

Best Practice Guidelines in Gastroenterology Disorders

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For no-charge textbooks in Gastroenterology, Hepatology, and
General Internal Medicine





THE WESTERN WAY



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CANMED OBJECTIVES

Medical Expert

The discussion of complex cases provides the participants with an opportunity to comment on additional focused history and physical examination. They would provide a complete and organized assessment. Participants are encouraged to identify key features, and they develop an approach to problem-solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic base provides the means for the candidate to establish an appropriate management plan based on the best available evidence to clinical practice. Throughout, an attempt is made to develop strategies for diagnosis and development of clinical reasoning skills.

Communicator

The participants demonstrate their ability to communicate their knowledge, clinical findings, and management plan in a respectful, concise and interactive manner. When the participants play the role of examiners, they demonstrate their ability to listen actively and effectively, to ask questions in an open-ended manner, and to provide constructive, helpful feedback in a professional and non-intimidating manner.

Collaborator

The participants use the “you have a green consult card” technique of answering questions as fast as they are able, and then to interact with another health professional participant to move forward the discussion and problem solving. This helps the participants to build upon what they have already learned about the importance of collegial interaction.

Manager

The participants are provided with assignments in advance of the three day GI Practice Review. There is much work for them to complete before as well as afterwards, so they learn to manage their time effectively, and to complete the assigned tasks proficiently and on time. They learn to work in teams to achieve answers from small group participation, and then to share this with other small group participants through effective delegation of work. Some of the material they must access demands that they use information technology effectively to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost-effective management plans.

Health Advocate

In the answering of the questions and case discussions, the participants are required to consider the risks, benefits, and costs and impacts of investigations and therapeutic alliances upon the patient and their loved ones.



Scholar

By committing to the pre- and post-study requirements, plus the intense three day active learning Practice Review with colleagues is a demonstration of commitment to personal education. Through the interactive nature of the discussions and the use of the “green consult card”, they reinforce their previous learning of the importance of collaborating and helping one another to learn.

Professional

The participants are coached how to interact verbally in a professional setting, being straightforward, clear and helpful. They learn to be honest when they cannot answer questions, make a diagnosis, or advance a management plan. They learn how to deal with aggressive or demotivated colleagues, how to deal with knowledge deficits, how to speculate on a missing knowledge byte by using first principles and deductive reasoning. In a safe and supportive setting they learn to seek and accept advice, to acknowledge awareness of personal limitations, and to give and take 360o feedback.

Knowledge

The basic science aspects of gastroenterology are considered in adequate detail to understand the mechanisms of disease, and the basis of investigations and treatment. In this way, the participants respect the importance of an adequate foundation in basic sciences, the designing of clinical research studies to provide an evidence-based approach, the relevance of their management plans being patient-focused, and the need to add “compassionate” to the Three C’s of Medical Practice: competent, caring and compassionate.

“They may forget what you said, but they will never forget how you made them feel.”

Carl W. Buechner, on teaching.

“With competence, care for the patient. With compassion, care about the person.”

Alan B. R. Thomson, on being a physician.



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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!

A warm and heartfelt thank you goes to **Dr. Naiyana Gujral** for her excellent assistance for helping to bring this project to a successful completion.

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 and Kim 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.





x



DEDICATION

“To Jeannette Mineault -Thomson”

Dr. Alan Thomson

Dedicated to my wife, Jennifer, and our child, Noah, as well as the numerous residents, fellows, and staff physicians, including Dr. Alan Thomson, whose support and career guidance have been invaluable and much appreciated.

Dr. David Hudson





ESOPHAGUS

Alajmi, Abdulaziz

Almudaires, Abdulaziz

Alsager, Mohammed

Malhi, Gurpreet

Natt, Navneet



DYSPEPSIA

Management of Dyspepsia: ACG and CAG Clinical Guideline (2017)

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

Recommendations

- Uninvestigated persons with dyspepsia
 - > 60 yr
 - EGD
 - If EGD negative (“functional dyspepsia [FD]”) as symptoms of gastroparesis → test and treat for H. pylori; repeat testing to prove eradication
 - If FD persists → trial of proton pump inhibitor (PPI)
 - If PPI trial not helpful, use tricyclic antidepressant (TCA) / prokinetic (PK) → psychological therapy
 - If symptoms of gastroparesis → consider study → PK trial
 - < 60 yr
 - Non-invasive test for H. pylori (urea breath test or stool antigen, not serology), treat infection if test is positive (prove eradication by repeat testing)
 - If alarm features present, or in the absence of alarm symptoms, give empirical trial of PPIs (normal dose, once daily, half an hour before first meal of the day, for 4-8 wk)
 - If no response to PPI or successful treatment of H. pylori infection
 - Empirical trial
- Patients
 - > 60 yr
 - EGD for investigation of dyspepsia, even if no alarm symptoms
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
 - < 60 yr
 - Patient with dyspepsia plus dysphagia (and no other alarm symptoms) do **not** require EGD.
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
 - Test for H. pylori with non-invasive test, and treat if positive
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong



- ❖ H. pylori eradication
 - Uninvestigated dyspepsia
 - A serological test for H. pylori is widely available and only a fraction of the cost of a urea breath test (UBT); if serology is negative, then the patient is not infected and further testing for H. pylori needs to be performed.
 - When doing a UBT, the patient must be off antibiotics, H2 receptor antagonists, and PPIs for 2 wk to prevent the test being falsely negative.
 - Other Guidelines (specifically for H. pylori) recommend that a non-serological test for H. pylori be performed after the triple- or quadruple therapy, to confirm eradication.
 - Functional dyspepsia (dyspepsia, EGD normal)
 - Patient with FD who has an H. pylori infection – treat the H. pylori infection
 - On completing the EGD, the following details should be reviewed and confirmed
 - The number of histological samples taken
 - The correct labelling of histological samples
 - The dose of sedation and/
 -
 - or analgesia given
 - Any specific post-procedure advice to be given to the patient
 - Follow-up arrangements
 - Small therapeutic gain ~9% (76.4% vs 67.7%)
 - RR for dyspepsia remaining = 0.91
 - Number needed to treat (NNT) ~12
- ❖ PPI empirical trial
 - Uninvestigated dyspepsia
 - If H. pylori test negative, then patient takes a trial of empirical PPI.
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
 - Use a PPI of your choice, po od, taken 30-60 min before the first meal of the day, and for 4-8 wk.
 - Do **not** use an empirical trial of histamine 2 receptor antagonist (H2RA)
 - Do **not** double the dose of PPI if the initial standard dose of PPI is ineffective.
 - Functional dyspepsia (EGD normal)
 - Eradication of H. pylori, normal EGD, continued dyspepsia
 - Treat with PPIs
 - Therapeutic gain ~6% (95.2% vs 69.6%; RR dyspepsia recovery = 0.87; 95% CI, 0.82 – 0.94, p = 0.00001; NNT, ~10 (95% CI, 7-20)
 - The subgroup of patients with prominent heartburn-related symptoms better than these patients with epigastric pain syndrome
 - If eradication of H. pylori infection proven (if H. pylori test positive), and empirical trial of PPI fails to relieve dyspepsia, offer the patient
 - Prokinetics
 - Note that there are no randomized studies comparing PK therapy with placebo
 - If the failed PPI course was 8 wk long, and a trial of PK is used for 8 wk, then considerable time will have passed before the patient will have their EGD.
 - Some guidelines suggests that if the patient fails a 4 – 8 wk trial of PPI, they should be booked for an EGD.



- Tricyclic anti-depressants (TCAs)
 - After proton pump inhibitor (PPI) failure +/- H. pylori eradication – use trial of TCAs
 - There are no randomized trial of anti-depressant therapies in undiagnosed dyspepsia.....the recommendation to use TCAs in the setting comes from other GI populations of patients with functional disease (irritable bowel syndrome [IBS])
 - RR for ↓ dyspepsia = 0.74, 95% CI, 0.61 – 0.71; NNT 6 (95% CI, 6 – 18)
 - SSRIs are not beneficial for functional dyspepsia (RR, 1.01; 95% CI, 0.89 – 1.15)
- Prokinetics
 - No gastroparesis
 - For FD not responding to PPIs, TCAs, proven H. pylori eradication therapy
 - Use prokinetic (PK) therapy
 - RR if remaining dyspepsia in the PK group vs placebo 0.92; 95% CI, 0.88 – 0.97; NNT, 12.5 (95% CI, 8 – 25)
 - RR in the group using domperidone, RR, = 0.71; 95% CI, 0.53 – 0.97; NNT 3 (95% CI, 2 – 8)
 - Gastroparesis
 - Gastroparesis (symptoms plus gastric emptying testing (e.g., 4-h solid phase emptying scan)
 - ~25% of patients with FD have ↓ rate of gastric emptying
 - Use prokinetics in FD if gastroparesis expected/proven
- Psychological therapies
 - Significant benefits of psychological therapies to ↓ symptoms of dyspepsia (RR, 0.53; 95% CI 0.44 – 0.65; NNT 3 (95% CI, 3 – 4)
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong
- Therapies for FD which are not recommended
 - Complementary and alternate medicines
 - Level of agreement: 90%
 - Grade of evidence: weak
 - Strength of recommendation: strong
 - Standard motility studies
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong

➤ Recommendations

- Perform EGD in dyspepsia patients ≥ 60 yr: Conditional recommendation, very low-quality evidence
- Do EGD: Conditional recommendation: moderate quality evidence.
- Dyspepsia patients < 60 yr, who do a non-invasive test for H. pylori, and give therapy for H. pylori infection if positive: Strong recommendation, high quality evidence.



- Dyspepsia patients < 60 yr should have empirical PPI therapy if they are H. pylori negative, or who remain symptomatic after H. pylori eradication therapy. Strong recommendation, high quality evidence.
- Dyspepsia patients < 60 yr not responding to PPI or H. pylori eradication therapy should be offered TCA therapy. Conditional recommendation low quality evidence.
- FD patients who are H. pylori positive should be prescribed therapy to treat the infection. Strong recommendation, high quality evidence.
- FD patients who are H. pylori negative or who remain symptomatic despite eradication of the infection, should be treated with PPI therapy. Strong recommendation, moderate quality evidence.
- FD patients, not responding to PPI or H. pylori eradication therapy (if appropriate) should be offered TCA therapy. Conditional recommendation, moderate quality evidence.
- FD patients not responding to PPI, H. pylori eradication therapy or tricyclic antidepressant therapy should be offered prokinetic therapy. Conditional recommendation, very low-quality evidence.
- FD patients not responding to drug therapy should be offered psychological therapies. Conditional recommendation, very low-quality evidence.
- Not recommended for routine use complementary and alternative medicine for FD. Conditional recommendation, very low evidence.
- Not recommended to do routine motility studies for patients with FD. Conditional recommendation, very low-quality evidence.
- Perform motility studies only for selected patients with FD. Conditional recommendation very low-quality evidence.

Abbreviations: CI, confidence interval; EGD, esophagogastroduodenoscopy; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; H. pylori, Helicobacter pylori, H2RA, histamine 2 receptor antagonist; NNT, number needed to treat; od, daily; P, probability; PKs, prokinetics; po, by mouth; PPI, proton pump inhibitor; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; UBT, urea breath test; yr, year



Normal Endoscopy Dyspepsia: ROME 4 Diagnostic Criteria (2018)

Poterucha J. MKSAP® 18 Gastroenterology and Hepatology. American College of Physicians – MKSAP.

➤ Definition

- Functional Dyspepsia
 - No evidence of structural organic/metabolic disease (including upper endoscopy) that is likely to explain the symptoms for the last 3 mon, with symptoms onset at least 6 mon before diagnosis.
 - Bothersome ≥ 1 of the following:
 - Postprandial fullness
 - Early satiety
 - Epigastric pain
 - Epigastric burning

Poterucha J. MKSAP® 18 Gastroenterology and Hepatology. American College of Physicians – MKSAP, Table 6, page 10

➤ Subtypes

- Functional Dyspepsia (FD)
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Epigastric Pain Syndrome (EPS)
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Postprandial Distress Syndrome
 - No evidence of organic, systemic, or metabolic disease (including upper endoscopy) that is likely to explain the symptoms for at least 3 mon, with symptom onset at least 6 mon before diagnosis.
 - 1 bothersome at least 3 days per week:
 - Postprandial fullness (i.e., severe enough to affect usual activities)
 - Early satiety (i.e., severe enough to prevent finishing a regular-sized meal)

Poterucha J. MKSAP® 18 Gastroenterology and Hepatology. American College of Physicians – MKSAP, Table 7.



- Epigastric Pain Syndrome

Criteria	Supportive Remark
○ ≥ 1 of the following symptoms, ≥ 1 day per wk – Bothersome epigastric pain and/or burning (i.e., severe enough to affect usual activities) ○ No evidence of structural, organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy), with symptoms for the last 3 mon with symptoms onset at least 6 mon before diagnosis.	– Induced by a meal, relieved by ingestion of a meal – May occur while fasting – Postprandial epigastric bloating, belching and nausea – Persistent vomiting suggests another disorder – Symptoms relieved by evacuation of feces / part of dyspepsia

Poterucha J. MKSAP® 18 Gastroenterology and Hepatology. American College of Physicians – MKSAP, Table 8, page .



QUALITY STANDARDS IN UPPER GASTROINTESTINAL ENDOSCOPY

Position statement of the British Society Gastroenterology (BSG), and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) (2017)

Beg S, et al. Gut 2017; 66: 1886-1899.

- Why now improve quality?
 - Impaired methods for detection of premalignant lesions
 - Known risk of failing to diagnose gastric adenocarcinoma on endoscopy – 10%

❖ Preprocedural Quality Standards

Recommendations

- Assess fitness of patient to have esophagogastroduodenoscopy (EGD)
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Inform patient of risks and benefits of EGD
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Obtain informed consent from patient before performing EGD
- Allocate appropriate time to perform quality examination in usually > 7 min (Bank M, et al. Gut 2019; 68: 15); Barrett's inspection time of > 1 min per cm
- For the above four recommendations
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Prepare patient for adequate mucosal visualization
 - Give premedication and mucolytic defoaming agent (simethicone, N-acetylcysteine or pronase) (10-30 min before)
- Develop and complete a safety checklist for the procedure before the patient leaves for the endoscopy suite.
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong

❖ Endoscopic Procedure

- Any person doing EGD on their own ("independently") must have appropriate training and proven relevant competencies.
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- For high-quality EGDs, the endoscopist must perform ≥ 100 EGDs per year
 - This is an absolute minimum number, and
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: weak



- UGI endoscopy should be performed with high-definition video endoscopy systems, with the ability to capture image and take biopsies.
 - In some Canadian endoscopy suits the recommendation is not being met, and the endoscopists may wish to consider using quality standards such as this to impress upon the hospital administration the essential nature of this budgetary request.
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Assess all relevant anatomical landmarks and high-risk areas (e.g., retroflex EGD in fundus; examine hiatus hernia for the diaphragmatic pinch).
 - Provide photodocumentation of all landmarks as well as all detected lesions
 - The quality of the visualization must be reported, and if complete views cannot be obtained, indicate why this is the case, and whether the EGD must be repeated.
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- It is appropriate to use the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) to acknowledge the recommendation to have photo documentation of all EGDs.
- During EGD
 - Provide adequate insufflation of air
 - Use pump-controlled water jet cleaning with mucolytic/defoaming agents
 - Perform frequent aspiration
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong
- Record the total length of mucosal inspection time (not just total endoscopy time), especially for surveillance of premalignant conditions, such as
 - Esophagus
 - Barrett's esophagus
 - Stomach
 - Chronic active gastritis (OAG)
 - Gastric atrophy (GA)
 - Gastric intestinal metaplasia (GIM)
 - Gastric dysphasia (GD)
 - Adenomatous polyp (AP)
 - Mucosal area around hyperplastic polyp (HP)
 - Fundic gland polyps (FGDs) in person with colonic adenomatous polyposis (FAP)
 - Level of agreement: 90%
 - Grade of evidence: weak
 - Strength of recommendation: weak
- When a lesion is identified, use
 - Photo-documentation
 - Targeted biopsies
 - Acceptable random biopsy protocol, e.g., Sydney system
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong



- Use safe sedation practice guidelines
 - Maintain internal audit of sedation-related complications, including need to
 - Administer flumazenil, naloxone, or ventilation
 - Cardiopulmonary arrest, or aspiration
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Use caution if intravenous sedation plus local anesthesia spray are used (use if necessary, but bare in mind ↑ risk of complications).
- Inlet patch (aka heterotrophic gastric mucosa, cervical inlet patch)
 - Seen in 3% of EGD, in proximal esophagus, may show presence of dysplasia
 - Perform photo documentation and biopsy to exclude dysplasia.
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong
- Hiatus hernia
 - Distance between top of gastric folds and diaphragmatic pinch ≥ 2 cm
 - Photodocumentation, in retroflexal position
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: weak
- Suspected disease-specific quality standards
- Barrett's esophagus (BE)
 - Use the Prague classification, including length and circumference of BE, obtained on withdrawal of the EGD.
 - Use the Paris classification of BE, including
 - Distance from incisors
 - Clock face position
 - Take targeted biopsies, where possible
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
 - “when no lesions are detected within a BE segment, biopsies should be taken in accordance with the Seattle protocol (quadratic biopsies at 2 cm intervals)
 - Level of agreement: 90%
 - Grade of evidence: moderate
 - Strength of recommendation: strong
- If squamous cell cancer of the esophagus suspected, use
 - Chromo-endoscopy with Lugol iodine (dysplasia → ↓glycogen uptake]; look for colour pale on dark brown background → pink colour), with controlled withdrawal of EGD
 - Narrow band imaging (NBI) may be a suitable substitute to Lugol iodine.
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong



