)

- Concept
  - DILI may mimic any non-DILI pattern of injury (on liver biopsy), such as idiopathic, immune-mediated AIH
  - There is no one histological feature on liver biopsy which is diagnostic for either DILI or DILI
  - The Ishak scoring system is used to suggest the diagnosis of AIH as being possible or probable – based on probable
  - Histopathological features which were present in both AIH and DILI
    - Portal inflammation
    - Interface hepatitis
    - Necrosis, focal
- A combination of histopathological features helps to differentiate between the two conditions
- Features which favour DILI vs. DILI
  - Plasma cells portal / intro-acinar
  - Rosette formation
  - Emperipolesis
- Features which favour DILI
  - Neutrophils, portal
  - Cholestasis inter-hepatocytes
  - Combinations of
    - Portal inflammation, neutrophils and plasma cells
    - Cholestasis hepatocellular
    - Fibrosis
- ↑ ANA (Anti-Nuclear Antibodies)
  - AIH (Autoimmune Hepatitis), 49%
  - PSC (Primary Sclerosing Cholangitis), 29%
  - HBV (Chronic Hepatitis B), 32%
  - HCV (Chronic Hepatitis C), 26%
  - NAFLD (Non-Alcoholic Fatty Liver Disease), 24%
  - AALD (Alcohol-Associated Liver Disease) 6%
- ↑ SMA (Smooth Muscle Antibodies), isolated
  - AIH, 63%
  - HCV infection (Chronic), 6%
  - PSC, 6%
  - AALD: 4%
- ANA plus SMA (concurrent)
  - AIH: 49%
  - Other liver diseases: <10%
  - Diagnostic accuracy
    - 1 of ANA/SMA, 58%
    - ANA plus SMA, 74%

- Anti-LKM1 (Liver-Kidney Microsomal Antibodies)
  - Usually positive where ANA/SMA negative
  - Sensitivity for AIH ~1% in US/Canada adults
- Anti-LC1 (Liver Cytosol Type 1)
  - In AIH patients positive for anti-LKM1, 32% are positive for liver cytosol type 1 (anti-LC1), 32%
- Anti-LKM3 positive in type 2 AIH in 17%
- Titer of ANA/SMA titers
  - Positive relationship
    - AIH severity
    - Response to treatment
  - Non-relationship
    - AIH activity
    - Outcome of treatment
- Antibodies to soluble liver antigen (anti-SLA)
  - Specificity for AIH, 99%
  - Only marker of AIH, 14% to 20%
  - Associated with
    - Severe AIH
    - ↑ risk of relapse when treatment stopped RA-like phenotype
- Atypical perinuclear antineutrophil cytoplasmic antibodies (p-ANCA)
  - Type 1 AIH, 50% to 92%
    - Low specificity
  - Differential of positive pANCA
    - Liver
      - AIH
      - PSC
      - PSC-AIH
      - DILI (minocycline)
    - Colon
      - Ulcerative colitis
    - Occasionally only pANCA positive in AIH
- Anti-nuclear (filamentous anti-actin)
  - A type of SMA
  - In AIH patients positive for AIH/SMA, anti-F is positive in 80% to 100%
  - Anti-α-actinin positive with
    - AIH, 42%
    - AIH positive for anti-actin, 66%
  - Anti-actin plus anti-α actinin positive
  - Associated with
    - Severe acute AIH
    - ↓ response to treatment
    - ↑ risk of relapse

➢ Treatment

- Pretreatment Evaluation
  - If considering use of azathioprine (AZA)
    - Screen for thiopurine (TPMT) activity to establish safety of use of AZA re development of severe immunosuppression (IMS)
  - When using AZA, monitor WBC count regularly to ensure no development of IMS from other metabolic pathways
  - Serology for HBV, HCV, and HIV-infection
    - If vaccinations for HAV/HBV not done previously, prefer before AZA therapy
    - Vaccination success (protective antibodies)
      - NAV, 100%
      - HBV, 76% (effect of concomitant of immunosuppressive therapy)
  - Guidance statement
    - Provide vaccinations against HAV/HBV infection in persons previously vaccinated
      - Also provide age-specific vaccinations for other infections
    - Prophylactic entecavir / tenofovir for ≥ 5 mon during / after use of AZA (≥ 12 mon after anti-CD20 drugs)
    - HBV Infection
      - Pretreatment (B-cell depleting drugs, calcineurin inhibitors)
        - Screen for HBsAg, anti-HBc q1-3 mon
      - Classification of risk and reactivation
        - Low, < 1% → monitor and treat as needed
        - Medium/moderate, 1% to 10%
        - High, >10%
      - Pretreatment, corticosteroids
        - HBsAg
        - ↑HBV DNA anti-viral prophylaxis for ↓ risk of revised seroconversion (HBsAg- plus anti-HBc → next viral prophylaxis for viral primary recirculation (HBsAg- plus anti-HBC → HBsAg plus HBV DNA
  - Guidance statement
    - AIH plus HBsAg- / anti-Hbc+ → when on prednisone +/- azathioprine serological monitoring for HBsAg and HBV DNA
    - AIH plus infection previously anti-viral therapy

- Bone Health
  - Risk factors for osteoporosis
    - Women > Men, especially post-menopausal women
    - Age
      - Women > 65 yr
      - Men > 10 yr
    - Smoker
      - ↓ body weight
      - ↓ mortality
    - Family history positive
    - In AIH, use of corticosteroids and prophylactic therapy
      - Calcium (elemental) 1 to 2 g/d, vitamin D 400 to 800 IU/day
  - Risk of low vitamin D concentration in blood of patients with AIH
    - Serum vitamin D
    - Insufficiency
      - < 29 ng/mL in 68% to 81%
      - < 20 ng/µL in 20%
  - Osteoporosis present
    - Achieve / maintain normal body weight
    - Exercise, weight-bearing
    - bisphosphonates
  - Guidance statements
    - Serum vitamin D (25-hydroxy vitamin D) performed at diagnosis, then
      - Vitamin D < 29 ng/mL, or glucocorticosteroids
        - Give element calcium, 1-2 g/d po, plus vitamin D 400-800 IU/d

- Metabolic Syndrome
  - Definition: presence of **≥ 3** of the following criteria:
    - Hypertension
    - ↑ body mass index (BMI > 30 kg/m²)
    - ↑ waist–hip ratio (central obesity; WHR)
    - Hyperglycemia
    - Hypertriglyceridemia
    - ↓ HDL (high-density lipoprotein cholesterol)
  - May be caused or worsened by corticosteroids
  - Guidance statements
    - Diagnose and treat components of metabolic syndrome (preferably before and during treatment)
      - Correct abdominal body weight (BMI, WHR)
      - Exercise

- Patient Coaching (before starting therapy for AIH)
  - Informal consent for benefits and drug-associated complications
  - Through discussion to achieve “buy in” by patient of importance of adherence to drug treatment
  - Beware of possible development of depression and anxiety, possibly related
    - Patient concern their AIH
    - Use of corticosteroids levels
    - ↓ quality of life
    - Past history of depression/anxiety
- Before starting therapy, inform patient of benefits and adverse effects of long term corticosteroids
  - Follow patient and consider periodic use of questionnaire to achieve/treat these complications of AIH / its treatment
    - Provide proper counseling and follow-up

- Reproduction and Family Planning
  - Patient (mother)
    - Maternal complication rate, conception to 12 mon postpartum, 38%
    - Amenorrhea (↓ fertility when AIH poorly controlled
  - Fetus
    - Birth rate in some mothers with AIH, 73%
    - ↑ preterm births, 20%
    - ↑ fetal loss / ↑ stillbirth, 27% vs. 7% to 15% for mothers with no chronic disease
    - ↑ risk of AIH flares / decompensation
      - AIH patient
        - Not on therapy
        - Not in remission for ≥ 1 yr before conception
    - Treat esophageal varices prophylactic with banding or use of non-specific β-blockers to ↓ risk of variceal bleeding
    - Post-partum flares (3x↑ risk of flares postpartum): follow patient carefully for possible flare
  - Guidance statements
    - Family planning to
      - Ensure biochemical remission > 1 yr before conception
      - If woman plans pregnancy
        - In the year before conception, perform upper endoscopy and prophylactic treatment, if varices present
        - If not assessment for varices preconception, do endoscopy in second trimester (T2)

➢ Pharmacological Treatment

- First-line indication
  - All patients with active AIH
  - Laboratory target
    - Normal ALT, AST, IgG concentrations
- Prednisone 40 to 60 mg po od, or
  - Prednisone, 20-40 mg po od, plus azathioprine (AZA), 1-2 mg po od
  - When using prednisone plus AZA, options
    - Start prednisone plus AZA together, or
    - Start prednisone, then AZA in 2 wks
- Monitor blood work q2 wk
  - When ↓ ALT / ↓ AST / ↓ IgG → slow taper (2.5 mg q2 wk) to active maintenance of 5-10 mg/day
  - If AZA not tolerated, use MMF but avoid of conception is planned (50-150 µg/d)
  - Do **not** use alternate only prednisone (may ↓ degree of immunosuppression)
- Budesonide 3 mg bid po plus AZA may be substituted for prednisone plus AZA to achieve remission
  - After remission continue budesonide 3 mg/d
- Do **not** use budesonide in patients with cirrhosis
  - Budesonide is 90% metabolized in gut and liver
  - In patients with cirrhosis, there is
    - ↓ hepatic metabolism
    - ↓ portal shunting

    } ↑ steroid-specific side effects
- Guideline Recommendations
  - For AIH, no cirrhosis or severe acute AIH, use prednisone plus AZA, or budesonide plus AZA
    - If patient has cirrhosis or severe acute AIH → use prednisone plus AZA

- Mycophenolate (MMF)
  - May be used to substitute for AZA in first-line treatment with prednisone plus AZA
    - Remission rate in 2 yr, ~75% (minimal data)
    - Success of MMF for former AZA intolerance 62% to 82%, vs, 38% treatment failure, 32%
    - MMF plus prednisone: remission rates
      - Biochemical, 60% to 79%
      - Histological, 89%

- Cyclosporine / Tacrolimus
  - Normalization of ALT/AST in 75% to 94%

➢ Predictors of response to CS

- Response
  - ↓ ALT/ ↓ AST is best predictor of outcomes
    - ↓ ALT/ ↓ AST in < 2 wk / HLA DRB1 *04:01
  - Biochemical remission in < 6 mon
    - ↓ progression to cirrhosis
    - ↓ need for liver transplant "prioritization"
  - Serum ferritin >2.1x ULN)
    - Predicts future remission, as also does
    - ↑ ferritin plus ↓ IgG

- Poor Response
  - ↓ vitamin D
  - ↑ angiotensin-converting enzyme (ACE) inhibitors

➢ "Stopping Rules": Treatment withdrawal

- Biochemical
  - Biochemistry (AST, ALT, IgG) normal for >2 yr of cirrhosis
  - If cirrhosis
    - Normal ALT/AST
    - ↑ IgG

    } > 2 yr

  - In the first year after withdrawal of treatment
    - 50% of relapses occur first 3 mon
    - After 1 yr of drug withdrawal, and for the next 3 yr, the risk of relapse is 3% per year
    - After 28 mon, 90% of relapse have occurred
  - Relapse after
    - Drug withdrawal, 50% to 87%
    - 2 yr of normal biochemistry, 46%
  - Monitor ALT/AST to spot and treat early recurrence of AIH so as to ↓ risk of progression to fibrosis

- Histopathology
  - Normalization of AST/ALT for > 2 yr in 30%
    - Normal ALT/AST for > 2 yr, relapse in 54%
    - No normalization of ALT/AST, 21%

- Normal AST/ALT plus normal biopsy, relapse in 46%
  - Greater benefit in children

- Venothrombotic Embolization (VTE)
  - VTE in treated AIH with normalized ALT/AST had liver stiffness
    - Those with persistently ↑ VTE (6.4 ± 3.2 kPa vs. 9.2 ± 9.2 kPa (P = 0.06)
  - The value of VCTE does **not** correlate with
    - Histopathology
    - Sustained remission
    - Predictive of relapse after drug withdrawal

- Risk factors for relapse after withdrawal of treatment
  - Duration/completeness of reactive AIH before stopping therapy
    - ↑ AST / ↑ ALT; ↓ IgG
    - Abnormal histopathology, including
      - ↑ plasma cells in portal area
    - Treatment: monotherapy, or multiple days

- Treatment after Drug Withdrawal-associated Relapse
  - Retreatment
    - Normalization of
      - ALT/AST in 4 mon, 94%
      - Histopathology in 8 mon, 59%
  - After one relapse, after 2 yr withdrawal retreatment may be effective, a second withdrawal is commonly associated with another relapse
    - Therefore, after one relapse, continue treatment long term, so as to
      - ↓ further relapses
      - ↓ risk of development of cirrhosis when there has been multiple relapses (10% vs. 38%, p = 0.02)
      - ↓ risk of death from liver disease or ↓ need for liver transplantation (3% vs 20%, p = 0.02)
  - Withdrawal of treatment may have a superior outcome if effective therapy is continued for > 2 yr, e.g., risk of relapse after 69 ± 8 mon of normal biochemistry is ~12%
  - Guidance statements
    - Only consider offering the withdrawal of effective therapy if ALT/AST and IgG have been normal for > 2 yr
    - Liver biopsy in the patient with normal biochemical tests may demonstrate unsuspected inflammation, and this leads to uninterrupted treatment, but the benefit is small and
      - Performing liver biopsy is not necessary in adults with AIH, tested and having normal biochemistry for > 2 yr

- After withdrawal of treatment in the AIH patient who have biochemical remission for > 2 yr, perform biochemical tests regularly (q3–6 mo) for 12 mon, then annually.
- If a relapse occurs in the AIH who relapses after drug withdrawal
  - Retest on the graph if successful program, plus
  - Continue therapy long term

- Guideline Recommendation (AASLD)
  - First-line therapy
    - AIH failure/incomplete response
    - Drug intolerance (thiopurine may be a suitable substitute to AZA in person who tolerate AZA, but data is limited

    } Use mycophenolate mofetil (MMF) or TIC to achieve/maintain biochemical remission (conditional recommendation, low certainty)
  - For second-line therapy
    - First try MMF rather than TAC (conditional recommendation, very low certainty)
- Drugs Under Study
  - Infliximab — Monoclonal antibody to TNF-α
  - Rituximab — Monoclonal antibody to B-cell surface receptor CD20

  } Under study
- Guidance Statement
  - Possibly future choices for first/second-line therapy for AIH, but cannot be recommended due to more studies are required.

Treatment Algorithm for Autoimmune Hepatitis (AIH)

- Patients with autoimmune hepatitis are typically initiated on predniso(lo)ne at 0.5–1 mg/kg/day.
  - In cases of good response
    - Azathioprine is added (1–2 mg/kg/day) and steroids are tapered, with individualized dosing guided by ALT and IgG normalization.
    - If azathioprine intolerance occurs, mycophenolate mofetil is considered as a second-line agent.
  - For insufficient response
    - Compliance should be assessed, and prednisolone may be escalated (e.g., 100 mg intravenously).
    - Persistent non-response warrants referral to a specialist centre for diagnostic confirmation, liver transplantation evaluation, or alternative immunosuppressive therapy.
    - If alternative diagnoses are suspected, appropriate management should be pursued.

Step	Intervention	Notes
○ Initial therapy	Predniso(lo)ne 0.5–1 mg/kg/day	Begin induction treatment
○ Good response	Add azathioprine 1–2 mg/kg/day	Taper steroids; aim for normal ALT/IgG
○ Azathioprine intolerance	Switch to MMF	Second-line therapy
○ Insufficient response	Check compliance; escalate prednisolone (100 mg i.v.)	Reassess
○ Persistent insufficient response	Refer to specialist centre	Confirm diagnosis, LTX evaluation, alternative immunosuppressives
○ Alternative diagnosis suspected	Investigate and manage accordingly	Rule out other causes

Adapted from: EASL. J Hepatol 2015; 63: 971-1004.

- ○ Once resolution occurs:
  - − Start/continue azathioprine (Imuran)
  - − Gradually taper prednisone by 2.5 mg q2–4 wks
- ○ Check liver AST/bilirubin and IgG q2–4 wks during withdrawal
  - − After withdrawal, check q3–6 mon
- ○ Risk of relapse within 6 mon after drug withdrawal
  - − Laboratory normal, ≥ 80%
  - − Laboratory plus liver biopsy normal, 15%
- ○ Recommendations
  - − Always perform baseline
    - ▪ Bone mineral density testing (DEXA scan)
    - ▪ Vaccination
    - ▪ HAV/HBV
  - − 20/10 continue maintenance until normal
    - ▪ Laboratory: ALT, bilirubin, IgG
    - ▪ Liver biopsy
  - − Imuran
    - ▪ Containing regimen has lower occurrence of steroid-related side effects (10% vs. 44%)
    - ▪ Always assess drug metabolizing enzymes (TPMT, thiopurine methyl transferase), mutations and WBC monitoring

Immunosuppressive Regimens (Adults)

Therapy	Week 1	Week 2	Week 3	Week 4	Maintenance
○ Prednisone monotherapy	60 mg	40 mg	30 mg	30 mg	≤20 mg
○ Prednisone + Azathioprine (USA)	30 mg + 50 mg	20 mg + 50 mg	15 mg + 50 mg	15 mg + 50 mg	10 mg + 50 mg
○ Prednisone + Azathioprine (EU)	30 mg + 1–2 mg/kg	20 mg + 1–2 mg/kg	15 mg + 1–2 mg/kg	15 mg + 1–2 mg/kg	10 mg + 1–2 mg/kg

- ○ Reasons for preference of
  - − Monotherapy
    - ▪ Cytopenia
    - ▪ Malignancy
    - ▪ Pregnancy
    - ▪ Short course (≤6 mon)
    - ▪ TPMT
  - − Combination therapy
    - ▪ Brittle diabetes
    - ▪ Emotional lability
    - ▪ Hypertension
    - ▪ Obesity
    - ▪ Osteoporosis
    - ▪ Postmenopausal state

- Endpoints

Treatment Terminology	Features	Action Plan
○ Remission	− Disappearance of symptoms − Normal serum aminotransferase, bilirubin, and γ globulin levels − Normal hepatic tissue or inactive cirrhosis	▪ Gradual withdrawal of prednisone over 6 wks ▪ Serum AST or ALT, total bilirubin levels determine q3 wks during and for 3 mon after drug withdrawal ▪ Then repeat laboratory tests q6 mon for ≥1 yr, then q1 yr
○ Treatment failure	− Worsening clinical/laboratory/ histological features despite compliance with therapy − Development of jaundice, ascites, or hepatic encephalopathy	▪ Prednisone 60 mg/day or prednisone 30 mg/day plus azathioprine 150 mg/day ≥1 mon ▪ ↓dose of prednisone by 19 mg and azathioprine by 50 mg of improvement, until standard treatment doses are achieved

Treatment Terminology	Features	Action Plan
○ Incomplete response	− Some/ no improvement in clinical, laboratory, and histological features despite compliance with therapy after 2-3 yrs − No worsening of condition	▪ ↓ dose of prednisone by 2.5 mg/mon until lowest level possible (≤10 mg/day) to prevent worsening of serum AST or ALT abnormalities ▪ Indefinite azathioprine therapy (2 mg/kg daily) as an alternative treatment if corticosteroid intolerance
○ Drug toxicity	− Development of ▪ Intolerable cosmetic changes ▪ Symptomatic osteopenia ▪ Emotional instability ▪ Poorly controlled hypertension ▪ Brittle diabetes, or ▪ Progressive cytopenia	▪ ↓ dose or discontinuation of offending drug ▪ Maintenance on tolerated drug in adjusted dose

- Treatment Failure
  - Return to original induction dosing
  - If ↓ ALT by 60 days, ↓ dosing as per previous interval, but monthly
  - Continue lifelong maintenance (otherwise relapse rates >90%)
- Relapse
  - Do **not** confuse treatment failure
  - Occurs in ~20% of patients with AIH, even with normal hepatic histopathology
  - Endpoints achieved, but then
    - ↑ ALT/AST >3× ULN +/- IgG >2× ULN
    - Does not require biopsy for confirmation
  - Number of relapses correlates with disease progression
  - ≥2 relapses associated with
    - Cirrhosis
    - Death
    - Liver failure
    - Liver transplant
  - Treatment of relapse

- Reinstitute initial regimen (prednisone + azathioprine)
- Ensure that patient is on AZA, 2 mg/kg
- Continue AZA indefinitely
- If AZA contraindicated use lowest dose of prednisone quired to normalize ALT (ALT at least <3x ULN)
- Usually, 10 mg prednisone tolerated long term

- Budesonide used in patients without cirrhosis / adrenal fibrosis as an effective treatment.
- If ALT < 5x ULN, Remission rates: 30–50%.
- Do **not** use in advanced fibrosis, cirrhosis, or ALT >5× ULN
- ↓ side effects due to extensive first-pass hepatic metabolism.
- **Not** effective in patients who failed glucocorticoids.
- **Not** endorsed as first-line therapy by most major associations

Manns MP et al. Gastroenterology 2016; 139:1198–206

- Mycophenolate Mofetil (MMF)
  - Second-line therapy
    - Usually given at 1 g bid.
  - Associated with biochemical and histological improvement
  - Indications
    - Treatment failure on AZA, or adverse reaction to AZA (but not if cytopenia to AZA)

Zachou K, et al. J Hepatol 2011; 55:636–46

- Tacrolimus & Cyclosporine shown effective in small studies for treating refractory autoimmune hepatitis.
- Side effects of these medications limit their extensive use.

Heneghan MA et al. Lancet 2013; 382:1433–44

➢ **Overlap Syndromes**

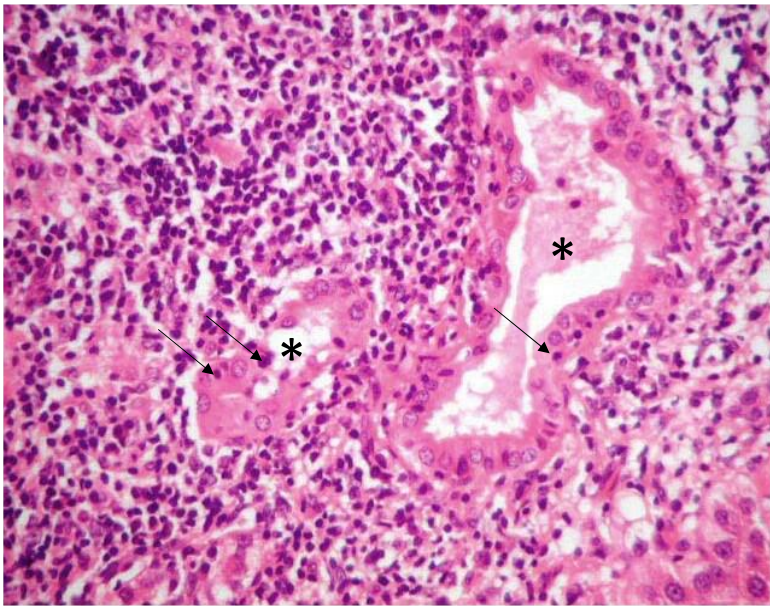
- Use the Paris Criteria for diagnosis of AIH-PBC and AIH-PSC, which may be treated differently then just AIH (Chazouillères O, et al. Hepatology. 1998; 28(2): 296-301)

- **AIH–PBC**
  - Seen in 5–8% of AIH patients.
  - Paris Criteria (need ≥2 of each in both AIH and PBC)

- Sensitivity 92%, Specificity 97%.
- Alert, Paris criteria perform less well if ALP/GGT not as ↑
- Superior to scoring system for AIH (do not use AIH scoring system to diagnose AIH-PBC

- For PBC
  - ALP >2× ULN, AMA positive, liver biopsy with florid duct lesion
  - GGT >5× ULN, IgG >18, plus liver biopsy with findings of AIH
- For AIH
  - Liver biopsy, interface hepatitis
  - ALT >5x ULN, plus
  - IgG ≥ 2x ULN, or SMA positive
- Treat for AIH plus
  - Often poor responders to UDCA
  - Treat dominant disease (ALT vs ALP predominance)
  - Treat second if poor response

Primary Biliary Cholangitis (PBC)



- The florid duct lesion is used to describe the textbook finding of PBC.
  - In the portal triad, inflammatory cells will surround the bile duct and duct-infiltrating lymphocytes may be present (there are several present in this irregularly shaped bile duct).
  - In this specimen, there is also a periportal rim of cellular debris-granulomatous tissue.
  - Remember, PBC is in the differential diagnosis of hepatic granulomas.

Courtesy of: Thomson ABR, Walsh JC. Images in Gastroenterology and Hepatology. Part 2; 2021. ISBN: 979-8743669325

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- In patients with no bile duct changes or loss on appropriate diagnostic testing, yet a possible serology for pyruvate dehydrogenase E2 (AMA)
  - The laboratory test is dales positive
  - The condition does not progress to PBC

- **AIH–PSC** (Primary Sclerosing Cholangitis)
  - Diagnosis
    - AIH, as per used
    - AMA negative
    - **No** diagnostic criteria, thus varied prevalence
      - Diagnostic/endoscopic imaging positive for large/small duct changes
      - When AIH criteria fulfilled including PSC features on cholangiogram (extra/intrahepatic or both), or
      - Onion-skin fibrosis / biliary findings on liver fibrosis biopsy
  - Imaging alone has ↓ specificity, but ↑ specificity if ALP elevated.
  - Suspect AIH-PSC, associated
    - AIH plus chronic idiopathic UC, or
    - Biliary involvement on biopsy
    - ↑ ALP / ↑ GGT which is unexplained
    - Poor response to corticosteroids
    - Abnormal cholangiogram
  - Guidance statements
    - Suspect AIH-PSC overlap syndrome
      - AIH plus
        - ↑ ALP / GGT
        - AMA positive
    - Suspect AIH overlap syndrome
      - AIH plus ↑ ALT/GGT
      - Onion skin histopathology on liver biopsy
    - Use the Paris criteria to diagnose AIH-PBC syndrome

- **AIH, Drug-induced**
  - Drug induced liver injury (DILI) may appear like AIH (drug cases of AIH-like condition seen in 2% to 17% persons with “classical” AIH
  - Numerous drugs implicated
    - Commonest
      - Infliximab
      - Minocycline
      - Nitrofurantoin

    } Latency interval > 12 mon

- Consult US Drug-Induced Liver Injury Network (US-DILIN)
  - LiverTox website, http://livertox.nlm.nih.gov/aboutus.html
- Clinical
  - Similar to AIH
    - Women > men
    - Acute onset in >60% vs, 20% for AIH
    - Responds to corticosteroids (plus stopping the offending drug)
  - Distinction from AIH
    - Hypersensitivity
    - Associated with pattern of drug intake
    - No cirrhosis at presentation, a progression to cirrhosis
    - Negative association to HLA
      - DRB1*03.01
      - DRB1*04.01
    - No/low association with autoimmune conditions (vs. 14% to 44%)
    - Mortality rate, 5%; need for LT, ~5%
    - No relapse after withdrawal of offending drug
- Histopathology
  - Similar
    - Hepatitis
      - Interface
      - Lobular
    - ↑ infiltration of
      - Lymphocytes
      - Plasma cells
      - Eosinophils
    - Necrosis
      - Centrilobular, zone 3
  - Differentiating rarely severe bridging fibrosis / cirrhosis
- Scoring systems (risk of death or liver transplantation [LT])
  - Hy's law
    - ↑ ALT/AST >3x ULN
    - ↑ bilirubin > 2x ULN

    } Risk of death / need for LT, 9% to 12%
  - Enhanced Hy's law (diagnosis of drug-induced acute AIH)
    - ALT > 17.3x ULN
    - Bilirubin > 6.6x ULN
    - AST/ALT > 1.5

    } Liver failure (ALF)
    Sensitivity (ALF), 80%
    Specificity, 82%
  - If these criteria met, begin treatment with drug-withdrawal, plus corticosteroids
- Guidance Statement
  - Exclude possibility of drug-induced AIH when patient present with AIH
  - Stop offending drug, follow anticipated ↓ transaminases / ALP
  - If Hy's law satisfied, stop suspected offending drug plus begin corticosteroids
  - If drug-induced AIH suspected, and there is improvement with withdrawal of the suspected offending drug, and then the AIH remains, suspected the correct diagnosis was AIH and not drug-induced and start corticosteroid therapy.