- LA grade D esophagitis / esophageal ulcers (≥ 5 mm depth)
 - Biopsy, then treat with PPIs for 6 wk and repeat EGD plus biopsies
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Eosinophilic esophagitis
 - Take ≥ 3 mucosal biopsies from at least 2 sites in the esophagus (low, mid, upper), even if mucosa ($\sim 15\%$ of suspected EOE will be normal appearing mucosa)
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong
- Esophageal varices
 - Use standardised classification, e.g., small and large
 - Treat photodocumentation as useful
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Strictures
 - Biopsy, then dilate after diagnosis known, unless the stricture is already known to have a benign cause (e.g., peptic, eosinophilic, radiotherapy, EMR/ESR, RFA)
 - Level of agreement: 90%
 - Grade of evidence: weak
 - Strength of recommendation: weak
- Gastric ulcers
 - Biopsy (≥ 6 mm) from the rim of ulcer (unless CMV suspected, when centre of ulcer is carefully biopsied)
 - Biopsy gastric antrum, incisura plus body (6 additional biopsies) for *H. pylori* infection
 - Treat *H. pylori* infection using guideline-based best practise
 - Repeat non-serological testing to prove eradication of *H. pylori* infection, and retreat if necessary
 - Treat known gastric ulcer (GU) with PPIs for 8-12 wk
 - Repeat EGD and rebiopsy gastric antrum, incisura and body to prove eradication of *H. pylori*
 - If GU not completely healed, repeat EGD to retake multiple biopsies to detect premalignant/malignant changes
 - Level of agreement: 90%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Duodenal ulcers
 - Regardless of history of use of NSAIDs, take 6 biopsies (gastric antrum, incisura, body) to exclude *H. pylori* infection
 - If *H. pylori* present, treat using best practise guidelines, and repeat non-serological testing to confirm *H. pylori* eradication
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong



- Endoscopic features of gastric atrophy (GA) / gastric intestinal metaplasia (GIM)
 - Make endoscopic diagnosis of GA/GIM using white light endoscopy (WLE), or preferentially intensified endoscopy.
 - Target biopsies from abnormal areas
 - If advanced endoscopy not available, use Sydney protocol for biopsies
 - Use separate bottles for biopsies from separate sites
 - Follow current guidelines for endoscopic / histological surveillance of GA/GIM/GD (Banks M, et al. Gut 2019;0:1-31)
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: weak
- Unexplained iron deficiency, biopsy
 - Gastric body, for gastric atrophy (poor digestion of iron, poor solubilization and poor digestion of iron, poor solubilization and poor absorption)
 - Gastric antrum, body for H. pylori infection and ↑ loss of blood from chronic active gastritis)
 - Duodenum, if celiac disease (iron malabsorption) suspected from family history / positive serology
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: weak
- Gastric polyps
 - Size, number, localization, and endoscopic type
 - Photodocument
 - Biopsy (gives some diagnosis (97%) as polypectomy biopsy)
 - If multiple polyps, take biopsies from multiple biopsies (no specific suggestion for number of polyps to be biopsied)
 - If biopsies adenomatous, or FAP, undertake surveillance as per best practise guidelines
 - Level of agreement: 100%
 - Grade of evidence: moderate
 - Strength of recommendation: strong
- Celiac disease
 - Describe and photodocument endoscopic changes in the first and second parts of the duodenum (D1 and D2)
 - Take ≥ 4 mucosal biopsies of D2/D2 (some guidelines recommend ≥ 6 duodenal biopsies)
 - Level of agreement: 100%
 - Grade of evidence: strong
 - Strength of recommendation: strong
- Malignant appearing lesion
 - Describe, photodocument, take ≥ 6 biopsies (unless otherwise contraindicated)
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong



❖ Post-endoscopy

- On completion of EGD, review and confirm
 - The number of histological samples taken
 - The correct labelling of histological samples
 - The dose [type] of sedation and/or analgesia given
 - Any complications of procedure
 - Any specific post-procedure advice to be given to the patient [and/or family]
 - Follow-up arrangements
- Before patient is discharged from the endoscopy suite, provide a written summary
 - Report describing main findings of EGD, including abnormalities/biopsies taken
 - Proposed management plan
 - Need for further endoscopy (surveillance and interval)
 - Follow-up as appropriate
 - Offer to provide a copy of written report to referring physician
 - Answer questions of patients/family
 - Remind patient, re safety issues of driving /work arising from sedation for EGD
 - Establish/maintain system for dictation report to referring physician is available within 24 h
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
- Biopsy results
 - “a method for ensuring histological results are processed must be in place”
 - Level of agreement: 100%
 - Grade of evidence: weak
 - Strength of recommendation: strong
 - It is appropriate to determine the maximal acceptable/safe results of standard biopsies to be available to the endoscopy as well as the referring physicians, and to the patient
 - This process should be subjected to audit
 - Note: although it is not specified it would be appropriate to expect the written report of the results of the biopsies within 3 working days of their submission from the endoscopy suite.
- Audit rates of failures to diagnose cancer withing 3 yr of the diagnosis of cancer post-EGD
 - Ensure the rate of post-EGD upper GI cancer (PEUGIC) is < 10%
 - Determine causes of these misdiagnosis, and take corrective action
 - Perform this audit evaluation every 3 yr
 - Level of agreement: 90%
 - Grade of evidence: weak
 - Strength of recommendation: strong

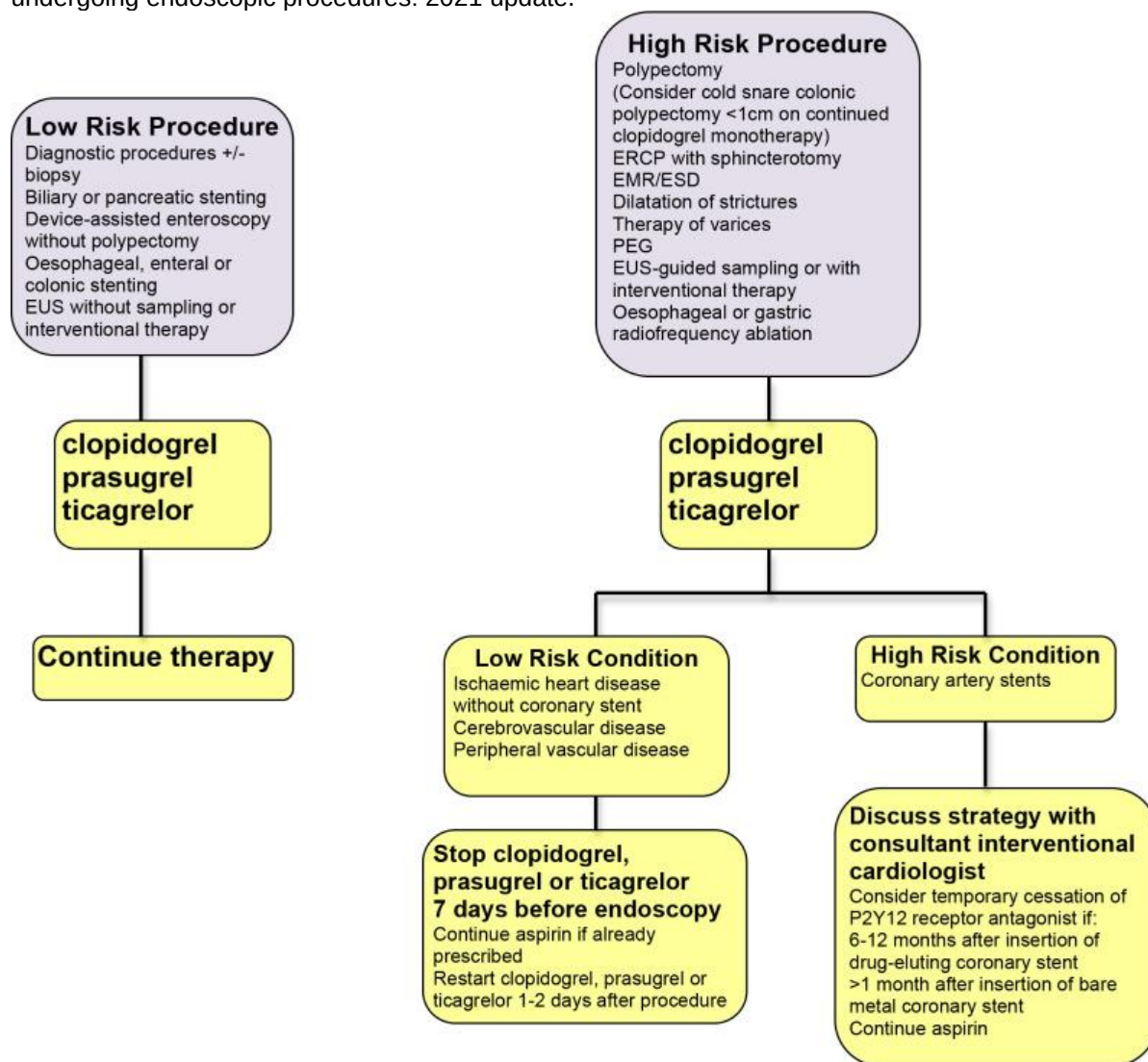
Abbreviations: AP, adenomatosis polyps; BE, Barrett's esophagus; BSG, British Society Gastroenterology; CAG, chronic active gastritis; D1, first part of duodenum (bulb); D2, second part of duodenum; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESR, endoscopic submucosal resection; FAP, familial adenomatous polyposis; FGP, fundic gland polyp; GA, gastric atrophy; GD, gastric dysplasia; GIM, gastric intestinal metaplasia; H. Pylori, Helicobacter pylori; HPs, hyperplastic polyps; LD, Los Angeles; NBI, narrow bowel imaging; PEUGIC, post-EGD upper GI cancer; PPIs; proton pump inhibitors; UGI, upper gastrointestinal



Endoscopy in Patients on Anti-platelet (AP) or Anti-coagulant Therapy: BSG/ESGE Guideline Update (2021)

Veitch AM, et al. Gut 2021; 70: 1611-1628

Guidelines for the management of patients on P2Y12 receptor antagonist antiplatelet agents undergoing endoscopic procedures: 2021 update.



Abbreviations: EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; PEG, percutaneous endoscopic gastroenterostomy

Printed with permission: Veitch AM, et al. Gut 2021; 70: 1611-1628 (Figure 1)



➤ Patient consideration

- Advise all patients of the ↑ risk of
 - Stopping AC/AP therapy → thrombosis
 - Not stopping AC/AP therapy → hemorrhage (Strong recommendation, low quality evidence)

➤ Therapies

❖ Anti-platelet agents

• Aspirin

- Primary prevention
 - No longer recommended
- Secondary prevention
 - Continue for all endoscopic procedures, except ampullectomy (weak recommendation, low quality evidence)
 - If to be discontinued, warn patient of ↑ risk of thrombosis vs hemorrhage (weak recommendation, low quality evidence)

➤ Risk stratification of endoscopic procedures based on the risks of hemorrhage and of intervention required to treat a complication

○ High-risk procedures	○ Low-risk procedures
– Endoscopic polypectomy* – ERCP with sphincterotomy – Ampullectomy – Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection – Endoscopic dilatation of strictures in the upper or lower GI tract – Endoscopic therapy of varices – Percutaneous endoscopic gastrostomy – Endoscopic ultrasound-guided sampling or with interventional therapy – Esophageal or gastric radiofrequency ablation	▪ Diagnostic procedures ± biopsy sampling ▪ Biliary or pancreatic stenting ▪ Device-assisted enteroscopy without polypectomy ▪ Esophageal, enteral or colonic stenting ▪ Endoscopic ultrasound without sampling or interventional therapy

*Cold snare resection of polyps <1 cm, consider keeping patient on continued clopidogrel monotherapy.

ERCP, endoscopic retrograde cholangiopancreatography.

Printed with permission: Veitch AM, et al. Gut 2021; 70: 1611-1628 (Table 1)



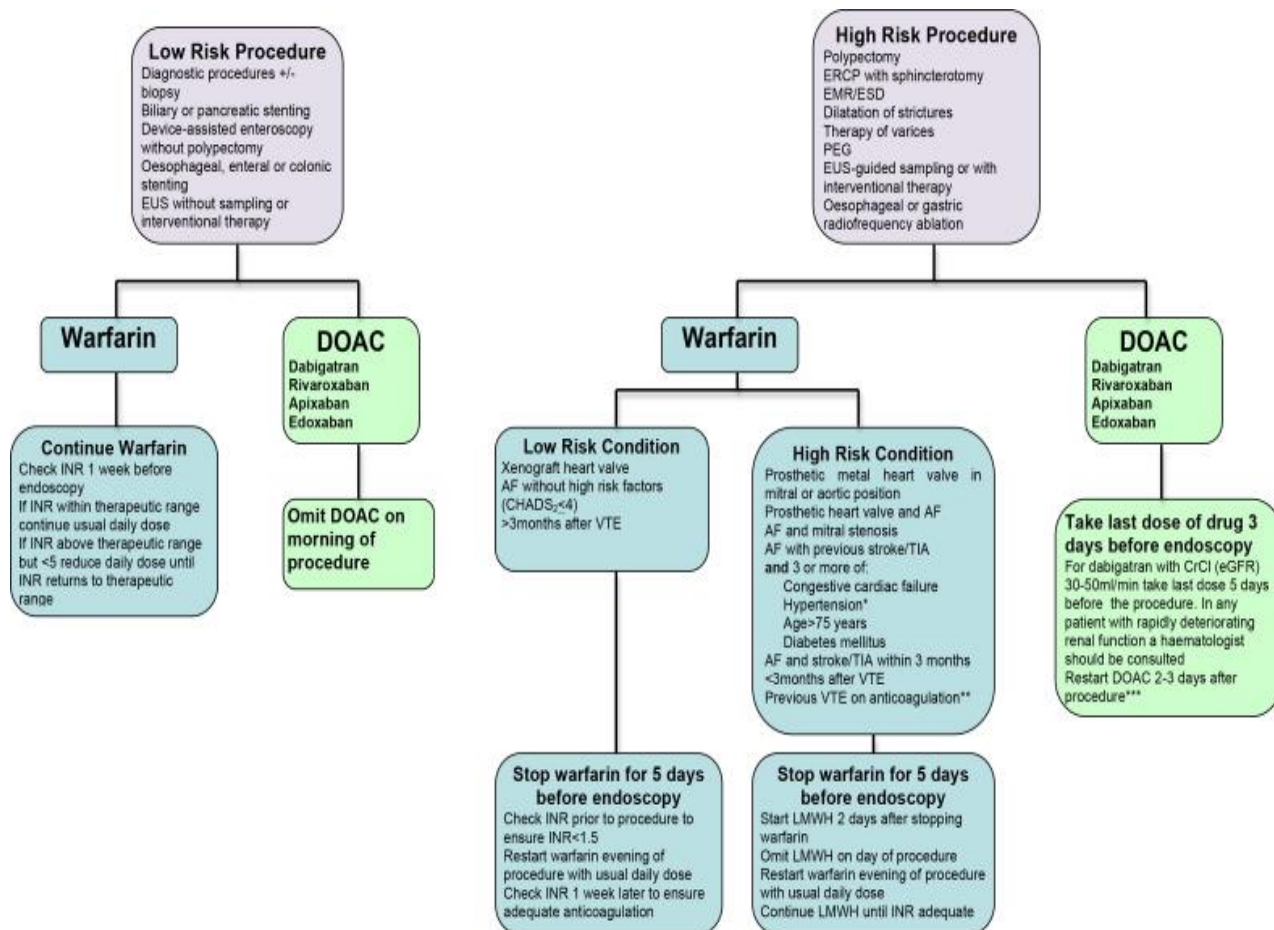
- ASA used for secondary prevention → ↓ risk
 - Vascular events, ↓ 30%
 - Vascular deaths, ↓ 15%
- Stopping ASA for secondary prevention → ↑ risk of cardiovascular events overall 3x (70% within 7-10 d)
- P2Y12 receptor antagonist (RA)
 - Low-risk endoscopic procedures
 - Continue single or double anti-platelet therapy (DAPT)
 - High-risk endoscopic procedures
 - Low patient risk of thrombosis
 - Single
 - Stop P2Y12 RA 7 days before procedure (strong recommendation, moderate quality evidence)
 - DAPT
 - Continue ASA, stop P2Y12 RA (strong recommendation, low quality evidence)
 - High patient risk of thrombosis
 - Continue ASA, plus consult interventional cardiologist re P2Y12 RA (strong recommendation, high quality evidence)
 - Irreversible ↓ platelet activity
 - Monotherapy
 - Clopidogrel, indications
 - Thromboembolic cerebrovascular accident
 - Peripheral vascular disease (PVD)
 - Elective percutaneous coronary intervention
 - DAPT plus ASA
 - Acute coronary syndrome (ACS)
 - Use prasugrel (clopidogrel if on ACS)
 - After placement of coronary stents
 - If DAPT stopped, continue ASA
 - Risk stratification for discontinuation of P2Y12 receptor antagonists clopidogrel, prasugrel or ticagrelor, based on the risk of thrombosis

High risk of thrombosis	Low risk of thrombosis
○ Drug eluting coronary artery stents within 12 mon of placement	– Ischemic heart disease without coronary stents
○ Bare metal coronary artery stents within 1 mon of placement	– Cerebrovascular disease
	– Peripheral vascular disease



❖ Anticoagulants

Guidelines for the management of patients on anticoagulants undergoing endoscopic procedures: 2021 update.



*Blood pressure >140/90 mm Hg or on antihypertensive medication.

**Previous VTE on anticoagulation and target INR now 3.5.

***Depends on hemorrhagic and thrombotic risk, consider extending interval for ESD.

Abbreviations: AF, atrial fibrillation; EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; INR, international normalized ratio; LMWH, low molecular weight heparin; PEG, percutaneous endoscopic gastroenterostomy; TIA, transient ischemic attack; VTE, venous thromboembolism

Printed with permission: Veitch AM, et al. Gut 2021; 70: 1611-1628 (Figure 2)



- Risk stratification for discontinuation of warfarin therapy with respect to the requirement for heparin bridging

High risk of thromboembolism	Low risk of thromboembolism
○ Prosthetic metal heart valve in mitral or aortic* position ○ Prosthetic heart valve and atrial fibrillation ○ Atrial fibrillation and mitral stenosis ○ Atrial fibrillation with previous stroke or transient ischemic attack+3 or more of: – Age>75 yr – Congestive cardiac failure – Hypertension† – Diabetes mellitus ○ Atrial fibrillation and previous stroke or transient ischemic attack within 3 mon ○ <3 mon after venous thromboembolism‡ ○ Previous venous thromboembolism on warfarin, and target INR to 3.5	– Xenograft heart valve – Atrial fibrillation without high-risk factors (CHADS₂ <4) – >3 mon after venous thromboembolism
○ Thrombophilia syndromes do not usually require heparin bridging, but individual cases should be discussed with a hematologist.	