- Liver Transplantation
  - ~10–20% of patients with AIH will require liver transplantation
    - For all persons requiring LT, AIH is the indication for < 5%
  - Survival, 5 yr
    - Graft, 74%
    - Patient, 80% to 90%
  - Patients typically referred with
    - Acute liver failure
    - Decompensated cirrhosis
    - Hepatocellular carcinoma (HCC).
  - Recurrence rate of AIH post-transplant: 20–30%.

Gleeson D et al. Gut 2011; 60:1611–29

  - ↑ risk of
    - Graft rejection, acute, 81%
    - Steroid resistance, 38&
    - Chronic, 9%
  - Mortality post LT
    - Most commonly due to early (days 30 to 180 post-LT) infection
  - Continuation of steroids after LT
    - Pro
      - ↓ rejection of AIH
      - ↑ recurrence of AIH
    - Anti
      - ↑ risk of infection
      - Steroid-associated adverse effects

  - Guideline Recommendation
    - Consider a slow taper and stopping of corticosteroids after LT (conditional recommendation, very low quality of evidence)

- Recurrence of AIH in transplanted liver
  - AIH, 5 yr after LT
    - 1, ~10%
    - 5, 36% to 68%

    } Similar rates independent of type of donor (living related/unrelated or dead donors

  - Differential
    - Alloimmune rejection, graft

- Histopathology changes used to differentiate recurrent AIH from rejection

	Recurrent AIH	Rejection
Lobule	– Hepatitis – Necrosis ▪ Focal” ▪ Confluent ▪ Bridging	– Blood works ▪ Endotheliosis – Bile ducts ▪ Damage
Interface	– Hepatitis – Lymphoplasmacytic infiltrate	

- Recurrent AIH after withdrawal of initial therapy
  - Patient
    - 5yr survival 86% to 100%
    - Recurrent AIH in retransplant liver, 33% to 100%
    - Required retransplantation, 33% to 60%
  - Graft
    - Failure, 8% to 50%

➢ De Novo AIH in liver transplant patients for non-AIH conditions

- Frequency, 1% to 3% of all LT
  - Median ~4 to 10%
- Common conditions treated by LT and develop de novo AIH
  - HCV infection, chronic
  - Primary biliary cholangitis
- Remaining
  - De novo AIH in patients with LT for chronic HCV treated with interferon
  - Definition
    - Graft dysfunction occurring >6 mon after [liver] transplantation in association with
      - Severe cholangitis, lymphocytic
      - Deposits of complement components 4d in portal vasculature
- Guidance statement
  - In patients with LT for
    - AIH who develop ↑ ALT/ ↑ AST, IgG antibodies
      - Suspect recurrent AIH
    - Non-AIH indicators, ↑ALT / ↑AST
      - Suspect de novo AIH, as well as other causes of allograft dysfunction
    - Perform liver biopsy to differentiate immune-mediated disease vs. other causes of allograft dysfunction
- Treatment of recurrent AIH
  - de novo AIH
  - Prednisone, azathioprine (for AIH) plus calcineurin inhibitor

Abbreviations: AALD, alcohol-associated liver disease; ACE, angiotensin-converting enzyme; AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; APS-1, autoimmune polyendocrine syndrome type I; ASGPR, asialoglycoprotein receptor; AST, aspartate aminotransferase; AZA, azathioprine; BMI, body mass index; Bregs, B regulatory cells; CD, cluster of differentiation; CD95, Fas/apoptosis antigen-1; CLD, chronic liver disease; CTLs, cytotoxic T lymphocytes; CTLA-4, cytotoxic T-lymphocyte antigen 4; CYP, cytochrome P450; DIW, drug-induced hepatitis; DILI, drug-induced liver injury; FTCD, formiminotransferase cyclodeaminase; γδ T cells, gamma delta T cells; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HE, hepatic encephalopathy; HLA, human leukocyte antigen; HCC, hepatocellular carcinoma; IgG, immunoglobulin G; IMS, immunosuppression; INR, international normalized ratio; ITP, immune thrombocytopenic purpura; LC1, liver cytosol type 1 antibody; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MMF, mycophenolate mofetil; MSK, musculoskeletal; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NK cells, natural killer cells; pANCA, perinuclear antineutrophil cytoplasmic antibody; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; RCT, randomized controlled trial; SLA, soluble liver antigen; SMA, smooth muscle antibody; Tregs, regulatory T cells; TNF-α, tumour necrosis factor alpha; TPMT, thiopurine methyltransferase; UGT1A, UDP glucuronosyltransferase family 1 member A; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography; VTE, venothrombotic embolization.

REPRODUCTIVE HEALTH AND LIVER DISEASE: PRACTICE GUIDANCE BY THE AASLD

Abdulaziz Alsihle

Sarkar M, et al. Hepatology 2021;73(1):318-365. doi:10.1002/hep.3155

Evidence Framework and Methodology

- Provides a data-supported, expert-informed approach
- Differs from formal AASLD Guidelines
- Developed by expert consensus due to limited randomized controlled trial data
- Based on formal literature review and analysis

Outlines

- Sexual Function Across Age in Patients with Chronic Liver Disease.
- Pregnancy Planning and Contraception in Adolescents and Adults with Liver Disease.
- Assisted Reproduction and Liver Disease.
- Menopause, Andropause, and Hormone Therapy in Liver Disease.
- Evaluation During Pregnancy.
- Pregnancy in Patients with Cirrhosis
- Management of Chronic Liver Diseases During Pregnancy.
- Liver Conditions Requiring Special Management During Pregnancy.
- Pregnancy-Specific Liver Diseases
- Management in Transplant Recipients

Guidance Statements: Sexual Function

- Sexual dysfunction is common in chronic liver disease and clinicians should routinely inquire about symptoms.
  - When identified, referral to a specialist may be needed for evaluation and treatment.

➢ **Sexual Function with Chronic Liver Disease**

- **In Women**
  - Chronic liver disease affects sexual and reproductive function across the lifespan
  - Severity increases with advanced and decompensated disease
  - Driven by hormonal imbalance and hypothalamic–pituitary axis dysfunction
    - Altered estrogen metabolism + HPA axis disruption
    - ↓ FSH/LH → anovulation, amenorrhea, infertility
  - Amenorrhea/oligomenorrhea:
    - 25% with advanced liver disease
    - ~75% awaiting liver transplant

- Alcohol excess worsens HPA or ovarian dysfunction
- Pregnancy can occur, even in decompensated cirrhosis

- **In Men**
  - Mechanisms: Low testosterone results from
    - Hypogonadotropic hypogonadism
    - ↑ Androgen to estrogen conversion.
    - ↓ Free testosterone due to ↑ SHBG
      - SHBG: Produced in the liver, estrogen-stimulated, rises early, falls in decompensation
    - ↑ Estrogen also from portosystemic shunting and increased circulating levels suppress the hypothalamic-pituitary axis
  - Clinical effects: ED, oligospermia, testicular atrophy, Gynecomastia.
  - Post Transplant:
    - Sex hormones often normalize post-LT → improved libido, but 20–50% may still have erectile dysfunction.
    - CNIs may reduce sperm counts/motility in animal models; sirolimus can impair spermatogenesis.
    - MPA (mycophenolate) requires contraception for 90 days post-discontinuation.

➢ Presentation and Causes

- Manifestations
  - Erectile dysfunction
  - Dyspareunia
  - Decreased libido due to chronic illness and hormonal abnormalities
- Differential diagnosis includes
  - Alcohol use
  - Autonomic dysfunction (e.g., diabetes)
  - Hypogonadism (including hemochromatosis)
  - Psychogenic causes
  - Medications (e.g., spironolactone, beta-blockers)

➢ Evaluation and Management Approach

- Open, directed questioning in clinic is essential
- History should assess:
  - Menstrual patterns
  - Psychosocial health
  - Sexual symptoms

- Evaluation may include:
  - Sex hormone levels
  - Thyroid function tests
- Patients should generally be referred to appropriate specialists for further evaluation and management

- **Pregnancy Planning and Contraception in Adolescents and Adults with Liver Disease.**
  - Guidance Statements: Pregnancy Planning and Contraception
    - Clinicians should routinely inquire about sexual activity and pregnancy intentions in all reproductive-aged adolescents and women with chronic liver disease or liver transplant.
    - Adolescents have an increased risk of unplanned pregnancy. Long-acting reversible contraceptives have advantages in this population.
    - Pregnant adolescents with chronic liver disease require increased psychosocial support, necessitating close collaborations between pediatric and adult hepatologists, patient support (e.g., social workers), and maternal-fetal medicine specialists.
    - Estrogen-containing agents should be avoided in patients with decompensated cirrhosis, BCS, hepatocellular adenomas, and transplant recipients with graft failure.
    - Patients using agents other than long-acting reversible contraceptives are encouraged to combine these with a barrier method given their higher failure rate; this is particularly important for women taking teratogenic medications, such as mycophenolic acid (MPA) products.
    - All forms of emergency contraception may be used in the setting of chronic liver disease.

- **Pregnancy Risks in Women with Liver Disease**
  - Women with chronic liver disease or prior transplant face unique pregnancy risks:
    - Worsening of underlying liver disease during pregnancy/postpartum
    - Increased obstetric and perinatal complications
    - Exposure to liver-related medications that may be unsafe in pregnancy/breastfeeding
  - Reproductive health counseling is critical:
    - Ensure safe and effective contraception if pregnancy is not desired
    - Plan pregnancy to minimize maternal and fetal risks

- **Pregnancy Planning in Liver Disease**
  - Clinicians should routinely ask about
    - Contraception use
    - Family planning
    - Pregnancy intentions
    - Sexual activity
  - Planning allows
    - Ensure liver disease stability
    - Inform patients of disease-specific risks to guide pregnancy decisions
    - Preconception liver evaluation
    - Switch from teratogenic meds to pregnancy-compatible regimens

- **Adolescent-Specific Considerations**
  - Adolescents may struggle with self-management and understanding liver disease
  - Scaffolding support from family, friends, or health services helps gradually build autonomy
  - 75% of adolescent pregnancies are unplanned → LARC preferred (Long-acting reversible contraception)
  - Collaboration among pediatric/adult hepatology and MFM specialists is essential
  - Adult providers must recognize adolescents' psychosocial needs in chronic liver disease

- **Contraception in Chronic Liver Disease: Principles**
  - Shared decision-making is essential to maximize adherence and satisfaction
  - A common reference for contraception safety: CDC U.S. Medical Eligibility Criteria (MEC) for women with medical conditions
  - AASLD provides specific guidance for:
    - Cirrhosis (compensated/decompensated)
    - Hepatocellular adenomas (HCAs)
    - Solid-organ transplant
  - Combined Hormonal Contraception (CHC), Projecting only, IUD and emergency contraception

- **Combined Hormonal Contraception** (CHC)
  - CHCs contain estrogen + progestin; typical failure rate ~9%
  - General risks: venous thromboembolism (VTE), hypertension, rarely a stroke.
  - Liver risk: Rare cholestatic liver injury has been reported, particularly with higher-dose estrogens. data in CLD are limited,

- Not recommended in:
  - Budd-Chiari syndrome (BCS)
  - Decompensated cirrhosis (impaired estrogen metabolism)
  - Graft failure post-liver transplant
  - Hepatocellular adenomas (estrogen promotes growth)
  - Multiple cardiovascular risk factors (esp. MASLD)
- Acceptable in:
  - Compensated cirrhosis
  - Other chronic liver diseases
  - Stable liver transplant recipients (data are limited)
- Drug interactions: CHCs affect CYP450 metabolism; review medications
- Always assess metabolic profile and cardiovascular risk before prescribing

- **Progestin-Only Contraceptive Options**
  - No estrogen-related risks → safe in cirrhosis, HCAs, transplant
  - Options & Failure Rates:
    - Progestin-only pills: ~9% failure, strict daily timing required
    - DMPA injections: ~6% failure, every 12 weeks, delayed return to fertility up to 18 months
      - Black box: bone density decrease, reversible after stopping
    - Subcutaneous implant: long-acting reversible contraception (LARC), failure 0.05%, minimal/no bone loss, lasts up to 3 years
  - Hepatocellular Adenoma growth: No prospective data on progestin-only agents

- **Intrauterine Devices** (IUDs)
  - Long-acting method; failure rate <1%
  - Copper IUD: hormone-free, effective ≥10 years, may increase menstrual bleeding
  - Levonorgestrel IUD: progestin-only, effective 3–5 years, lightens or stops bleeding
  - Adolescents: highly effective, adherence-independent
  - Liver considerations: no expected risk in decompensated cirrhosis or HCAs (no estrogen)
  - Transplant recipients: safe, including in graft failure; early concerns about infections or reduced efficacy not supported

- **Perioperative & Emergency Contraception**
  - Perioperative use:
    - Estrogen-containing contraception does **not** need to be stopped unless prolonged immobility
    - Other agents continued regardless of mobility
    - Contraceptive risk in the perioperative setting is **not** well studied.
  - Emergency contraception (first 5 days post-intercourse):
    - Copper IUD: highest efficacy (<1% failure)
    - Hormonal pills:
      - Progestin-only: avoid if BMI >30
      - Estrogen-containing: limited data, short-term use likely safe, but avoid in HCAs, BCS, decompensated cirrhosis, graft failure

- **Contraceptive Options for Women with Liver Disease**

Method	Benefits	Drawbacks	Suitability in Liver Conditions*
○ Copper IUD	Very effective (<1% failure), long duration (≈10 yrs), hormone-free, no estrogen risks, no daily adherence	May worsen cramps or bleeding; less ideal if anemia or low platelets	Cirrhosis: Compensated = Safe; Decompensated = Generally safe. BCS/HCC/Graft failure: Acceptable. Post-transplant: Acceptable
○ Hormonal IUD (progestin)	Very effective (<1% failure), long duration (≈5 yrs), lighter periods, no estrogen risks, no daily adherence	Irregular bleeding common	Cirrhosis: Compensated = Safe; Decompensated = Generally safe. BCS/HCC/Graft failure: Acceptable. Post-transplant: Acceptable
○ Combined hormonal (pill/patch/ring)	Predictable cycles, lighter bleeding, acne benefits	Higher failure (~9%), requires strict adherence, contraindicated in severe liver disease (decompensated cirrhosis, tumours, graft failure)	Cirrhosis: Compensated = Acceptable; Decompensated = Contraindicated. BCS/HCC/Graft failure: Contraindicated. Post-transplant: Acceptable

Method	Benefits	Drawbacks	Suitability in Liver Conditions*
○ Progesterone-only pill	No estrogen risks	Higher failure (~9%), strict timing needed, irregular bleeding, possible bone density loss, metabolism may be impaired in liver disease	Cirrhosis: Compensated = Acceptable; Decompensated = Generally safe. BCS/HCC/Graft failure: Acceptable. Post-transplant: Acceptable
○ DMPA injection	No estrogen risks, given every 3 months	Failure ~6%, requires clinic visits, irregular bleeding, possible bone density loss, metabolism may be impaired in liver disease	Cirrhosis: Compensated = Acceptable but less favored; Decompensated = Generally safe but less favored. BCS/HCC/Graft failure: Acceptable but less favored. Post-transplant: Acceptable
○ Subcutaneous implant	Very effective (<1% failure), long duration (≈3 yrs), no estrogen risks, no daily adherence	Irregular bleeding common	Cirrhosis: Compensated = Acceptable; Decompensated = Generally safe. BCS/HCC/Graft failure: Acceptable. Post-transplant: Acceptable

*Categories simplified:
- Safe/Acceptable = generally recommended
- Contraindicated = not recommended due to health risks
- Less favored = usable but with caution

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365.

- **Assisted Reproduction and Liver Disease.**
  - Guidance Statements
    - There is **no** absolute contraindication to assisted reproduction in women with cirrhosis or prior transplant. Preconception counseling for risk stratification is recommended.
    - For patients with cirrhosis, the degree of hepatic decompensation is important when considering assisted reproduction, with caution used in Child-Pugh B or C.
    - For liver transplant recipients, stability of graft function should be assessed when considering assisted reproduction.
    - Infertility defined as
      - <35 yr: no pregnancy after 12 months of unprotected sex
      - ≥35 yr: no pregnancy after 6 months
    - Compensated cirrhosis → fertility similar to general population
    - History of decompensation → fertility reduced by ~40%
    - Hypothalamic–pituitary dysfunction → poor response to gonadotropin therapy or Clomiphene.
    - Data are limited: assisted reproduction is understudied in women with chronic liver disease
    - **No** Data on hepatic decompensation risk
    - Post-liver transplant (LT) pregnancies after assisted reproduction have been reported
    - Retrospective Review
      - 18 women with liver disease
      - 7 post-LT, 6 autoimmune hepatitis, 2 PBC, 1 hepatitis B, 1 PCS, 1 noncirrhotic PHTN
      - 7 had cirrhosis
      - 16 underwent IVF → 3 (18%) failed after 3 cycles
    - Adverse events
      - 1 post-LT: severe graft worsening with hormonal treatment → improved with steroids
    - Pregnancy outcomes
      - Live birth: 50% in cirrhosis, 67% in non-cirrhotic liver disease

- **Menopause, Andropause, and Hormone Therapy**
  - Guidance Statements:
    - Menopausal hormone therapy should not be used in women with decompensated liver function, or hepatocellular adenomas
    - Testosterone replacement may be used in hypogonadal men with chronic liver disease

- **Menopause & Hormone Therapy in Liver Disease**
  - Estrogen benefits
    - Inhibits hepatic stellate cell activity >> decrease fibrogenesis, supports metabolism, prevents bone loss/fractures
  - Liver disease risks
    - Advanced disease → poor bone health, sarcopenia, malnutrition, immobility
  - Hormone therapy
    - Effective for menopausal symptoms and bone health
    - Caution: cholestatic effects in cholestatic liver disease
    - Safe in PBC (topical, oral, parenteral)
    - Avoid in hepatic adenoma (promotes growth), decompensated liver function
    - Other risks: VTE, stroke, breast cancer; individualized risk-benefit decisions needed

- **Andropause & Testosterone Therapy**
  - Andropause: age- or liver-related decline in testosterone → sexual dysfunction, fatigue, mood changes, bone loss.
  - In advanced liver disease: low testosterone → sarcopenia (predictor of mortality)
  - Testosterone therapy benefits: improves muscle/bone mass, may lower mortality
    - Risks: myocardial infarction, stroke, transient liver enzyme elevation
    - Clinical decision: tailor to symptoms and testosterone levels
  - Sinclair M et al. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone. Journal of Hepatology.
    - Design: 12-month, double-blind, placebo-controlled RCT
    - Population: 101 men with cirrhosis + low testosterone
    - Intervention: IM testosterone undecanoate vs placebo
    - Primary outcome: ↑ total lean mass +4.74 kg
    - Key secondary outcomes:
      - ↓ fat mass −4.34 kg
      - ↑ bone mass and femoral neck bone mineral density (BMD) by DEXA scan
      - ↑ hemoglobin, ↓ HbA1c
    - Safety: No increase in adverse events
    - Mortality: Lower with testosterone (16% vs 25.5%), not statistically significant

- **Evaluation During Pregnancy**
  - Guidance Statements:
    - Elevation in aminotransferases, bilirubin, or bile acids in pregnancy is abnormal and requires investigation.
    - Abdominal US without contrast is the preferred imaging modality throughout pregnancy. Limited Doppler study of hepatic vasculature can be used, but exposure time should be minimized.
    - MRI/MRCP without gadolinium is preferred over CT imaging. Gadolinium is contraindicated in pregnancy.
    - Abdominal CT without contrast is generally safe, but the cumulative ionizing radiation exposure should be as low as possible and less than 50 mGy.
    - There are insufficient data to recommend use of elastography during pregnancy.
    - Breastfeeding is safe after iodinated or gadolinium contrast.

- **Normal Physiologic & Biochemical Changes in Pregnancy**
  - ↑ Plasma volume, heart rate, cardiac output (up to 50% by 3rd trimester)
  - ↓ Systemic and splanchnic vascular resistance
  - Absolute hepatic blood flow unchanged, but ↓ % of cardiac output to liver
  - Hyperdynamic state resembles decompensated cirrhosis
  - ↓ Hepatic drug clearance
  - ↓ Gallbladder motility → ↑ gallstone risk
  - Esophageal varices may appear late in pregnancy (IVC compression)
  - Spider angiomas & palmar erythema (hyperestrogenic state)
  - Liver usually non-palpable; displaced upward by gravid uterus
  - Exacerbated by pregnancy: gallstones, vascular liver disease, cirrhosis

- **Pregnancy-related Hemodynamic Changes and Portal Hypertension**
  - Pregnancy-related physiologic changes:
    - ↑ blood volume
    - ↑ splanchnic vasodilation
    - ↑ collateral circulation
    - ↑ portal flow and intrahepatic resistance
    - ↓ systemic vascular resistance and blood pressure
  - Leads to worsening portal hypertension:
    - Enlarged varices → higher risk of bleeding
    - Ascites
    - Hepatic encephalopathy

- **Liver Biochemistry Changes During Normal Pregnancy**

Marker	First Trimester	Second Trimester	Third Trimester
ALT / AST	Generally unchanged	Generally unchanged	Generally unchanged
Gamma-glutamyl transferase	Within normal range	Within normal range	Within normal range
Bilirubin	Typically normal	Typically normal	Typically normal
Bile acids	Normal	May rise	Often elevated
Alkaline phosphatase	Normal	Increased	Increased
Albumin	Normal or slightly lower	Normal or slightly lower	Normal or slightly lower
Alpha-fetoprotein (AFP)	Normal or mildly higher	Elevated	Elevated

  - Notes
    - “Normal” = values remain within expected reference ranges.
    - “Elevated” = physiologic rise due to pregnancy changes, not necessarily pathologic.
    - Albumin tends to decline slightly across trimesters due to hemodilution.
    - Alkaline phosphatase increases later in pregnancy because of placental production.

↑ Clotting factors II, V, VII, X, XII, fibrinogen → hypercoagulable state

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365. (Table 2)

- **Abdominal Imaging in Pregnancy**
  - Ultrasound (US) is first-line: no ionizing radiation, no known fetal risk.
    - Doppler US is safe in all trimesters; minimize exposure time.
    - US contrast agents are generally avoided (animal data suggest potential risk).
  - If additional imaging is required:
    - MRI without gadolinium is preferred in all trimesters.
    - Gadolinium-enhanced MRI should be avoided: gadolinium crosses the placenta and increases fetal exposure.
    - CT can be used if necessary, but MRI is favored.
    - MRCP without contrast is useful for suspected choledocholithiasis not seen on US.

- Fetal Radiation Considerations
  - Risk depends on dose and gestational age, <50 mGy
  - before implantation: possible “all-or-none” effect.
  - Weeks 2–8: highest teratogenic risk.
  - Weeks 8–25: risk of neurocognitive effects (lower after week 15).
  - After week 25: minimal risk.
  - Accepted cumulative fetal exposure: <50 mGy.

- **Radiation Exposure from Common Imaging Procedures**

Procedure / Modality	Approximate Fetal Dose (mGy)	Approximate Maternal Dose (mSv)
Abdominal X-ray	~0.1–0.3	~0.01–1.1
Barium enema (double contrast)	~1–20	~2–18
Chest X-ray (two views)	~0.0005–0.01	~0.06–0.29
CT scan of abdomen/pelvis	~13–25	~3–45
ERCP (fluoroscopy-guided)	~0.1–0.3*	~2–6*
Small-bowel series	~7	~3–7.8

*Values for ERCP vary depending on fluoroscopy time and technique.

- Notes
  - Doses are approximate ranges, not absolute values.
  - Fetal dose is expressed in mGy (absorbed dose).
  - Maternal dose is expressed in mSv (effective dose).
  - Clinical context and necessity should always guide imaging decisions in pregnancy.

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365. (Table 3)

- **Approach to Abnormal Liver Tests in Pregnancy**
  - Cholestatic Pattern
    - Initial step: Ultrasound (without Doppler)
    - If negative, consider:
      - Drug-induced injury
      - Primary biliary cholangitis (PBC)
      - Primary sclerosing cholangitis (PSC)
    - Additional tests:
      - Anti-mitochondrial antibodies, PBC-specific ANA
      - MRCP (non-contrast) if suspicion for biliary disease is high

- Pregnancy-specific Conditions (based on gestational age)
  - Acute fatty liver of pregnancy
  - Hyperemesis gravidarum
  - Hypertensive disorders of pregnancy:
    - HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets)
    - Preeclampsia / Eclampsia
  - Intrahepatic cholestasis of pregnancy (ICP)
  - Suggested labs: bile acids, coagulation profile, reticulocyte count, haptoglobin, uric acid, platelet count, urine protein
- Hepatocellular Pattern
  - Possible causes:
    - Autoimmune hepatitis
    - Celiac disease
    - Drug-induced liver injury
    - Steatohepatitis (NAFLD/ALD)
    - Vascular disease (consider Doppler)
    - Viral hepatitis (HAV, HBV, HCV, HDV, HEV, HSV, CMV, EBV)
    - Wilson disease
  - Additional tests:
    - Autoimmune markers (ANA, SMA, IgG)
    - Celiac antibody testing
    - Ceruloplasmin, 24-hour urine copper, slit lamp exam
    - Viral serologies and DNA/antibody panels

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365. (Figure 3)

- **Pregnancy in Patients with Cirrhosis**
  - Frequency & Prognosis: (In a population-based study of 2,106 women with cirrhosis)
    - Rare: ~1 per 3,000–6,000 pregnancies.
    - Maternal mortality historically 20%; recent data <2%, 6% in decompensated cases
    - Cirrhosis and portal hypertension not absolute contraindications, given improved mortality.
    - Preconception MELD ≥10 → high risk of hepatic decompensation (83% sensitivity & specificity).
    - Prior decompensation → ↑ risk of liver-related complications during and up to 1 year postpartum (13% vs 1.2% in compensated cirrhosis).
  - Maternal Outcomes
    - Hepatic decompensation in 15%: ascites (11%), variceal hemorrhage (5%).
    - ↑ risk: preeclampsia, gestational hypertension, cesarean delivery, placental abruption, uterovaginal hemorrhage.

- Fetal Outcomes
  - ↑ risk: preterm delivery, growth restriction, low birth weight, neonatal death (up to 12% in decompensated cases).
  - Other outcomes (small for gestational age, congenital malformations, stillbirth) similar to general population.
- Counseling
  - Women with cirrhosis, especially with prior decompensation or MELD ≥10, should be counseled on the risk of worsening liver disease and fetal/maternal complications.

- **Portal Hypertension (PHT) in Pregnancy and Delivery**
  - Guidance Statements:
    - Endoscopic procedures require preoperative consultation with specialists for maternal sedation and fetal monitoring.
    - Pre-pregnancy variceal screening recommended; if not done, screen early in second trimester or if ongoing liver injury/decompensation occurs.
    - Sedation: meperidine, midazolam, propofol, fentanyl acceptable; minimize duration.
    - Small GEV: consider NSBBs for primary prophylaxis.
    - Medium/large GEV: band ligation or NSBBs recommended; propranolol preferred.
    - Acute variceal hemorrhage: octreotide/somatostatin, PPI, cephalosporins, endoscopy; avoid terlipressin.
    - Mode of delivery should follow obstetric indications only.

➢ Management: Prophylactic Approach

- Risk of Variceal Bleeding
  - Most serious complication in cirrhosis/PHT during pregnancy.
  - Incidence has decreased from 18–33% → 5–8.5%. Likely due to effective prophylaxis before and during pregnancy.
  - Risk highest second trimester (↑ intravascular volume) and during delivery (uterine compression, Valsalva).
- Screening Recommendations:
  - All women with cirrhosis: EGD within 12 months preconception.
  - Non-cirrhotic PHT → similar screening.
  - Non-invasive markers (liver stiffness <20 kPa, platelets >150 ×10^9/L) identify low-risk patients, but small varices may be missed (~30%).
  - EGD is the preferred preconception test; if not done, perform early second trimester.
  - Repeat EGD only if ongoing liver injury or new decompensation.

- Primary Prophylaxis
  - NSBBs: for medium/large varices; may be considered for small varices.
  - Endoscopic variceal ligation (EVL): preferred for high-risk stigmata (red wale, cherry red spots).
  - Choice guided by variceal size, liver disease severity, comorbidities, and patient preference.
- Safety of EGD in Pregnancy
  - ~95% of patients undergoing EGD deliver healthy infants.
  - Procedures ideally deferred to second trimester.
  - Sedation options: midazolam, meperidine, fentanyl, propofol.
  - Minimize fetal exposure to anesthetics; prolonged/frequent exposure in 3rd trimester may impact neurodevelopment.
  - Use lowest possible dose of sedation and be quick!
  - Pre-op evaluation by maternal-fetal medicine (MFM) specialist recommended.

Variceal Screening in Pregnancy

- Women with cirrhosis should undergo variceal screening within 12 months before conception.
  - If no varices are found, no treatment is indicated.
  - Small varices (≤5 mm) warrant consideration of NSBB therapy
  - Medium or large varices (>5 mm) require NSBB or EVL until obliteration, with EVL preferred if high-risk bleeding stigmata are present.
- If screening was not performed prior to conception, esophagogastroduodenoscopy (EGD) is recommended early in the second trimester.
- Management follows the same principles: NSBB for small varices, NSBB or EVL for medium/large varices, with EVL preferred in the presence of high-risk features.

Screening Status	Findings	Recommended Action
○ Screening within 1 year prior to conception	No varices	No treatment indicated
○ Screening within 1 year prior to conception	Small varices (≤5 mm)	Consider non-selective beta-blocker (NSBB)
○ Screening within 1 year prior to conception	Medium/large varices (>5 mm)	NSBB or endoscopic variceal ligation (EVL) until obliteration*
○ No screening prior to conception	Perform EGD in 2nd trimester	If small varices → consider NSBB; if medium/large varices → NSBB or EVL*

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365.

- **Variceal Bleeding in Pregnancy**

➢ Management

- Secondary Prophylaxis
  - Non-specific Beta Blockers (NSBBs)
    - Propranolol preferred >> established safety profile, extensive clinical experience, and predictable pharmacology
    - Nadolol: very long half-life → accumulation and prolonged fetal exposure
    - Carvedilol: additional α1-blockade → higher risk of maternal hypotension and reduced uteroplacental perfusion; limited pregnancy data
  - Esophageal variceal ligation (EVL): for medium/large varices; continue until obliteration.
- Active Bleeding
  - Immediate maternal resuscitation and emergent endoscopy.
  - Octreotide or somatostatin initiated; avoid terlipressin (uterine contractions, reduced blood flow).
  - Antibiotic prophylaxis: cephalosporins preferred.
- Recurrent or Gastric Variceal Bleeding: Data is limited
  - Cyanoacrylate ± coiling depending on expertise.
  - TIPS: rescue therapy for uncontrolled bleeding or pre-cesarean decompression.

- **Portal Hypertension at Delivery and Postpartum**

➢ Management

- Delivery Considerations
  - Mode of delivery guided by obstetric indications.
  - Vaginal delivery ↑ intra-abdominal pressure → ↑ portal pressure → risk of variceal rupture.
  - Assisted vaginal delivery can reduce straining/second-stage duration >> to reduce the risk
  - Cesarean delivery: ↑ risk of bleeding from abdominal wall varices & postpartum ascites.
    - Platelets >50,000/mL → recommended for cesarean.
- Postpartum Risks
  - ↑ postpartum hemorrhage due to thrombocytopenia or higher cesarean rate
  - Prevention: active management of third stage of labor.

- **HBV Infection**
  - Guidance Statements:
    - All pregnant women should be tested for HBsAg.
    - HBsAg-positive pregnant women
      - Should be informed of the increased risk of mother-to-child transmission (MTCT) with invasive pregnancy procedures, such as amniocentesis.
      - Require quantification of HBV DNA in the second trimester, and if maternal HBV DNA is greater than 200,000 IU/mL, antiviral therapy should be started between gestational weeks 28 and 32, to reduce the risk of MTCT. Antiviral therapy can be stopped at delivery or up to 3 months postpartum.
      - If antiviral therapy is required, TDF is preferred. There are insufficient safety data to recommend entecavir or tenofovir AF.
      - Monitoring of ALT and HBV DNA for 6 months postpartum or after cessation of antivirals is recommended.
      - Breastfeeding is **not** contraindicated, even in women who continue on antiviral therapy.

➢ Management

- Hepatitis B in Pregnancy & Lactation
  - Care should be co-managed by hepatology, MFM, and pediatrics
  - Universal screening: HBsAg with prenatal labs
  - If HBsAg positive → check HBV DNA
  - Vaccination is safe in pregnancy for non-immune women
  - Antiviral therapy in pregnancy
    - TDF preferred: extensive safety data, no teratogenicity
    - Lamivudine / telbivudine: safe but higher resistance
    - Entecavir & TAF: insufficient pregnancy data → not recommended
    - Peg-interferon: option before conception only.
  - If pregnancy occurs on antivirals
    - Decide to continue vs stop based on flare risk. Stopping therapy requires close monitoring for hepatitis flares
    - If continuing and not on TDF → switch to TDF
    - Women with advanced fibrosis should not stop therapy, given concerns for decompensation with a clinically significant flare.
  - Brown RS Jr, et al. Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: findings from the Antiretroviral Pregnancy Registry. Journal of Hepatology 2012.
    - Large prospective data from the Antiretroviral Pregnancy Registry (1989–2011)

- Overall major birth-defect rate with antiviral exposure: 2.8%, comparable to population controls
- No increased risk of major congenital malformations with lamivudine (LAM) or tenofovir disoproxil fumarate (TDF)
- Similar risk with first-trimester vs later exposure
- No specific pattern of defects identified
- Supports fetal safety of LAM and TDF when used during pregnancy for chronic HBV

- **Prevention of Mother-to-Child Transmission** (MTCT) **of HBV**
  - MTCT prevention is critical despite neonatal HBV vaccine + HBIG, as failure occurs in up to 15%
  - Timely neonatal immunoprophylaxis is essential
    - HBV vaccine + HBIG within 12 hours of birth
  - Maternal HBV viral load at delivery is the strongest risk factor
    - MTCT is rare if HBV DNA <200,000 IU/mL
    - Third-trimester antiviral therapy reduces MTCT from ~18% → 5%
      TDF preferred
    - Start at 28–32 weeks' gestation
    - Reduces MTCT Earlier antiviral initiation should be considered if HBV DNA ≥ 7 log IU/mL, to reach target viral load by delivery
    - Antivirals can be stopped at delivery or 1–3 months postpartum (No clear difference in ALT flare risk)
  - Cesarean delivery does NOT reduce MTCT
  - Prolonged labor or rupture of membranes
    - Theoretical risk, but mitigated by proper neonatal prophylaxis
  - Amniocentesis
    - May increase MTCT risk in highly viremic mothers
    - Risk should be discussed; consider earlier antivirals if invasive procedures anticipated

- **Hepatitis C in Pregnancy**
  - Guidance Statements:
    - Pregnant women should be tested for HCV during each pregnancy, and those testing positive should be evaluated for antiviral therapy after completion of pregnancy and breastfeeding.
    - Preconception antiviral therapy should be prioritized for HCV-infected women of childbearing age, to eliminate the risk of MTCT during pregnancy.
    - For women or men whose HCV therapy includes ribavirin, highly effective contraception is required, and conception should be deferred for at least 6 months following last ribavirin use.

  - There are insufficient safety data on DAAs to recommend their use in pregnancy as a means of reducing MTCT.
  - HCV-infected women requiring invasive pregnancy procedures, such as amniocentesis, should be informed of the possible risk of MTCT.
  - To reduce MTCT in HCV-infected women
    - Avoid prolonged rupture of membranes
    - Invasive fetal monitoring.
- Monitoring for ALT flares in HCV-infected women is **not** required during pregnancy and postpartum.
- Breastfeeding is not contraindicated in HCV-infected women but **not** recommended during antiviral therapy. In addition, caution is needed if skin breakdown occurs with associated bleeding of nipples.

➢ Epidemiology and screening

- Prevalence of HCV in reproductive-aged women has doubled, driven largely by IVDU
- Universal screening is recommended in every pregnancy
- Women who screen positive during pregnancy should be linked to care for postpartum antiviral treatment
- Treating HCV before conception is a priority

➢ Fertility and Pregnancy Outcomes

- HCV does not clearly impair fertility, but data are limited
- Associated with adverse pregnancy outcomes, including:
  - ~1.6× higher odds of preterm birth
  - Markedly increased risk of intrahepatic cholestasis of pregnancy (ICP)
- Pregnancy does not worsen the course of HCV
- Spontaneous postpartum clearance can occur (up to ~25%); confirm HCV RNA before starting treatment

➢ Mother-to-child transmission (MTCT)

- Overall MTCT risk:
  ~6% with HCV viremia
  ~11% with HCV–HIV coinfection
- No clear viral load threshold identified
- Transmission occurs mainly peri-/intrapartum
- Mode of delivery does not affect MTCT risk

- To reduce risk:
  - Avoid prolonged rupture of membranes
  - Avoid invasive fetal monitoring and episiotomy
- If invasive prenatal testing is needed:
  - Amniocentesis preferred over CVS or fetal blood sampling
  - Avoid placental contact when possible

➢ Management

- Breastfeeding: Not contraindicated
- HCV may be detectable in breast milk at very low levels
  - No proven association between breastfeeding and transmission
  - Temporary interruption advised if nipple bleeding or skin breakdown
- Antiviral therapy
  - DAAs are not routinely recommended during pregnancy Limited safety data
  - If pregnancy occurs on therapy, decision to continue is individualized
  - Avoid breast feeding, Data are very limited for both Epclusa and Mavyret
  - Ribavirin is contraindicated
    - Embryocidal and teratogenic
    - Both women and men must use highly effective contraception
    - Defer conception for ≥6 months after last dose
- Infant testing and follow-up
  - Passive maternal anti-HCV can persist up to 18 months
  - Test infants for anti-HCV at ≥18 months
  - If anti-HCV positive → check HCV RNA
  - Refer infected infants to pediatric HCV specialists

- **Wilson Disease and Pregnancy**
  - Guidance Statements:
    - Preconception counseling should include genetic counseling and discussion of medication safety in pregnancy.
    - Use of zinc is safe in pregnancy and delaying conception until the patient is on zinc monotherapy should be encouraged.
    - Chelating agents should be continued during pregnancy due to the high risk of spontaneous abortion if withdrawn.
      - Dose reductions in the second and third trimesters are required. Chelating agents require up-titration to pre-pregnancy doses after delivery.
    - Close monitoring of copper balance is necessary to avoid over chelation during pregnancy.
    - Breastfeeding is associated with infant risks if on treatment, as all WD drugs are excreted in breast milk, and there is risk for copper deficiency in the infant.

- Demography
  - Overall congenital anomaly rate similar to general population when treated
  - Pregnancy outcome data in Wilson disease are limited, making it difficult to determine whether birth defect risk is increased
- Pathophysiology
  - Caused by mutation in ATP7B, encoding a copper-transporting P-type ATPase
  - ATP7B expressed in ovaries, uterus, placenta → copper may directly affect pregnancy outcomes
  - ↑ infertility and spontaneous abortion
  - May cause oligomenorrhea or amenorrhea due to hormonal dysregulation
- Treatment Options
  - Chelators: D-penicillamine, trientine → ↑ urinary excretion
  - Zinc salts → ↓ intestinal copper absorption
  - Teratogenicity
    - D-penicillamine: teratogenic in humans
    - Trientine: teratogenic in animal studies
    - Zinc: not teratogenic
- Outcomes
  - In a cohort of 282 pregnant women with WD, 162 received chelation therapy (D-penicillamine, trientine, or chelator + zinc)
    - Birth defects occurred in ~3%, comparable to the general population
    - Smaller case series reported no birth defects in women treated with chelating agents
  - Spontaneous abortion rates:
    – 10% in women treated with zinc or D-penicillamine
    – 17% in undiagnosed women
    – 36% in women who discontinued therapy
- Management During Pregnancy
  - Continuing therapy ↓ spontaneous abortion
  - Stopping therapy ↑ risk of miscarriage
  - Treated women have better pregnancy outcomes than untreated
  - Avoid over-chelation (risk of fetal copper deficiency)
  - Reduce chelator dose to 25–50% of pre-pregnancy dose

- No dose adjustment for zinc
- Postpartum
  - Gradually uptitrate chelators to pre-pregnancy dose
  - Monitor with 24-hour urine copper and serum free copper
- Breastfeeding
  - Breastfeeding generally not recommended
  - All WD medications excreted in breast milk
  - Risk of infant copper deficiency
- Contraception
  - Copper IUD is acceptable
  - Systemic copper absorption is minimal

- **Autoimmune Hepatitis in Pregnancy**
  - Guidance Statements:
    - Preconception counseling should include discussion of medication safety in pregnancy and potential for disease exacerbation, including decompensation.
    - Delaying conception until liver disease is well controlled on stable doses of immunosuppressants for at least 1 year is suggested.
    - Counseling regarding the potential risks of azathioprine and 6-mercaptopurine (6-MP) is recommended, although these drugs are considered safe in pregnancy and lactation.
    - Prednisone and budesonide are considered low risk in pregnancy and lactation.
    - MPA products are contraindicated in pregnancy and lactation.
    - Liver test monitoring during each trimester is suggested. More frequent monitoring (every 2–4 weeks) is advised for the first 6 months postpartum.
    - Breastfeeding is not contraindicated.

- Autoimmune hepatitis & fertility
  - Fertility is preserved in women without cirrhosis
  - No evidence of reduced fertility unless advanced liver disease

- Disease course during pregnancy
  - Aminotransferases often improve during pregnancy
  - Spontaneous remission can occur
  - Flares may occur during pregnancy or postpartum
  - Rare cases of urgent liver transplant reported

- Postpartum risk
  - Highest flare risk occurs within first 3 months postpartum
  - Reported flare rates ~13–55%
  - Higher risk if immunosuppression stopped or remission <1 year before conception
  - De novo AIH can present postpartum
- Maternal outcomes
  - Main risk is flare with worsening liver function
  - Serious maternal events in ~11% of pregnancies
  - Risk significantly higher in women with cirrhosis
- Fetal outcomes
  - Increased risk of preterm birth
  - Increased risk of small-for-gestational-age infants
  - Fetal loss reported in up to ~29% (includes early miscarriage in some series)

➢ Treatment

- Immunosuppression management
  - Continuing therapy reduces flare risk
  - Minimal dose adjustment preferred during pregnancy
  - Anticipate postpartum flares
    - If dose reduced in pregnancy, increase back to baseline postpartum
    - Close ALT monitoring postpartum required
- Azathioprine
  - No proven increase in congenital malformations in humans
  - Acceptable to continue during pregnancy
  - Low levels detected in breast milk without clear harm
- Corticosteroids
  - Prednisone considered low risk
  - Can be used as monotherapy in stable disease
  - Use lowest effective dose
  - Limited data for budesonide
- Contraindicated therapy: Mycophenolic acid (MPA)
  - High risk of congenital malformations
  - Increased spontaneous abortion risk
  - Must be stopped ≥6 weeks before conception
  - Strict contraception required

Reproductive Considerations for Common Immunosuppressive Agents

Medication Group	Pregnancy	Breastfeeding	Fertility	Historical FDA Category*
○ Thiopurines (6-MP, Azathioprine)	Generally considered compatible. 6-MP not linked to birth defects; azathioprine may be associated with low birth weight or preterm delivery.	Usually acceptable; occasional reports of mild, self-limited neutropenia in infants.	6-MP: ovarian function preserved; mixed data in men (some reports of birth defects, others show no increased risk). Azathioprine: no clear adverse impact on fertility in either sex.	D
○ Calcineurin inhibitors (cyclosporine, tacrolimus)	Compatible. Cyclosporine sometimes linked to low birth weight; tacrolimus occasionally associated with hypertension, preeclampsia, or preterm birth.	Compatible.	No known fertility concerns in men or women.	C
○ Glucocorticoids (prednisone, budesonide)	Compatible. Prednisone has rare associations with oral clefts; budesonide may reduce fetal exposure.	Compatible.	Budesonide: no fertility effect in animal studies; human data limited. Prednisone: no adverse reproductive outcomes reported in men.	C
○ mTOR inhibitors (sirolimus, everolimus)	Not recommended due to limited human data.	Not recommended due to limited human data.	Sirolimus: reports of irregular ovulation, ovarian cysts, reduced sperm counts. Everolimus: rare reports of reduced sperm count and male fertility.	Sirolimus: C; Everolimus: not assigned
○ Mycophenolate products (MMF, myco-phenolate sodium)	Contraindicated. Strongly associated with miscarriage and congenital malformations.	No adverse events reported, but use discouraged given pregnancy risks.	No fertility concerns in men or women; women should discontinue ≥6 weeks before conception.	D

*Historical FDA categories:

- **C** = Risk cannot be ruled out
- **D** = Evidence of risk, but benefits may outweigh in certain cases

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365 (Table 5)

- **Primary Biliary Cholangitis** (PBC) **and Primary Sclerosing Cholangitis** (PSC)
  - Guidance Statements:
    - Measurement of total serum bile acids may be considered in the first trimester to aid in excluding ICP in the setting of new-onset or worsening pruritus during pregnancy.
    - UDCA is safe in pregnancy and lactation, although no data support a therapeutic benefit in PSC.
    - Obeticholic acid and fibrate use is not recommended in pregnancy or lactation in women with PBC due to lack of safety data.
    - Clinically significant pruritus typically requires a multifaceted approach with cholestyramine, rifampin, SAMe, and antihistamines considered, although evidence is low.
    - Vitamin K deficiency related to cholestasis should be corrected, and regular monitoring of PT is recommended.

- **Primary Biliary Cholangitis (PBC) in Pregnancy**

➢ Diagnosis and baseline assessment
  - ~1/3 of new PBC diagnoses occur during pregnancy.
  - Check total serum bile acids in the first trimester to help interpret later elevations if ICP develops (PBC may be associated with elevated total serum bile acid)

➢ Fertility and pregnancy outcomes
  - Limited data; fertility and overall maternal outcomes appear similar to non-PBC controls.
  - Interpretation confounded when cirrhosis is present.

➢ Symptoms
  - New or worsening pruritus in ~50% during pregnancy.

➢ Disease course
  - During pregnancy
    - ~70% have stable or improved liver tests.
  - Postpartum
    - 60–70% experience increased disease activity.
    - IgM levels and antimitochondrial (M2) antibody titers may fall during pregnancy and rebound postpartum.

➢ Fetal considerations
  - Fetal/neonatal complications may be higher; data limited and confounded by cirrhosis.

- Medications in pregnancy & lactation
  - UDCA: safe in pregnancy and breastfeeding.
  - Obeticholic acid: no human safety data → not recommended.
  - Fibrates: no human pregnancy data; adverse maternal effects at high doses in animals → not recommended.
  - Excretion of obeticholic acid and fibrates into breast milk is unknown → avoid during lactation.

- Vitamin K and bleeding risk
  - Cholestasis can cause vitamin K deficiency.
  - Cholestyramine may worsen deficiency.
  - Rare cases of low prothrombin and hemorrhage reported
  - Responds to parenteral vitamin K.

- **Primary Sclerosing Cholangitis** (PSC) **in Pregnancy**
  - Published pregnancy data are limited and often confounded by IBD activity.
  - Fertility is **not** impaired by PSC.
  - Pregnancy outcomes
    - Higher risk of preterm birth (~10–30%) and cesarean delivery.
    - Active IBD at conception or during pregnancy is a major driver of adverse fetal outcomes.
  - Disease course
    - Most women have stable liver tests during pregnancy.
    - Up to one-third have increased liver enzymes postpartum, usually without clinical consequences.
    - Women on UDCA more likely to maintain stable liver enzymes, though UDCA is not formally approved for PSC.
  - Evaluation of worsening symptoms
    - Consider dominant stricture with new symptoms or rising liver tests.
    - Symptoms: pruritus & abdominal pain.
    - Initial imaging: ultrasound.
    - Further evaluation (if needed): cross-sectional imaging or ERCP, guided by symptom severity and gestational age.
  - Pruritus management
    - Often requires combination therapy: lifestyle measures, antihistamines, cholestyramine, rifampin, UDCA.
  - Vitamin K and bleeding risk
    - Cholestasis can cause vitamin K deficiency.
    - Cholestyramine may worsen deficiency.
    - Consider PT monitoring during pregnancy in cholestatic patients.

- **MASLD and Reproductive Health and Pregnancy**
  - Guidance Statements
    - Evaluation for symptoms associated with polycystic ovary syndrome is recommended.
    - Preconception counseling should include review of maternal and fetal risks associated with obesity and diabetes and the benefits of optimizing weight and metabolic comorbidities before conception.
    - Optimal gestational weight gain through healthy diet and appropriate exercise should be emphasized.
    - Monitoring of liver tests should be similar to non-pregnant women.
    - Pregnant patients with MASLD: breastfeeding is encouraged, and longer duration of lactation is associated with lower rates of future MASLD among offspring and reduced maternal metabolic complications, including MASLD.

➢ Infertility

- MASLD itself ≠ infertility.
- Higher infertility often due to PCOS, obesity, or cirrhosis.
- MASLD prevalence in PCOS: 42% overall.
- Screen for PCOS in young women with MASLD (menstrual irregularities, hirsutism, infertility).

➢ Pregnancy Risks

- Hypertensive complications: OR 3.1.
- Preterm birth: OR 1.6.
- Postpartum hemorrhage: OR 1.7.
- Gestational diabetes: ↑ risk independent of BMI/age.
- Delivery outcomes
  - ↑ cesarean (64% vs 17%)
  - ↑ preterm (16% vs 5%)
  - ↑ small for gestational age (6% vs 3%)
- Long-term offspring risk
  - Maternal obesity & diabetes → ↑ MASLD risk in children
  - Mechanisms: epigenetic changes, mitochondrial dysfunction, dysbiosis, inflammation.
- Breastfeeding (protective)
  - Improves insulin sensitivity
  - Promotes postpartum weight loss
  - Lowers systemic inflammation
  - Hormones (prolactin, oxytocin) support healthy metabolism

- Management
  - Lifestyle modification: weight optimization, metabolic comorbidity treatment.
  - Pregnancy goal: prevent excessive gestational weight gain; individualize care if underweight.
  - No MASLD-specific medications approved in pregnancy.

- **Alcohol-Associated Liver Disease** (ALD) **and Reproductive Health**
  - Guidance Statements:
    - Pregnant women should be screened for alcohol use and referred for management when appropriate.
    - For women with ALD, counseling should include delaying conception until abstinence is achieved.
    - Medication use to treat alcohol use disorder during pregnancy should be individualized, with careful weighing of the risks of alcohol use versus those of medication exposure.

- **Trends in Alcohol Use**
  - Increasing among reproductive-aged women
  - 2012–2013: 75% any alcohol use, 36% heavy/episodic use during pregnancy
  - Lower alcohol use in 2nd & 3rd trimesters than 1st

- **Pregnancy Risks**
  - Alcohol → ↑ preterm birth & small-for-gestational-age infants
  - Fetal alcohol spectrum disorder: long-term complications

- **Screening & Preconception Care**
  - Ask all women about alcohol use, especially preconception/pregnancy
  - Alcohol abstinence is crucial for women with ALD

- **Medications for Alcohol Use Disorder**
  - Safety in pregnancy limited:
    - Disulfiram: potential fetal abnormalities
    - Naltrexone: used in pregnancy; no fetal abnormalities reported
    - Acamprosate: animal studies show risk; limited human data suggest safety

- **Benign Hepatic Lesions in Pregnancy**
  - Guidance Statements:
    - Reproductive-aged women with HCAs should be counseled about the possibility of adenoma growth and rupture in pregnancy.

- Ultrasound monitoring of HCAs during each trimester and up to 3 months postpartum is reasonable.
- Pregnancy in women with HCAs <5 cm is not contraindicated.
- For HCAs >5 cm, prophylactic treatment with embolization or resection should be considered before conception to reduce risk of rupture.
- Hepatic hemangiomas, regardless of size, do not require monitoring, but new symptoms should prompt evaluation.
- Focal nodular hyperplasia, regardless of size, does not require monitoring.

- **Hepatocellular Adenomas (HCAs)**
  - Overview
    - HCAs are benign liver lesions, mostly in reproductive-aged women.
    - Strong association with estrogens; estrogen receptors in ~1/3 of HCAs.
    - Stopping estrogen-containing contraception → HCA regression.
    - Modern low-dose contraceptives → lower HCA risk.
  - Pregnancy Risks
    - Estrogen-rich state may increase risk of tumour growth, rupture, hemorrhage.
    - Historical data (1970): rupture in 83% of pregnant women with HCA; maternal death reported.
    - Contemporary data: smaller HCAs (<5 cm) → low risk of rupture; minimal maternal/fetal complications.
    - 2011 study: 17 pregnancies, 4 HCAs enlarged, no ruptures.

Management of HCA Prior to and During Pregnancy

Lesion Size	Management	Follow-up
HCA < 5 cm	Ultrasound monitoring each trimester and at 12 weeks postpartum	No intervention if lesion remains < 5 cm; if lesion grows ≥ 5 cm → consider bland embolization
HCA ≥ 5 cm	Consider bland embolization or surgical resection	If eradicated or resected → no follow-up required during pregnancy; if reduced to < 5 cm → ultrasound monitoring each trimester and at 12 weeks postpartum

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365.

- **Hepatic Hemangioma in Pregnancy**
  - Overview
    - Most common benign liver lesion (prevalence 0.4–8%, contemporary ~2.5%).
    - Usually asymptomatic; intervention rare (<1%) for pain, bleeding, or rupture.
    - More common in women; estrogen link not well established.
    - CHC use or pregnancy: generally safe, no routine monitoring needed.

- Cavernous/Giant Hemangiomas
  - Defined as >5–10 cm.
  - Pregnancy risks: ↑ intra-abdominal pressure, ↑ blood volume, cytokine changes → rare risk of growth/rupture.
  - Resection during pregnancy: rare but safe in 2nd trimester (reported in 3 cases, no maternal/fetal deaths).
- Management
  - New symptoms → prompt evaluation.
  - Intervention decisions: case-by-case, guided by symptoms and maternal/fetal risk.

- **Focal Nodular Hyperplasia** (FNH) **in Pregnancy**
  - Overview
    - Second most common benign liver lesion (prevalence 0.3–3%).
    - Mostly in reproductive-aged women.
    - Can coexist with vascular lesions (e.g., hemangiomas) in ~20% of cases.
  - Estrogen & Pregnancy
    - Association with estrogen not well established.
    - CHC use or pregnancy → generally safe.
    - Studies: 12 pregnancies showed no significant lesion growth, no maternal or fetal deaths.
    - Only one case of rupture reported in literature.
  - Management
    - Routine monitoring not required during CHC use or pregnancy.

- **Budd-Chiari Syndrome**
  - Guidance Statements
    - Doppler US is the imaging modality of choice for diagnosing BCS.
    - Treatment of acute BCS is similar to non-pregnant patients, except for limited anticoagulation options and insufficient safety data for thrombolysis in pregnancy.
    - Low molecular weight heparin (LMWH) is the anticoagulant of choice during pregnancy and lactation.
    - Vitamin K antagonists are contraindicated during pregnancy but acceptable during breastfeeding.

- **Gallstone Disease in Pregnancy**
  - Guidance Statements
    - Abdominal ultrasound (US) is the imaging modality of choice for suspected gallstone disease in pregnancy.
    - Initial management is supportive, though ERCP and laparoscopic cholecystectomy can be considered, ideally in the second trimester.
    - If ERCP is required, fetal radiation should be minimized using short fluoroscopy and lead shielding of pelvis/lower abdomen.