*Heparin bridging for a metal aortic valve is recommended by European Society of Cardiology and by the European Association for Cardio-Thoracic Surgery guidelines 2017, but this varies between international guidelines and local guidance should be established in conjunction with cardiology or cardiothoracic services.

†Blood pressure>140/90 mm Hg or on antihypertensive medication.

‡The majority of patients are now on direct oral anticoagulants (DACs) for venous thromboembolism and bridging is not appropriate. Consider deferring a high-risk procedure beyond 3 mon therapy in this high-risk group for thromboembolism.

Abbreviation: INR, international normalized ratio.

- Warfarin

- Low-risk endoscopic procedures, is
 - Continue ASA, but ensure INR in the therapeutic range in the wk before the procedure (low quality evidence, strong recommendation)
- For low-risk endoscopic procedures
 - Warfarin therapy should be continued (low quality evidence, moderate recommendation).
 - Ensured that the INR does not exceed the therapeutic range in the week prior to the procedure (low quality evidence, strong recommendation).



- Continue warfarin and check the INR during the week before the endoscopy.
- If INR
 - Within therapeutic range → continue with the usual daily dose.
 - Above the therapeutic range, but less than 5 → ↓the daily warfarin dose until the INR returns to within the therapeutic range.
 - > 5, defer the endoscopy and contact the anticoagulation clinic, or a medical practitioner, for advice.
- For high-risk endoscopic procedures
 - Patients at low thrombotic risk
 - Discontinue warfarin for 5 days before the procedure (strong recommendation, high quality evidence).
 - Check INR prior to the procedure to ensure <1.5 (strong recommendation, low quality evidence).
 - Warfarin can be resumed on the day of the procedure, with the usual dose that night.
 - Restart the daily therapeutic dose of LMWH on the day after the procedure.
 - Continue LMWH until a satisfactory INR is achieved.
 - Updated literature searches were conducted on the use of warfarin and heparin in patients undergoing endoscopy.
 - There were no new data to indicate a change to the existing protocols above.
 - Any new data relevant to interventional therapy are discussed in the sections on specific endoscopic procedures
- High-risk endoscopic procedures
 - Low thrombotic risk
 - Stop warfarin 5 d before procedure (strong recommendation, high quality evidence)
 - Before procedure INR must be < 1.5 (strong recommendation, low quality evidence)
 - High thrombotic risk
 - Stop warfarin and bridge with low molecular weight heparin (LMWH; moderate quality evidence, strong recommendation)
- Stop warfarin for 5 days before the endoscopy.
 - Check the INR prior to the procedure to ensure its value is <1.5.
 - On the day of the procedure restart warfarin with the usual daily dose that night.
- Check INR 1 wk later to ensure adequate anticoagulation.
 - For high-risk endoscopic procedures in patients at high thrombotic risk, warfarin should be temporarily discontinued and substituted with LMWH (moderate quality evidence, strong recommendation).
- Warfarin should be stopped for 5 days before the procedure.
 - Two days after stopping warfarin
 - Commence daily therapeutic dose of LMWH.
 - Administer the last dose of LMWH at least 24 h prior to the procedure.



- Heparin (bridging for warfarin)
 - Anti-coagulation bridge
 - Unfractional heparin (uFH) IVI (intravenous infusion)
 - Low molecular weight heparin (LMWH), SC (subcutaneous) injection
 - Controversy
 - Heparin bridging required for
 - Bileaflet mechanical aortic valve replacement, with no atrial fibrillation (AF)
 - No
 - American College of Cardiology (ACC)
 - American Heart Association (AHA)
 - British Society of Hematology (BSH)
 - Yes
 - European Association for cardiothoracic surgery
 - European Society of Cardiology (ESC)
- ❖ Direct Oral Anti-coagulants (DOACs)
 - DOACs plus ASA stent
 - Discuss with interventional cardiologist.
 - Mechanisms of action
 - Dabigatran inhibits thrombin
 - Apixaban, doxaban, rivaroxaban inhibit FXa
 - DOACs
 - Low-risk endoscopic procedures
 - Stop DOAC on day of procedure (weak recommendation, low-quality evidence)
 - High-risk endoscopic procedures
 - eGFR CrCl > 50 mL/min
 - Stop DOAC 3 d before procedure (strong recommendation, low-quality evidence)
 - CrCl (eGFR) 30-50 mL/min
 - Stop DOAC 5 d prior to procedure (strong recommendation, low quality evidence)
 - Consult hematologist if renal function is deterioration rapidly
 - CrCl < 30 mL/min
 - Dabigatran **contraindicated**
 - Heparin bridging required for
 - Non-valvular atrial fibrillation (AF) with CHADS2 score > 5 (comorbidities such as diabetes, hypertension, heart failure)
 - Patients on warfarin with high-risk of thromboembolism
- Recent (within 3 mon) venothrombolism (VTE)
 - ↑ risk of recurrence
 - Low-risk procedure
 - Continue DOAC
 - High-risk procedure
 - Continue DOAC for 3 mon, then do procedure



- Thrombophilia syndromes

- Low risk
 - Factor V Leidin
 - Prothrombin mutation
 - Protein C/S deficiency
 - Use heparin bridging

} No heparin bridging

- ❖ Acute GI Bleeding and ACs/Aps (anti-platelets)

- Aspirin (ASA)
 - Secondary prevention
 - Continue ASA
 - If stopped, restart as soon as hemostasis is achieved
- DAPT
 - Consult interventional cardiologist (strong recommendation, moderate quality of evidence)
 - If major bleeding
 - If P2Y12RA stopped
 - Continue ASA (strong recommendation, moderate quality evidence)
 - Restart P2Y12RA within 5 d, if still indicated (strong recommendation, moderate quality evidence)
 - If patient has coronary stent, restart P2Y12RA as soon as possible after endoscopic hemostatic therapy (EHT)
- Anticoagulants (AC)
 - Stop AC and proceed with therapeutic endoscopy/radiological intervention (strong recommendation, low-quality evidence)
 - Vitamin K agonist (VKA), hemodynamic instability
 - Give vitamin K IV, plus
 - Four factor (FP) PCC (strong recommendation, low-quality evidence), or
 - Fresh frozen plasma (FFP) if PCC not available (weak recommendation, very low-quality of evidence)
- DOACs
 - Hemodynamic therapy: give reversal agents

DOAC	Reversal Agent
- Dabigatran	▪ Idarucizumab
- Anti-FXa	▪ Andexanet (weak recommendation, low-quality evidence), or FF PCC (weak recommendation, very low-quality evidence)



- Restart AC after GI bleed (GIB)
 - If an indication for long-term anti-coagulation (AC) (strong recommendation, low-quality evidence)
 - Low thrombotic risk
 - Start AC 7 d after stopping AC (weak recommendation, low-quality evidence)
 - High thrombotic risk
 - Use heparin bridging, restart AC within 3 d (strong recommendation, low-quality evidence)
- Mortality rate is 20% in patients with acute U/LGIB vs ~10%, “....mainly related to patients comorbidities)
 - “Anticoagulants are independent predictors of neither mortality nor in-hospital bleeding, provide they are managed appropriately.”
 - “temporary discontinuation of anticoagulation is the “standard of care” in patients with clinically significant GI bleeding.”

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- In patients with severe acute GI bleeding and hemodynamic instability, it is necessary to rapidly reverse anti-coagulation from vitamin K antagonist, using PCC rather than FFP.
- Give why PCC is preferred to FFP.
 - Faster onset of action
 - Lower volume
 - No need to check patient blood group
- Concomitant vitamin K
 - To prevent “INR rebound”

Abbreviations: AC, anti-coagulant; ACS, acute coronary syndrome; AP, anti-platelet; ASA, aspirin; BSG, British Society of Gastroenterology; CrCl, creatinine clearance; d, day; DAPT, double anti-platelet therapy; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; EHT, endoscopic hemostatic therapy; ESGE, European Society of Gastrointestinal Endoscopy; FFP, fresh frozen plasma; GI, gastrointestinal; Hg, hemoglobin; INR, international normalized ratio; LGIB, lower gastrointestinal bleeding; mon, month; PCC, prothrombin complex concentration; PVD, peripheral vascular disease; UGIB, upper gastrointestinal bleeding; VKA, vitamin K antagonist; VTE, venous thromboembolism



Endoscopy and Sedation: AGA Guidelines (2022)

Hepner D and Siddiqui UD. Am J Gastroenterol 2022; 117: 33-38

- Physiologic alterations during pregnancy and anesthetic considerations
- Respiratory
 - Pregnancy causes gradual
 - ↑ O₂ consumption
 - ↑ minute ventilation and
 - ↓ supply of backup oxygen due to
 - ↓ residual volume
 - ↓ functional resident capacity
 - This decrease in functional residual capacity is further diminished due to
 - Obesity
 - General anaesthesia
 - Certain body positions (such as supine, Trendelenburg, and Lithotomy)
 - Airway
 - Inhibition is more challenging due to
 - ↑ anteroposterior chest wall diameter
 - ↑ breast size
 - Laryngeal edema
 - ↑ body weight
 - Use smaller ET tube and gentle maneuvers
- Gastrointestinal
 - The context of challenging intubations causes 73% of maternal deaths associated with anesthesia in parturient (labour)
 - Mechanisms (anatomical changes)
 - Stomach is pushed up towards the left hemidiaphragm by the gravid uterus
 - Intraabdominal section of the esophagus displaced into the thorax, and
 - The axis rotates 45° to the right of its normal vertical position
 - These anatomical changes and progesterone ↓ lower esophageal sphincter tone
 - Peristaltic time ↑ risk of gastroesophageal reflux (GERD)
 - Reflux is more common as gestational age increases
 - By the third trimester, 72% of pregnant patients report symptoms of GER
 - Duration of fast before surgery
 - Light, non-fatty meal, 6 h
 - Otherwise, 5 h
 - May use non-particulate antacids may
 - ↑ gastric motility
 - ↓ H⁺ damage to lungs



- Induction agents
 - Avoid propofol
 - Delivery is not usually a planned event right after endoscopy, but
 - Propofol crosses the placenta, and
 - Neonatal blood levels of propofol can be clinically significant if it happens within 10 min of administration
- Procedure-related considerations
 - Anatomic changes of pregnancy
 - The expanding uterus → aortocaval compression → moves stomach into thorax → ↓ blood flow middle of the second trimester
 - It is advised to move the left uterus to reduce aortic compression and the resulting hypotension
 - Postpone, elective non-obstetric procedures until after delivery, or in second trimester (T2)
 - Procedure-related considerations
 - Left uterine displacement is recommended to minimize aortocaval compression and associated hypotension
 - Elective non-obstetric procedure should be delayed until after delivery to limit maternal and fetal risks
 - Non-emergent (but non-elective) procedures should be performed in the second trimester
 - Emergent procedures should be performed according to the maternal disease process
 - Provide thromboprophylaxis, aspiration prophylaxis, and antibiotic prophylaxis when warranted
 - Fetal monitoring should be performed when appropriate and when personnel are available to interpret the results
 - At a minimum, the fetal heart rate and uterine activity should be monitored both before and after surgery
 - Drugs administered for sedation during endoscopy
 - Deep sedation is safe using midazolam, fentanyl and propofol
 - No teratogenic potential in human
 - Post-operative management: Lactation
 - Safe to use drug lactation
 - After procedural sedation, nursing is permitted as long as the nursing patient is awake, conscious, and able to feed.
 - Breastmilk pump and discarded is controversial
 - Fentanyl and propofol do not require breastfeeding interruptions, but lactating patients may want to delay breast feeding for at least 4 h after receiving midazolam.



GASTROINTESTINAL REFLUX DISEASE (GERD)

Esophageal Manometry and Reflux Monitoring: British Society of Gastroenterology (BSG) Guidelines (2019)

Trudgill NJ, et al. Gut 2019; 66: 1-20.

➤ Equipment

- Measure pressure profiles of muscle of body of esophagus and upper/lower sphincters

• Qualities

○ Comparisons	High-resolution Manometry (HRM)	Standard Manometry (SM)
- Sensors	Solid state	Water perfused
- Number	Up to 36	3-8
- Reusable	+	-
- Dynamic performance	Immediate	Delayed
- Topographical analysis (2-D/3-D contour plots)	+	-
- Average procedure time, min	31	42

• Recommendation

- HREM is superior to SM as related to interpretation, performance and reproducibility
 - Grade evidence: high
 - Strength recommendation: strong

• Performance

- HRM is superior to standard manometry (SM) for
 - Quality
 - Reproducibility
 - Accuracy
 - Diagnostic yield
 - Multi-channel impedance added to HRM (HRIM) measurement of bolus movement through esophageal body to EGJ (movement of bolus disrupted/resistance develops)
- Note that 80% of persons with dysphagia but no manometric abnormality may have abnormal bolus movement, as shown on HRIM.

➤ Patient preparation

- Usually a barium swallowing study/esophagogastroduodenoscopy (EGD) has been performed before HRM/SM.
- Instruct patient to stop medications which might affect HRM/SM at least 48 h beforehand
 - Anticholinergics
 - Calcium channel blockers
 - Nitrates
 - Opiates
 - Prokinetics



- Stop food/fluids beforehand
 - Usually 6 h
 - Known esophageal retention 12 h
 - Suspected achalasia
 - Liquid diet for 2-3 days
 - Fast for 12 h or longer
- Make decision whether tests should be done on or off PPIs
- Test INR if patient is on warfarin
 - Do **not** do HRM/SM if INR is supratherapeutic

➤ Manometry Procedure

- Position
 - HRM
 - Upright/supine
 - SM
 - Supine
- Wet swallows
 - 10x 5 mL fluid, 20°C (room temperature)
 - q20-30sec
- Adjunctive testing (upright position)
 - Rapid drink challenge (RDC)
 - 200 mL, freely taken
 - Multiple rapid swallows (MRS)
 - 2 mL, every few seconds
 - Single bolus swallows, solid/viscous
 - Test meal
- HRM measured parameters
 - Integrated relaxation pressure (IRP)
 - Definition
 - “the lowest mean deglutitive esophagogastric junction [EGJ] pressure referenced to gastric pressure for 4 continuous or non-continuous seconds during a 10s window after the onset of swallowing, measured from the start of upper esophageal sphincter (UES) opening”
 - Interpretation
 - IRP reflects the degree of EGJ relaxation during swallowing
 - Distal contractile integral (DCI)
 - Definition
 - “...the product of the mean amplitude of contraction with distal smooth muscle esophagus (mm Hg) multiplied by the duration of contraction(s) and the length of the distal esophageal segment (cm) from the transition zone to the proximal margin of the LOS”
 - Interpretation
 - Peristalsis integrating is present if DCI > 450, there are no peristaltic breaks > 5 cm within a 20 mm isobaric contour.



- Contractile deceleration point (CDP)
 - Definition
 - “.... the inflation point along the 30 mm Hg isobaric contour (or pressure greater than intrabolsus pressure in instances of compartmentalized pressurization) at which propagate velocity slows”.
 - Must be localized within 3 cm of the proximal margin of the LES
 - Interpretation
 - “..... demarcating peristalsis from ampullary emptying”
- Distal latency (DL)
 - Definition
 - “.... Measurement from the beginning of UOS [UES] swallowing induced relaxation to the CDP
 - Note that the normal values for IRP, DCI, CDP and DL vary between the measurements of the equipment and the specific catheter which is used.

- Examples
 - Using a rice meal, ≥ 2 swallows

▪ Achalasia, esophagogastric junction (OGJ)	IRP > 25 mm Hg
▪ Spasm	DL < 4.5 sec
▪ Hypercontractility	DCI > 8000 mm Hg x sec x cm

- Minor disorders of peristalsis may be seen, e.g., “fragmented peristalsis”
 - 5 yr follow up
 - 70% become spontaneously asymptomatic
 - Consider performing challenge swallows (solid or liquid)
- Rapid drinking challenge (RDC) and multiple rapid swallows (MRS)
 - Rapid swallowing from RDC/MRS → “deglutitive inhibition” (↓ peristalsis of motility of body of esophagus, plus ↓ tone (↑ relaxation) of OGJ (↓ pressure of lower esophageal sphincter (LES)
 - This is then followed by a clearing contraction
 - RDC-IRP > 12 mm Hg → indicates esophageal obstruction due to achalasia
 - RDC-IRP > 8 mm Hg → indicates “all cause” EGJ obstruction
 - MRS may be better than RDC to detect ineffective/fragmented single water swallows, and thereby identifying “peristaltic reserve”
 - Peristaltic rescue can be testing using liquids or solids
 - Causes of peristaltic rescue NERD (negative/normal endoscopy gastroesophageal reflux disease)
 - Definition
 - Hypotensive absent peristalsis with water but not with swallows
 - Interpretation
 - Excludes a major disorder of esophageal motility



- Solids can be used to detect “peristaltic reserve”, as also can water (“wet”) swallows, but using a standardized often leads to a change in diagnosis.
 - Manometric classification, 67% } Also, solids provide for better management and outcomes
 - Clinical diagnosis, 39%

		Swallows	
		Solids	Liquids
- Detection of	▪ Dysphagia/dysmotility	70%	30%
	▪ Outlet obstruction	26%	7%

❖ Approaches to patients

- Esophageal dysphagia
 - After careful history and physical examination – perform EGD
 - Some endoscopists wish to see barium swallow before performing an EGD so as to anticipate the possible need for therapeutic measures, and to outline structural lesions which might offer safety challenges.

Recommendation

- The patient with esophageal dysphagia should have EGD plus biopsies of the esophagus from the different recommended sites to rule out eosinophilic esophagitis, before having manometry studies (HRM/SM)
 - If EGD is not readily available, at least do a barium swallow
 - Before HRM/SM (also especially useful to detect
 - If EGD not readily available → barium swallow
 - Barrett’s esophagus (BE)
 - Flat lesions
 - Zenker diverticulum
 - May be useful in suggesting
 - Other causes of dysphagia, e.g., dysphagia, e.g., infections of esophagus
 - Degree of gastroesophageal reflux
 - Possible motility disorder

• Achalasia

- In the patient having an esophageal manometry study for suspected achalasia, perform HREM rather than SM because of its superior performance characteristics and diagnosis potential
- Advantage of HREM vs SM to diagnose achalasia
 - Performance characteristic

	Sensitivity	Specificity
▪ HREM	98%	96%
▪ SM	52%	-
 - Determination of subtypes of achalasia
 - Selection of optimal initial therapy based upon achalasia subtype e.g., type III achalasia responds poorly to all treatments
 - Distal (diffuse) esophageal spasm (DES), hypercontractile esophagus, absent peristalsis (non-achalasia major motility disorders)



Recommendation

- HREM is superior to SM for diagnosis and for functional information regarding the non-achalasia motility disorders
 - GRADE evidence: Moderate
 - Strength recommendation: Conditional/weak

➤ Definition

- Distal Esophageal Spasm (DES)

- Specific-premature contractions, DI < 4.5 sec
- Non-specific
 - HREM water, ≥ 2 simultaneous contractions
 - Fast wave contractile front velocity (CFV) > 8 cm/s in > 20% of wet swallows with amplitude > 30 mm Hg
 - Normal peristalsis in ≥ 1 out of 10 swallows
 - Minor criteria
 - Body contraction waves
 - $\uparrow$ amplitude
 - Multi peaked
 - LES (EGD)
 - Resting
 - Relaxing
 - $\uparrow$ pressure
 - Incomplete/impaired
- EGJ (LES) relaxation
 - Incomplete/impaired EGJ relaxation (function obstruction) must not be called DES on the basis of some normal peristalsis

	“Best Technique”	
▪ EGJ (LES) relaxation	HRM	
▪ DES	SM	

- Absent peristalsis (“absent contractility”)

- Use HREM plus MRS, RDC, or a test meal to distinguish absent peristalsis from achalasia, type I

- Hypercontractile esophagus (HE; previously called “nutcracker esophagus” [NE])

- Non-hypercontracted esophagus is defined as $\geq 20\%$ of swallows with DCI > 8000 mm Hg.s.cm.
 - Three patterns of hypercontractile swallows
 - Multi peaked
 - Synchronized with breathing
 - Not synchronized with breathing
 - Not multi peaked
 - Often associated with EGJ obstruction
- In the past, HE (“hypertensive peristalsis”) was defined as HREM as DCI > 5000 mm Hg.s.cm
 - Often asymptomatic with repetitive contractions, and usually symptomatic (“spastic nutcracker”)



- Catheter-based (SM) Monitoring of pH/impedance

Recommendation

- Esophageal monitoring is the preferred method to identify the lower esophageal sphincter (LES), 5 cm above which by convention an esophageal pH probe is placed
 - GRADE: evidence: High
 - Strength recommendation: Strong
- The positioning of the pH probe by manometry is superior to pH step-up approach, i.e., pulling the pH probe back from the stomach into the lower esophagus.
 - Comparing the manometry-based versus the step-up based positioning of the pH probe, in 58% of patients the step-up approach did not correctly correlate with the position found on manometry.
 - The ideal approach is a combination of the manometry approach to find the LES (the pH step-up), followed by the patient eating immediately afterwards.

- Before Anti-reflux Surgery

Recommendation

- Before performing anti-reflux surgery (fundoplication), all patients should have esophageal manometry to ensure that they do **not** have
 - Achalasia (LES dysfunction)
 - Distal esophageal spasm (major motor dysfunction of the body of the esophagus)
 - GRADE evidence: moderate
 - Strength recommendation: strong
- Notwithstanding the above strong recommendation, this is not supported by the expected quality of evidence
 - Dysphagia is common after anti-reflux surgery
 - Early, 20%
 - Late (> 6 mon), ~6%
 - Patients with abnormal esophageal motility do **not** have ↑ risk of post-operative dysphagia
 - Patients with no dysphagia before surgery, and who have a preoperative motility study, this prospective motility study “does not predict the likelihood of dysphagia after surgery”
 - “Even abnormalities in esophageal motility preoperatively (altered primary peristalsis or distal contraction amplitude) does “... not have an impact on post-operative dysphagia scores”
 - Preoperative abnormalities in
 - LES pressure/relaxation
 - Peristalsis, bolus transient
 - The only prediction of post-operative dysphagia is the degree of the fundoplication.



- Symptoms after esophageal surgery
 - HREM (but not SM) with MRS/solid test meal may demonstrate gastroesophageal outlet obstruction as a cause of post-operative symptoms.
 - The presence of outflow obstruction with solid swallows predicts a positive response to esophageal dilation in 59% of patients.
 - It is not known yet whether the occurrence of post-operative dysphagia can be predicted on the basis of a new HREM term, the “esophagogastric junction contraction integral”.
 - Rumination
 - Definitions (Rome III diagnostic criteria)
 - ≥ 3 mon of regurgitation without preceding nausea only during and up to 2 h after 2 meals and never at night.
 - The regurgitated food tastes “pleasant” (not “acidic” so the food can be chewed or swallowed.
 - Pathophysiology
 - Voluntary but subconscious contraction of the abdominal wall $\rightarrow$ $\uparrow$ intra gastric pressure > 30 mmHg $\rightarrow$ relaxation of LES/UES $\rightarrow$ regurgitation of non-acid food/fluid, but not gas
 - Diagnostic Testing
 - HREM plus pH/impedance testing
 - GER of food/fluid, non-acidic
 - No gastric/supragastric belching (regurgitated air)
 - pH/impedance monitoring
 - Purpose
 - Detection of gastroesophageal fluid or gas; insensitive of their pH or content (i.e., liquid, solid, gas)
 - Procedure
 - Ideally perform EGD before pH/pl study, with patient off PPIs for ≥ 2 wk
 - Fast for 6 h
 - Test to ensure warfarin associated INR is in the therapeutic range
 - pH/PI Probe placed 3 cm proximal to lower esophageal sphincter (LES) as determined by manometer measurement, or based on pH step up technique (Please see previous section)
 - Stop food/fluid intake 6 h before testing, or longer if gastroesophageal obstruction / esophageal retention of food/fluid suspected
 - Monitor pH/pl for 24 h
- | | <u>Total time pH 4</u> |
|----------------|------------------------|
| ▪ Normal | 4% to 6% |
| ▪ Intermediate | 4% to 6% |
| ▪ Abnormal | $> 6\%$ |



- Definition of “acid reflux event”
 - ↓ esophageal pH to < 4
 - % of total time esophageal pH < 4 (over 24 h)
 - The Meissner score described components of pH such as % time pH < 4 when supine or upright, number of events < pH 4, or for 5 min, or longest event
 - This composite score has no advantage over simpler percentage total time esophageal pH 4
- Suggested reporting of pH data
 - % pH <4
 - Total
 - Upright
 - Supine
 - Number of episodes of pH < 4 which lasts for > 5 min
 - Those numbers may be calculated automatically by the movement including SAP/SI, explained below
 - GRADE evidence: Low
 - Strength recommendation: strong
 - Proceed with determination of the symptom index (SI)
- Symptom Index (SI)
- Definition
 - “The number if symptom events associated with GER as a percentage of the total number of symptom events”
 - A SI > 50% suggests a clinical positive association, but
 - False positive result may occur if there are only a few recorded symptoms and many reflux events
 - SI is less reproducible than is SAP so SI should not be done alone

Recommendations

- “patients should undergo all pH monitoring **off** all acid suppression to maximize the choice of diagnosing excess acid reflux and a significant symptom association with acid reflux”
 - GRADE evidence: Moderate
 - Strength recommendation: Strong
 - When taking PPI b.i.d., < 4% have persistent abnormal acid exposure, but 30% do when taking PPI od
- Patients with symptoms of heartburn or regurgitation which does not respond to PPI b.i.d., the decision is whether PPIs are stopped or not before pH/Pi testing depends upon the finding at EGD.
 - Abnormal EGD or previous abnormal pH monitoring
 - Perform study with patients **on** PPI (high probability of abnormal test)
 - No abnormal EGD or previous normal pH monitoring
 - Perform study with patient **off** PPI (lower probability of abnormal test)
 - Better possibility too demonstrate GER symptom association.
 - GRAD Evidence: Low
 - Strength recommendation: conditional/weak



- The qualitative analysis of acid exposure, number of reflux episodes, and association of symptoms with GER episodes provides superior data, for example may help to differentiate between refractory normal endoscopy reflux disease (NERD) versus functional heartburn.

Recommendation

- SAP/SI symptom associations should be used only for heartburn/regurgitation, and **not** for throat/respiratory symptoms.
 - GRADE evidence: Low
 - Strength recommendation: conditional/weak
- ❖ Patients with symptoms which are clinically suspicious of GERD
- Undiagnosed dyspepsia (no EGD) or NERD (EGD normal)

Recommendations

- Use empiric trial of PPI b.i.d. for 4 wk, with the target of > 75% ↓ frequency of GERD symptoms
 - GRADE evidence: Moderate
 - Strength recommendation: strong
 - If the patient symptoms respond to PPI trial stop PPI after 4 wk
 - If symptoms recur, use PPI in minimal dose to control GERD symptoms
- In those patients who do **not** respond to empirical trial of PPI b.i.d., pH/ Pi monitoring is not necessary unless the patient/physician are considering anti reflux surgery.
 - In this case reflux monitoring is recommended before surgery
 - GRADE evidence” Moderate
 - Strength recommendation: Strong

Recommendation

- “Patients should undergo all pH monitoring off all acid suppression to maximize the choice of diagnosing excess acid reflux and a significant symptom association with acid reflux”

Clinical Diamond

- “.... responding to a proton pump inhibitor (PPI) is associated with better long term symptomatic outcome following anti-reflux surgery”



- With supraesophageal symptoms
 - If gastroesophageal reflux is suspected to be a cause of chest pain, throat or respiratory symptoms, and an empirical trial of PPI b.i.d. is not successful → perform pH/PI monitoring.
 - GRADE evidence: Low
 - Strength recommendation: Strong
 - Explanation for combined pH/PI monitoring
 - Diagnosis/exclusion of
 - GER, pathological
 - Symptoms association of GER of acid/non-acid
 - GER into of upper esophagus (↑ risk of microaspiration)
 - When performing pH/PI monitoring for patients with suspected supraesophagus symptoms from GER:
 - What to do about PPI use
 - Previous abnormal EGD or pH study abnormal (suggesting pathological GER and ↑ likelihood of abnormal pH/PI testing)
 - Performed with patient on PPI
 - No previous abnormal EGD or normal pH study (likely GER not present)
 - Perform off PPI
- Suspected GERD in patients with cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), or lung transplantation (LT)

Recommendations

- Patients with CF or IPF who may require future lung transportation should have pH/PI monitoring, and if abnormal acid/non-acid reflux – PPI b.i.d.
 - GRADE evidence: Low
 - Strength recommendation: Conditional/weak
- In CF/IPF, there may be GER without symptoms, but the GER predisposes the patient to microaspiration.

MCQ Pearl

- Patients with idiopathic pulmonary fibrosis (IPF), the ↑ risk of gastroesophageal reflux is due to IPF-associated
 - ↓ lower esophageal pressure (LESP) → proximal reflux and possible micro-aspiration
 - ↓ peristalsis of body of esophagus (↓ clearance of reflux acid and non-acid material)



- Suspect GER as cause of symptoms, symptoms responsive to PPI's and anti-reflux surgery planned

Recommendations

- GRADE evidence: Moderate
 - Strength recommendation: Strong
- Perform pH study (pH/PI study not necessary) to confirm
 - Abnormal GER
 - Symptom association
 - Superior response to fundoplication if patient had demonstrated abnormal pH study
 - Excellent 5-yr results in 85%
- Suspected GER as cause of symptoms, symptoms not responsive to PPIs, and anti-reflux surgery planned:

Recommendation

- Perform pH/PI study (off PPIs) to confirm
 - Excess esophageal acid exposure, +/-
 - Symptom association with acid/non-acid GERD
 - GRADE evidence: Low
 - Strength recommendation: Strong
- Post-fundoplication symptoms
 - Symptoms after fundoplication may be due to GER of
 - Acid/non-acid
 - Air (belching)

➤ Definition

- Belching of swallowed air

➤ Types

- Gastric belching
 - Swallowed air vented from the stomach
- Supragastric belching
 - Swallowed air vented from the esophagus

➤ Pathophysiology

- Fundoplication alters belching
 - ↓ gastric
 - ↑ supragastric



Recommendations

- Patients who have had anti-reflux surgery and who have persistent/recurred GER symptoms should be studied with pH/PI monitoring (not pH alone) to diagnose/exclude persistent GER and to exclude other causes, such as supra-esophageal belching
 - GRADE evidence: Low
 - Strength recommendation: Conditional/weak

❖ Wireless Monitoring of Esophageal pH

➤ Definition

- “...radiotelemetry pH capsule attached to a delivery system and an external receiver”
 - Perform off PPI therapy
 - Capsule placed by EGD 6 cm above squamocolumnar junction, using suction device
 - Monitor for 48 h for better symptom correlation

Recommendations

- Perform wireless pH monitoring for 48 h
 - GRADE evidence: High
 - Strength recommendation: Strong
- ↓ variability
- ↑ abnormal GER detected
- ↑ reporting of symptoms
- ↑ symptom correlation
- If the result of the 48 h capsule wireless pH monitoring is indeterminate, the procedure may be extended to 96 h, as long as
 - The capsule is still attached
 - the “average analysis” plus the “worst day” analysis or the 3-day average analysis may be used to determine if the correct diagnosis is GERD
 - GRADE evidence: Moderate
 - Strength recommendation: Conditional/weak
- While the extension of monitoring from 48 h to 96 h ↑ diagnostic yield, achieving this ↑ yield depends upon when data is included in the analysis; details of the methodology will not be discussed here.
- Patients suspected of having GERD
 - Who do **not** respond to PPI b.i.d. (refractory), and
 - Cannot tolerate nasoesophageal pH catheters, or
 - Results of pH, or pH/PI testing are inconclusive
 - GRADE evidence: Moderate
 - Strength recommendation: Strong
 - Consider wireless capsule monitoring



❖ Quality Improvement: Auditing MD/monitoring

- Physician/assistants
- Placement of pH probes graded by manometry
 - Pre-operatively
 - pH monitoring
 - Manometry
- Monitoring for dysphagia
 - Perform premanometry EGD +/- biopsies
 - Perform at least one adjunctive testing (large volume water/solid-viscous swallows / test meal)

Abbreviations: BE, Barrett's esophagus; b.i.d., twice a day; BSG, British Society of gastroenterology; CDP, contraction deceleration point; CF, cystic fibrosis; CFV, contractor front velocity; DCI, distal contractile integer; DEO, disturbed esophageal obstruction; DOS, distal esophageal spasm; EGD, esophagogastroduodenoscopy; EGJ, esophagogastric junction; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HE, hyper contractile esophagus; h, hour; HRM, high resolution manometry; INR, international normalized ratio; IPF, idiopathic pulmonary fibrosis; IRP, Integrated relaxation pressure; LES, lower esophageal sphincter; LT, liver transplantation; MCQ, multiple choice question; MRS, multiple rapid swallows; PPIs, proton pump inhibitors; RDC, rapid drink challenge; s, seconds; SAP, symptom association probability; SI, symptom index; SM, standard manometry



Symptoms Association Analysis in Patients with Symptoms of Suspected Gastroesophageal Reflux Disease (GERD)

Kamal AF, et al. Am J Gastroenterol 2020; 115: 1950-1959.

- GERD symptoms do **not** always (~50%) correlate with EGD-demonstrated mucosal disease
 - Proof of GER by esophageal manometry is not practical or available on a wide basis.
 - Some persons are hypersensitive to even small amounts of GER (“reflux hypersensitivity”), and it is important to be able to correlate the GER event with the patient’s experience of GER symptoms.
 - Thus, esophageal reflux monitoring has become important
 - To quantitate acid exposure times by pH, and
 - To assess the reflux and symptoms relationships, rather than just focusing on pathological acid exposure by itself.
- Prolonged measurements (24-48 h) of esophageal pH has satisfactory performance characteristics for establishing abnormal values for esophageal acid exposure.
 - Sensitivity, 77% to 100%
 - Specificity, 85% to 100%
 - However, those values are for patients who are already known to have GERD by way of their having EGD-demonstrated erosive esophagitis.
- Multi-channel pH impedance pH-MII monitoring adds the benefits of measuring reflux of acid, as well as non-acid and reflux of air (a belch).
 - With pH-MII
 - Acid reflux (refluxate, pH < 4)
 - Weekly acid reflux, pH 4 to 7 (esophageal pH is normally ~pH7)
 - Alkaline reflux, decreasing pH, but an impedance events

	Impedance Event Retrograde Decrease from Baseline
▪ Fluid reflux	↓
▪ Air reflux	↑

▪ Fluid reflux	↓
▪ Air reflux	↑
- pH monitoring (Lyon GERD Consensus)
 - Outcome measured
 - Presence of GER (pH < 4)
 - GER duration (best measure: acid pH < 4 exposure time (normal, < 4% of the monitored time; abnormal, > 6%; false negative exposure result (patients with confirmed reflux esophagitis, 20%)
 - Number of reflux events: > 80 reflux episodes per 24 h
 - May be abnormal
 - Adjunctive data for proving that a patient’s symptoms are due to reflux, especially when acid exposure time is inclusive at 4% to 6%
 - Number of reflux events lasting > 5 min



- Impedance monitoring
 - Number of results episodes per 24 h (best use is to interpret acid exposure time between 4% and 6%)
 - Normal, < 45
 - Abnormal, > 80
- ❖ Symptoms association methods
- Cough
 - pH-MII catheter, measures pressure in the lumen of both the esophagus and stomach
 - Interpretations
 - Reflux, then cough → GER causes cough
 - Cough, then reflux → cough causes GER
- GER
 - Time window of evaluating GER symptoms
 - 2 min between a reflux episode and considering whether symptoms are due to the reflux episode.
 - This 2 min time window applies for assessing cough or GER, but not other symptoms such as non-cardiac chest pain (NCCP).
- Symptom index (SI)
 - The number of GER-related symptom episodes as a percentage of the total number of symptom episodes.
 - Do **not** include non-GER symptoms (heartburn/regurgitation, cough) in the numerator
$$SI = \frac{\text{Number of reflux-related symptom episodes}}{\text{Total number of symptom episodes}} \times 100\%$$
 - Performance characteristics of SI for heartburn
 - Sensitivity and specificity, 50%
 - Limitation of SI
 - The number of reflux episodes is not taken into account, just the number of reflux-related symptom episodes → ↑ risk of false positive SI if there are
 - Many GER events, but
 - Few GER symptoms episodes
 - Probability of a positive SI ↑ with ↑ number of reflux episodes.