- **Hyperemesis Gravidarum** (HG)
  - Guidance Statements
    - Supportive care: rehydration, electrolyte correction, thiamine supplementation, anti-emetics.
    - Liver chemistry abnormalities usually resolve with symptom control; persistent abnormalities warrant evaluation for another cause.

➢ Incidence
  - 0.35–2% of pregnancies

➢ Timing
  - Typically first trimester

➢ Clinical Features
  - Persistent vomiting
  - Weight loss ≥5% of pre pregnancy weight
  - Dehydration and ketonuria
  - Rarely persists throughout pregnancy

➢ Liver Findings
  - Abnormal enzymes in ~50%; usually ALT > AST, rarely >1,000 Jaundice uncommon
  - Resolves with hydration and vomiting control

➢ Maternal and Fetal Outcomes
  - Early treatment → usually no major adverse outcomes
  - Possible low birth weight and preterm delivery
  - High recurrence in subsequent pregnancies
  - No association with chronic liver disease

➢ Treatment
  - Supportive care: rehydration, electrolyte correction, nutrition
  - Thiamine supplementation to prevent Wernicke's encephalopathy
  - Anti-emetics: ondansetron, metoclopramide, promethazine
  - Corticosteroids: only for severe cases; oral prednisolone not proven

- **Intrahepatic Cholestasis of Pregnancy** (ICP)

➢ Incidence
  - 0.4–10% of pregnancies; higher in Latina, Chilean Araucanian, Swedish, Baltic populations

➢ Risk Factors
  - Genetic: ABCB4, ABCB11, ATP8B1 variants
  - Hormonal: ↑ estrogen & progesterone sulfates
  - Maternal: age, multiparity, metabolic syndrome, HCV
  - Personal/family history → recurrence 40–92%

➢ Clinical Features:
  - Pruritus (palms and soles, no rash), usually 2nd–3rd trimester
  - Labs: ↑ AST/ALT (2–30×), ↑ total bile acids (TBA)
  - Rarely occurs in first trimester

➢ Diagnosis:
  - Symptoms and labs sufficient; US to exclude biliary obstruction
  - Repeat TBA if initial test normal (pruritus may precede lab abnormalities)

➢ Risks
  - Maternal
    - Minimal; symptoms resolve postpartum
  - Fetal
    - Preterm birth, meconium-stained amniotic fluid, neonatal respiratory depression, asphyxia
    - Intrauterine fetal death (IUFD): 0.1% (>40 μmol/L), 3.4% (≥100 μmol/L)

➢ Management:
  - Ursodeoxycholic acid (UDCA) first-line for pruritus
  - Antihistamines, cholestyramine, rifampicin, same for refractory symptoms
  - Postpartum follow-up to ensure normalization of labs
  - Consider genetic testing for severe, recurrent, or early-onset ICP

- **Liver Disorders Unique to Pregnancy**

Hyperemesis Gravidarum (HG)

- Typical timing – Early pregnancy (mainly 1st trimester; occasionally later)
- Frequency – ~0.3–2% of pregnancies
- Predisposing factors – Prior episode in earlier pregnancy
- Clinical features – Severe nausea/vomiting, ≥5% weight loss, dehydration
- Laboratory findings – AST/ALT mildly elevated (rarely >1000 U/L), improve with hydration; ketonuria, electrolyte imbalance; jaundice uncommon
- Diagnosis – Clinical; endoscopy rarely needed

Intrahepatic Cholestasis of Pregnancy (ICP)

- Typical timing – Usually 2nd–3rd trimester
- Frequency – ~0.4–10% depending on population
- Predisposing factors – Multiparity, metabolic syndrome, hepatitis C, family history, genetic variants (ABCB11, ABCB4, ATP8B1)
- Clinical features – Intense itching (palms/soles), no rash
- Laboratory findings – AST/ALT 2–30× upper limit; bile acids >10 µmol/L
- Diagnosis – Clinical + bile acids >10 µmol/L; liver enzymes supportive but not required; ultrasound may exclude other causes

HELLP Syndrome

- Typical timing – 2nd–3rd trimester
- Frequency – ~0.2–0.6% (within preeclampsia spectrum)
- Predisposing factors – Chronic hypertension, diabetes, older maternal age, multiple gestations, prior preeclampsia
- Clinical features – Abdominal pain, nausea/vomiting, often with preeclampsia
- Laboratory findings – AST/ALT often >500 U/L; platelets reduced; bilirubin <5 mg/dL; hemolysis (schistocytes, reticulocytes); ↑ LDH; hyperuricemia
- Diagnosis – Clinical + maternal organ dysfunction (renal, hepatic, neurologic, hematologic) or fetal growth restriction

Acute Fatty Liver of Pregnancy (AFLP)

Typical timing	Late 3rd trimester or early postpartum
Frequency	Rare (~0.005–0.01%)
Predisposing factors	First pregnancy, multiple gestations, male fetus
Clinical features	Abdominal pain, nausea/vomiting, jaundice, hypoglycemia; encephalopathy if liver failure
Laboratory findings	AST/ALT 300–1000 U/L; ↑ bilirubin, ↑ LDH; ↓ fibrinogen, ↓ antithrombin III; prolonged PT; platelets <100,000; coagulopathy, hypoglycemia, DIC if severe
Diagnosis	Clinical; Swansea criteria often used (sensitive but not specific)

Adapted from: Sarkar M, et al. Hepatology 2021;73(1):318-365.

- **Pregnancy in Liver transplant Recipient**
  - Guidance summary
    - Delay pregnancy ≥1 yr post-LT, with ≥6 months stable graft function.
    - CNIs, azathioprine/6-MP, corticosteroids: acceptable.
    - mTOR inhibitors & MPA: contraindicated.
    - Monitor CNI troughs, graft function closely during pregnancy/postpartum.
    - Mode of delivery based on obstetric indications.

- Pregnancy trends & planning:
  - Pregnancies in LT recipients are rising; reproductive counseling is essential.
  - ~40% of pregnancies in LT recipients are unplanned—more common in younger women and those conceiving <1 year post-LT.
  - Preconception counseling allows:
    - Optimization of graft function
    - Review of immunosuppressive regimen
    - Risk counseling for maternal and fetal outcomes

- Lactation
  - Tacrolimus, cyclosporine, corticosteroids, azathioprine are safe.
  - MPA, sirolimus, everolimus: avoid.

- Maternal risks
  - Higher rates of hypertensive disorders (preeclampsia: 22–73% depending on immunosuppressant).
  - Increased risk of GDM (~10%; higher with tacrolimus).

- Fetal outcomes:
  - Live birth rate ~75%; preterm birth more common (27% vs. 11%).
  - Low birth weight and IUGR more frequent.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; BCS, Budd-Chiari syndrome; BMD, bone mineral density; CHC, combined hormonal contraception; CLD, chronic liver disease; CNIs, calcineurin inhibitors; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; DMPA, depot medroxyprogesterone acetate; EBV, Epstein–Barr virus; EGD, esophagogastroduodenoscopy; EVL, endoscopic variceal ligation; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCAs, hepatocellular adenomas; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ICP, intrahepatic cholestasis of pregnancy; IgG, immunoglobulin G; IUD, intrauterine device; IVC, inferior vena cava; IVF, in vitro fertilization; LH, luteinizing hormone; LT, liver transplant; MASLD, metabolic dysfunction-associated steatotic liver disease; MEC, medical eligibility criteria; MELD, Model for End-stage Liver Disease; MFM, maternal-fetal medicine; MPA, mycophenolic acid; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MTCT, mother-to-child transmission; NAFLD, non-alcoholic fatty liver disease; NSBBs, non-selective beta blockers; PBC, primary biliary cholangitis; PCS, portocaval shunt; PHTN, portal hypertension; PSC, primary sclerosing cholangitis; RCT, randomized controlled trial; SHBG, sex hormone-binding globulin; SMA, smooth muscle antibody; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TIPS, transjugular intrahepatic portosystemic shunt; US, ultrasound; VTE, venous thromboembolism.

HEPATOCELLULAR CARCINOMA (HCC)

David Hudson

- Demography
  - Hepatocellular carcinoma (HCC) is currently the third leading cause of cancer death worldwide
    - Incidence will ↑ 55% between 2020 to 2040
  - 5- year survival rates exceed 55% in patients with early-stage HCC
  - Most (90%) HCC occurs in the setting of advanced cirrhosis
  - The global prognosis of HCC is poor - on average patients present with advanced disease and 5-yr survival rates without treatment, < 20%
  - Advanced disease/tumours have a survival in q1-2 yr
  - Liver cancer is a major cause of death in many countries, Efforts to reduce the incidence of preventable liver cancer should be prioritised to avoid the predicted rise in people diagnosed with liver cancer.
  - Hence, recommendations to complete,
    - Screen q6 mon with AFP
    - Abdominal ultrasound (US) q6 mon plus α-fetoprotein for HCC screening in all patients with cirrhosis, advanced fibrosis (F3) or high risk of HBV.
  - Previously viral hepatitis (HBV/HCV) were the leading causes for the development of HCC.
    - Globally, trends are shifting towards alcohol and MASLD as being the leading drivers of advancing liver disease
  - Alcohol currently causes 25% of global deaths due to liver disease
    - 20% of all HCC related cancer deaths are due to alcohol related liver disease
  - There has been a shift from HCC being a disease of low socioeconomic status to moderate-high socioeconomic demographics.
  - Reducing Risk of HCC
    - Early diagnosis and effective treatment of all liver disease with potential to progress
    - Vaccination for HBV infection

- **Types of Prevention**

Types of Prevention	Primary	Secondary	Tertiary
Definition	Prevent disease before it occurs	Early diagnosis ↓ impact of a disease	↓ impact interventions to decrease ongoing disease

Types of Prevention	Primary	Secondary	Tertiary
○ Proven Strategies	HBV vaccination Anti-viral treatment for HBV and HCV	Ultrasound and AFP scoring	Anti-viral therapy after curative therapy Adjuvant therapy
○ Emerging Strategies that are undergoing evaluation	Aspirin Coffee Metformin Statins	GALAD Model Liquid biopsy panels	Neoadjuvant therapy

- ○ Pros and cons of Scoring for HCC
  - − Benefits
    - ▪ Early HCC detection
    - ▪ Curative treatment receipt
    - ▪ ↑ survival
  - − Harms
    - ▪ Physical complications
    - ▪ Psychological distress
    - ▪ Financial burden
  - − Alter balance
    - ▪ Risk of HCC
    - ▪ Liver dysfunction
    - ▪ Medical comorbidities
    - ▪ Older age
    - ▪ Patient preference / goals of care

➢ Screening Methods for Early HCC

- ○ Common scoring method for HCC
  - − Abdominal ultrasound plus AFP
    - ▪ Specificity, 61%
    - ▪ Specificity, 91%

- **The GALAD Model**

G	**A**	**L**	**A**	**D**
Gender (males)	↑ Age	L3-AFP	AFP	DCP

Abbreviations: AFP, alpha-fetoprotein; DCP, des-carboxy-prothrombi; L3-AFP, lentil-lectin-reactine 3%

- ○ Increasing age and male gender are associated with HCC in individuals with chronic liver disease and are included in the model
  - − Sensitivity, 54–72%
  - − Specificity, 90%

- Other tests

	Sensitivity	Specificity
– Alpha-fetoprotein (AFP)-L3	62%	90%
– DCP	40%	81%
– Multitarget algorithms	82%	87%

- HCC Visualization Score (VIS)
  - A – No/minimal limitations
  - B – Moderate limitations
  - C – Severe limitations

Score	Concept	Examples
No or minimal limitations	– Limitations, if any, are unlikely to meaningfully affect sensitivity	▪ Liver homogeneous or minimally heterogeneous ▪ Liver visualized in near entirety ▪ Minimal beam attenuation or shadowing
B. Moderate limitations	– Limitations may obscure small masses	▪ Liver moderately heterogeneous ▪ Moderate beam attenuation or shadowing ▪ Some portions of liver or diaphragm not visualized
C. Severe limitations	– Limitations significantly lower sensitivity for focal liver lesions	▪ Liver severely heterogeneous ▪ Severe beam attenuation or shadowing ▪ Majority (>50%) of liver not visualized ▪ Majority (>50%) of diaphragm not visualized

Abbreviations: AFP, alpha-fetoprotein; LI-RADS, Liver Imaging Reporting and Data System; US, ultrasound; VIS, visualization score

➢ Diagnosis

- CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10–19	≥ 20
Count additional major features – Enhancing "capsule" – Nonperipheral "washout" – Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4/LR-5
	One	LR-3	LR-4	LR-4	LR-4	LR-4/LR-5
	≥ Two	LR-4	LR-4	LR-5	LR-5	LR-5

Observations in this cell are categorized based on one additional major feature:

- LR-4 – if enhancing "capsule"
- LR-5 – if non-peripheral "washout" or threshold growth

LI-RADS	Description	Management
Negative	No observations detected	Return to surveillance in 6 months
LR-NC	Not categorizable due to image degradation or omission	Repeat or alternative imaging in < 3 mon
L1-RADS	Definitely benign observation	Return to surveillance in 6 mon
LR-2	probably benign	Consider repeat diagnostic imaging in 6 mon
LR-3	Intermediate probability of malignancy	Repeat or alternative imaging in 3–6 mon
LR-4	Probably HCC	Multidisciplinary discussion for further work-up
LR-5	definitely HCC	Multidisciplinary discussion for management consensus
LR-M	probably/definite malignancy not HCC specific	Multidisciplinary discussion, consider biopsy
LR-TIV	definite tumour in vein	Multidisciplinary discussion, may include biopsy

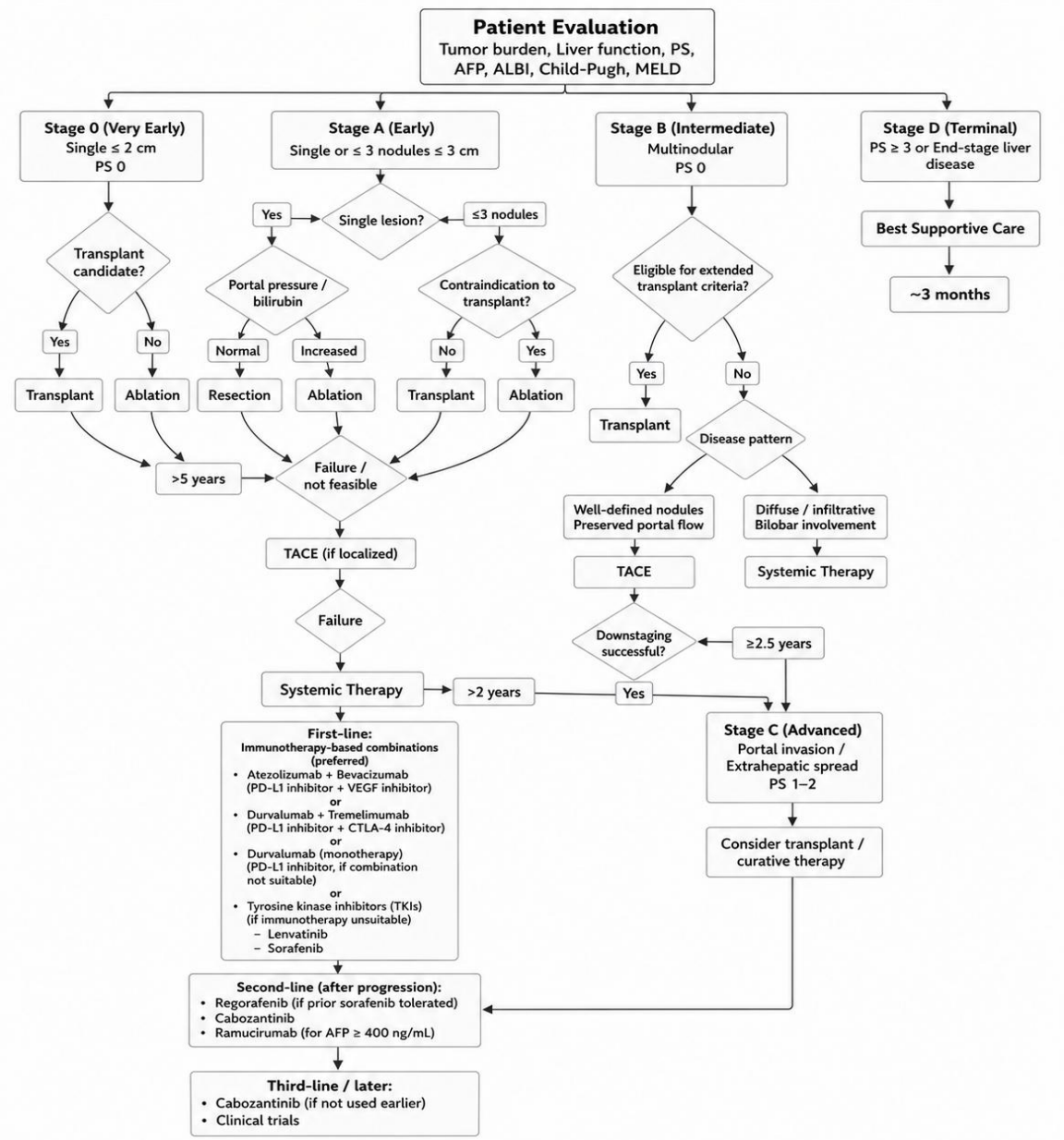
➢ Treatment

Suggested Algorithm for Treatment of Hepatocellular Cancer (HCC)

Patient Background	Condition / Criteria	Recommended Action
○ History of HCC	− Any liver mass	▪ Apply LI-RADS
○ Cirrhosis	− Vascular etiologies (e.g., cardiogenic)	▪ LI-RADS does not apply → biopsy required
	− Other etiologies, ≥10	▪ Apply LI-RADS
○ Chronic HBV infection	− PAGE-B score ≤9	▪ LI-RADS not validated → biopsy recommended

Adapted from Vogel A, et al., Ann Oncol. 2025;36(5):491–506 and EASL Clinical Practice Guidelines, J Hepatol. 2025;82(2):315–374).

Algorithm for the Evaluation, Staging, and Management of Hepatocellular Carcinoma



Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin score; Child-Pugh, Child-Pugh score (liver function classification); CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HCC, hepatocellular carcinoma; IO, immuno-oncology (immunotherapy); MELD, Model for End-stage Liver Disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance status; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

Adapted from: Reig M, et al. J Hepatol. 2022; 76(3): 681-693

➢ Classification

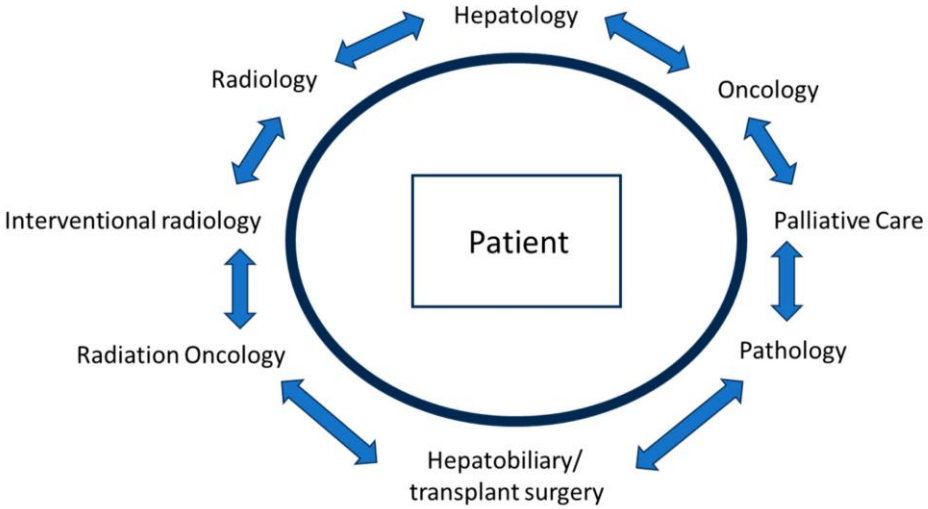
- **Barcelona Classification**

Period	Key Developments	Ongoing Issues / Limitations
1999–2002	Initial BCLC staging and treatment framework introduced	No major refinements
2003–2007	Addition of very early stage; portal invasion defines advanced disease	No distinction between intra- vs extrahepatic invasion
2008–2011	Sorafenib established for advanced HCC	Unclear role in intermediate stage
2012–2017	Transplant eligibility incorporated into surgical decision-making	Limited consensus for very early-stage transplant strategies
2018–2021	Expansion of systemic therapies; shift toward liver function–based assessment	Inconsistent terminology across guidelines
2022–present	Subclassification of intermediate stage; emphasis on multidisciplinary care	MDT role mainly supports stage migration

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; MDT,

Adapted from: Trevisani F, et al. J Hepatol 2024;80(4):661-669.

- The Multidisciplinary Team in HCC Care (Liver Transplant Program)



Courtesy of: Kinsey E, et al. Cancers 2024; 16(3):666 (Figure 1)

- **Locoregional Therapy – Ablation**
  - When liver transplantation (LT) and resection are contraindicated.
    - Ablation alone with the application of Radiofrequency Ablation (RFA) or Microwave Ablation (MWA)
    - Use for curative intent for treatment of HCC lesions ≤ 3 cm
    - Lesions < 3 cm are currently ideal for treatment by RFA/MWA, with similar outcomes to resection/LT.
    - Reserved for patients not surgical candidates given risk of recurrence (73–80%).
  - Approach
    - Laparoscopic
    - Percutaneous
      - Proximity to major blood vessels/bile ducts needs to be avoided (heat sink)
      - Dome lesions – thermal injury to diaphragm
    - Transarterial chemoembolization (TACE), then RFA may be effective for unresectable non-early HCC
  - Ideal
    - ≤ 3 separate lesions
    - Lesion < 3 cm for RFA, possible (< 4.5 cm for MWA)

Oncologic Outcomes for 3- to 5-cm Hepatocellular Carcinomas by Locoregional Therapy

Outcome (%)	Ablation	TACE–Ablation Combination
Local tumour progression (%)		
Overall	2.9–59.4 [28–32, 65, 67]	1.4–40 [65, 67, 79]
1-yr	45 [79]	1.8–9.5 [69, 72, 75, 79]
3-yr	76	3.9–40
Recurrence-free survival (%)		
1-yr	21–66.7 [65, 67]	54–89.2 [65, 67, 70, 74]
2-yr		
3-yr	10–44.2	40–69.4
5-yr	10	20
Progression-free survival (%)		
1-yr		
2-yr		
Overall survival (%)		
1-yr	77–92.3 [31–33, 65, 67]	84.6–97.4 [65, 67, 70, 74–76, 80]
3-yr	23–72.2	66.6–79
5-yr	14.9–53.3	39–67.7
Complications (%)		
Minor complications	53.7–64.2 [65, 67, 79]	60.6–96 [65, 67, 74, 76, 79]
Major complications	2.8–3	0–8.7

Courtesy of: Young and Golzarian. AJR. 2020;215(1):223–234.

- Accepted safe remnant/residual liver volume / Functional Liver Remnant (FLR)
  - Non-cirrhotics
    - ~30% of Estimated Liver Volume
    - >0.7% of body weight
  - Cirrhotics
    - 50 to 70%
    - Confounding Variables
      - Steatosis
      - Age
      - Active hepatitis
- Techniques to induce contralateral hypertrophy
  - Portal vein embolization (+/– TACE)
  - Radioembolization (Radiation Lobectomy)
- Typically, major resection is avoided in patients with cirrhosis – especially in cases of portal hypertension (risk of small-for-size syndrome)

Truant S, et al. *J Am Coll Surg*. 2007;204(1):22–33.

- **Recurrence HCC After Resection**
  - Recurrence after
    - Hepatic resection
    - Up to 70% of patients
    - Post-liver transplantation
  - There is a need to identify patients at high risk of recurrence
    - Multiple prognostic/risk nomograms are available
  - Early Recurrence Score (ERS)
    - 6 variables prognosticate recurrence
      - AFP
        - AFP >100 ng/mL – strongest predictor
      - Size of largest tumour ≥4 cm
      - Multifocality / Satellite nodules
      - Surgical margin positivity
      - Vascular invasion

- **Adjuvant Therapy**
  - Principle goal of adjuvant therapy
    - ↓ risk of cancer recurrence, and
    - ↑ proportion with cure
    - Adjuvant endpoints
      - Rare recurrence
      - Recurrence-free or disease-free survival (RFS, DFS)
      - Overall survival (OS)
    - Tumours within 2–3 yr are likely to recur; at later time points

- Secondary goal
  - Delay recurrence, improve outcomes
  - Endpoints: DFS, RFS, time to recurrence (TTR), OS
  - Imperative to account for risk of adjuvant therapy if considered cured
    - Toxicity
    - Cost
    - Quality of life impact
    - Adjuvant setting is higher risk than advanced disease

NCI, Dictionary of Cancer Terms: www.cancer.gov

- **STORM Trial: Adjuvant Sorafenib vs Placebo**
  - A phase 3, randomized, double-blind placebo-controlled trial
    - N = 1114 patients with intermediate or high risk for recurrence randomized to sorafenib or placebo for 4 yr
    - 81% post-resection, 19% post-ablation
    - 46% “high risk”
      - Microvascular invasion
      - Poor differentiation
      - Satellites / multifocal
    - 54% “intermediate risk”
      - Tumour >2 cm + absence of microvascular invasion (MVI) or satellites
      - Median AFP < ng/mL, 91% solitary tumour
  - Median duration of sorafenib: 12.5 mon
  - Median RFS: 33.3 mon vs. 33.7 mon (HR 0.94)
  - Conclusion
    - Adjuvant
      - Sorafenib of **no** benefit

- **IMBRAVE 050: Atezolizumab** (PDL1) **+ Bevacizumab** (VEGF) **vs Active Surveillance** (Adjuvant) **Post Ablation/Resection**
  - 668 patients randomized 1:1 to Atezolizumab + Bevacizumab q3 wk for 1 yr vs. surveillance
  - At a median follow-up: 17 mon, the primary endpoint of centrally assessed relapse-free survival (RFS) was superior for
    - Atezolizumab/Bevacizumab: 78%
    - Surveillance, 65%
    - Hazard ratio, 0.72
    - P = 0.012

- Conclusion
  - Adjuvant therapy in selected patients had statistically significant, but the benefit was considered to be clinically insignificant

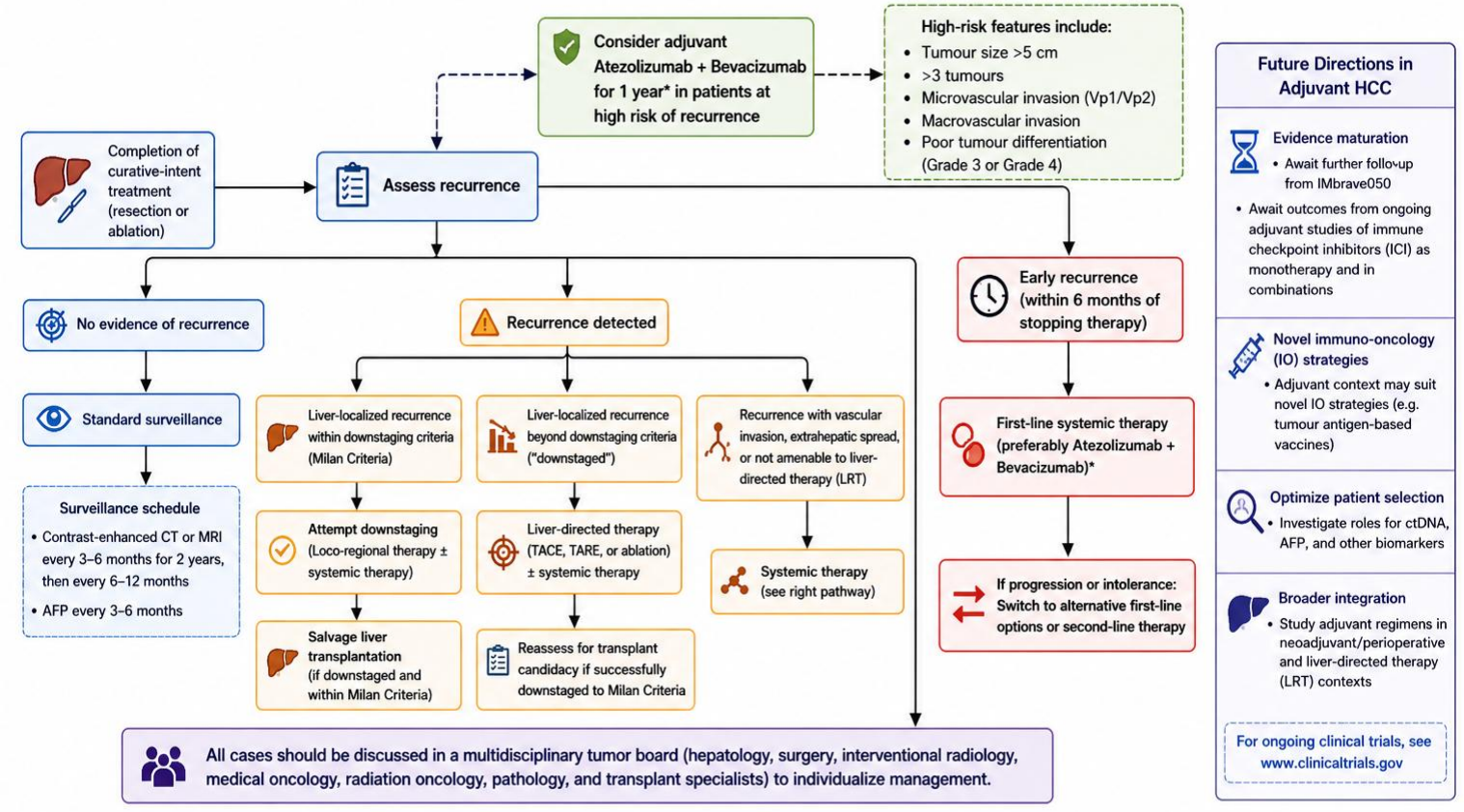
Qin S, et al. *Lancet*. 2023; 402(10425):1833–1845.