- Symptom association probability (SAP)
 - Overcomes the risk of the high number of false positive SI results by taking into account the total number of reflux episodes.
 - 24 h recording with data analysed from 2 min intervals being positive (R+) or negative (R-) for reflux.
 - Then a “2x2 contingency table is set up of R+/R- versus symptoms (S) positive (S+) or absent (S-)”

	S+	S-
R+		
R-		

Abbreviations: R, reflux of acid; S, GER symptom; $SAP = (1 - \text{probability}) \times 100\%$

- Thus, SAP is a calculation, a “statistical parameter” that does not necessarily imply a casual relationship”.
- Notwithstanding, an SAP value of $\geq 95\%$ is interpreted as “...the probability of an association occurring by chance is $< 5\%$.”

- SAP represents “the probability of a relationship, i.e., the preferred symptom-association index”.
 - “SAP is recorded with stronger statistical validity for reflux symptom correlation...”.

- Ghillebert probability estimate (GPE)
 - “This method consists of a calculation of the sum of partial possibilities of all reflux associated symptoms among the total number of symptoms, considering total pH impedance study duration and total exposure time”.
- Comparisons
 - Discordance between SAP and GPE is only ~3%
 - Can be used interchangeably
 - SI and GPE ~1%
 - Comparing SI and SAP
 - Longer monitoring affects SAP values: (SAP- to SAP+) is 5% to 10%
 - Day-by-day variability of SI (SI- to SI+) is 5%, i.e., lower reproducibility, with Rendall coefficient of concordance [K-value]; 0.86.
 - Use of SI and SAP symptom indices only modestly predict value for proton pump inhibitor (PPI) treatment success.



- Interobserver agreement of SI and SAP in patients on PPIs varies by symptom.

Symptom	K-Value
- Regurgitation	0.68
- Indigestion	0.64
- Chest pain	0.51
- Heartburn	0.48
- Cough	0.33
- Throat clearing	0.29

- Symptom response with PPI

	Sensitivity	Specificity
- SI	35%	80%
- SAP	65%	73%

- GPE score directly/linearly correlates with ↓ global symptom severity.

- Strength of symptom

Terminology	Acid Exposure Time (AET)	SAP	
- Strong	AET+	SAP+	} ■ Best symptomatic response to medical/surgical therapy
- Good	AET+	SAP-	
- Equivocal			
- Hypersensitivity (not sure to abnormal acid reflux)	AET-	SAP+	

- Reflux hypersensitivity

➤ Definition

- A disease of heightened esophageal visceral sensitivity, and not because of pathological acid disease.
 - Normal esophageal mucosa on EGD, but normal esophageal acid response, but abnormal symptom correlation.
 - Typical of patient with GERD symptoms and no response to high-dose PPIs
 - Treat with TCAs/SSRIs



- Functional heartburn

	GERD Symptoms	Normal Acid Response	Normal EGD	Symptom Correlation (SI/SAP*)	Response to PPIs
- Esophageal reflux hypersensitivity	+	+	+	-	-
- Functional heartburn	+	+	+	-	-
- GERD	+	-	+	+	
▪ Non-GERD	+	-	+/-		
▪ PPIR-GERD (resistant)	+	-	-	+/-	

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the features required by the Rome IV criteria to support the diagnosis of functional heartburn.
 - "Dyspepsia", i.e., that is burning retrosternal discomfort/pain
 - No symptom relief with proton pump inhibitors (PPIs)
 - No GERD / EoE
 - No major esophageal motor disorder
- Give data suggesting that SI/SAP may have limited use in patients with PPI refractory GERD (PPIR-GERD) to distinguish between esophageal hypersensitivity and functional heartburn.

○ pH negative	No esophagitis	}	Minimal differences in SAP calculation score
○ pH positive	No esophagitis		
	Esophagitis		

PPI therapy may have some role in patients with acid hypersensitivity

- Give the likely significance of symptom association of the GERD symptoms of regurgitation.
 - False positive SI/SAP indices with rate of refluxes < 10% (~33% are false positive if no reflux rate).
 - This may represent the rumination syndrome (please see next page)
 - Intake of acid food beverages during ambulatory reflux monitoring and analysis of symptom association → artifacts in false positive



- Rumination Syndrome
- Definition (Rome IV criteria)
 - “Persistent or recurrent regurgitation of recently ingested food and subsequent spitting or and mastication and swallowing and
 - Regurgitation not preceded by retching for the past 3 mon”
- Demography
 - Occurs in ~20% of PPI-R non-responsive (refractory) GERD (GERD-like symptoms)
- Clinical clues
 - Criteria for Rome IV definition, plus
 - Gastroesophageal reflux of non-acid post-prandial material
 - Proximal reflux episodes, frequent

TINY TRIVIA

- Give the classification of belching, based upon impedance measurements.
 - Gastric air distends fundus → movement of air into esophageal / oral cavity (mouth).
 - Supra gastric belch
 - Air in environment sucked through mouth into oral cavity into esophagus → air in esophagus returned to oral cavity / out through the mouth (expelled air has not reached the stomach before being released back into the mouth)
 - Air or liquid mixed (air plus liquid) belches occur with both gastric/supragastric belching.
 - Belching may be air → liquid, liquid → air, or mixed

Abbreviations: AET, acid exposure time; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GPE, Ghillebert probability estimate; min, minute; NCCP, non-cardiac chest pain; NERD, Normal endoscopy reflux disease; pH-MII, multi channel pH impedance; PPI, proton pump inhibitor; PPI-R, proton pump inhibitor resistant; RR, refractory reflux; S, symptoms; SAP, symptom association probability; SI, symptom index; SSRI, selective serotonin receptor inhibitors; TCA, tricyclic antidepressant; W, coefficient of concordance

Useful additional reading: the Lyon consensus, Gyawal CP et al. Gut 2018; 67: 135-62.



Clinical Use of Esophageal Physiologic Testing: ACG Guideline (2020)

Gyawali CP, et al. Am J Gastroenterol 2020; 115: 1412-1428.

➤ Clinical

- Do **not** use symptom questionnaires by themselves "...to diagnose specific esophageal conditions such as GERD, EoE, esophageal motility disorder (i.e., achalasia)
 - For example, the Eckardt score (ES) "... was developed without rigorous evaluation for validity and reliability.
- GERD questionnaires should not be used to diagnose GERD because of poor performance characteristics.
 - Sensitivity, 62 % to 100%
 - Specificity, 37% to 67%
- However, patient-related outcomes (PRO) may be used to assess treatment outcomes for achalasia when done in conjunction with ... an objective measure of esophagus function such as timed barium esophagus (TBE).

➤ Diagnostic imaging

- In patients with obstructive esophageal symptoms (dysphagia), if a barium esophagram is performed, also do a timed barium swallow using a standardized, upright, timed protocol and include a barium tablet with the liquid barium.
- Timed barium swallow (TBS)
 - Evaluate the height of the barium swallow at 1 min (abnormal, > 5 cm) and at 5 min (abnormal, > 2 cm)
- Esophagram to detect esophageal dysmotility is "suboptimal with poor performance characteristics"
 - Sensitivity ~70% Positive predictive value (PPV) ~60%
 - Specificity 50% Negative predictive value (NPV) ~60%

• Esophageal Manometry

- High resolution manometry (HRM) is superior to conventional manometry to diagnose achalasia, and to direct the choice of optimal therapy.
 - Use provocative maneuvers such as Rapid Drink Challenge (RDC) or standardized test meal (STM) → ↑ yield for
 - Obstruction of esophagogastric junction (EGJ) outflow
 - Esophageal spasm
 - Also measure high resolution intraluminal impedance (HRIM) to better assess bolus clearance



- Functional Lumen Imaging Probe (FLIP)
 - Measure
 - Pressure
 - Area (minimal cross-sectional area, CSA)
 - Distensibility (abnormal response to esophageal distention found in 50% of patients with non-occlusive esophageal contraction (provides another possible subclassification of achalasia with predictive value for therapeutic outcome)
 - Ineffective esophageal motility (IEM), or normal HRM study
 - Can provide diagnosis of achalasia when EGJ relaxation is normal on HRM / normal integrated relaxation pressure (IRP).
 - EGJ relaxation / distensibility products
 - In persons with obstructive esophageal symptoms and borderline findings on HRM, use if FLIP to complement HRM.
 - To diagnose an esophageal motility disorder
 - To assess possible ↑ risk of bolus impaction in EoE
 - To determine adequacy of pneumatic balloon dilation (PBD) (EGJ distensibility, minimal cross-sectional area)

Abbreviations: AET, acid exposure time; ARS, anti-reflux surgery; BE, Barrett's esophagus; CSA, cross sectional area; EGJ, esophagogastric junction; EoE, eosinophilic esophagitis; FLIP functional lumen image probe; HRM, high resolution surgery; IEM, ineffective esophageal manometry; IRP, integrated relaxation pressure; LA, Los Angeles EGD grading system for severity of esophagitis; PBD, pneumatic balloon dilation; PPI, proton pump inhibitor; PRO, patient related outcomes; SAP, symptom association probability; SRA, symptom reflux association

Typical Gastroesophageal Reflux Symptoms

- Monitoring of intraesophageal pH or pH impedance is standard for assessing abnormal esophageal acid exposure, and not the GERD questionnaire, an empiric trial of PPI, or EGD.
 - Persons with suspected GERD symptoms but failing a PPI trial should have ambulatory pH/PI reflux monitoring while **off** PPIs to make the diagnosis of GERD, rather than EGD, and use prolonged 48 to 76 h wireless pH monitoring if symptoms are
 - Infrequent
 - Vary from day to day
 - “The clearest need for objective reflux monitoring for a conclusive GERD diagnosis is in
 - Symptomatic patients who do **not** respond to acid suppressive therapy*
 - Patients on whom invasive/surgical reflux management is planned in patients concerned about long-term PPI therapy”.

*Editor's note: Some authorities would suggest that GER surgery not be performed in persons who have had no response to PPI, and that the phrase be “patients who do **not** respond adequately to optimal acid suppressive therapy”.



- Empiric PPI trial of 1 to 4 wk vs. acid exposure time (AET) per by ambulatory testing.
 - Sensitivity, ~80%
 - Specificity, ~55%
- vs. esophagitis on EGD
 - vs. positive SAP
- Response to PPI in persons with GERD, 69%
 - No GERD, 51%
 - Positive likelihood ratio, 1.52
 - Negative likelihood ratio, 0.71
- This represents “limited diagnostic utility of PPI test to conclusively identify patients with GERD”.
- Suspected GERD from
 - Symptoms
 - PPI response
 - EGD esophagitis LA grade A/B
 - pH/PI ambulatory reflux monitoring (e.g., ↑ acid exposure time)
 - LA grade C/D esophagitis / Barrett’s esophagus (BE)
- Unproven GERD
- Esophagitis on EGD does not correlate with symptoms or AET.
 - In fact, about 50% of persons with GERD symptoms or ↑ AET will have a normal EGD.
- AET does predict symptom improvement from pharmacotherapy / anti-reflux surgery.
 - An abnormal AET > 5.5% is predicted by
 - ↑ haitus hernia
 - BMI > 25

Tests	Evidence for GERD
- AET+, RSA+	Strong
- AET+, RSA-	Good
- AET-, RSA+	Reflux hypersensitivity
- AET-, RSA-	None (normal) ▪ Visceral ▪ Hypersensitivity motor disorder of esophagus ▪ EoE ▪ Behavioral disorder

Abbreviations: AST, aid exposure time; RSA, reflux system association

- Give when ambulatory reflux monitoring (ARM) is done while patient is **on** PPI therapy.
 - ARM is done when the patient is off therapy, except
 - When they have proven GERD (e.g., LA C/D esophagitis)
 - When doing PI monitoring, looking for weak acid reflux.
 - When patient is off PPI, they are less likely to be detected to have abnormal PI testing, indicating weak acid reflux (WAR); thus if looking for WAR, the patient should be on PPIs.



- If patient has GERD symptoms and proven GERD (LA grade C/D esophagitis), perform pH/PI monitoring on PPI, rather than just doing pH monitoring or EGD.
 - Indications for surgery for GERD
 - Inadequate response to PPIs
 - Patients wish not to be on long term PPIs
 - Large hiatus hernia / regurgitation
 - ↑ acid reflux burden (ARB) on ambulatory reflux monitoring (ARM)
 - Perform esophageal HRM to ↑ diagnostic yield to identify
 - Motility-related causes/associations of non-cardiac chest pain, e.g.,
 - Achalasia
 - Distal esophagitis spasm (DES, previously called diffuse esophageal spasm)
 - hypercontractility (e.g., Jackhammer esophagus)
 - Hiatus hernia (HH; with functional significance to GER symptoms)
 - Because HRM provides morphological details of the EGJ, it is superior to conventional manometry (CM), EGD and barium esophagram to identify the presence of a hiatus hernia (HH).
 - Performance characteristics for HH > 2 cm at surgery
 - False positive 5% vs. 32% (P = 0.01)
 - False negative similar, ~50%
- | | HRM | EGD | Barium Esophagus |
|---------------|-----|-----|------------------|
| - Sensitivity | 94% | 96% | 70% |
| - Specificity | 92% | 95% | 98% |
- Positive diagnosis of GERD (EGD, LA grade C/D; acid exposure time [AET] > 4.2% →
 - Positive symptom index (SI) predicts improvement of GERD symptoms on PPI
 - AET 4% to 6%, borderline for GERD; AET > 6%, pathological: confirmed GERD.
 - AET and RSA (reflux symptom association) off PPI predicts testing treatment success from anti-reflux surgery (ARS).

Abbreviations: AET, acid exposure time; ARM, ambulatory reflux monitoring; ARS, after anti-reflux surgery; BI, baseline impedance; EPR, esophagopharyngeal reflux; HRIM, high resolution impedance manometry; LPR, laryngopharyngeal reflux; MNBI, mean nocturnal baseline impedance; RSA, reflux symptom association; SI, symptom index

- Basal Impedance (BI) Testing
 - Terms
 - Basal impedance (BI) testing (pH/PI recording) for 24 h
 - Mean nocturnal baseline impedance (MNBI)
 - Nocturnal portion of 24 h pH/PI recording
 - Mucosal impedance (MI) - balloon catheters measure mucosal impedance
 - Basal impedance high resolution impedance monitoring (BI-HRIM)



- Correlation
 - Basal impedance (BI)
 - Correlates inversely with
 - Esophageal acid burden
 - Mucosal integrity
 - Mean Nocturnal Baseline Impedance (MNBI)

	Sensitivity	Specificity
▪ $< 2292 \Omega \rightarrow$ diagnosis of erosive GERD	~90%	~85%
▪ $> 2292 \Omega \rightarrow$ pH-positive GERD (NERD)	~85%	~85%

 - MNBI $< 2292 \Omega$ is predictive of symptom improvement with
 - PPIs
 - Surgery
 - Post-reflux swallow induced peristaltic waves (PSPW)
 - A marker of esophageal chemical clearance
 - Persons with esophageal symptoms who were being considered for ARS should have a test which may predict success of the surgery, such as a AET, RSA or MNBI.
 - PSPW index: "the proportion of reflux episodes with PSPW within 30 sec among the total number of reflux episodes on a pH/PI study.
 - Lower in GERD (erosive or non-erosive) than in functional heartburn.
 - Predict response to PPIs in persons with NERD (endoscopic-negative heartburn)
- Testing after ARS
 - In a patient with esophageal symptoms after ARS, perform EGD +/- barium esophagram to examine EGJ gastric cardia for possible "slip page, displacement and recurrence of hiatus hernia.
- Extraesophageal symptoms
 - Laryngeal symptoms and laryngoscopic signs may represent an extraesophageal association/complication of GERD (laryngopharyngeal, LPR).
 - However, LPR does not correlate with pH/PI
 - Has poor diagnostic accuracy (44%)
 - Does not predict response to PPIs
 - In patients with suspected LPR but no response to PPIs, pH/PI monitoring will show acid reflux in $< 50\%$ ($> 50\%$ have non-acid reflux).
 - pH/PI is superior to PPI trials to identify the patients
 - With GERD associated with laryngeal symptoms, and likelihood of PPI response
 - Chronic cough may be associated with GERD pH/PI predicts the probability of PPI response.
 - Those who respond to PPIs using help weakly acidic esophagopharyngeal reflux (EPR) or swallow induced EPR.
 - In the patient with extraesophageal reflux symptoms, but without concurrent typical reflux symptoms, first performed ambulatory reflux monitoring (ARM) rather than an empiric trial of PPIs.



- Rumination syndrome

- Definition

- "...repetitive, effortless regurgitation of recently ingested food into the mouth, followed by either spitting or remastication and reswallowing, without nausea, retching, or vomiting" (Stanghellini V, et al. Gastroenterology 2016; 150: 1380-92)
- "Persistent or recurrent regurgitation of recently ingested food and subsequent spitting or and mastication and swallowing and
 - Regurgitation not preceded by retching for the past 3 mon"

- High resolution impedance manometry (HRIM)

- Findings
 - ↑ intragastric pressure > 30 mm Hg is associated with proximal movement of gastric content.
 - "Proximal movement of the EGJ from the intraabdominal cavity into the thorax with the increased intrabdominal pressure that occurs at the onset of rumination episodes".
 - Pressurization (↑ intraesophageal pressure)
 - Each episode of rumination detected by HRIM
 - Sensitivity, 80%
 - Specificity, 100%
- Rumination cannot be distinguished from GERD or pH/PI or on baseline impedance (BI).
- Consider confirming the clinical diagnosis of rumination syndrome with HRIM performed after meals (post-prandial protocol).



Test after meals (post-prandial monitoring)

- Supragastric belching

- Definition

- "...frequent, repetitive, bothersome belching episodes occurring more than 3 days a week, with the criteria fulfilled for 3 mon and symptom onset at least 6 mon prior (the Rome IV criteria).
 - Disappears when sleeping

- Diagnostic imaging

- pH/pl monitoring
 - Air in esophagus (rapid ↑ impedance in esophagus)
 - Detection of directionality of air movement
 - Sensitivity, 95%
 - Specificity, 75%



➤ Clinical

- Association with GERD in 50% of supragastric belches.

Characteristics	Supragastric	Gastric
○ Time	Day	Day and night
○ Severity	+++	+
○ Frequency	+++	+

- What's on the horizon?

- Catheter-based oropharyngeal pH monitoring for supraesophageal reflux episodes.
- Pepsin concentration in saliva diagnosis of GERD +/- reflux hypersensitivity (pepsin > 210 ng/mL, 98% specific).
- FLIP during ARS/EGD reflux procedure to "...tailor the intervention to prevent postoperative dysphagia".
- Configure the clinical diagnosis of supragastric belching with pH/PI monitoring.

Recommendations

- Patients with obstructive esophageal symptoms without a mechanical cause
 - Use high-resolution esophageal manometry for the evaluation for esophageal motility disorders (conditional recommendation, very low quality of evidence).
- Perform in patients with obstructive esophageal symptoms.
 - Use HRM rather than conventional line tracing manual tree to diagnose esophageal motility disorders (strong recommendation, moderate quality of evidence).
 - Use supplementary/provocative maneuvers with the manometry protocol to improve the diagnosis of esophageal motility disorders (conditional recommendation, low quality of evidence).
- Use barium tablet with a barium esophagram during the evaluation of obstructive esophageal symptoms (conditional recommendation, very low quality of evidence).
- Use reflux monitoring rather than patient-reported symptoms on GERD questionnaires for a conclusive diagnosis of GERD in patients with esophageal reflux symptoms (conditional recommendation, very low quality of evidence).
- In patients with symptoms of GERD who do **not** respond to PPIs,
 - Uses esophageal ambulatory reflux monitoring (conditional recommendation, very low quality of evidence).
 - Use ambulatory esophageal reflux monitoring over EGD if the EGD is not definitive (conditional recommendation, very low quality of evidence).
- In patients with typical reflux symptoms and unproven GERD.
 - Use ambulatory reflux monitoring performed off antisecretory therapy over ambulatory reflux monitoring on antisecretory therapy for a conclusive diagnosis of GERD (conditional recommendation, very low quality of evidence).
- In adults with infrequent symptoms or day-to-day variation in esophageal symptoms.
 - Use prolonged wireless pH monitoring over 24 h catheter-based monitoring for the diagnosis of GERD (conditional recommendation, very low quality of evidence).



- In adults with typical esophageal reflux symptoms and previous confirmatory evidence of GERD (proven GERD),
 - Use ambulatory pH impedance monitoring on PPI therapy over endoscopic evaluations or pH monitoring alone to diagnose persisting GERD (conditional recommendation, very low quality of evidence).
- Patients with esophageal symptoms being evaluated for anti-reflux surgery,
 - Abnormal AET is a predictor of treatment outcome.
 - RSA and mean nocturnal BI provide adjunctive value (conditional recommendation, very low quality of evidence).
- In patients with esophageal symptoms after ARS,
 - EGJ and gastric cardia anatomy should be inspected endoscopically and/or radiographically to assess mechanical abnormalities (conditional recommendation, very low quality of evidence).
- For diagnosis of extraesophageal reflux
 - Use ambulatory reflux monitoring, specifically pH impedance monitoring performed off acid suppression, over laryngoscopy (strong recommendation, low quality of evidence).
- For extraesophageal reflux symptoms without concurrent typical reflux symptoms,
 - Use ambulatory reflux monitoring off acid suppression rather than an empirical trial of PPI therapy (conditional recommendation, very low quality of evidence).
- For patients with excessive belching, confirm the diagnosis of supragastric belching
 - Use pH impedance monitoring (conditional recommendation, very low quality of evidence).
- In patients with esophageal symptoms suspicious for rumination syndrome,
 - Use HRIM with postprandial monitoring to confirm the diagnosis if clinically necessary (conditional recommendation, low quality of evidence).

Surgery versus radical endotherapies for early cancer and high-grade dysplasia in Barrett's oesophagus (Bennett C, et al. Cochrane Database of Systematic Reviews 2020(5): CD007334. DOI: 10.1002/14651858.CD007334.pub5)

This Cochrane review has indicated that there are no RCTs to compare management options in this important area.



Proton Pump Inhibitors (PPIs)

Malfertheiner P, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 697-708.

- Microbiome
 - PPIs → ↓H⁺
 - ↑ IL-1B, ↑ non-Hp organisms, ↑ NH₄ (from bacterial nitrogen cycle)
 - Patients who will require long-term PPIs should be tested/treated for H. pylori infection to ↓ risk of an accelerated morphological progression from chronic gastritis, to atrophic gastritis, to metaplasia/dysplasia, to adenocarcinoma (European Mastricht V / Florence consensus report [Malfertheiner P, et al. Gut 2017; 66: 6-30])
- Changes in gut microbiota in long-term users of PPIs
 - ↓ bacteroides
 - ↓ diversity
 - ↑ firmicutes
 - ↑ C. difficile / Clostridial in colon
 - ↑ bacterial/fungal overgrowth (SIBO)
- ↑ enteric infections
 - Salmonella, Shigella spp.
 - Campylobacter spp.
 - Toxigenic E. coli
- Hepatic complications
 - ↑ risk of
 - Spontaneous bacterial peritonitis (SBP), OR 1.72 (95% CI 1.1 – 2.69)
 - Hepatic encephalopathy (HE)
 - No ↑ risk of esophageal variceal bleeding (EVB)
- Dementia (cognitive impairment)
 - OR, 1.44; 0.95% CI 1.36-1.52)
 - Controversial data, multiple confounding factors
- Parietal cell hyperplasia (PCH) and fundic gland polyps (FGP)

➤ Pathophysiology

PPI → H⁺ → G cell ↑ gastrin → parietal cell hyperplasia
 – 2x ↑ risk of FGP
ECL cell → ↑ chromogranin

→ D cell ↓ somatostatin

- PPI → ↓ H⁺
 - ↑ G
 - ↓ SOM
 } → parietal cell hyperplasia (PCH)
 → ↑ FGP (2-4x↑; fundic gland polyps)

Abbreviations: CI, confidence interval; ECL, enterochromaffin-like cells; EVB, esophageal variceal bleeding; FGP, fundic gland polyps; G, gastrin; H⁺, hydrogen ion; IL, interleukin; NH₄, ammonium; OR, odds ratio; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth; SOM, somatostatin;



- Endoscopic Appearance of Fundic Gland Polyps
 - Characteristic endoscopic images of multiple fundic gland polyps of the oxyntic mucosa.
 - Multiple fundic gland polyps
 - Histomorphological characteristics of a cystic gland dilatation
 - These polyps are
 - Located in the fundic or corpus mucosa between gastric rugal folds.
 - Also appear in a single polypoid structure.
 - The size varies from a few millimetres up to 10 mm.
 - The underlying lesion is not a mucosal neof ormation, but
 - cystic gland dilatation (histomorphology).
- Kidney disease
 - ↑ acute kidney injury (AKI), idiosyncratic reaction
 - ↑ risk 5x HR, 2.52; 95%CI 2.27 – 2.79
 - ↑ risk of acute interstitial nephritis: HR 3.2; 95%CI 1.47 – 6.14
 - ↑ chronic kidney disease (CKD)
 - Risk associated with age of user, and PPI dose/duration
- Hypomagnesemia
 - PPI
 - ↓ H^+ → ↓ intestinal absorption of magnesium (Mg^{2+}) by ↓ TRPM6/TRPM7 (channel-dependent paracellular Mg^{2+} transport)
 - ↑ Cr_s (↑ serum creatinine, i.e., renal dysfunction) → associated with ↓ Ca^{2+} absorption by ↑ H^+ -associated inhibition of paracellular Ca^{2+} transport
- Drug interactions
 - Metabolism
 - Clopidogrel and omeprazole are both metabolized by same cytochrome P450 pathway (CYP2C19), so it is postulated that PPIs might ↓ effect of this drug by blocking oxidative hydrolysis of clopidogrel (prodrug) to active metabolites.
 - Controversial whether anti-platelet effect impaired by the PPI
 - ↑ digoxin, nifedipine, alendronate, warfarin (potential anti-coagulation effect of vitamin K antagonists)
 - ↓ efficiency of tyrosine kinase inhibitors
 - Sunitinib
 - Erlotinib
 - Absorption
 - ↓ 66% concentration
 - Ketoconazole, itraconazole, atazanavir, cefpodoxime, L-thyroxine, α-methyldopa, enoxacin, dipyridamole
 - Long-term use of PPIs may alter vascular hemostasis through their inhibitory effect on asymmetric dimethyl arginine (ADMA) to ↓ nitric oxide synthase (NOS)
 - ↑ endothelial senescence

Abbreviations: ADMA, asymptomatic dimethylarginine; AKI, acute kidney injury; Ca, calcium; CI, confidence interval; HR, hazard ratio; Mg, magnesium; NOS, nitric oxide synthase; PPI, proton pump inhibitor



- Effect of Acid Inhibition with PPIs on Helicobacter Pylori Gastritis
 - A shift from antrum-predominant inflammation to fundus–corpus-predominant inflammation occurs with acid inhibition via proton-pump inhibitors (PPIs).
 - The occurrence of Helicobacter pylori gastritis
 - Varies according to H. pylori virulence and host susceptibility genes and
 - Is related to diverse clinical outcomes
 - Corpus-predominant gastritis is associated with a markedly higher risk of developing malignancy than antrum-predominant gastritis.
 - As antrum-predominant H. pylori infection shifts to the gastric body, there is
 - IL-1 β (pro-inflammatory)
 - $\uparrow$ NH₄
 - $\uparrow$ atrophy of fundus/body region
 - Altered other micro-organisms
 - PPIs alter the gastric milieu by contributing to $\uparrow$ IL-1 β , a potent pro-inflammatory factor, and ammonia (NH₄).
 - The catalytic activity of H. pylori urease on urea leads to the formation of NH₄, and PPIs could $\uparrow$ production of NH₃ through the biological nitrogen cycle involving other gut bacteria.
 - $\uparrow$ IL-1 β and $\uparrow$ NH₄ contribute to as well as result from the fact that H. pylori shifts from the antrum to the corpus.
 - Consequently, H. pylori might even totally disappear from the antrum, but it increases the inflammation in the fundus–corpus.

➤ Evidence Levels for the Association between PPIs and Various Complications

Complications Associated with PPI use	Level of Evidence*
○ CNS – Dementia	3b
○ Lung – Pneumonia	2a/2b/2c 2a/2b
○ Heart – Reduced clopidogrel activation with increased cardiovascular risks	1c 2a
○ GI – Effects on Helicobacter pylori gastritis – Gastrointestinal infection	1c 2a 2a/b
○ MSK – Fractures and osteoporosis	2a
○ Endocrine – Myopathies – Hypomagnesemia – Hypocalcemia	4 3b 4



Complications Associated with PPI use	Level of Evidence*
○ Structural/functional	
– Abnormalities	2a
	2a
	2b
	1c
○ Kidney	
– Acute intestinal nephritis (AIN)	2b
– Chronic kidney disease (CKD)	2b

* Interpretation:

1a, systematic review of RCT of good methodological quality and with homogeneity;

1b, individual RCT with narrow 95%CI;

1c, individual RCT with risk of bias;

2a, systemic review of cohort studies (with homogeneity);

2b, individual cohort study (including low-quality RCT, for example < 80% follow-up);

2c, non-controlled cohort studies or ecological studies;

3a, systemic review of case-control studies (with homogeneity);

3b, individual case-control study;

4, case series or poor-quality cohort or case-control studies

Abbreviations: AIN, acute interstitial nephritis; Ca²⁺, calcium; CI, confidence interval; CKD, chronic kidney disease; Cr_s, serum creatinine; ECL, enterochromaffin-like; EVB, esophageal variceal banding; FGP, fundic gland polyp; G, gastrin; H⁺, hydrogen ion; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IL, interleukin; Mg²⁺, magnesium; NH₄, ammonium; NO, nitric oxide; NOS, nitric oxide synthetase; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis; SOM, somastatin

Adapted from: Malfertheiner P, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 697-708 (Table 1)



Extra (Super) Esophageal Reflux (EER): AGA Practice Update (2023)

➤ Definition

- Extraesophageal reflux (EER) is "...a subset of gastroesophageal reflux (DER) that leads to troublesome symptoms/conditions that are not normally attributed to the esophagus"...such as sinus/ear disease; cough/asthma, pulmonary fibrosis, laryngeal hoarseness, dysphonia; dental erosions/carries; post nasal drip; throat clearing
 - These supraesophageal symptoms. Conditions are approached differently if the GER occurs alone, or with GER (EER + GER)

➤ Pathophysiology

- EER may relate to GER of acid, or non-acid
 - Microaspiration
 - Reflex pathway by the vagus (CN X) nerve

➤ Clinical

- Best practice advice
 - The physician who deals with patients with GER/GERD should take an appropriate history for EER
 - A multidisciplinary approach and investigations performed for suspected EER should be multidisciplinary

➤ Diagnosis

- There is not a
 - Single gold standard test for the diagnosis of GER
 - PPI trial
 - A test for diagnosis of GER which has poor performance characteristics
 - Sensitivity, 71-78%
 - Specificity, 41-54%
 - Perform tests for reflux before performing empirical PPI trial
 - PPI improvement of GER symptoms may be due to a non-acid cause (e.g., placebo)
- Best practice advice
 - "the contribution of GER to EER symptoms should be based on the global clinical impression derived from the patients' symptoms, response to GER therapy, and results of endoscopy acid reflux testing"
- Do **not** only use the PPI trial to rule in / rule out GER or an association of GER to EER

Important Concept

- About only a half of patients with EER symptoms have GER
- EER symptom relief better on b.i.d. than od, and 12 wk better than 8 wk trial



- Ambulatory Esophageal Reflux Monitoring
 - Options for measurement of GER pH if pH and symptom association for GER symptoms optimally performed with patient **not** on PPIs
 - Catheter
 - Wireless pH capsule
 - Impedance
 - Does **not** determine “reflux burden”
 - Does **not** establish reflux causation for EER symptoms
 - Preferably do acid reflux monitoring first to establish pathological gastroesophageal reflux, and to perform reflux monitoring off PPI

Best Practice Advice

- If 12 wk empirical PPI test fails to ↓ EER symptoms
 - Do **not** continue PPIs longer or switch PPIs
 - Perform esophagogastrosocopy (EGD) and acid monitoring studies, with patient **off** PPIs
- If GER proven (pH monitoring, EGD) but patient’s EER symptoms do **not** respond to high doses of PPI
 - Perform pH impedance testing while on high dose PPI
 - pH impedance shows proximal reflux, and acid weak-acid and non-acute refluxate
- GER symptoms may also respond to
 - Lifestyle changes
 - Neuromodulators
 - Cognitive behaviour therapy (CBT)
 - Hypnotherapy
 - External upper esophageal sphincter (UES)
 - Compression device (20-30 mmHg pressure on cricoid)
 - Add benefit to PPI: 55%, 31%
- Acid Suppression Therapy for GER
 - PPI therapy for no benefit for
 - Chronic cough
 - GERD-related chronic laryngitis
 - Asthma (statistically significant but not clinically meaningful)
- Surgery and Endoscopic Therapies for GER
 - “...a look of response to PPIs predicts lack of response to anti-reflux surgery”;
 - “...response to PPI therapy before operation...associated with effectiveness of surgery”



BARRETT'S ESOPHAGUS (BE)

Barrett's Esophagus: Recommendations of BSG (2018)

di Pietro M and Fitzgerald RC. Gut 2018;67(2):392-393.

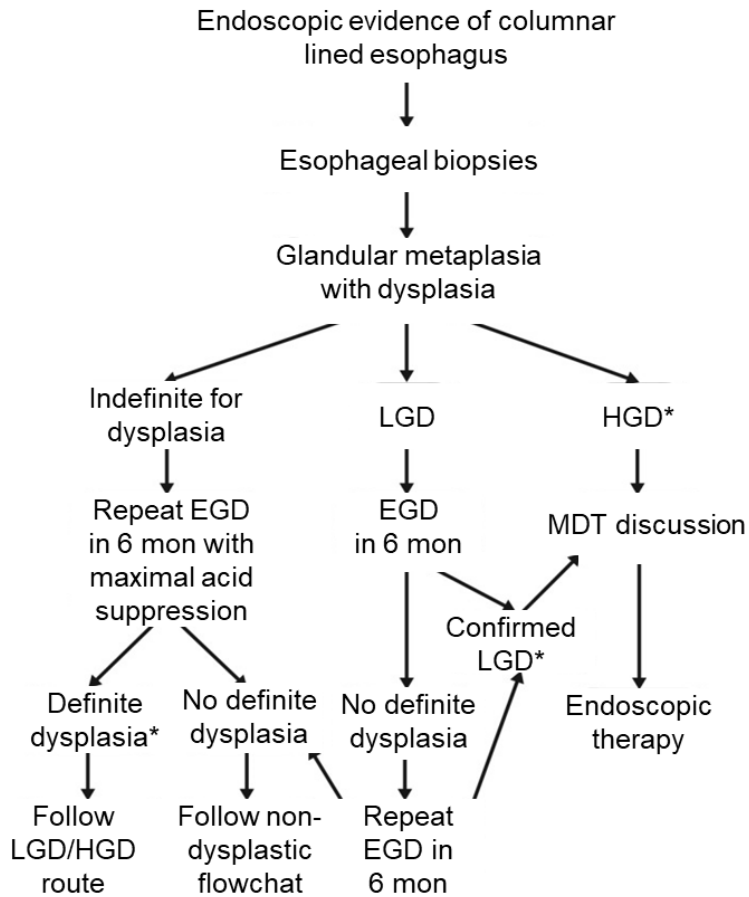
➤ Diagnosis

- The histopathological diagnosis of dysplasia alters the management of patients with Barrett's esophagus (BE), i.e., just metaplasia
 - Retrospective review of mucosal biopsies showed low-grade dysplasia (LGD) has emphasized the challenges of making this histopathological diagnosis; Revised Histopathological Diagnosis of LGD.
 - Confirmed LGD 27%
 - Down grading from LGD to BE metaplasia / indefinite for dysplasia (IND), 73%
 - When confirmed diagnosis ("more stringent and robust dysplasia diagnosis) of LGD, follow-up showed
 - Progression to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) – 9% per year
 - When diagnosis downgraded to non-dysplastic Barrett's esophagus (metaplasia) or IND
 - Conversion rate to HGD/EAC 0.6% and 0.9% per year respectively
 - These findings have been confirmed, in patients with LGD treated, with radiofrequency ablation (RFA)
 - 1% developed HGD.ECA in 3 year, versus ~27% who were followed by annual EGD.
 - Summary: there is a clinically important (high) rate of progression of LGD/HGD/ECA, and this risk of progression/conversion may be markedly reduced by RFA.
- Management of LGD in patients with BE
 - Patients with LGD
 - Repeat EGD in 6 mon
 - If any repeat EGD biopsy shows LGD, and
 - If expert GI pathologist confirms LGD in ≥2 biopsies
 - ↓
 - Offer patient
 - Endoscopic ablation therapy, preferably RFA, or
 - EGD plus biopsies q6mon (continued surveillance)

Recommendation grade A for endoscopic therapy (for surveillance). Agreement: A+ 56%, A 33%; U 0%; D 11%; D+ 0%



Updated Flow Chart for the Management of Dysplastic Barrett's Esophagus



* Dysplasia needs to be confirmed by 2 independent GI pathologists

- A pathological finding of indefinite for dysplasia (IND) does not exclude the presence of dysplasia
 - Therefore, do a 6-mon follow-up
- Endoscopic follow-up in 6 mon is recommended for LGD.
 - If LGD is also found at follow-up, EGD even if not consecutive, EGDs provided that the diagnosis of dysplasia on two occasions is confirmed by two independent GI pathologists (ideally from a different institution)
 - Endoscopic ablation should be considered.
- A diagnosis of high-grade dysplasia (HGD) also needs to be confirmed by a second GI pathologist. Patients with dysplasia should be offered endoscopic therapy following discussion within multidisciplinary (MDT) setting.