- Efficacy
  - Improved RFS on interim analysis (12-month RFS: 78% vs. 65%, median: NE, HR 0.72, p = 0.012)
  - No difference in OS, but
    - Data is immature with few events (27 events in A+B arm, 20 events in control arm)
    - Next OS analysis will occur at final RFS analysis
  - Unclear whether benefit reflects curing vs. delaying recurrence
  - Would like to see outcomes stratified by AFP and ctDNA to determine if these may help identify patients likely to be cured without adjuvant therapy
- Safety
  - Higher rates of Grade 3–4 adverse events (AE) and serious adverse events (SAE) in treatment arm (41% vs. 13%, SAE: 24% vs. 10%)
- Question
  - Is the RFS improvement sufficient for adoption?

Reig M, et al. *J Hepatol*. 2022.

➢ Current Recommendation

Management of Recurrence After Curative Treatment for HCC (Post-resection or Post-ablation)



Developed based on BCLC strategy updates, EASL and AASLD guidelines, and pivotal trials (IMbrave150 and IMbrave050).

- **Selected Adjuvant Trials on the Horizon**

Agent	Design	Sample Size	NCT Number
○ Nivolumab (CheckMate 9DX)	RP3	545	NCT03383458
○ Pembrolizumab (KEYNOTE-937)	RP3	950	NCT03867084
○ Camrelizumab + Apatinib	RP3	687	NCT04639180
○ Durvalumab + Bevacizumab (EMERALD-2)	RP3	908	NCT03847428
○ Durvalumab + Tremelimumab	Phase 2	28	NCT05440864

  - Selection criteria: multicenter, phase 2 or 3, with ≥1 site in North America

➢ **Liver Transplantation Criteria**

- Milan Criteria
  - Single lesion ≤ 5 cm, or
  - ≤ 3 nodules, each ≤ 3 cm
  - No vascular or extrahepatic invasion
- UCSF Expanded Criteria
  - Single lesion ≤ 6.5 cm, or
  - ≤ 3 nodules, with largest tumour ≤ 4.5 cm and total tumour diameter ≤ 8 cm
  - No vascular or extrahepatic invasion
- Expansion Beyond Milan Criteria – Global Evolution of Liver Transplant Eligibility for HCC

Year	Country	Criteria	5-Year Outcomes
2001	United States (UCSF)	Solitary ≤6.5 cm or ≤3 nodules ≤4.5 cm & total ≤8 cm	OS: 81%
2007	United States (Dallas)	Solitary ≤6 cm or ≤4 nodules ≤5 cm	RFS: 63.9–64.6%
2008	Spain (Valencia)	≤3 nodules ≤5 cm, total ≤10 cm	OS: 69%
2009	Italy	Up-to-7 (size + number ≤7, no microvascular invasion)	OS: 71.2%

Year	Country	Criteria	5-Year Outcomes
2012	France	Point-based: size (≤3/6/6 cm), number (≤3/24), AFP ≤100,000 ng/mL	OS: 68% (score ≤2 = low risk)
2015	China (Hangzhou)	Total tumour diameter ≤8 cm or >8 cm with AFP ≤400 ng/mL	OS: 73.8%
2015	Canada (Ontario)	Total Tumour Volume (TTV ≤145 cm^3) and AFP ≤1000 ng/mL	OS: 74.6%
2018	Italy (Metroticket 2.0)	Up-to-7: AFP ≤200 ng/mL; Up-to-5: AFP ≤400 ng/mL; Up-to-4: AFP ≤1000 ng/mL	OS: 70%

Abdelrahim M, et al. *Cancers*. 2021;13(19):4911.

- **The Extended Toronto Criteria for Liver Transplantation in Patients With HCC**
  - Overall survival
    - Patients meeting Milan criteria had actuarial survival ~80–85% at 5 years.
    - Patients meeting Extended Toronto criteria (M+) had similar survival (~75–80% at 5 years).
    - The difference was not statistically significant (p = 0.3), meaning expansion beyond Milan did not compromise survival outcomes.
  - Recurrence risk
    - Milan group recurrence: 13.1% at 5 years.
    - Extended Toronto group recurrence: 29.8% at 5 years.
    - The difference showed a numerical increase in recurrence for the extended group, but it was not statistically significant (p = 0.08).

Adapted from: Sapisochin G, et al. Hepatology. 2016;64(6): 2077-2088.

- **TGLN: HCC Criteria**
  - Exception Points Criteria for Liver Transplant Allocation (HCC):
    - Tumour Size
      - One nodule ≥ 2 cm
      - Multiple nodules ≥ 1 cm
      - One nodule 1–2 cm (non-curable by other means)
      - Recurrent nodule ≥ 1 cm
    - Additional Criteria (All Must Be Met):
      - Total Tumour Volume (TTV) ≤ 145 cm^3
      - AFP (Alpha Fetoprotein) ≤ 1,000
      - Imaging: Diagnostic for HCC (biopsy if unclear)
      - No vascular invasion or extrahepatic spread
      - No cholangiocarcinoma features on histology

- **Bridging and Downstaging Therapy**

➢ Definition

- **T**reatment of accepted transplant candidates within Milan criteria while on the transplant waiting list.

➢ Discussion

- The patients are at very high risk of drop-out due to tumour progression especially when wait times exceed 6 mon.
  - ~10–20% of patients with HCC will drop off the list while waiting for transplantation.
- Bridging locoregional therapy (LRT) has been shown to ↓ drop-outs, but effect on postoperative HCC recurrence remains not well defined.
- Tumour response to LRT appears to be the best predictor of HCC recurrence and recurrence-free survival (RFS): complete response is preferred over partial response.
  - >2 cm of residual viable tumour tissue at explant is a strong indicator of recurrence.
- Patients who respond to 1–2 applications of LRT have
  - Improved survival
  - ≥ 3 treatments, unclear benefit
- A combination of AFP (tumour biology) is likely to replace conventional transplant eligibility criteria
  - Response to adjuvant therapy, tumour size, and number of nodules
- Downstaging Therapy is intended to treat patients whose tumour is outside accepted transplantation criteria.
  - Most of trials will downstage until within Milan Criteria as acceptable (EASL 2018 HCC Guidelines)
- Some studies have demonstrated that even without upfront restriction, if downstaging can be obtained, there is no difference in overall survival
  - NOTE: Metro-ticket 2.0 can be applied to re-stratify patients after LRT with viable tissue to determine 5-yr post-HCC survival http://www.hcc-olt-metroticket.org/#calculator_pre (hcc-olt-metroticket.org)

Abbreviations: EASL, European Association for the Study of Liver; HCC, hepatocellular cancer

- **UNOS Downstaging Protocol**
  - Pretreatment Disease Criteria:
    - 1 lesion >5 cm and ≤8 cm, or
    - 2 or 3 lesions each >3 cm and ≤5 cm, with total diameter of all lesions ≤8 cm, or
    - 4 or 5 lesions, each <3 cm, with total diameter of all lesions ≤8 cm
  - Locoregional Therapy (LRT) *(intervening step)*
  - Post-Treatment Disease Criteria:
    - 1 lesion ≥2 cm and ≤5 cm, or
    - 2 or 3 lesions each ≥1 cm and ≤3 cm
  - Meta-analysis
    - T1: <2 cm, solitary
    - T2: One tumour >2 cm and <5 cm, or 2–3 HCCs all ≤3 cm
    - T3: One HCC ≤5 cm, two or three HCCs, at least one >3 cm and <5 cm
    - T4: >4 HCCs any size
  - Dropout rate (bridging therapies versus no therapy) for adults with cirrhosis awaiting LT and HCC (T2)
  - Mortality Rate (bridging therapies versus no therapy) for adults with cirrhosis awaiting LT and HCC (T2)
  - LRT Bridging and Downstaging – Systematic Review and Meta-analysis (Kulik LM, et al. Hepatology. 2018;67(1):381–400)
    - T1 HCC
      - No good quality evidence
    - T2 HCC
      - Non-significant ↓ risk of waitlist dropout secondary to progression
      - Non-significant post-LT survival benefit
    - T3 HCC
      - ↑ in 1- and 5-year post-LT survival

- Hepatocellular Carcinoma (HCC) after Downstaging Without Up-Front Stage Restrictions
  - Overall 1-, 3-, 5-, and 10-yr survival rates in the B-UCSF group (89%, 73.2%, 66%, 50%) were comparable to those in W-UCSF (94%, 94%, 85%, 63%) and W-MC (93%, 83%, 74%, 62%) (p = 0.29)
  - Conclusion
    - Suggests aggressive downstaging for LT candidates beyond Milan criteria
    - Selective approach yields long-term outcomes akin to earlier-stage disease

- Predictors of success
  - Sample size, number, tumour diameter
  - Response to LRT (CR)
  - ↓ AFP
  - Mode of DS / TARE / TACE
  - Observation period 3–6 mon
  - Degree of liver disease
  - Vascular invasion

- Upper Limits of Downstaging for Hepatocellular Carcinoma in Liver Transplantation?
  - Expanding Transplant Criteria
    - Debate on including patients previously excluded due to high disease burden but responding well to treatments
      - Examples: HCC patients with large nodules responding to radioembolization or those with macrovascular invasion responding to new systemic treatments
  - Effective Downstaging Strategies
    - Combining systemic treatment with locoregional therapy offers effectiveness
    - Tailoring treatments to target largest nodules while using systemic therapy for others can expedite downstaging and reduce dropout risk, consider hepatic functional reserve
  - Challenges and Future Perspectives
    - Long-term post-transplant survival and relapse rates crucial, but data is limited
    - Prospective multicenter studies needed
    - Dynamic list management and monitoring biological markers vital for success, balancing waiting list dynamics and patient outcomes

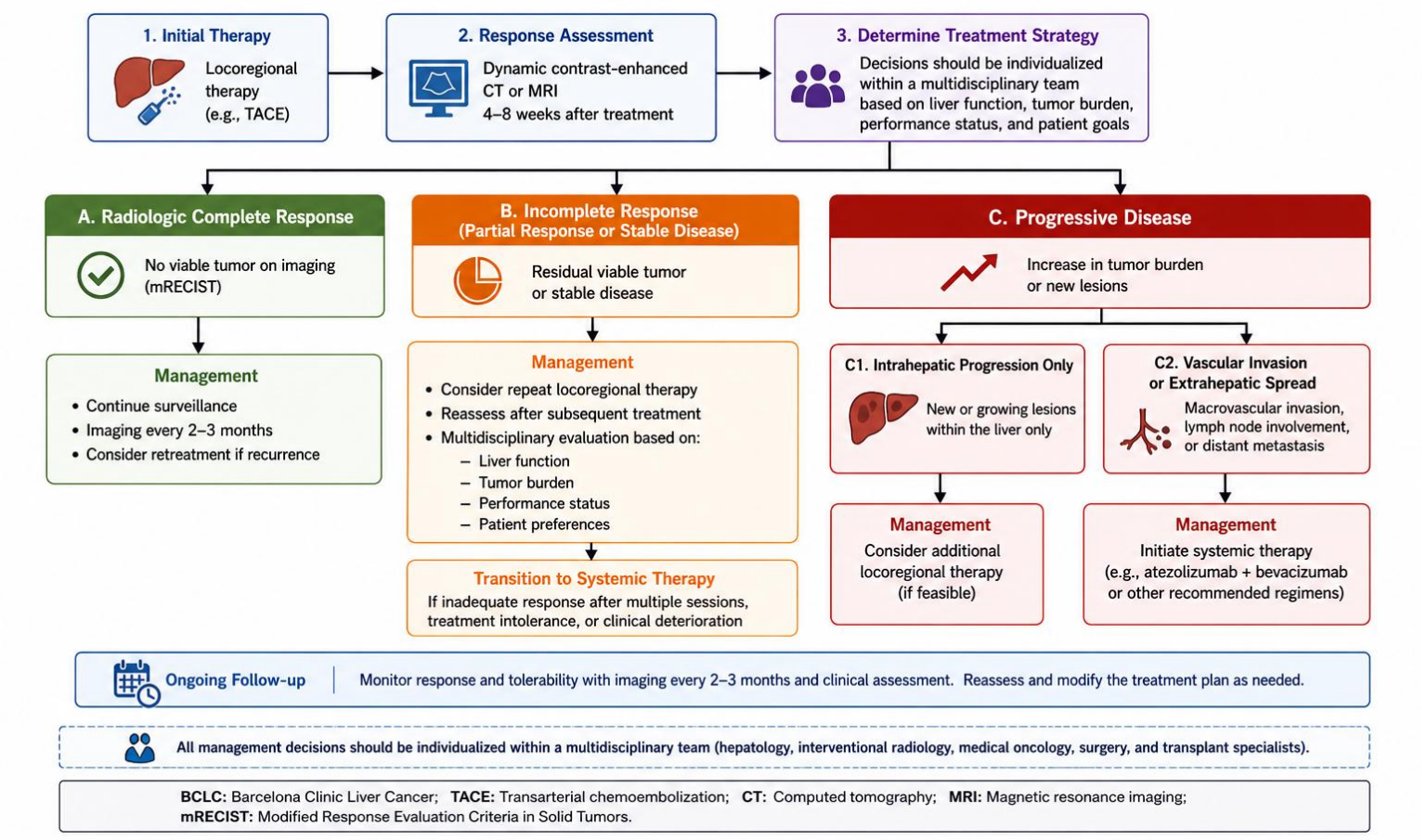
- Current LRT – TACE/TARE
  - Absolute Contraindications to Locoregional Therapy (TACE/TARE)
    - Decompensated Cirrhosis (CTP ≥ B8), ALBI > 1
    - Extensive Tumour/Diffuse infiltration
    - Severely Reduced Portal vein flow / Vp4 PVT
    - Technical Limitations
  - TACE Relative Contraindications
    - Portal Vein thrombosis
    - Severe cardiopulmonary comorbidities
    - Tumour Size ≥ 10 cm (some advocate applying “Up to 7 Criteria”)
    - Untreated varices as high risk of bleeding
    - Risk of bile-duct occlusion

- TARE Relative Contraindications
  - Portal vein thrombosis (may still be feasible)
  - 20% lung shunting of hepatic artery flow
  - Vascular anomaly resulting in increasing hepatic arterial blood flow to other organs
    - Requires two procedures (mapping, treatment)

➢ **Y90 Radiation Segmentectomy vs TACE**

Response Type (mRECIST)	Y90 (%)	TACE (%)	P-value (adj)
Primary tumour CR	92	74	P < 0.001
Overall tumour CR	84	58	P < 0.001
Partial response	6	36	—
Stable disease	2	5	—
Progression	1	3	—
− Progression at 1 year	7.2	15	P < 0.001
− Progression at 2 years	30	42	P < 0.001

Management After Locoregional Therapy (e.g., TACE) in Intermediate-Stage Hepatocellular Carcinoma (BCLC Stage B)



Developed based on contemporary hepatocellular carcinoma guidelines and clinical evidence, including the Barcelona Clinic Liver Cancer (BCLC) strategy update, practice guidance from the American Association for the Study of Liver Diseases, and key studies on locoregional and systemic therapy sequencing.

➢ Locoregional Therapy and ICI's

- Background
  - TACE has been the standard of care for HCC eligible for embolization for over 20 yr
    - However, median PFS for HCC treated with TACE remains 7–8 mon
  - The population of people with HCC who receive embolization is highly heterogeneous, based upon
    - Tumour burden
    - Liver function, and
    - Comorbidities
  - Immunotherapy + Anti-VEGF is hypothesized to
    - ↑ antitumour activity via
      - Immune activation
      - Inhibition of tumour neovascularization
  - TACE may prime the tumour microenvironment (TME) for
    - Immunotherapy and
    - Anti-VEGF (vascular endothelial growth factor) therapy via neoantigen release as a response to ischemia
  - The EMERALD-1 study (NCT03778957) evaluated TACE plus durvalumab (anti-PD-L1 immunotherapy) ± bevacizumab (anti-VEGF) in participants with unresectable HCC eligible for embolization

- EMERALD-1 Study Design
  - A global, double-blind, placebo-controlled Phase 3 study
    - Study Population
      - Adults with confirmed HCC
      - Not amenable to curative therapy (e.g., resection, ablation, transplantation)
      - No extrahepatic disease
      - Child-Pugh A to B7
      - ECOG PS 0 or 1
      - Measurable disease per mRECIST
      - Excludes Vp3 and Vp4
      - No prior systemic therapy or TACE†
    - Stratification Factors
      - TACE modality (DEB-TACE vs cTACE)
      - Geographical region (Japan vs Asia [excluding Japan] vs other)
      - Portal vein invasion (Vp1 or Vp2 ± Vp1 vs none)

- Endpoints
  - Primary
    - PFS for Arm B vs Arm C using BICR per RECIST 1.1
  - Key Secondary
    - PFS for Arm A vs Arm C
    - OS
    - QoL
  - Other Secondary
    - ORR and TTP using BICR per RECIST 1.1
    - Safety
    - PFS/ORR/TTP via investigator and BICR per mRECIST

Abbreviations: BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead TACE; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; mRECIST, modified RECIST; ORR: objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q4W/Q2W/Q3W, q4/2/3 wks; QoL, quality of life; RECIST, response evaluation criteria in solid tumours; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression; VEGF, vascular endothelial growth factor

➢ Systemic Therapy

- HCC is not resistant to conventional cytotoxic chemotherapy
  - Patients with BCLC B or BCLC C HCC who have adequate performance status and liver function, but are no longer candidates for LRT, either due to disease burden or extrahepatic spread, should be considered for systemic therapy
- Untreated BCLC B and BCLC C HCC
  - Poor prognosis ~~9 mon and 3 mon, respectively
  - Effective therapies are essential to improve outcomes
- HCC is resistant to conventional cytotoxic chemotherapy due to:
  - Autophagy activation
  - Apoptosis evasion
  - Expression of drug efflux pumps
  - Development of DNA repair mechanisms

- Objective Response Rates with Systemic Therapy

Trial	Design	Arms	OS (mon)	ORR
CELESTIAL	2nd/P3	Cabo vs plac	10.2 vs 8.0*	4% vs 1%
CheckMate 040	2nd/P2	Ipi/Nivo	22.8	32%
CheckMate 459	Front/P3	Nivo vs Soraf	16.4 vs 14.7	15% vs 7%
COSMIC-312	Front/P3	Cabo/Atezo vs Sor	15.4 vs 15.5	11% vs 3.7%
HIMALAYA	Front/P3	Durva/Treme vs Sor	16.4 vs 13.8*	20.1% vs 5.1%
IMBRAVE-150	Front/P3	Atezo/Bev vs Sor	19.2 vs 13.4*	29.8% vs 11.3%
KEYNOTE-240	2nd/P3	Pembro vs Plac	13.9 vs 10.6	18% vs 4.4%
LEAP-002	Front/P3	Len/Pembro vs Len	21.2 vs 19.0	26.1% vs 17.5%
REACH-2	2nd/P3	Ramucirumab vs plac	8.5 vs 7.3	5% vs 1%
REFLECT	Front/P3	Lenvatinib vs Soraf	13.6 vs 12.3	18.8% vs 6.5%
RESORCE	2nd/P3	Regoraf vs plac	10.6 vs 7.8*	10% vs 4%
SHARP	Front/P3	Soraf vs Plac	10.7 vs 7.9*	2% vs 1%

  - **mRECIST for HCC – Response Assessment**

Response	Definition
CR	Disappearance of any intratumoural arterial enhancement in all target lesions
PR	≥ 30% ↓ SoD* of viable portions (enhancement on arterial phase) of target lesions from baseline
PD	≥ 20% ↑ SoD* of viable portions of target lesions with nadir as a reference point
SD	Neither PR nor PD with nadir** as a reference point

  - The treatment options in 2025 for first-line treatment for HCC include targeted therapies such as
    - Multikinase inhibitors (MKIs)
    - Anti-VEGF therapies
    - Immune checkpoint inhibitors (ICIs), or
    - Combinations

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SB, sustained benefit / stable benefit; SD, stable disease; VEGF, vascular endothelial growth factor

Note: in RECIST viable tumour eradication based or arterial phase enhancement on imaging (not the usual evaluation on the basis of diameter of tumour

Efficacy Outcomes of First-Line Systemic Therapies In Advanced Hepatocellular Carcinoma.

Study	Design	Intervention vs. Control	ORR Intervention vs. Control	DCR Intervention vs. Control	Survival (Months)
○ SHARP	Randomized, double-blind, placebo-controlled, phase III	Sorafenib vs. placebo	RECIST: 2% vs. 1%	RECIST: 43% vs. 32%	10.7 vs. 7.9
			RECIST: 18.8% vs. 6.5%	RECIST: 72.8% vs. 59.0%	
○ REFLECT	Randomized, open-label, non-inferiority phase III	Lenvatinib vs. sorafenib	mRECIST (investigator): 24.1% vs. 9.2%	mRECIST (investigator): 75.5% vs. 65.5%	13.6 vs. 12.3
			mRECIST (masked review): 40.6% vs. 12.4%	mRECIST (masked review): 73.8% vs. 58.4%	
○ IMBRAVE-150	Randomized, open-label, phase III	Atezolizumab/ bevacizumab vs. sorafenib	RECIST: 27.3% vs. 11.9%	RECIST: 75.6% vs. 55.7%	19.2 vs. 13.4
			mRECIST: 33.2% vs. 13.3%	mRECIST: 72.3% vs. 51.1%	
○ HIMALAYA	Randomized, open-label, sponsor-blind, phase III	Durvalumab/ tremelimumab vs. sorafenib	RECIST: durva/treme 20.1% vs. durva 17% vs. soraf 5.1%	RECIST: 60.1% vs. 58.4% vs. 60.7%	16.43 vs. 16.56 vs. 13.77

Abbreviations: DCR, disease control rate; ORR, objective response rate

Courtesy of: Llovet JM, Ricci S, Mazzaferro V, et al. N Engl J Med. 2008;359(4):378-390; Kudo M, Finn RS, Qin S, et al. Lancet. 2018;391(10126):1163-1173; Finn RS, Qin S, Ikeda M, et al. N Engl J Med. 2020;382(20):1894-1905; Abou-Alfa GK, Lau G, Kudo M, et al. N Engl J Med. 2022;386(20):1899-1911.

- **Single Tremelimumab Regular Interval Durvalumab** (STRIDE) **vs. Sorafenib**

PHASE III HIMALAYA STUDY

- Inclusion Criteria
  - Age ≥ 18 years
  - Histologically confirmed HCC
  - BCLC B or C
  - Child-Pugh A
  - ECOG 0 to 1
- Intervention
  - Tremelimumab (CTLA-4 inhibitor) + Durvalumab (anti-PD-L1)
  - Durvalumab monotherapy
  - Sorafenib (multi-tyrosine kinase inhibitor)
- Primary Endpoint
  - Time from randomization until death (any cause)
  - Median Overall Survival of 16.56 months [14.01–19.12] vs. 13.77 months [12.25–16.13]
- Adverse Events
  - Grade 3/4, events
    - STRIDE: 50.5%
    - Durvalumab: 37.1%
    - Sorafenib: 52.4%
  - **No** treatment-related gastrointestinal or esophageal varices hemorrhagic events noted (*In contrast to IMBRAVE-150)*

➢ **Positive Studies**

- **CARES-310 – Camrelizumab and Rivoceranib vs. Sorafenib**

PHASE III STUDY – FDA ACCESSING/APPROVAL PENDING

- Inclusion Criteria
  - Age ≥ 18 years
  - Histologically confirmed HCC
  - BCLC B or C
  - Child-Pugh A
  - ECOG 0 to 1
- Intervention
  - Camrelizumab (anti-PD1) + Rivoceranib (VEGFGR2) vs. Sorafenib
- Primary Endpoint
  - Dual outcome
  - Progression-free survival (progression or death)
  - Overall survival

- Median Overall Survival 22 mon [19.1–27.2] vs. 15.2 mon [13.0–18.5]; Hazard Ratio: 0.62 [0.49–0.80]
- Adverse Events
  - Camrelizumab–Rivoceranib group, and 6% in the sorafenib group

➢ **Negative Studies**

- **Leap 002**
  - Background
    - Systemic therapies have advanced the treatment of hepatocellular carcinoma.
    - Need for improved survival in first-line advanced stages persists.
    - Evaluation of pembrolizumab (anti-PD1) addition to lenvatinib versus lenvatinib alone initiated to address this need.
  - Methods
    - Global, double-blind, phase 3 study (LEAP-002) conducted.
    - Patients with unresectable hepatocellular carcinoma enrolled (N = 794).
    - Randomized to receive lenvatinib plus pembrolizumab or lenvatinib plus placebo.
  - Findings
    - Median overall survival
      - 21 mon with lenvatinib + pembrolizumab vs,19 mon with lenvatinib + placebo (HR 0.84 [95% CI 0.71–1.00])
    - Median progression-free survival
      - 8 mon with lenvatinib + pembrolizumab vs. 8 mon with lenvatinib + placebo (HR 0.87 [95% CI 0.73–1.02])
  - Adverse Events
    - Common, with treatment-related deaths occurred in 1% of patients in both groups

- **COSMIC-312**
  - Background
    - Cabozantinib has demonstrated clinical efficacy when combined with checkpoint inhibitors across solid tumours.
    - COSMIC-312 trial aimed to evaluate cabozantinib plus atezolizumab (PD-L1) versus sorafenib as first-line therapy for advanced hepatocellular carcinoma.
  - Methods
    - Open-label, randomized, phase 3 trial conducted across 32 countries.
    - Patients with advanced hepatocellular carcinoma, not amenable to curative therapy, enrolled (N = 837).
    - Randomized to receive Cabozantinib + Atezolizumab, Sorafenib, or Single-agent Cabozantinib

- Findings
  - Median progression-free survival
    - 7 mon with combination therapy vs. 4.2 mon with sorafenib alone (HR 0.63, p = 0.0012)
  - Interim analysis of overall survival
    - No significant difference between combination therapy and sorafenib alone
- Adverse Events
  - Common
  - Serious events more frequent in the combination therapy group

Morpheus-Liver (RECENT PHASE 1B/2 STUDY)

- Intervention
  - Atezolizumab (PD-L1) and Bevacizumab (VEGF) with the addition of tiragolumab (TIGIT); An immune receptor present on some T cells and natural killer cells which ↑ checkpoint inhibitor therapy
- Primary Endpoint
  - Objective Response Rate (% of patients with a partial response or complete response to therapy)
    - Atezo/bev: 11.1% vs. Atezo/bev + tira, 43%

➢ Summary

- Multidisciplinary Approach
  - Crucial for the effective management of hepatocellular carcinoma (HCC)
  - Ensures that all aspects of the disease, from diagnosis to treatment planning, are addressed comprehensively.
- Treatment Options
  - Based on the patient's **Barcelona Clinic Liver Cancer (BCLC) stage**.
- This staging system helps guide decisions on therapies such as surgery, locoregional treatments, or systemic therapy.