Abbreviations: LGD, low-grade dysplasia; HGD, high-grade dysplasia; MDT, multidisciplinary team; EGD, esophagogastroduodenoscopy

Printed with permission: di Pietro M and Fitzgerald RC. Gut 2018;67(2):392-393 (Figure 1)



Screening and Subsequent Surveillance in Barrett's Esophagus: AGA Clinical practice Update (2022)

Muthusamy VR, et al. Clin Gastroenterol Hepatol 2022; 20: 2696-2706.

Recommendation

- Perform EGD screening for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) with ≥ 3 risk factors
 - Old
 - Fat
 - White (non-Hispanic "white")
 - Men who smoke
 - Have a family history of BE/EAC / chronic GERD symptoms
- Others is similar to previous guideline recommendations, except with the new wording, the patient does not necessarily have GERD, since it is one of the choices of several risk factors, but if there are ≥ 3 other risk factors besides GERD, the EGD screening would be performed.
 - There is an important distinction, because only a few ($<10\%$) of persons who develop EAC (in US/Canada) have a past history of symptomatic GERD
 - In patients with GERD, the risk of BE is $\sim 3\%$
 - The previous screening guidelines were thus changed because of this relatively low sensitivity ($<50\%$)
 - The number of "3" risk factors for screening was based upon expert opinion

Take Home Message

- Screening for BE/EAC "...is not restricted to patients with GERD symptoms.

Recommendation

- Screening for BE/EAC can be done with EGD, or collection of esophageal cells for histology examination, using
 - Transnasal endoscopy
 - Cytosponge
 - EsoCheck
 - EsophaCap
- If endoscopic screening is selected for screening, use
 - High-definition white light endoscopy (HD-WLE), plus
 - Virtual chromoendoscopy (VC), plus
 - Perform a high-quality endoscopy
 - "Spend" adequate time inspecting the Barrett's segment



- Adding VC to HD-WLE increase the rate of detection of high-grade dysplasia (HGD) EAC from 10% to ~15%
- Implicate in this recommendation is the need to train and become competent in VC and treatment chromoendoscopy, including narrow band imaging (NBI)
- Recommended procedure inspection times EGD ≥ 7 min, plus ≥ 1 min procedure for each cm of the circumferential extent of the Barrett's mucosa (European Society for Gastrointestinal Endoscopy [ESGE], and United European Gastroenterology [UEG], Bisschops R, et al., Endoscopy 2016; 48: 843-864)
- Surrogates for performance of a high-quality endoscopic examination for screening and surveillance of non-dysplastic BE (NDBE), high grade dysplasia (HGD) and esophageal adenocarcinoma (EUS)
 - Endoscopy
 - Performed by a physician with BE diagnosis/management (Wani S, et al. Am J Gastroenterol 2017; 112: 1032-1048)
 - Use a distal attachment cap to the endoscopy
 - Use ND-WLE plus chromoendoscopy of the Barrett's segment
 - Also consider using confocal laser endomicroscopy (CLE) or volumic lesion endomicroscopy (VLE)
 - CLE
 - Sensitivity (Sn), 77%
 - Specificity (Sp), 89%
 - CLE plus NB + per-lesion detection of neoplasia in BE 19% (but same Sn/Sp)
 - Procedure
 - Wash the mucosa
 - Insufflate and desufflate
 - Inspect for adequate duration
 - Identify landmarks
 - Diaphragmatic hiatus
 - Gastroesophageal junction (GEJ)
 - Squamous columnar junction (SCJ)

Recommendation (classifications)

- Use classifications (please also see below recommendation)
 - Prague
 - Maximal length (L)
 - Circumference ©, maximal
 - Paris
 - Visible, superficial neoplasia
 - Seattle
 - Multiple quadrant biopsies
 - Screening, q2cm
 - Surveillance, q1cm
 - Plus, biopsies from visible lesions
 - Using Seattle biopsy protocol $\rightarrow$ $\uparrow$ detection rate of BR-dysplasia (RR, 2.75)
 - Not using Seattle biopsy protocol $\rightarrow$ $\downarrow$ detection rate of dysplasia (OR, 0.53)



- Wide-area transepithelial sampling (WATS-3D)
 - Abrasive brush, larger surface areas → sheets of cells, analysed by neural network software
 - Benefits of WATS-3D
 - ↑ detection of dysplasia, 7%
 - ↓ interobserver variable of interpretation of dysplasia (kappa value, 0.86) (also endorsed by ASGE Standards of Practice Committee, Qumseya B, et al. Gastrointest Endosc 2019; 90: 335-359e2)

➤ Treatment

- Use proton pump inhibitors (PPIs) po od (b.i.d. if still symptomatic) for all patients with BE
- Role of PPIs in patients with BE
 - ↓ progression of NDBE to HGD/EAC
 - aHR, 0.29; 95%CI 0.29; CI, 0.12-0.79
 - Second study, aHR 0.32 (95% CI, 0.15-0.67)
- In the presence of erosive esophageal LA grade C/D
 - Biopsy for BE, if BE / suspected BE
 - Treat with PPI b.i.d. for 8 wk, then
 - Repeat EGD + biopsies (second / follow-up EGD reveals BE in ~10%)
 - PPI po b.i.d. was superior to once daily dosing, but because of the design of the supporting studies
 - The recommendation was for once daily dosing in BE, except
 - b.i.d. (twice daily dosing)
 - If necessarily for control of symptoms
 - If planned endoscopic mucosal resection (EMR) / endoscopic submucosal dissection (ESD) for BE HGD/EAC

➤ Surveillance

- After screening shows BE (NDBE) q3-5 yr (please see use if risk stratification models / (PBES below)
- q3-5 yr (please see use of risk stratification models / PBES below)
 - Note: ACG guidelines suggest longer intervals for NDBE if length of BE is < 3 cm (Shaheen NJ, et al. Am J Gastroenterol 2022; 117: 559-587)
- Use tissue systems pathology assay (TSPA) progressing to HGD/EAC (Lyer PG, et al. Clin Gastroenterol Hepatol 2022; 20: 2772-2779)
 - Validated to assess low, intermediate and high risk of NDBE
 - If high risk by TSPA, then risk of progression is also high (risk of progression ↑4.7x)
 - Sensitivity (Sn), 30% → ↑ Sn to 95% of multiple levels are examined
 - Specificity, 95%
 - Independent indication of likely progression to OR, 14.2 (95% CI: 5-39, P < 0.001)
- After endoscopic eradication therapy (EET, i.e., EMR, ESD)



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the components measured in the Tissue Cypher tissue system pathology-based prediction assay (TSPA).

- Endocrine - Architecture
- Nucleus - Morphology
- Biomarkers - AMACR, CD45Ro, Cd63, COX-2, cytokeratin 20, HER2, HIF-1 alpha (protein-based)

- Use Progression in Barrett's Esophagus Score (PBES) to determine the optimal surveillance interval

- Components ▪ Low-grade dysplasia (LGD) ▪ Males, smokers ▪ Length (L) of BE (Prague classification)	}	- Grade of risk of progression ▪ Low, 0.13% ▪ Intermediate, 0.73% ▪ High, 2.1%

- Recommendation (surveillance after EET)

○ 4 quadrant biopsies from - Neosquamous epithelium (NSE) - Esophagogastric junction (EGJ) - Gastric cardia	}	▪ This protocol detects - Recurrence after EET of ~20% - Subsquamous/tangential extension up to 1 cm beyond the proximal end of the SCJ



Diagnosis and Management of Barrett's Esophagus (BE): ACG Clinical Guideline (2016)

Shaheen NJ, et al. Am J Gastroenterol 2016; 111: 30-50.

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

➤ Definition of BE

- "...metaplastic change in the distal esophagus, whereby the normal squamous epithelium is replaced by specialized columnar epithelium with goblet cells."
 - It is important to include the presence of goblet cells to the definition of BE
 - Not to do so would increase diagnosis of BE by 147%
 - Note that in some countries (not including Canada), BE is overdiagnosed because of there being no need to include goblet cells in the histopathological definition of BE

➤ Diagnosis

- Suspect BE
 - When there are salmon-pink coloured tongues or circumferential mucosa extending $\geq$ 1 cm above the gastroesophageal junction (GEJ) into the tubular esophagus
 - When there is an abnormal Z line, or a Z line with > 1 cm of variability
- Take multiple mucosal biopsies of this salmon-coloured mucosa
 - For short segments of 1 to 2 cm take ≥ 4 biopsies per cm of
 - Tongues of BE
 - Circumferential BE
 - For > 2 cm of suspected BE, take 4 quadrant biopsies every
 - 2 cm for suspected BE (screening)
 - 1 cm for follow-up of biopsy-proven BE (surveillance)
- The biopsies must demonstrate intestinal metaplasia (IM) before this is called BE [IM consists of columnar cells plus goblet cells].
 - IM consists of intestinal metaplasia (columnar cells), and in the US, BE includes both IM plus goblet cells)
- If biopsies from the salmon-pink coloured do **not** show intestinal metaplasia
 - Repeat EGD plus biopsies in 1 to 2 yrs (to determine if the abnormally coloured tissue has developed into IM)

➤ Endoscopic description

- The Prague classification of the endoscopic features of the suspected intestinal metaplasia includes
 - The circumferential and maximal extent of the columnar mucosa in esophagus, and
 - The proximal margin of the gastric folds and diaphragmatic hiatus



➤ Diagnosis

- FLIP (esophageal functional lumen imaging probe)
 - Determine the role of the esophagogastric junction outflow obstruction (EGJOO) in the hypercontractility
 - “Measurement of lumen diameter across a space-time domain along the distal esophagus and through the EGJ” (panometry)
 - Normal, repetitive anterograde contractions
 - In HE, ↑ LES lift; prolonged contractions along entire distal esophagus or absent peristalsis
- At EGD describe
 - The portion of the circumference of the tubular esophagus
 - The height of the tallest tongue of salmon-coloured mucosa
 - The location of
 - The gastroesophageal junction (GEJ)
 - The squamocolumnar junction (SGJ)
 - The endoscopy could be done with usual endoscope with sedation, or a transnasal endoscopy without sedation.
- If the salmon-pink coloured mucosa showing exists in an area of esophagitis, treat the esophagitis with PPIs for 8-12 wk, and repeat the EGD plus biopsies to ensure that the histologically demonstrated changes showing regenerative changes were not misinterpreted as IM, and the patient was mislabelled as showing BE.

Recommendation

- The diagnosis of BE requires the presence of intestinal metaplasia in the tubular esophagus (conditional recommendation, very low quality evidence)
- When **not** to biopsy
 - The minimal length of altered mucosa is > 1 cm before diagnosing BE, because
 - The reliability coefficient of the Prague criteria is low (0.22) for BE < 1 cm
 - The risk of progression of BE to high grade dysplasia (HGD) or to esophageal adenocarcinoma (EAC) is very low when < 1 cm
 - Persons with a normal or regular Z line should not have biopsies “...in the absence of a clear abnormality”

Recommendation

- The length of the columnar mucosa must be ≥ 1 cm before making the diagnosis of BE
- Patients with a normal Z line should not have esophageal mucosa biopsies
 - Do **not** do esophageal mucosal biopsies in patients with < 1 cm displacement of the Z line, and without any visible lesions, from the top of the gastric folds (quality of evidence: low; strength of recommendation: conditional)



- Number of biopsies to be taken
 - Partially desufflate esophagus to ↓ need of
 - Flattening gastric folds
 - Making a hiatus hernia look like BE
 - For BE segments < 4 cm, take ≥ 8 biopsies, if possible (yield for IM, 94%)
 - If not possible, take
 - ≥ 4 biopsies for each cm of circumferential BE, and
 - 1 biopsy per cm in tongues of BE
- Histopathologists
 - “Expert pathologists must be used to assess biopsies taken for BE
 - An expert pathologist has been defined as “...a pathologist with a special interest in BE-related neoplasia who is recognized as an expert in the field by his/her peers” (Clinical Practice Update Committee, American Gastrointestinal Association in Gastroenterology 2016; 151: 822-835)
 - When low grade dysplasia (LGD) is confirmed, the risk of progression to high grade dysplasia (HGD/ esophageal adenocarcinoma [EAC]) is 9% per year.
 - Diagnostic interpreting BE
 - ↓ by 5 yr of professional experience (OR 0.48, 95% CI 0.31–0.74)
 - ↑ by being a pathologist in a non-teaching hospital (OR 1.76, 95% CI 1.15–2.69)
 - “...neither case volume nor self-identifying as an expert predicted diagnostic proficiency
 - ↑ 1 pathologist increases accuracy by ~20%

Recommendation

- Confirm the presence of LD/HGD by using two pathologists expert in the area of diagnosis of BE (quality of evidence, low; strength of recommendation: strong)



➤ Screening

- Only a small proportion (12%) of patients with EAC have been in a surveillance program for BE
 - < 50% of persons with EAC have chronic symptoms of GERD
 - While a surveillance program is important to ↓ risk of EAC, other approaches are necessary
- Screening for BE may be considered in
 - Men with GERD symptoms (heartburn/regurgitation) which are
 - Chronic ≥ 5 yr in duration (low sensitivity of only 39-43%; specificity of 67-76%)
 - Frequent ≥ every weekplus
 - ≥ 2 additional risk factors
 - Age > 50 yr
 - Caucasian
 - Central obesity
 - Waist circumference > 102 cm, or
 - Waist-hip ratio (WHR) > 0.9
 - Smoking, current/past
 - Family history, confirmed first-degree relative with BE or esophageal adenocarcinoma (EAC)
 - Each risk factor ↑ risk of BE by ~12%, and supports the surveillance of persons with multiple risk factors
 - Men with GERD symptoms and multiple risk factors, make decision to screen made on a person-to-person basis.
 - Screening should be performed only after consideration of
 - Patient's life-expectancy
 - Future need of surveillance EGD plus biopsy
 - Therapy if screening is positive for BE
 - If initial screening for BE is negative, do **not** repeat
- Male predominance of BE complications
 - Prevalence
 - BE: M, 67%; F, 33%
 - EAC: M, 89%; F, 11%
 - Progression to EAC, M > F (aOR 2.2; 95%CI, 1.8-2.5)



Recommendation

- Perform screening for BE in persons with symptoms of chronic GERD, plus ≥ 3 of the above risk factors
 - An acceptable non-endoscopic swallowable capsule sponge device and a biomarker is an acceptable alternative (Strength of recommendation: conditional; quality of evidence: very low)
- Advanced imaging
 - Confocal laser endomicroscopy
 - IV fluorescein and laser blue light
 - Performance characteristics compared to histopathology
 - Particularity useful compared to histopathology
 - Targeted biopsies
 - Guide therapy
 - Volumetric laser endomicroscopy
 - “...optical coherence tomography technology” with “...a computer assisted detection algorithm” to visualize depth of 3 mm (mucosa, submucosa)
 - Correct labeling
 - Non-dysplastic, 52%
 - Dysplastic, 73%
 - Artificial intelligence
 - “...deep learning computer-aided detection system”

Recommendation

- Use white light endoscopy and chromoendoscopy for endoscopic surveillance of BE (quality of evidence: moderate; strength of recommendation: strong)

➤ Surveillance

Repeat EGD after initially negative EGD screening

- Low yield overall
 - ↑ yield if initial EGD showed esophagitis
 - Repeat EGD after 11 wk PPI for erosive esophagitis, 12%

LA Grade	Esophagitis BE (%)
C/D	17%
A/B	9%



Recommendation

- Do **not** repeat EGD for BE screening
 - If initial EGD was “negative” (strength of recommendation: conditional; quality of evidence: low)
 - However, in the text, it is recommended that “...patients with esophagitis on initial endoscopic evaluation should undergo repeat endoscopy 8-12 wk after treatment with PPIs to ensure healing of esophagitis and to determine the presence of BE”.
- Inform patient of risk and benefits of surveillance

MCQ Trick – Not Stated Clearly in Published Recommendations

- BE suspected → surveillance EGD performed
 - NERD
 - Do **not** repeat EGD surveillance for BE
 - Erosive esophagitis (EE)
 - Give PPIs for 8-12 wk and repeat EGD to
 - Ensure healing of BE
 - Repeat esophageal mucosal biopsies to determine possible presence of BE

- Endoscopic equipment and technique
 - Technique
 - Retroflex EGD in cardia
 - Adequate duration of inspection (longer)
 - Equipment
 - Chromoendoscopy (↑ detection of dysplasia/EAC)
 - Vital dyes
 - Electronic methods
 - Acetic acid
 - Sensitivity, 92%
 - Specificity, 96%
 - Narrow band imaging (NBI) vs. white light endoscopy (WLE): 30% vs. 21%, P=0.01
 - NBI also shows
 - Irregular mucosa/vascular pattern
 - NBI targeted biopsies vs. WLE standard protocols
 - Sensitivity, 94%; Specificity, 94%

Cautionary Note

- “Chromoendoscopy-directed biopsies should not yet be used as a substitute for the standardized biopsy protocol.”