➢ **Liver-directed therapies**

Therapy	Advantages	Disadvantages
○ Ablation	– Curative – Well tolerated	▪ Limited to small lesions, ideal for <3 cm ▪ Be mindful of location ▪ Avoid dome lesions ▪ Adjacent to major vessels \ bile ducts ▪ Can be expensive
○ Y90	– Can be used in the presence of portal vein thrombosis – Outpatient procedure performed in two sessions (mapping + treatment) – Well tolerated	▪ Must pass mapping procedure requirements (avoid hepatopulmonary shunting or reflux)
○ TACE	– One-time treatment – Recommended as first-line liver-directed therapy for BCLC stage B patients	▪ Overnight hospital stay required to monitor post-procedure pain and complications ▪ Cannot be used in patients with portal vein thrombosis
○ External beam radiation	– Minimal risk of liver damage – Can be used in the presence of portal vein thrombosis – Dome lesions can be treated	▪ Often requires multiple days of treatment ▪ Caution advised if bowel is in close proximity (e.g., caudate lobe lesions)

- **HCC, 2nd Line if Failure of 1st Line Chemotherapy**
  - After progression on first-line immunotherapy, about half of patients remain eligible for further systemic therapy.
  - Retrospective data support sorafenib, lenvatinib, or nivolumab plus ipilimumab, while prospective studies include cabozantinib and pembrolizumab plus regorafenib.
  - The other half are ineligible and receive palliative care. Among those eligible, ~40% with oligoprogression may benefit from locoregional therapy such as TACE, SBRT, TARE, or ablation.

Clinical Scenario	Next Step	Evidence Source
○ HCC progression on first-line immunotherapy	Eligible for systemic therapy (~50%)	Retrospective: Sorafenib, Lenvatinib, Nivolumab+Ipilimumab; Prospective: Cabozantinib, Pembrolizumab+Regorafenib
○ HCC progression on first-line immunotherapy	Ineligible for systemic therapy (~50%)	Palliative care
○ Oligoprogression (~40% of systemic-eligible)	Locoregional therapy (TACE, SBRT, TARE, ablation)	Clinical practice data

Adapted from: https://dailynews.ascopubs.org/do/systemic-therapy-hepatocellular-carcinoma-s-next-after-immunotherapy

Kaplan-Meier Curve – PFS: D+B + TACE vs. Placebos + TACE

- Key Findings
  - Median PFS improved by 6.8 mon with D+B + TACE vs. Placebos + TACE

Group	Median PFS (95% CI), mon	Participants (n)
− D+B + TACE	15.0 (11.1–18.9)	204
− Placebos + TACE	8.2 (6.9–11.1)	205

  - Hazard Ratio (HR): 0.77 (95% CI: 0.61–0.98)
  - Stratified log-rank p-value: 0.032*

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin score; APHE, arterial phase hyperenhancement; APRI, AST to platelet ratio index; BCLC, Barcelona Clinic Liver Cancer; BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; CR, complete response; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCP, des-carboxy-prothrombin; DFS, disease-free survival; DCR, disease control rate; DEB-TACE, drug-eluting bead TACE; ECOG, Eastern Cooperative Oncology Group; ERS, early recurrence score; EASL, European Association for the Study of the Liver; FLR, functional liver remnant; FS, FibroScan; FT, FibroTest; GALAD, gender, age, L3-AFP, AFP, DCP model; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; IO, immuno-oncology; LI-RADS, Liver Imaging Reporting and Data System; LRT, locoregional therapy; LR-NC, LI-RADS not categorizable; LR-TIV, LI-RADS tumour in vein; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-stage Liver Disease; MVI, microvascular invasion; mRECIST, modified Response Evaluation Criteria in Solid Tumours; MWA, microwave ablation; OS, overall survival; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial

response; PS, performance status; RFA, radiofrequency ablation; RFS, recurrence-free survival; SD, stable disease; STRIDE, single tremelimumab regular interval durvalumab; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor; TTV, total tumour volume; UNOS, United Network for Organ Sharing; UCSF, University of California, San Francisco; US, ultrasound; VEGF, vascular endothelial growth factor; VIS, visualization score.

Suggested Reading:

Abou-Alfa GK, Lau G, Kudo M, et al; HIMALAYA Investigators. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *N Engl J Med.* 2022;386(20):1899-1911. doi:10.1056/NEJMoa2109685

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182-236. doi:10.1016/j.jhep.2018.03.019

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Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology.* 2018;67(1):358-380. doi:10.1002/hep.29086

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Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol.* 2022;76(3):681-693. doi:10.1016/j.jhep.2021.11.018

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PANCREAS

DIAGNOSIS AND MANAGEMENT OF PANCREATIC CYSTS

Brian Yan and Hisham Akhtar

- Demography
  - Prevalence
    - 75% of pancreatic cysts are asymptomatic/incidental
      - 80% of resected asymptomatic cysts are benign
      - 25% of patients >70 have incidental cysts
  - Age of onset
    - Usually 40 to 60 yrs, except for
      - Pseudopapillary neoplasms (20s)
      - Pseudocyst (any age)
      - Gender distribution, except more females with SCN, SPN, MCI
  - Autopsy study, ~50% had cysts
  - Malignancy in $2/10^4$ incidental cysts
  - Rate of malignant transformation, 0.24%/year

Take Home Message

Pancreatic cysts are very common, and malignant ones are rare.

  - 3% of CT and up to 45% of MRIs have an incidental pancreatic cysts
  - Only 0.8% of cysts are >2 cm
  - Systematic review of 17 studies (only 3 prospective)
    - 48,860 patients
    - Prevalence
      - USA, 12.6%
      - Asia, 3.1%
    - Prevalence of mucinous lesions: 4.3%
      - Only 0.7% have worrisome/high-risk stigmata

The European Study Group on Cystic Tumours of the Pancreas. *Gut* 2018; 67: 789–804
Zerboni G, et al. *Pancreatology* 2019; 19: 2–9
Scheiman JM, et al. AGA Technical Review. *Gastroenterol* 2015; 148: 824–848
Elta GH, et al. ACG Clinical Guideline. *Am J Gastroenterol* 2018; 113: 464–479
Vege SS, et al. *Gastroenterol* 2015; 148: 819–822
Spinelli KS, et al. Ann Surg. 2004;239(5):651-657.
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- Classification
  - Benign
    - Pseudocyst
    - Serous cystadenoma (SCN)

- (Pre)Malignant
  - Mucinous cystic neoplasm (MCN)
    - Mucinous cystadenoma
    - Mucinous cystadenocarcinoma
  - Intraductal papillary neoplasm (IPMN)
    - Main pancreatic duct
    - Branched ducts

➢ Differential

Group (An Extension of Classification)	Tumours
Epithelial neoplastic	Mucinous ▪ IPMN ▪ Mucinous neoplasms Non-mucinous ▪ Acinar cell carcinoma ▪ Cystic ductal adenocarcinoma ▪ Cystic hamartoma ▪ Cystic neuroendocrine tumours ▪ Cystic teratoma ▪ Serous cystic neoplasms (SCN) ▪ Solid-pseudopapillary neoplasms (SPN)
Epithelial non-neoplastic	Congenital cyst Lymphoepithelial cyst Retention cyst Simple cyst
Non-epithelial neoplastic	Lymphangioma Sarcoma
Non-epithelial non-neoplastic	Pseudocyst Parasitic cyst Walled-off necrosis

Adapted from: Kloth C, et al. Diagnostic 2023; 13: 454-475

➢ Diagnostic Imaging

Characteristics of the major types of cystic lesions of the pancreas

Type	Diagnostic Imaging
Branch duct IPMN	Dilation of side branches of PD Grape-like cystic lesion

Type	Diagnostic Imaging
○ Cystic pancreatic neuroendocrine tumours (cPNET)	− Well-demarcated − Mixed solid cystic tumours − Seen anywhere in pancreas
○ Main duct IPMN	− Dilation of PD
○ Mucinous cystic neoplasm (MCN)	− Unilocular/septated − Some have peripheral calcifications − Usually tail of pancreas
○ Pseudocyst	− Well-circumscribed − Oval or sound − Anechoic on EUS − Low attenuation on EUS
○ Serous cystic neoplasms (SCN)	− Microcystic/honeycomb, ± central scar (30%)
○ Solid-pseudopapillary neoplasms (SPN)	− Well-demarcated − Mixed solid-cystic tumours − Seen anywhere in pancreas

Abbreviations: CEA, carcinoembryonic antigen; CT, computerized tomography; EUS, endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PD, main pancreatic duct

- Only IPMN, main/branched duct, and some pseudocysts connect to the main pancreatic duct
  - Cyst aspirate has
    - ↑ amylase in IPMN (MD, BD)
    - ↑ CEA in IPMN (MD, BD) and MCN
- Solitary cysts
  - SCN, SPN, MCN, cPNET (cystic pancreatic neuroendocrine tumour)
  - Others may be single or multiple
- Ovarian stroma
- ↑ risk of malignancy
  - All except pseudocyst, SCN
  - In the other types of pseudocyst, risk of malignancy with ↑ size (>2 to >3 cm)

Burlein R and Shami VM. Ther Adv Gastrointest Endosc 2021; 14: 1-21

Key Points:

- Look for mass/nodule/cyst
- Look for characteristics: connected to the pancreatic duct (IPMN)
  - Microcystic / honeycomb (SCN)
  - Central scar (SCN)
  - Well-circumscribed (SPN, cPNET)
  - Unilocular/septated, calcifications, tail of pancreas (MCN)

- Endoscopic ultrasound (EUS)
  - Indications ACG guidelines (2018)
    - If any of the following present:
      - Change in PD caliber with upstream atrophy
      - IPMN or MCN ≥3 cm
      - Jaundice due to cyst
      - Pancreatitis due to cyst
      - PD ≥5 mm
      - Presence of mural nodule or solid component
      - Size increase >3 mm/year during surveillance

Clinical or radiological features of concern for malignancy can be alternated or done in conjunction with MRI during surveillance

  - Outcomes using AGA (2018) vs. International consensus (2017) guidelines
    - Mortality rates related to management of PCN
      - No difference
    - Costs per patient / per cancer identified ~~50% lower using AGA guidelines

Lobo JM, et al. Am J Gastroenterol 2020; 115; 1689-1697

- Endoscopic ultrasound (EUS) and EUS Guided Needle Confocal Laser Endomicroscopy (NCLE)
  - Detection of advanced neoplasia in IPMNs
    - Epithelial thickness
    - Darkness of epithelium
    - Density of papillae
    - Intricate vascularity
    - Intracystic cellularity

Ardeshna DR, et al. World J Gastroenterol 2022; 28; 624-634

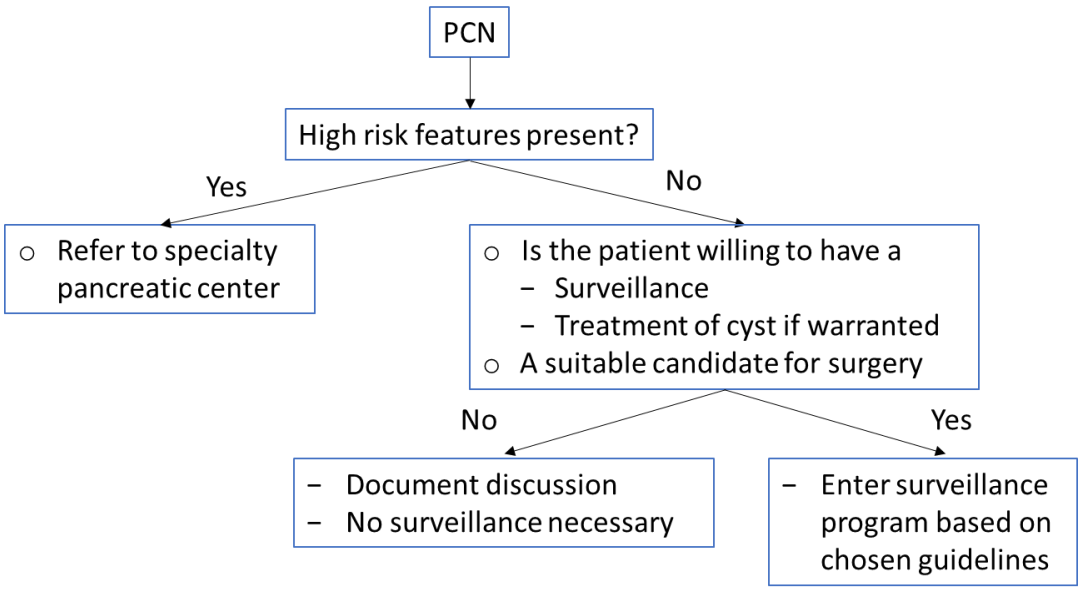
➢ Surveillance

Cyst size	2018 ACG	2018 European
<1 cm	MRI q2 yrs ×4 yrs (then consider lengthening)	Year 1: MRI/EUS q6 mon + CA-19-9 + clinical evaluation After Year 1: MRI/EUS q1 yr + CA-19-9 and clinical evaluation; ≥4 cm: resection

Cyst size	2018 ACG	2018 European
○ 1–2 cm	– MRI q1 yr ×3 yrs, then q2 yrs ×4 yrs (then considering lengthening)	—
○ 2–3 cm	– MRI/EUS q6–12 mon ×3 yrs, then q1 yr ×4 yrs (then lengthen)	—
○ >3 cm	– Refer to multidisciplinary group; alternate EUS/MRI q6 mon ×3 yrs, then yearly ×4 yrs (then consider lengthening)	—

Abbreviations: CEA, carcinoembryonic antigen; CT, computerized tomography; EUS, endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PD, main pancreatic duct

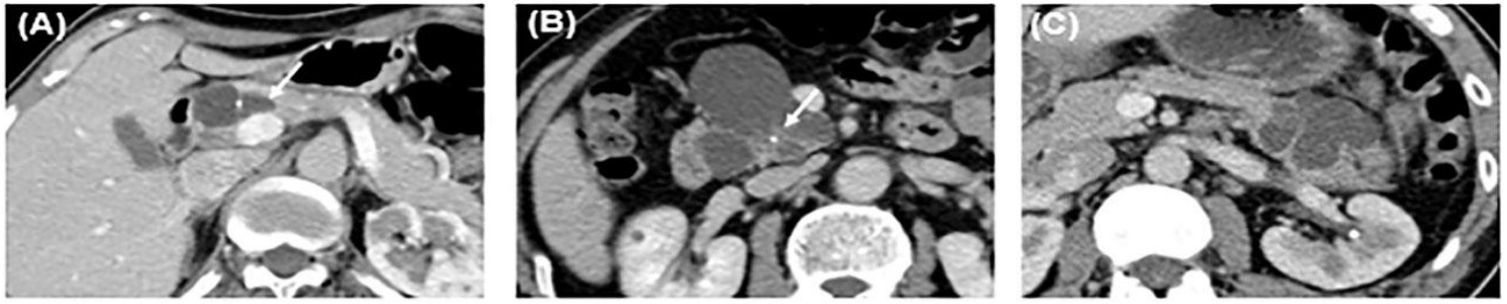
Algorithm to Approach Pancreatic Cysts



- ○ High-risk features
  - – Mural nodule
  - – Solid component
  - – Dilation of main pancreatic duct (≥5 mm)
  - – Cyst size ≥3-4 cm, and
  - – Positive cytology on fluid aspiration

Adapted from: Burlein R and Shami VM. Ther Adv Gastrointest Endosc 2021; 14: 1-21.

Differences in the characteristics of SCNs and MCNs



- (A) shows a macrocystic SCN in the head of the pancreas, and a small cyst can be seen outside the mother cyst (white arrow), called the extracapsular cystic sign.
- (B) shows an SCN presenting as a central scar with dotted calcification, which is typical of this kind of neoplasm.
- (C) presents an SCN with multiple cysts that is difficult to diagnose.
- (D) shows a septal wall inside an MCN, which forms a small cyst called the intracapsular cystic sign.
- (E) depicts an MCN with calcification on the septal wall.
- (F) shows an MCN with a single cyst and a smooth contour.

Courtesy of: Chen H-Y, et al. Front. Oncol 202111: 745001.

Take Home Message

- Unfortunately
  - Morphology is not good to determine if lesion is malignant or not
- Kappa statistics vary from 0.010 to 0.463, when reporting agreement between 8 reviews, excluding data noted as “indeterminate by ≥ 2 review (Ahmad et al, GIE 2003)

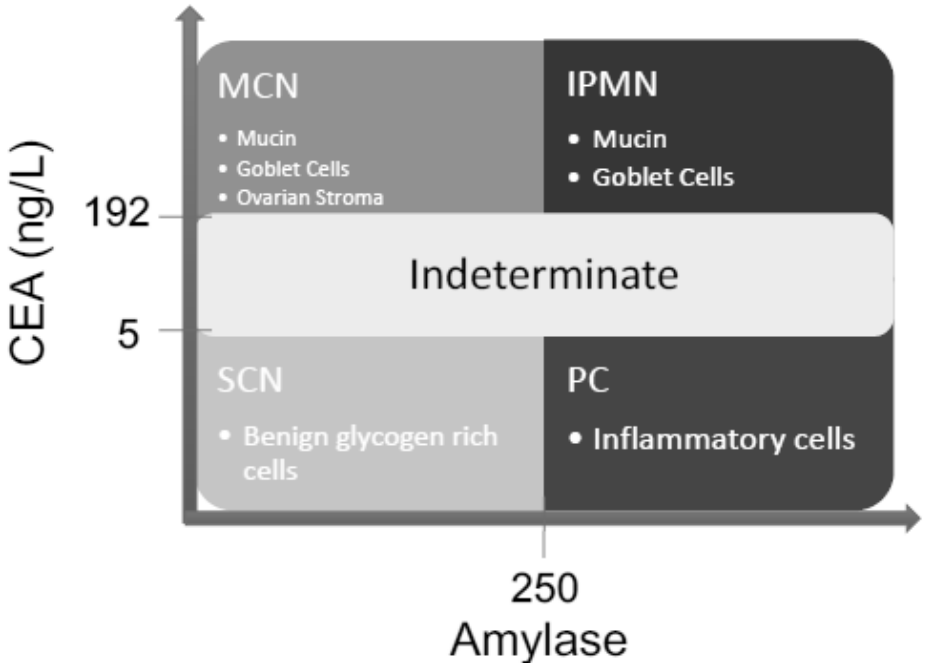
- The future of pancreatic imaging – Radiomics
  - Analysis of mathematically derived textural features from cross-sectional imaging studies
  - Beyond human perception
  - Quantify individual pixels and their associated gray-scale value from cross-sectional imaging in a temporal and spatial plane to create a cyst impression
  - C**ategories**
    - Differentiating types of PCNs
    - Risk Stratification

Ardeshna DR, et al. World J Gastroenterol 2022; 28: 624-634

➢ Laboratory

- Analysis of aspirate of pancreatic cyst
  - Amylase
  - CEA
  - Cytology
  - Glucose
  - Molecular Analysis (KRAS, GNAS)
  - Mucin Profiling
  - Mucin Stain
  - String Sign

Ardeshna DR, et al. *World J Gastroenterol* 2022; 28: 624–634



- Tumour Markers in Pancreatic Cyst Fluid Glucose

Differentiating Between Mucinous and Non-mucinous Lesions

Tumour Marker	Sensitivity	Specificity	Accuracy	ROC	P Value	Cut-off
CEA*	0.73	0.84	0.79	0.930	<.001	192
CA 125	0.83	0.37	0.60	0.501	0.183	9
CA 15-3	0.19	0.94	0.57	0.501	0.815	121
CA 19-9*	0.58	0.62	0.66	0.654	0.004	2900
CA 72-4*	0.80	0.61	0.72	0.742	0.001	7

*Only the tumour marker carcinoembryonic antigen (CEA), CA 19-9, and CA 72-4 have statistically significant P-values to differentiate between mucinous and non-mucinous lesions.

van der Waaij LA, et al. Gastrointest Endosc. 2005;62(3):383-389.
Brugge WR, et al. Gastroenterology 2004;126(5):1330-1336.

- Glucose in Pancreatic Cyst Fluid
  - Cystic fluid glucose < 28 mmol (50 mg/dL)
    - Performance characteristics to differentiate mucinous from non-mucinous pancreatic cysts
      - Sensitivity, 91%
      - Specificity: 86%
      - Accuracy: 94%

McCarty TR, et al., GIE 2021; 94: 678-712

- Mutational/Molecular Analysis
  - Mucinous
    - KRAS
    - RNF43
    - TP53
    - P16/CDKN2A
    - SMAD4
  - Mucinous – IPMN
    - GNAS
  - Malignancy
    - DNA Aneuploidy/tetraploidy
  - SPN
    - VHL
    - CTNNB1 (Beta-catenin)
  - Malignancy – SMAD4

	Mucinous		Malignant	
Test	Sensitivity	Specificity	Sensitivity	Specificity
KRAS	11–57%	93–100%	20–91%	71–93%
LOH	43–70%	66–100%	50–100%	36–83%
DNA Quantity/Quality	29–46%	68–100%	40–83%	75–93%

Abbreviations: Sn, sensitivity; Sp, specificity

Levy MJ, et al. Gastrointest Endosc. 2016;83(5 Suppl): AB148. Presented at Digestive Disease Week (DDW), San Diego, CA, May 21–24, 2016.

- Comparison of EUS-FNA Markers

Test	Sensitivity	Specificity
○ Mucinous		
− CEA >192 ng/mL	75%	81%
− Glucose <50 mg/dL	89%	78%
− String sign ≥1 cm	95%	94%
− KRAS/GNAS mutation	89%	100%
○ SCN, pseudocyst, cystic NET		
− CEA <5 ng/mL	50%	95%
○ Excludes pseudocyst		
− Amylase <250 U/L	44%	98%

Adapted from: Lee LS. World J Gastroenterol 2021; 27; 5700-5714

- Other Aids
  - Cystoscopy
    - Spyglass
  - Needle-based Confocal Laser Endomicroscopy (nCLE)
  - Optical Coherence Tomography (OCT)
  - Microbiopsy forceps
  - Artificial intelligence (AI)
    - Machine learning algorithm

Rangwani S, et al. Biomimetics 2022; 7: 79-93

Take Home Message (The European Study Group on Cystic Tumours of the Pancreas. Gut 2018; 67: 789–804)

- Perform pancreatic cyst fluid analysis for CEA, cyst fluid lipase levels, and cytology to adhere the highest accuracy for differentiating mucinous from non-mucinous PCN (GRADE 2C, strong agreement).
- Do **not** perform EUS-FNA
  - If results are expected to change clinical management (GRADE 2C, strong agreement).
  - If the diagnosis is already established by cross-sectional imaging, or
  - Where there is a clear indication for surgery (GRADE 2C, strong agreement).

- Natural History
  - IPMN
  - MD-IPMN: ~40% malignant risk

Predictor	Positive LR (95% CI)	Negative LR (95% CI)
– Mural nodule ≥10 mm	5.5 (2.3–13.3)	0.18 (0.08–0.41)
– Positive cytology	20.3 (3.0–137)	0.23 (0.12–0.44)
– Mural nodule ≥10 mm OR positive cytology	6.1 (2.5–14.9)	0.07 (0.02–0.29)

  - SB/BD-IPMN
    - Risk of malignancy
      - Positive cytology
      - Development of pancreatic duct adenocarcinoma (PDCA)
        - 10 yr, ~4%
        - 15-yr, 12%

Oyama H, et al. Gastroenterology 2020; 158; 226-237

    - Malignant features
      - ↑ size > 3 cm, size growing
      - ↑ number of multifocal lesions
      - Presence of nodule (solid components) / papillae
  - MCN
    - Prevalence of invasive cancer, 7% to 36%
  - Pancreatic hepatic neoplasm (PCN)
    - Rate of malignant transformation, 0.12% per yr

Take Home Message

- Most pancreatic cysts do **not** become malignant.

- Treatment: Surgical resection of pancreas
  - Indications for surgical resection
    - 2015 AGA
      - Positive cytology on EUS-guided FNA of both a solid component and dilated PD

- 2017 International Consensus
  - Obstructive jaundice with PCN in head of pancreas
  - Enhanced mural nodules ≥5 mm
  - PD ≥10 mm
  - MD-IPMN
  - Cytology suspicious / positive for malignancy
- 2018 ACG
  - All MD-IPMNs; cytology with high-grade dysplasia or malignancy; mural nodule; concerning features on EUS

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; BD-IPMN, branch duct intraductal papillary mucinous neoplasm; CA-19-9 carbohydrate antigen 19-9; EUS, endoscopic ultrasound; FNA, fine needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PCN, pancreatic cystic neoplasm; PD, main pancreatic duct.

Burlein R and Shami VM. Ther Adv Gastrointest Endosc 2021; 14: 1–21

- European Guidelines (2018)
  - Absolute Indications:
    - Positive cytology for malignancy/HGD
    - Solid mass
    - Jaundice (tumour related)
    - Enhancing mural nodule (≥5 mm)
    - MPD dilatation ≥10 mm
  - Relative Indications:
    - Grow-rate ≥5 mm/year
    - Increased levels of serum CA 19.9 (>37 U/mL)*
    - MPD dilatation between 5 and 9.9 mm
    - Cyst diameter ≥40 mm
    - New onset of diabetes mellitus
    - Acute pancreatitis (caused by IPMN)
    - Enhancing mural nodule (<5 mm)

*In the absence of jaundice

Abbreviations: HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct.

Adapted from: The European Study Group on Cystic Tumours of the Pancreas. Gut 2018; 67: 789–804

- Indications for surgery (Radiologically Suspected IPMN)
  - SCN usually doesn't need surgery
  - First Year from Diagnosis:
    - Clinical evaluation
    - Serum CA19.9
    - MRI and/or EUS
  - After First Year (yearly)
    - Clinical evaluation
    - Serum CA19.9
    - MRI and/or EUS
- Relative** Indication for Surgery
  - Patient Scenarios
    - Significant co-morbidities + only one relative indication
    - Significant co-morbidities + two or more relative indications
    - No significant co-morbidities + one or more relative indications
  - Management
    - Intensive surveillance (q6 mon)
      - Clinical evaluation
      - Serum CA19.9
      - MRI and/or EUS
- Absolute* Indication for Surgery
  - Lifelong follow-up for patients post-partial pancreatectomy
- Patients Unfit for Surgery
  - No follow-up required
  - Consider palliative care

*Absolute Indications:

- Cytology for positive malignancy or high-grade dysplasia
- Jaundice (tumour-related)
- Main pancreatic duct (MPD) dilatation ≥10 mm
- Mural nodule enhancing, and ≥5 mm
- Solid mass

**Relative Indications:

- Acute pancreatitis caused by IPMN
- Cyst diameter ≥40 mm
- Enhancing mural nodule <5 mm
- Growth rate ≥5 mm/yr
- MPD dilatation 5–9.9 mm
- New-onset diabetes mellitus
- Serum CA19.9 ≥37 U/mL (in absence of jaundice)

Abbreviation: EUS, endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm

Adapted from: The European Study Group on Cystic Tumours of the Pancreas. Gut 2018;67:789–804.

- Risk of pancreatic surgery for pancreatic cystic neoplasms
  - Morbidity, 30% to 50%
  - Motaliry, 4%

➢ Summary

- Pancreatic cysts are common, malignant cysts are not
- Morphology alone is not sufficient to determining if cyst is mucinous or malignant
- EUS can help to look at worrisome/high risk features to rule out cancer, and FNA may help if it changes management
  - Cyst fluid analysis
    - Amylase/lipase
    - CEA
    - Cytology
    - Glucose
- Surveillance: Pick a guideline, look for development of high risk features
- Natural history: The majority of cysts will never become malignant
- Pancreatic surgery carries mortality and morbidity
- Surgery for a select group based on high risk features of the cyst

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; BD-IPMN, branch duct intraductal papillary mucinous neoplasm; CA 19-9, carbohydrate antigen 19-9; CA 72-4, carbohydrate antigen 72-4; CA 125, carbohydrate antigen 125; CA 15-3, carbohydrate antigen 15-3; CEA, carcinoembryonic antigen; CT, computerized tomography; cPNET, cystic pancreatic neuroendocrine tumour; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GNAS, guanine nucleotide-binding protein alpha subunit; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; KRAS, Kirsten rat sarcoma viral oncogene; MCN, mucinous cystic neoplasm; MPD, main pancreatic duct; NCLE, needle confocal laser endomicroscopy; NET, neuroendocrine tumour; OCT, optical coherence tomography; PCN, pancreatic cystic neoplasm; PD, pancreatic duct; PDCA, pancreatic ductal adenocarcinoma; SCN, serous cystic neoplasm; Sn, sensitivity; Sp, specificity; SPN, solid-pseudopapillary neoplasm; VHL, von Hippel–Lindau gene.

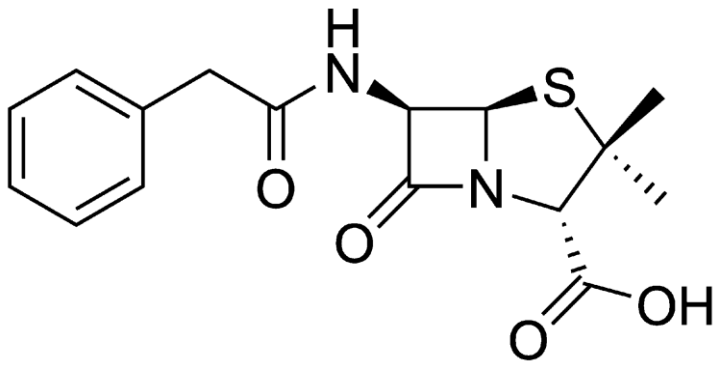
MISCELLANEOUS

SYPHILIS OF THE GI TRACT AND LIVER

Khalid Alseiari

- History of Syphilis
  - Discovery and Early Epidemics
  - Syphilis was first recognized in Europe during the late 15th century.
    - Treponema pallidum was identified in 1905 by Schaudinn and Hoffmann.
    - Initial treatments were rudimentary e.g., mercury, arsenicals.
  - Syphilis was first recognized in Europe during the late 15th century.
  - Cultural and Historical Context
    - The name 'Syphilis' comes from Girolamo Fracastoro's 1530 poem about a shepherd.
      - Often referred to as the 'French disease' or 'Italian disease', in depending upon where is the speaker.
  - Depicted in art and literature as a moral and social commentary.

- Penicillin and Syphilis
  - Discovery
    - Alexander Fleming identified penicillin in 1928 from *Penicillium notatum
  - Clinical Trial
    - In 1943, John F. Mahoney tested penicillin on syphilis patients.
    - Rapidly killed Treponema pallidum
    - Safe and effective; replaced toxic traditional treatments
  - Impact
    - Penicillin became the standard cure for syphilis, revolutionizing treatment and patient outcome



Courtesy of: Silva J, et al. Clean Technologies. 2019; 1(1):114-124 (Figure 1)

- Epidemiology
  - There is a recent global ↑ in syphilis cases, particularly among high-risk groups such as men who have sex with men (MSM), and person with HIV.
  - WHO estimates 1 million pregnant women are diagnosed with syphilis annually.
  - Even in some high-income countries, there are ↑ rate of each year of syphilis in men and women of childbearing age.
  - Infectious syphilis and congenital syphilis in Canada, 2022
    - Infectious Syphilis
      - There were 13,953 cases of infectious syphilis reported in 2022, a rate of 364 cases per 10^5 population.
        - ↑ 11% rate increase since 2021
        - ↑ 109% rate increase since 2018
      - The ↑ rates in males (M) and females (F) was in ~50% M>F
    - Congenital Syphilis
      - There were 117 cases of confirmed early congenital syphilis*, reported in 2022, rate of ~32 cases per 10^5 live births.
        - 7% ↑ rate increase since 2021
        - 599% ↑ rate increase since 2018

Rates of syphilis in men and women of childbearing age across high-income and middle-income settings

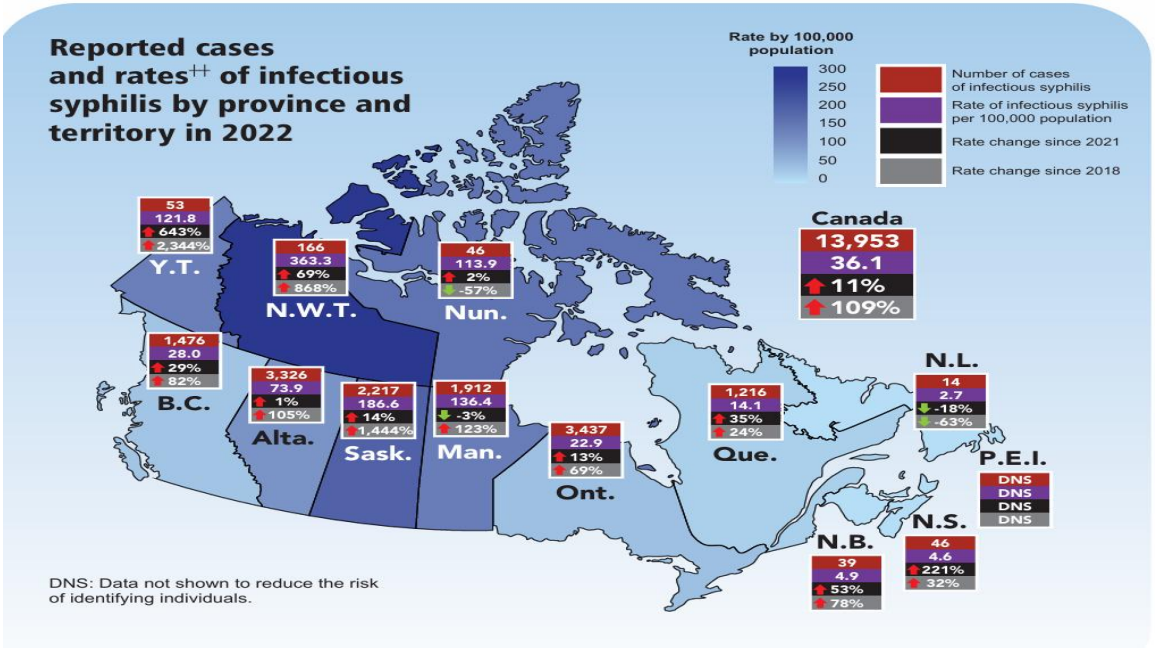
Country (age, yr)	Approximate Cases per 10^5 (Women, Men) 2019
Australia (15–44 yrs)	17
Brazil	22‡
Canada (15–39 yrs)	19†
Chile	28‡
England (15–44 yrs)	3
EU or EEA (25–44 yrs)	4
USA (15–44 yrs)	9

Abbreviations: EEA, European Economic Area; NA, Not available

Data from 2018
†Primary and secondary syphilis only
‡Antenatal screening rate

Courtesy of: https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2023-49/issue-10-october-2023/infectious-congenital-syphilis-canada-2022.html

Syphilis Rates in Canada



Courtesy of: https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2023-49/issue-10-october-2023/infectious-congenital-syphilis-canada-2022.html

- Microbiology
  - Causative Agent
    - Treponema pallidum
      - A spiral-shaped bacterium (spirochete)
  - Transmission
    - Sexual Contact
      - Most common route
    - Congenital
      - Mother-to-fetus, during pregnancy
    - Rare Cases
      - Blood transfusion, or
      - Contact with infected lesions

➢ Pathophysiology

- Early Local Infection
  - Treponema pallidum enters through microscopic abrasions in skin or mucosa.
  - Replication and Spread
    - Slow division (~30 hr)
    - Forms a painless ulcer (chancre)
    - Spreads to lymph nodes and bloodstream
  - Immune Response
  - Early Cellular Response:
    - Polymorphonuclear leukocytes → $CD4^+$ and $CD8^+$ T cells
    - Paradox
      - Resolves chancre, but
      - Allows dissemination
  - Hematogenous Spread
    - Leads to secondary syphilis
    - Involves multiple organs

- Latent Syphilis
  - Prolonged asymptomatic phase with possible reactivation
  - Key Manifestations
    - Gummas
      - Granulomatous soft-tissue lesions in skin, bones, and visceral
    - Cardiovascular Syphilis
      - Vasculitis (*endarteritis obliterans*)
      - Arterial damage including aortic
    - Neurosyphilis
      - CNS damage at any stage, leading to
        - ↓ coagulation
        - ↑ neurological defects
  - Gastrointestinal (GI) Involvement:
  - Mechanism
    - Direct invasion of rectal mucosa by *T. pallidum*
    - Inflammatory response in lamina propria
    - Mimics conditions like ulcerative colitis
    - Requires colonoscopy and biopsy for diagnostic confirmation

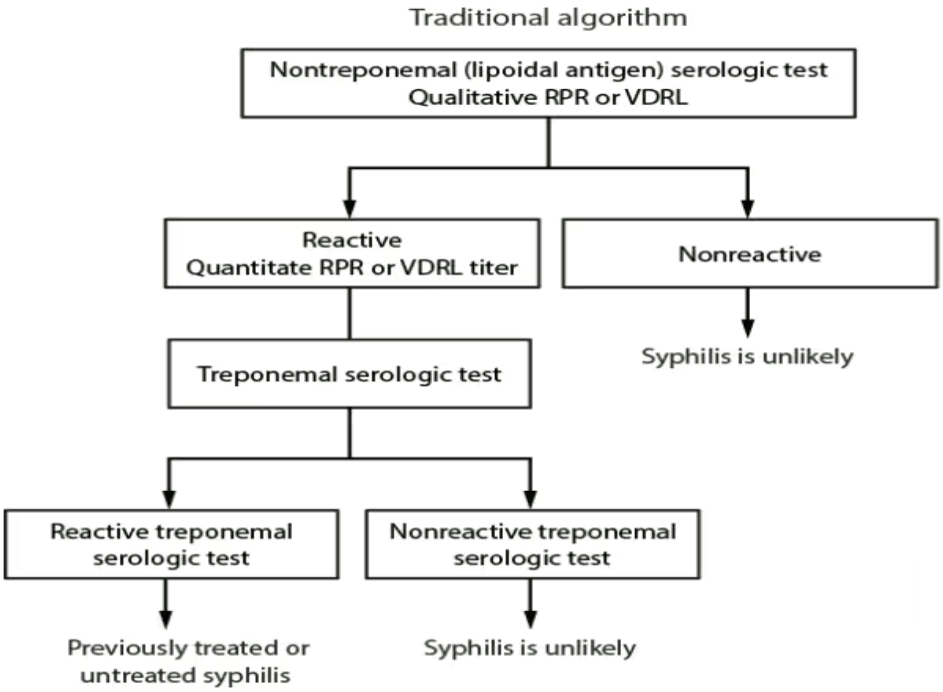
- Laboratory
  - Non-treponemal tests (NTT) *(VDRL, RPR)*
    - Non-specific antibody released during infection
  - Treponemal test (TT) *(immunoassays, TPPA, FTA-ABS)*
    - Specific antibody against *T. pallidum*, persist over lifetime
  - Who to test (PHAC, 2023)
    - Sexually active adults *(q3–6 months)*
    - Pregnant people (first visit, again at 28–32w, and once again at time of delivery only if in an outbreak area at risk of reinfection)
    - Suggest q3month opt-out programs for high-prevalence communities such as:
      - Gay, bisexual, and other MSM
      - People living with HIV infection
      - Person who is/was incarcerated
      - People who use substances / access addiction services
      - Some Indigenous communities

- Direct Detection Methods
  - Darkfield Microscopy and Molecular Tests (e.g., polymeric chain reaction [PCR])
    - Detecting *T. pallidum* directly from lesion exudate or tissue
    - Gold standard for diagnosing early and congenital syphilis
    - PCR tests for *T. pallidum* DNA
      - Available in specialized laboratories but
      - Not commercially standardized

- Serologic Testing (Presumptive Diagnosis)
  - Requires two types of tests to be positive to diagnose syphilis
    - Screening
      - Nontreponemal Test (e.g., RPR or VDRL)
        - Detect antibodies to cardiolipin–lecithin–cholesterol antigens
        - Reflect disease activity and monitor treatment response
      - Titers (Quantitative Results
        - Correlate with disease activity
        - A fourfold change in titers (e.g., 1:16 → 1:4) indicates treatment success
      - Limitations
        - False positives can occur with:
          - Other infections (e.g., HIV)
          - Pregnancy
          - Age
          - Autoimmune conditions
          - Drug use

        - Titers may persist ("serofast state") or fail to revert to nonreactive after treatment
        - Treponemal Test (e.g., TP-PA, EIA, CIA, or immunoblot)
            - Using one test type is sufficient to ↑ risks of false positives in conditions like pregnancy, autoimmune disorders, or previous syphilis treatment
            - Detect antibodies specific to *T. pallidum* antigens
            - Confirm diagnosis after a positive nontreponemal test
            - Limitations
                - Remain positive for life in most patients (even after treatment)
                - Cannot monitor treatment response
    - When Tests Disagree
        - Positive treponemal + negative nontreponemal
            - Second treponemal positive → Evaluate history, treat if untreated
            - Second treponemal negative → No further action if risk is low
    - Traditional Algorithm
        - Start with nontreponemal test (RPR or VDRL)
        - Confirm positives with treponemal test (e.g., TP-PA)

- Algorithms that can be applied to screening for syphilis with serologic tests — CDC laboratory recommendations for syphilis testing in the United States, 2024

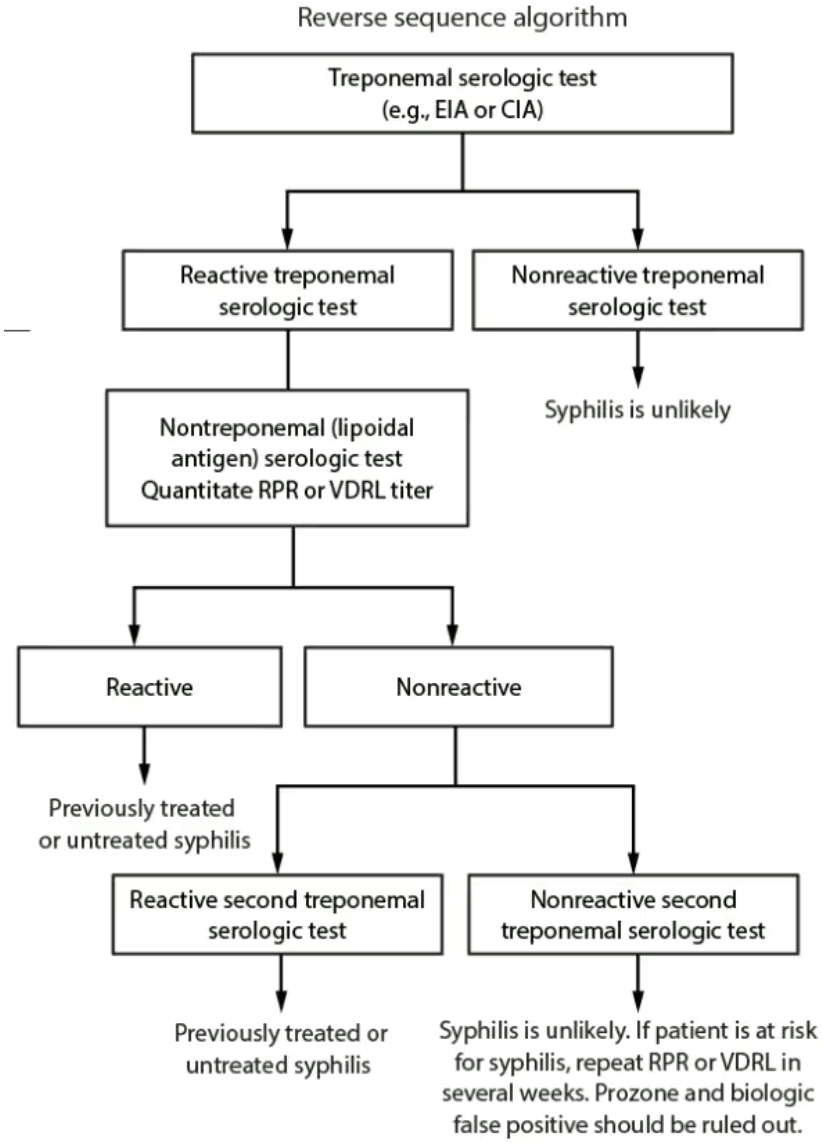


Courtesy of: Papp JR, et al. CDC laboratory recommendations for syphilis testing, United States, 2024. MMWR Recomm Rep. 2024;73(1):1-32.

– Parameter	▪ Traditional algorithm with a nontreponemal (lipoidal antigen) test as the initial test
– Reagent cost	▪ Rapid and inexpensive reagents
– Specimen throughput	▪ Good for small-throughput laboratories ▪ Less suitable for high-throughput laboratories because of labor and resources needed and occupational hazard of pipetting of individual specimens
– Performance characteristics of the first test in the algorithm	▪ Results of nontreponemal (lipoidal antigen) tests can be subjective, and there is laboratory variability in titers ▪ Possible prozone reaction that might be falsely interpreted as negative unless the serum sample is diluted ▪ Biologic false-positive resulting from nonspecific reactivity resulting from conditions other than syphilis ▪ Might be less sensitive for detecting early and late/latent syphilis
○ Screening applications	▪ Good for populations with a high likelihood of previous syphilis

- ○ Reverse Sequence Algorithm
  - – Automated treponemal test (e.g., EIA, CIA) as initial screen
  - – Reflexively perform nontreponemal test to confirm disease activity
  - – If non-treponemal is negative
    - ▪ Use a second treponemal test (e.g., TP-PA) for discrepancy resolution

- Algorithms that can be applied to screening for syphilis with serologic tests — CDC laboratory recommendations for syphilis testing in the United States, 2024



Courtesy of: Papp JR, et al. CDC laboratory recommendations for syphilis testing, United States, 2024. MMWR Recomm Rep. 2024;73(1):1-32.

- Parameter
  - Reverse algorithm with a treponemal test as the initial test
- Reagent cost
  - Higher reagent cost per specimen; Automated treponemal tests widely available with high throughput and lower human labor costs
- Specimen throughput
  - Possible batching of samples that could delay test result turnaround time
- Performance characteristics of the first test in the algorithm
  - Treponemal tests produce objective results; No prozone reaction; Detects antibodies against Treponema pallidum antigens; Might have increased detection of patients with early syphilis
- Screening applications
  - If algorithm is used in populations with a high likelihood of previous syphilis, an increased number of primary screening tests could be false positives*

- Special consideration: neurological disease
  - Indications for lumbar puncture
    - Neurologic, ocular, or auditory symptoms
    - Inadequate serologic response to treatment
    - Tertiary syphilis
    - HIV with CD4 < 350 or RPR ≥ 1:32: maybe

CMIA (TT)	RPR (NTT)	TPPA (TT)	Interpretation
–	Not Done	Not Done	Negative or early incubating syphilis
+	–	–	False positive
+	+	–	Early infection, late latent/tertiary, previously treated
+	Indeter	–	Inconclusive, repeat
+	–	+	Indeter
+	+	+	Previously treated, early infection, late latent/tertiary
+	–	+	Current or previously treated infection

Abbreviations: NTT, non-treponemal; RPR, rapid plasma; TPPA, treponema pallidum particle agglutination assay; TT, treponemal tests; VLD, lower limit of detection

➢ Stages of Syphilis Infection

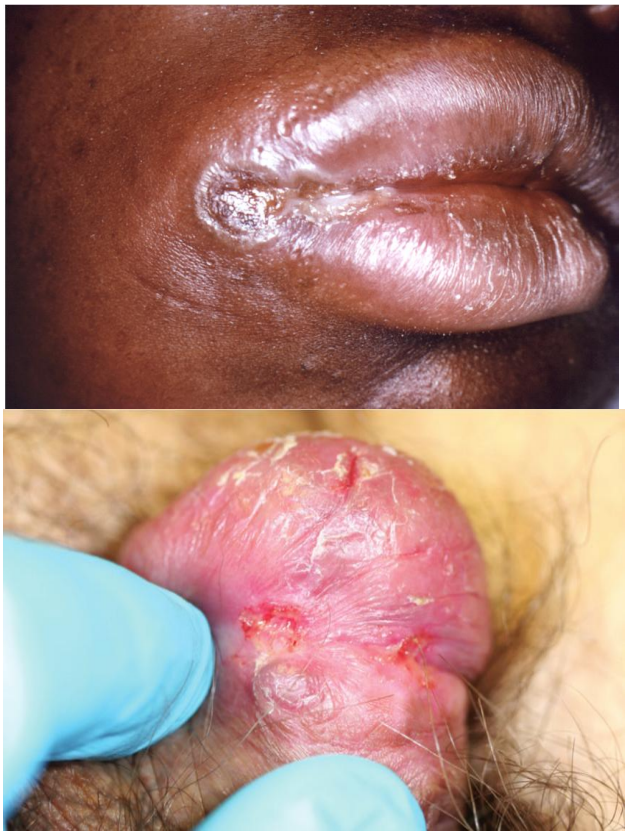
Treponema pallidum infection progresses through primary, secondary, latent, and tertiary stages. Latent syphilis may resolve spontaneously or advance to tertiary disease. Neurosyphilis, ocular syphilis, and otosyphilis can occur at any stage of infection.

Stage of Syphilis	Description	Notes
○ Primary	− Initial lesion (chancre)	▪ Occurs at site of infection
○ Secondary	− Rash, mucocutaneous lesions	▪ Systemic dissemination
○ Latent	− Asymptomatic phase	▪ May resolve or progress
○ Tertiary	− Cardiovascular, gummatous, neurologic	▪ Late complications
○ Neurosyphilis / Ocular / Otosyphilis	− Can occur at any stage	▪ Requires specific evaluation

Adapted from: https://www.std.uw.edu/go/comprehensive-study/syphilis/core-concept/all

➢ Types

- **Primary Syphilis**
  - Incubation period
    - 10 to 90 days (median, 21–25 days)
  - Characteristic Lesion
    - Solitary, nontender genital chancre
    - Caused by *T. pallidum* invasion
      - May also occur on non-genital sites like digits, nipples, tonsils, or oral mucosa
  - Other findings include
    - Lymphadenopathy

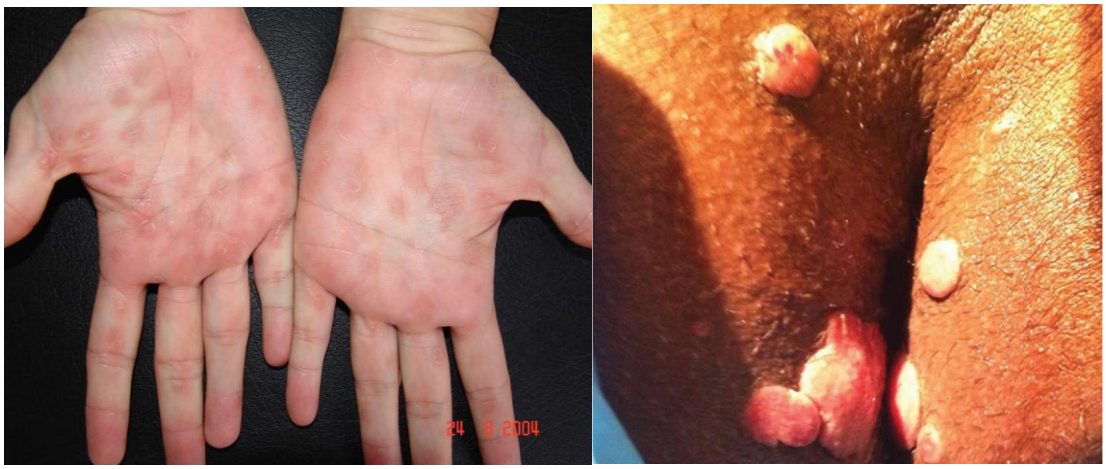


Courtesy of: https://www.aafp.org/pubs/afp/issues/2012/0901/p433.html

- **Secondary Syphilis**
  - Appears 6–12 wk after the primary infection.
  - Clinical Features:
    - Non-specific symptoms
      - Alopecia
      - Arthralgias
      - Condylomata lata
      - Fatigue
      - Fever
      - Hepatitis
      - Lymphadenopathy
      - Malaise
      - Meningitis
      - Rash
      - Uveitis

- Highly contagious during this stage
- Characteristic findings
  - Syphilitic dermatitis
    - Widespread rash (often involving palms and soles)
  - Condylomata lata
    - Moist, wart-like lesions (especially in genital areas)
- Clinical course primary and secondary syphilis resolve spontaneously
  - No scarring even without

Secondary Syphilis



Courtesy of: https://healthjade.com/syphilis/

- **Latent** (Positive serology, **no** clinical manifestations)
  - An asymptomatic phase lasting years; infection persists without outward signs.
    - Early (<1 year)
    - Late (>1 year) or unknown duration
- **Tertiary**
  - Cardiovascular
    - Aortic aneurysms and other cardiovascular complications from arterial damage.
  - Gummas
    - Destructive soft-tissue lesions appearing on skin, bones, or internal organs.

- Neurosyphilis (central nervous system involvement leading to neurological deficits and cognitive decline)
  - Late
    - Tabes dorsalis
    - General paresis
  - Early or late
    - Asymptomatic
    - Meningitis
    - Otic symptoms
    - Headaches
    - Ocular symptoms
    - Argyll-Robertson pupil, dementia

- **Syphilis and the Gastrointestinal Tract**

➢ Pathophysiology

- Hematogenous dissemination of *Treponema pallidum* during secondary syphilis
- Bacterial invasion of GI mucosa triggers localized inflammation

➢ Clinical

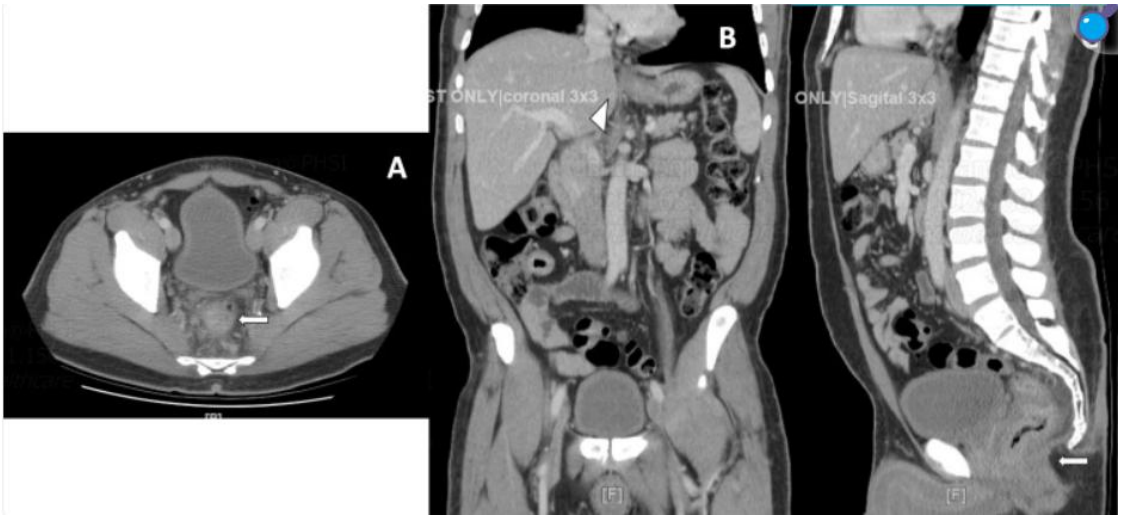
- Common
  - Anorexia
  - Abdominal pain
  - Nausea
  - Diarrhea (often nonspecific)

- Rare
  - Syphilitic Colitis
    - Erythema
    - Ulcerations
    - Friability, and
    - Hematochezia
    - Mimic inflammatory bowel disease (IBD) or malignancy
  - Syphilitic Hepatitis
    - ↑ liver enzymes, cholestatic pattern
    - May resemble primary biliary cholangitis (PBC)
  - Proctitis / Rectal Masses
    - Mimics rectal tumours; associated with extraintestinal manifestations (EIM)
      - Rash
      - Arthralgia

- Laboratory
  - Non-Treponemal Test (e.g., RPR)
  - Treponemal Tests (e.g., TP-PA, FTA-ABS)
    - Confirms syphilis in patients with non-specific histological findings usability.

- Diagnostic Challenge in GI Syphilis
  - Clinical Mimics
    - Symptoms overlap with:
      - Inflammatory bowel disease (IBD)
      - Primary biliary cholangitis (PBC)
      - Malignancy
  - Serology and Staining
    - Serologic tests (e.g., RPR, TP-PA) essential but may show low titers
    - Special stains (e.g., Warthin-Starry, immunohistochemistry) needed for confirmation
  - Histopathology
    - Nonspecific findings:
      - Lymphoplasmacytic infiltrates
      - Crypt loss
      - Ulceration
    - Routine H&E staining often misses spirochetes
  - Delays in Diagnosis
    - Low clinical suspicion and nonspecific findings often lead to delayed treatment
    - Sexual history and systemic evaluation are critical for accurate diagnosis

- Diagnostic Imaging
  - CT/MRI
    - Diffuse colitis
    - Rectal wall thickening
    - Perirectal lymphadenopathy
    - Mimic malignancy or severe proctitis



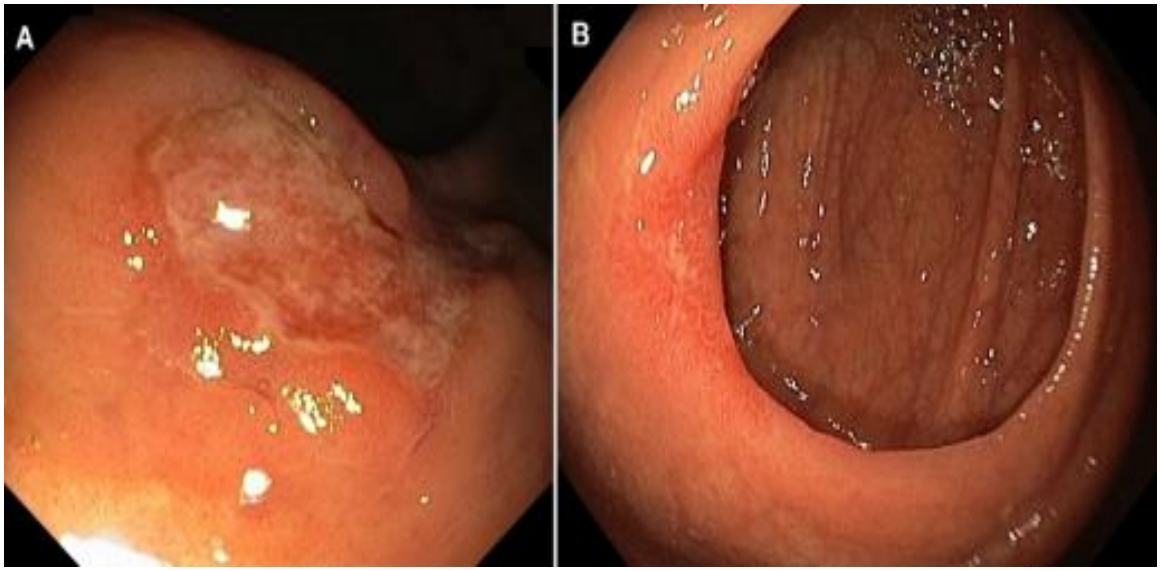
Images showing hepatic steatosis with a normal caliber of the biliary system (arrowhead), focal moderate wall thickening of the rectum (arrows), and multiple enlarged perirectal adenopathy (A. Axial; B. Coronal; C. Sagittal)

Courtesy of: Cantu Lopez C, et al. Cureus. 2024;16(4):e59222 (Figure 1)

- Endoscopy
  - Patchy Erythema
    - Reddened areas of the mucosa (often misinterpreted as inflammatory bowel disease [IBD])
  - Ulcerations and Friability
    - Ulcers vary in size and depth
      - Friable mucosa that bleeds easily
    - Mimics ulcerative colitis or malignancy
  - Rectal/or Colonic Masses
    - Polypoidal lesions / near-luminal obstruction that resemble tumours
    - Mimics
      - IBD
      - Rectal malignancy, or
      - Infectious colitis (e.g., CMV, HSV, bacterial pathogens)

Ulceration

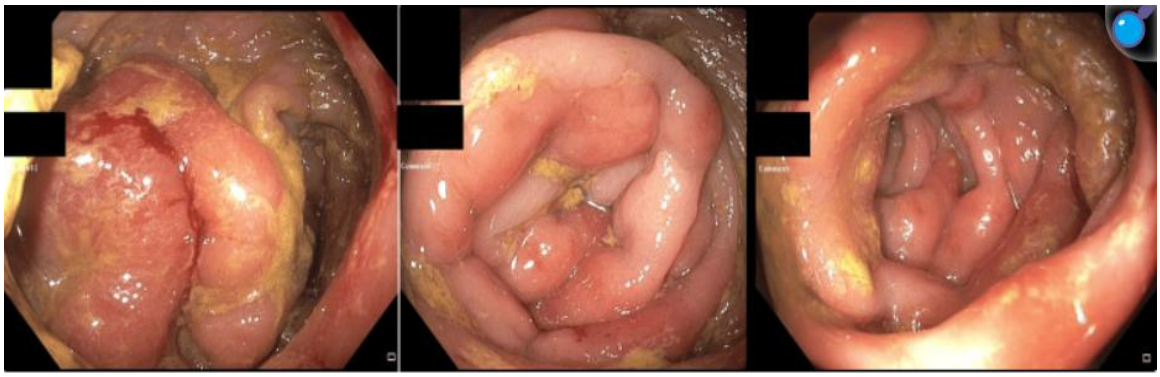
Syphilis of the Rectum



Rectal Ulcer Sessile Polyps

Courtesy of: https://online.reed.es/DOI/PDF/ArticuloDOI_10621.pdf

Syphilis of Rectum

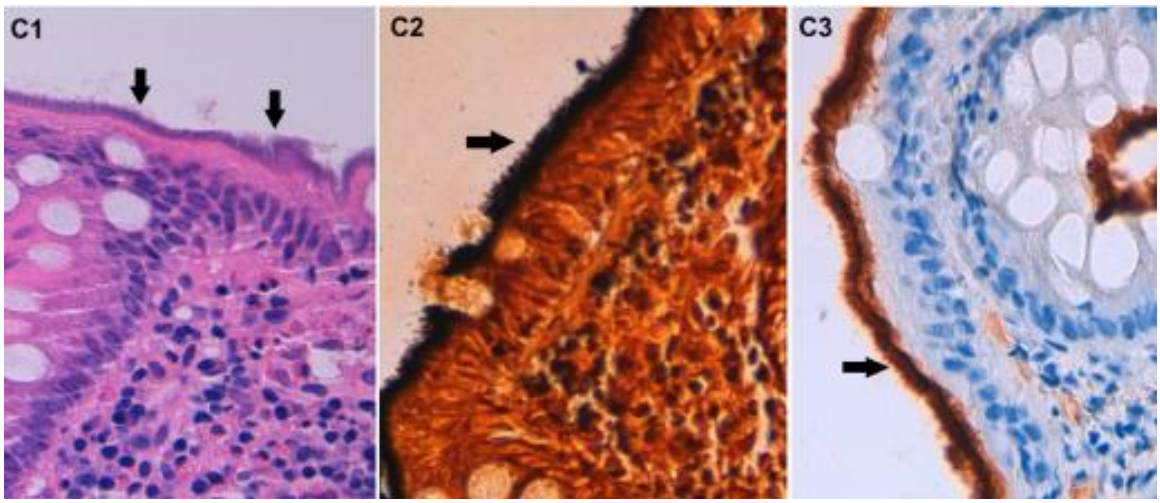


- Severe inflammation, erythema, and thickened rectal folds with near luminal obstruction prior to the initiation of syphilis treatment (blacked out identifying patient information in the left upper corner of images).
- Mimicking a rectal mass.

Courtesy of: Cantu Lopez C, et al. Cureus. 2024;16(4): e59222 (Figure 2)

➢ Histopathology

Syphilis of Rectum



- Histological images of the fourth case showing
  - Spirochetes adhered to the mucosa (indicated by black arrows) with hematoxylin-eosin staining (C1)
  - Warthin-Starry staining (C2), and
  - Treponema immunohistochemistry (IHQ) (C3)
  - Not shown here
- GI tract
  - Lymphoplasmacytic infiltration
  - Crypt destruction
  - Mucosal ulceration
- Liver
  - Intrahepatic bile duct infiltration → cholestatic hepatitis

Courtesy of: https://online.reed.es/DOI/PDF/ArticuloDOI_10621.pdf

Abbreviations: CDC, Centers for Disease Control and Prevention; CIA, chemiluminescent immunoassay; CMIA, chemiluminescent microparticle immunoassay; CMV, cytomegalovirus; CNS, central nervous system; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; GI, gastrointestinal; H&E, hematoxylin and eosin; HIV, human immunodeficiency virus; IHQ, immunohistochemistry; MMWR, Morbidity and Mortality Weekly Report; MSM, men who have sex with men; MRI, magnetic resonance imaging; NA, not available; NTT, non-treponemal test; PCR, polymerase chain reaction; PHAC, Public Health Agency of Canada; PBC, primary biliary cholangitis; RPR, rapid plasma reagin; STD, sexually transmitted disease; TP-PA, Treponema pallidum particle agglutination assay; TT, treponemal test; VDRL, Venereal Disease Research Laboratory test; VIS, visualization score.

Suggested Reading:

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MONKEY POX (MPOX) AND GASTROENTEROLOGICAL PERSPECTIVES

Yifan Han

- History
  - 1958
    - First isolated among outbreaks of a pox-like disease in a colony of crab-eating macaques.
  - 1970's
    - First instance of mpox causing disease in humans in the area now known as the DRC.
  - 1980
    - The end of routine smallpox vaccination by the WHO.
  - 2003
    - US outbreak, first instance of mpox in Western hemisphere.
  - 2022
    - Global multi-country outbreak of the Clade 2 virus.
    - Over 100,000 cases in total.
  - 2024
    - DRC
    - Previously unaffected areas and neighboring countries.

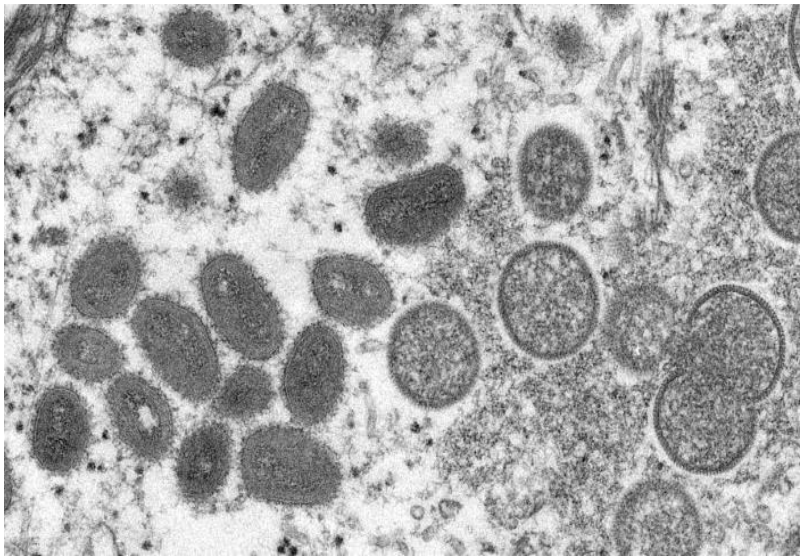
- Etymology
  - Mpox = monkeypox
    - First named in 1950s after the discovery of the disease in captive monkeys.
    - 2015 - WHO best practices in naming diseases:
      - "Disease names should be given with aim to minimize unnecessary negative impact of names on trade, travel, tourism, animal welfare."
    - 2022 - WHO recommends new name of mpox to reflect above aims.
    - Although disease names are the responsibility of the WHO, the International Committee on the Taxonomy of Viruses are currently in the process of reconsidering all viruses in the orthopoxvirus genus.

World Health Organization. WHO recommends new name for monkeypox disease. Published November 28, 2022. https://www.who.int/news/item/28-11-2022-who-recommends-new-name-for-monkeypox-disease

- The Virus and Trivia
  - The mpox virus is classified within the orthopoxvirus genus.
    - Smallpox, cow pox ...
    - Cow pox was named variolae vaccinae by the British physician Edward Jenner.
    - "Vaccines" are named after Jenner's work in pioneering this method of inoculation.

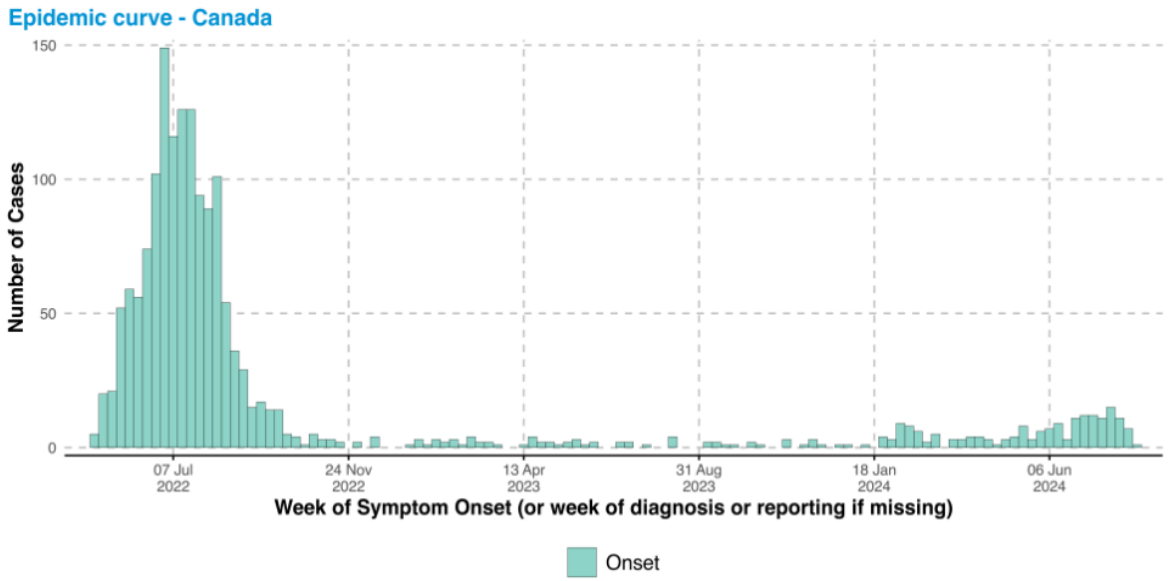
- Two strains of mpox virus
  - Clade 1 and Clade 2

Monkey Pox



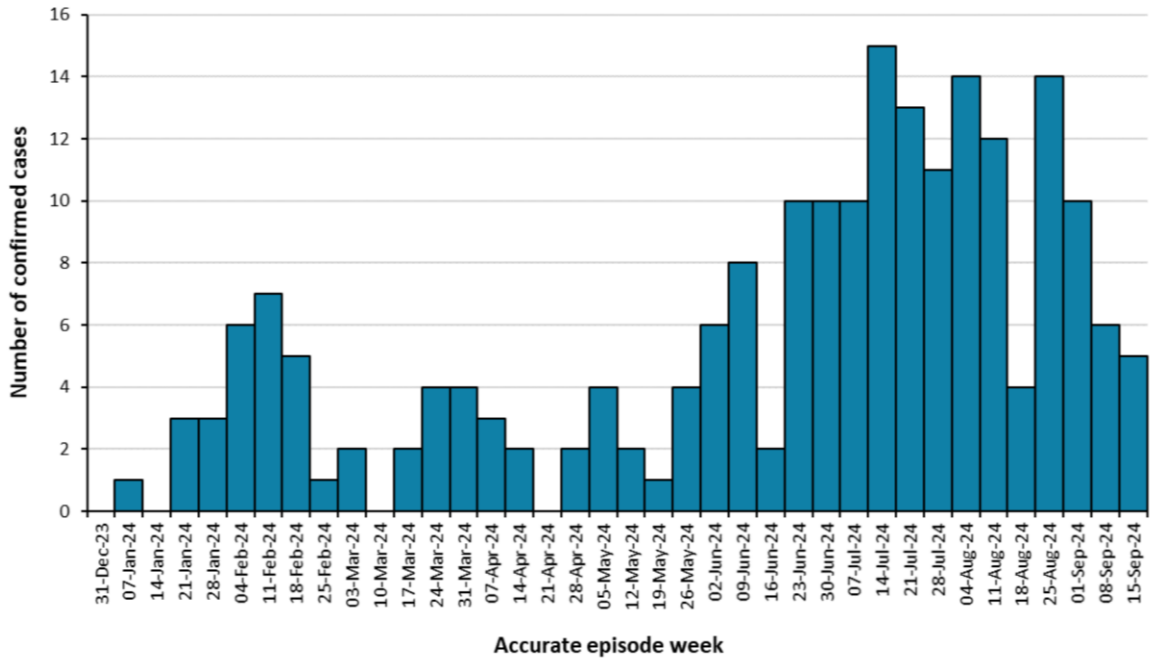
- This electron microscopic (EM) image depicted mpox virus particles, obtained from a clinical sample associated with the 2003 prairie dog outbreak.
  - It was a thin section image from of a human skin sample. On the left were mature, oval-shaped virus particles, and on the right were the crescents, and spherical particles of immature virions.

Courtesy of: https://phil.cdc.gov/Details.aspx?pid=22664



Courtesy of: WHO

- Ontario
  - More cases compared with 2023
    - 206 compared to 33.
    - 98% are male
      - Median age 36
      - 97% from age 20-49.
  - ·86% reported intimate contact with same sex partner.
    - 2 were in the Middlesex-London Health Unit (Ontario, Canada)



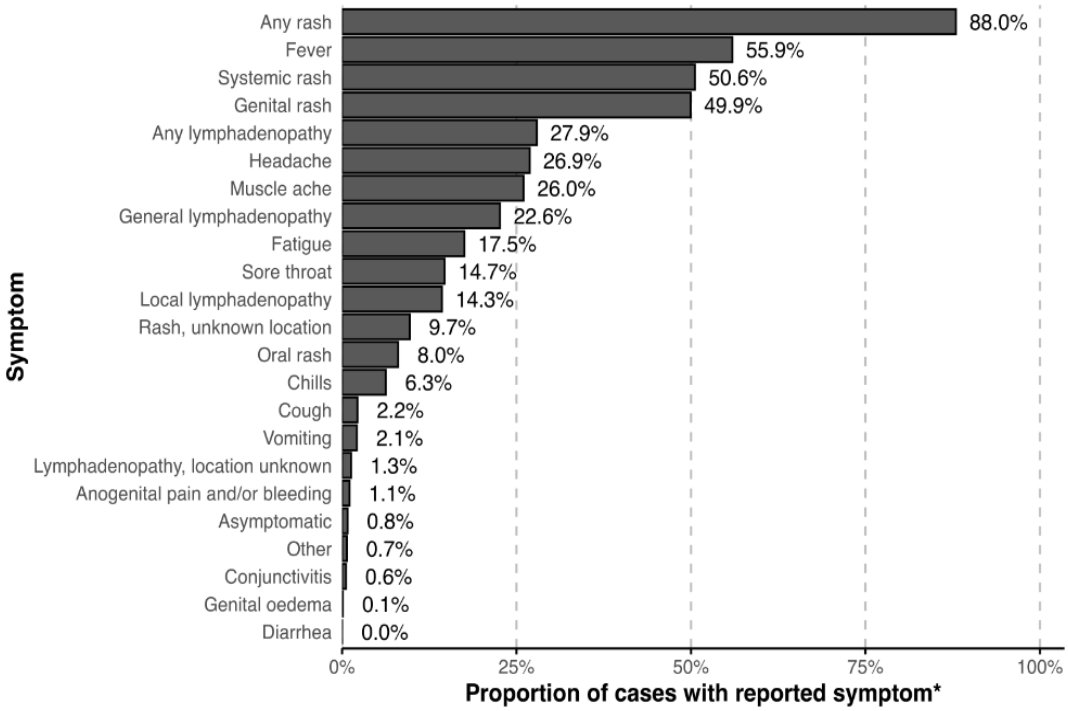
Courtesy of: Ontario's integrated Public Health Information System (iPHIS)

➢ Transmission

- Animal to human
  - Bodily fluids, bite, raw meat.
  - ↑ risk the more invasive the contact, e.g., bite vs. touching an animal
  - Animals
    - Dormice
    - Gambian pouched rats
    - Monkeys.
    - Rope squirrels
    - Tree squirrels

- Human to human
  - Direct contact with sores, scabs, bodily fluids.
  - Via breach of skin or mucous membrane
    - Fomites
    - Mother-to-fetus
    - Percutaneous injection
    - Respiratory secretions
    - Vaginal/semen
  - Viral shedding from skin lesions, 25 days

➢ Clinical Manifestation



Source: WHO
*36,478 cases with at least one reported symptom from a country where at least two unique symptoms reported used as denominator

- Eyes
  - Blepharitis
  - Periocular
  - Keratitis
  - Cellulitis
  - Blindness
- Central Nervous System (CNS)
  - Encephalitis

- Skin
  - Incubation period
    - 7–10 days, average ~7 days
      - Longer duration if more benign exposure
  - Systemic illness
    - 1-5 days
    - Fever/chills
    - Myalgias
    - Sore throat
    - Headache
    - Lymphadenopathy
  - Rash
    - 2–3 weeks
    - Characteristic rash, painful, then itchy when crusted over
    - Few to countless
    - Site(s)
      - Perioral
      - Oral
      - Consistent with (at inoculation site)
- GI tract
  - Mouth
    - Oral Ulcers, 33%
  - Esophagus
    - Odynophagia, 31%
    - Dysphagia, 12%
  - Stomach
    - Abdominal pain, 9%
    - Vomiting, 12%
    - Nausea, 10%
    - Anorexia, 47%
  - Colon
    - Proctitis / rectal pain / bleeding, 11-25%
    - Diarrhea, 5%
  - Liver
    - ↑ ALT, ↑ AST (hepatocellular enzymes)
      - ↑ AST, 8% (mean value 66 U/L)
      - ↑ ALT 10% (mean value 66 U/L)
    - ↓ albumin, 8%
    - Hepatic lesions.
      - Mpox spreads to liver which results in replication and secondary viremia.
    - Cidofovir (treatment of Mpox)
      - Associated with mild to moderate ALT elevations.

- Causes
  - Self-limited, and does not require dose modification.
  - Acute liver failure (ALF), lactic acidosis, steatosis when patients take other known hepatotoxins – zidovudine, stavudine, didanosine.
- Post-transplant patients
  - Case series describes 11 patients with Mpox in the US.
    - 10 kidney transplants, 1 liver transplant
    - 7 had co-existing HIV infection with mean CD4 count 632
    - Most were on prednisone, tacrolimus, MMF
  - All received tecovirimat
  - All had limb/trunk rash
  - 2 patients had concurrent CMV reactivation, 1 had syphilis, and another had new hepatitis B infection
  - Outcomes
    - Symptom duration of 3–14 days
    - 8/11 were hospitalized
    - 1/11 died (CMV reactivation, pneumonitis, and shock)
- Immunosuppression
  - Mpox is controlled via T cells
  - The use of immunosuppressive drugs could lead to worse outcomes.
  - Tecovirimat is an inducer of CYP3A and 2B6 → may ↓ tacrolimus levels.

- Resolution
  - After 2–4 wk, most people have resolution of symptoms
  - Hospitalizations, rare in North America
  - Mortality
    - North America (US), ~0.1%
  - Fatality rate in
    - Congo, 4%

Higgins E, et al. Clinical features, treatment, and outcomes of mpox in solid organ transplant recipients: A multicenter case series and literature review. Am J Transplant. 2023;23(12):1972-1979.

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Alakunle E, et al. A comprehensive review of monkeypox virus and mpox characteristics. Front Cell Infect Microbiol. 2024;14:1360586.

➢ Diagnosis of Mpox

- Suspected
  - When patients with typical symptoms like rash and have risk factors (close contact with suspected/confirmed Mpox, travel to Africa)
  - Consider concurrent infections: syphilis, gonorrhea, chlamydia, HSV, HIV.

- Laboratory
  - PCR for DNA – Test of choice at LHSC.
  - Serology
- Diagnostic Imaging
  - On electron microscopy
- Endoscopy
  - Mpox transmitted by aerosols
    - Endoscopy can cause aerosolization, as well as direct bodily fluid contact.
  - Can last days to weeks at room temperature and be transmitted via fomites.
  - No known history of endoscopic transmission of mpox to date.
  - Wet-cleaning methods recommended over sweeping/dusting/vacuuming.
  - Esophageal intubation should probably be performed under airborne precautions.
    - CDC recommended N95 while LHSC recommends contact droplet +
  - Common disinfectants are effective against other orthopox viruses.
- Treatment
  - Supportive care
    - Symptom relief (topical lidocaine, sitz baths)
    - Hydration
    - Antinauseant
    - Eye drops
    - Nutrition.
  - Tecovirimat ± cidofovir, brincidofovir
    - Immunocompromised
    - Active skin conditions
    - Pregnant/lactating
    - <18 years
    - Ocular, life-threatening manifestations.

Ontario Ministry of Health. Mpox antiviral guidance for health care providers.

- Prevention
  - Community
    - Avoid close contact, Use of barriers could lower risk.
    - Minimize contact with objects used by people with Mpox.
    - Avoid contact with rodents and primates, especially in endemic settings.
  - Health care environment
    - LHSC: Contact droplet plus.
  - Vaccination: IMVAMUNE
    - Indications
      - MSM with multiple partners
      - History of STIs
      - Sex workers;
      - Pre-exposure or post. Ideally within 4 days of high-risk exposure.

The Center for Disease Control. Preventing Mpox.
Health Canada. Summary: Interim Guidance on the Use of Imvamune in the Context of a Routine Immunization Program.

- Prognosis
  - Nausea, vomiting, dysphagia
    - Higher likelihood to be hospitalized
  - Dysphagia
    - Higher likelihood of severe illness

- Take home points
  - Mpox tends to cause systemic symptoms and a characteristic skin rash.
  - Mpox can affect the upper and lower GI tracts.
  - Screen for concomitant infections.
  - Post-transplant patients have higher risk of severe disease and could benefit from anti-viral therapy.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALF, acute liver failure; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CMV, cytomegalovirus; CYP3A, cytochrome P450 3A; CYP2B6, cytochrome P450 2B6; DRC, Democratic Republic of the Congo; EM, electron microscopy; GI, gastrointestinal; HIV, human immunodeficiency virus; iPHIS, integrated Public Health Information System; LHSC, London Health Sciences Centre; MMF, mycophenolate mofetil; Mpox, monkeypox; MSM, men who have sex with men; N95, N95 respirator mask; PCR, polymerase chain reaction; STI, sexually transmitted infection; US, United States; WHO, World Health Organization.

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