- Equipment
 - High-definition / high-resolution white light EGD
 - Electronic chromoendoscopy also useful, but
 - At this stage in the surveillance algorithm, do **not** use other advanced imaging techniques until use is more evidence-based
- Biopsies
 - Random
 - 4-quadrant biopsies
 - Interval
 - BE, no prior dysplasia, q2cm
 - BE, prior dysplasia, q1cm
 - Targeted
 - Nodular mucosal in the BE segment → remove by endoscopic mucosal resection (EMR) without doing prior endoscopic ultrasound (EUS)
- Biopsy protocol
 - Seattle protocol to biopsy for BE
 - All visible lesions seen by endoscopy
 - 4 quadrant biopsies every 2 cm from the lower esophageal sphincter (LES) to the squamocolumnar junction (SGJ)
 - 4-quadrant, q2cm protocol superior to high-definition white light endoscopy to biopsy targeted lesion, 73% vs. 27%
 - The ↑ detection of LGD/HGD by 13x
 - Issue: the longer the length of BE, the lower the physician's adherence to the protocol

Recommendation

- Use a structural biopsy protocol to reduce detection bias in patients having endoscopic surveillance for BE (quality of evidence: low; strength of recommendation: strong)
- Indeterminant Dysplasia (IND)
 - Definition
 - “when the pathologist is unable to determine whether the histology truly represents dysplasia or may be due to inflammatory changes”
 - LGD
 - Rate of progression of IND to HGD/EAC is similar to rate of progression of LGD to HGD/EAC
 - Similar to the rate of progression of LGD/HGD/EAC, 0.6 per 100 person-years



Recommendation

- Use an experienced GI pathologist to confirm diagnosis of IND
 - If IND is confirmed, treat with PPI for up to 6 mon, and then repeat EGD plus biopsies
 - If IND redefined/downgraded after PPI therapy to non-dysplastic BE (NDBE) or intestinal metaplasia (IM)
 - Follow recommendations below
 - If IND use is confirmed, then two choices
 - Follow approach for NDBE or
 - Repeat EGD/biopsies q6-12 mon
 - If IND → LGD/HGD
 - Follow recommendations below
- Presence of esophagitis A, B, C, D
 - Similar to screening,
 - At surveillance EGD when erosive esophagitis, treat with PPIs / ↑ dose of current PPIs to induce healing on EGD, and then do biopsies for BE surveillance.
- Interpretation
 - Biopsies with dysplasia
 - Assess biopsies independently by two experienced pathologists, at least one of whom has specialized expertise in GI pathology
- Biomarkers for risk stratification of patients with BE
 - Not recommended at this time
 - The biomarkers include trefoil factor 3 (TFF3), methylated DNA markers (MDMs) (polymerase chain reaction [PCR] based test)
 - The Cytosponge-TFF3 has a high likelihood of confirmatory EGD, on EGD “only if the provider thought was indicated”)

Non-endoscopic swallowable cell collection capsule sponges, plus biomarkers (all studies from US, British [UK] 30-mm Cytosponge)

	Sensitivity	Specificity
○ Trefoil factor 3 (TFF3)		
– US	76	77
– UK	80	92
Methylated DNA marker (MDM)	92-94%	62-94%
○ Biomarkers		
– p53 (tumour suppressor gene)		
– Tissue-cypher system (fluorescent images of 9 protein-based biomarkers, nuclear morphology, tissue architecture)		
	Low sensitivity and specificity	

Recommendation

- At this time, do **not** use p53 or tissue-cypher system in addition to standard histopathology in patients having surveillance BE.



- Use "...published quality indicators to benchmark your [endoscopy] unit's performance against published standards"
- Intervals for surveillance
 - Screening shows
 - BE (IM, no dysplasia)
 - Do **not** require a repeat endoscopy in 1 yr for dysplasia surveillance
 - BE, indefinite for dysplasia
 - PPI for 3 to 6 mon, then repeat EGD + biopsies
 - If biopsies remain indefinite for dysplasia, repeat EGD plus biopsies
 - Low-grade dysplasia (LGD)
 - Endoscopic eradication therapy, but
 - EGD + biopsies q1yr is still an "acceptable alternative"
- Endoscopic Ablative Therapy (EAT)
 - Should not be used for non-dysplastic BE
 - EMR used for BE with LGD/HGD
- Benefit of surveillance of BE
 - ↓ mortality of EAC (surveillance vs. no/incomplete surveillance), RR, 0.64 (95%CI, 0.50-0.71)
 - Perform endoscopic surveillance in persons with known BE at intervals which are determined by the degree of dysplasia noted in previous biopsies (Strength of recommendation: Conditional)

Recommendation

- Stop performing BE surveillance when patient is no longer going to benefit
 - Too old for endoscopic eradication therapy (EET)
 - Too old for repeat endoscopy
 - Estimate life survival < 5 yr
- Intervals for repeat EGD/biopsies

NDBE/HGD

- Use the length of the BE to determine the surveillance intervals (EGD per # yr)
 - ↑ BE length → ↑ risk of progression of NDBE → LGD/HGD → EAC (OR, 1.25; 95%CI, 1.16-1.36)

Length of BE	EAC	EAC plus HGD
< 3 cm	0.07%	0.25%, P = 0.001
> 3 cm	0.29%	0.91, P = 0.001



Recommendation

- In patients with non-dysplastic BE (NDBE), surveillance intervals are determined by length of BE (quality of evidence: moderate; strength of recommendation strong)
- WATS-3D
 - A wide area transepithelial cytology brush with computer-assisted 3-dimensional analysis
 - Not recommended for BE surveillance, since at best only 2% absolute ↑ detection of LGD/HGD

Recommended Endoscopic Surveillance Intervals based on Degree of Dysplasia and Segment Length

Baseline endoscopic finding	Suggested endoscopic surveillance
○ Non-dysplastic BE of < 3 cm length	– EGD q5yr
○ Non-dysplastic BE of ≥ 3 cm length	– EGD q3yr
○ BE indefinite for dysplasia, any length (confirmed by a second pathologist)	– Repeat EGD within 6 mon after ↑ PPI to b.i.d. dosing, if not already on high-dose PPI
	– If repeat EGD yields diagnosis of NDBE or LGD ▪ Treat using that algorithm
	– If repeat EGD demonstrates BE indefinite for dysplasia ▪ EGD q1yr
○ BE with LGD (confirmed by a second pathologist and opting for endoscopic surveillance)	– EGD at 6 mon from diagnosis
	– EGD 12 mon from diagnosis
	– EGD annually thereafter

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

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➤ Therapy

- Prevention
 - PPI po od
 - b.i.d. PPI not recommended unless patient has symptoms or esophagitis
 - No other chemoprevention recommended, including ASA/NSAIDs



- Endoscopic therapy: endoscopic mucosal resection (EMR), endoscopic ablative therapy (EAT)
 - Nodularity in the BE segment → remove by EMR
 - If biopsy specimen removed by EMR shows HGD/IMC → EAT
 - If biopsy specimen shows neoplasia at a deep margin
 - Surgery
 - Systemic therapy
 - Additional endoscopic therapies
 - Non-nodular BE with dysplasia → EAT by radiofrequency ablation
 - Esophageal adenocarcinoma (EAC)
 - T1a EAC → endoscopic therapy
 - T1b EAC → multidisciplinary surgical oncology team
 - Perform EUS for FNA of regional lymph nodes
 - T1b, SM 1 → endoscopic therapy considered rather than esophagectomy +/- multi-modality therapies if lesion is
 - Well-differentiated
 - No lymphovascular invasion
 - High surgical risk patient
- Surgery
 - If patient has GERD symptoms which are refractory to PPIs
 - Perform anti-reflux surgery for the GERD
 - Do **not** use anti-reflux surgery as an “anti-neoplastic measure”
 - T1b, SM2-3
 - Esophagectomy +/- neoadjuvant therapy
 - T1a, T1b SM1 EAC
 - Surgery
 - Multi-modality therapy if
 - Poor differentiation
 - Lymphovascular invasion
 - Good surgical risk
 - Incomplete EMR
- Post-endoscopic complete elimination of intestinal metaplasia (CE-IM)
 - Continue EGD plus biopsy surveillance to detect recurrent IM +/- dysplasia
 - Interval of surveillance depends on histopathology before ablation
 - HGD/IMC q3mon x4, then q6mon x2, then q1yr
 - LGD q6mon x2, then q1yr
 - Surveillance after CEIN should be with high-resolution white light endoscopic imaging plus narrow band imaging



- Recurrence of IM/dysplasia
 - Treated as recommended before ablation (please see above)
- Continue EGD plus biopsy surveillance to detect recurrent IM +/- dysplasia
- Treatment of BE
- ❖ Non-endoscopic
- Proton Pump Inhibitors (PPIs)
 - Evidence that BE associated with presence, severity and duration of GERD symptoms, but
 - Control of GERD symptoms does not completely ↓ risk of BE progression because there may still be asymptomatic reflux
 - PPI therapy in BE → 71% ↓ risk of HGD/EAC
 - The only consistent proven adverse effect of PPI use is enteric infection
 - OR 1.33; 95%CI: 1.01-1.75
 - Number needed to harm, 900 for each yr on PPI
 - Double-dose PPI (esomeprazole 40 mg b.i.d.) was superior to lower dose to ↑ time to all cause mortality, including HGD/EAC (time ratio [TR] 1.27 (95% CI: 1.01-1.58, P = 0.038).

Recommendations

- In patients with BE, use PPI po od, unless there is
 - Allergy
 - Contraindication
 } To PPI
- Aspirin (ASA) / nonsteroidal anti-inflammatory drugs (NSAIDs)
 - Rational
 - Inhibition of cyclooxygenase pathway reduces inflammation-induced upregulation of oncogenic factors
- Anti-reflux surgery

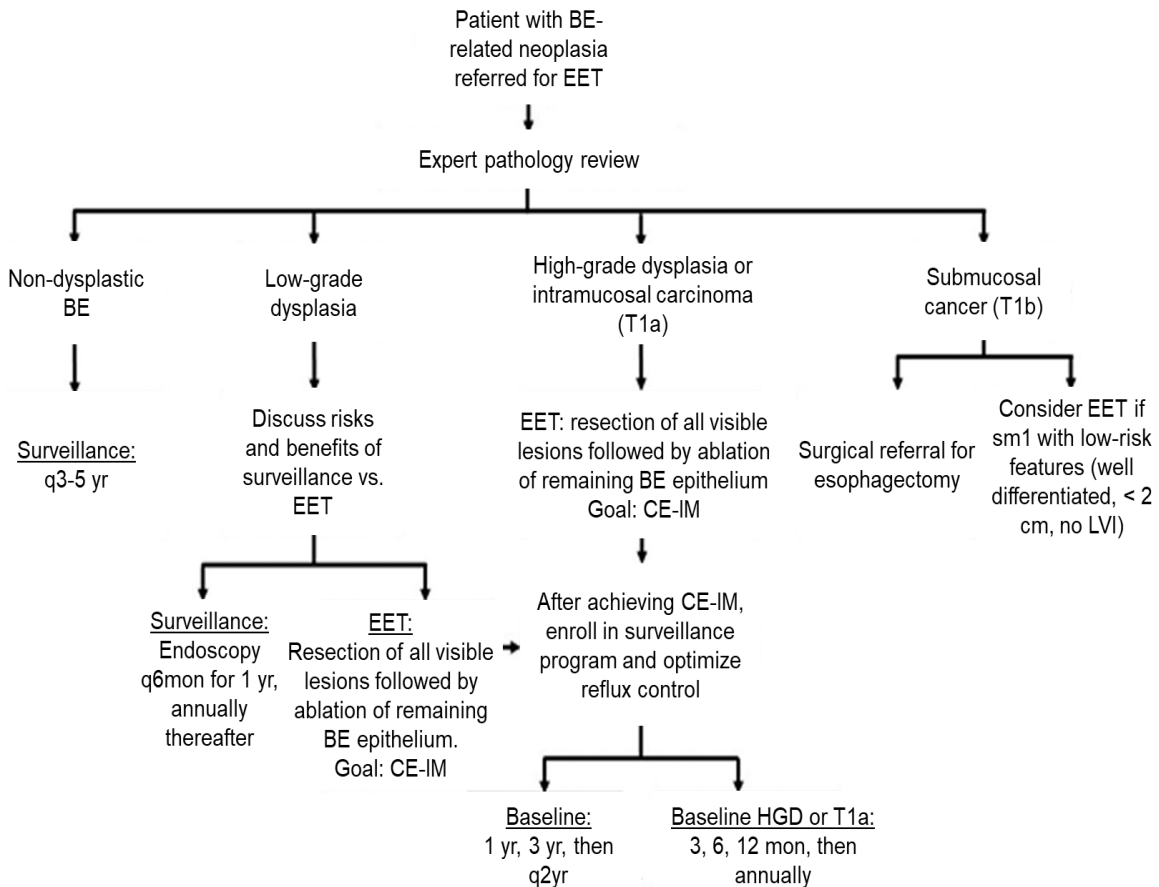
Recommendation

- Do **not** use anti-reflux surgery "...as an anti-neoplastic measure in patients with BE (Strength of recommendation: conditional; quality of evidence: low)



❖ Endoscopic

Algorithm for patients referred for consideration of EET.



- Note that these procedures are to be performed using high-definition white light endoscopy and virtual chromoendoscopy and are generally performed after initiation of maximal acid suppressive therapy (twice-daily PPI). Resection of visible lesions should always precede ablative therapy.
 - This mucosal resection may upstage the BE
 - This case the algorithm for the most severe histology should be followed

Abbreviations: BE, Barrett's esophagus; CE-IM, complete eradication of intestinal metaplasia; EET, endoscopic eradication therapy; HGD, high-grade dysplasia; LGD, low-grade dysplasia; LVI, lymphovascular invasion; PPI, proton pump inhibitor

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❖ High Grade Dysplasia (HGD)

- Endoscopic eradication therapy (EET) vs. esophagectomy (EGS)
 - EET = EGS
 - Complete eradication
 - 5-yr survival rate (no different)
 - Superiority of EET vs. EGS
 - AE's of EET (radiofrequency ablation [RFA] +/- endoscopic mucosal resection [EMR])
 - Stricture, ~6%
 - Bleeding, 1%
 - Perforation, 0.6%
 - EET (RFA +/- EMR)
 - 3 sessions usually needed for complete eradication of intestinal metaplasia (CE-IM)

MCQ Pearl

- The role of EET may be adequate for T1b EAC, or esophagectomy which has been previously recommended for EAC with superficial submucosal invasion (SM-1 invasion < 500 µm into the submucosa)

Recommendation

- In patients with BE with high grade dysplasia (HGD) or intramucosal cancer (IMC) undergo EET compared with esophagectomy (strength of recommendation: strong; quality of evidence: moderate).
- Contemporary practice includes ER of any visible lesion within EE segment, following
 - Ablative techniques (e.g., cryotherapy) to achieve complete eradication of
 - Dysplasia (CED)
 - Intestinal metaplasia (CE-IM)

❖ Low grade dysplasia (LGD)

- LGD may progress to HGD/EAC
 - ~2% per patient year
 - Because of this high variability in the rate of progression of LGD
 - Confirm diagnosis of LGD by reading of histopathology by expert pathologist
 - It is controversial whether the risk of progression is high in the first year after diagnosis, which would suggest possible underdiagnosis of the LGD)



- Choices for treatment of LGD
 - Repeat EGD BE surveillance within 6 mon, or then again at 12 mon
 - EET is possibly preferable
 - RFA / sham RFA, plus surveillances
- | | At 12 mon | No RFA | |
|---|-----------|--------|-----------|
| - Complete eradication | | | |
| ▪ LGD | 90% | 23% | P < 0.001 |
| ▪ IM | 81% | 4% | P < 0.001 |
| - Risk of progression to | | | |
| ▪ HGD/EAC | ~2% | ~27% | P < 0.001 |
| ▪ EAC | 2% | ~9% | P = 0.03 |
| - EET/ablation → ↓ neoplastic progression by 25% (NNT, 4) | | | |
- Rational for sequence of BE ER (EMR/ESD) → ablation
 - Remove tissue by ER
 - Improve histopathological interpretation with larger forceps biopsies
 - Histological grading

}

Upstage
Downstage

} Alters management in 30-40%
 - Endoscopic ultrasound (EUS) inferior to EMR/ESD biopsy material
 - In the staging of early EAC
 - In determining lateral and depth margins for resection
 - Obtaining prognostic factors
 - Grade of differentiation
 - Invasion (lymphovascular, perineural)
 - Role EUS
 - Stage T1b EAC
 - Stage T1a EAC

Clinical Diamond

- Long-term outcome for early-stage EAC is better for EET than for surgery.
- Do **not** use Paris classification of superficial EAC.

Techniques for ER

- Endoscopic mucosal resection
 - Cap-assisted EMR
 - Multiband EMR (usually the preferred technique)
- Endoscopic submucosal dissection
 - Indicates
 - Larger lesions which are **not** suitable for EMR
 - Possible submucosal invasion or lesions arising postablation, making EMR challenging due to scarring.



- Always remove residual BE segment, even if just non-dysplastic BE (NDBE) to
 - ↓ risk of metachronous HGD/ECA
 - Methods
 - Radiofrequency ablation (RFA) thermal
 - Cryotherapy (spray or balloon direct contact tissue necrosis)
 - Liquid nitrogen
 - Liquid nitrous oxide
- } Risk of strictures, 9-12%
- Sequence with EET: ER, then ablation therapy

Recommendations

- Use EET in BE plus confirmed (expert pathologist) to ↓ risk of progression of LGD → HGD/ECA, or
 - Endoscopic surveillance of confirmed LGD (strength of recommendation: conditional; quality of evidence: moderate)
- In patient with LGD having EET
 - First do EMR/ESR of any visible lesion in the BE segment
 - Then do ablative therapy (strength of recommendation: conditional; quality of evidence: very low)
- Quality Consideration for EET/Ab for BE
 - Centralize the care of patients with “BE-related neoplasia”
 - Impaired outcomes with large volumes of treatments
 - ↓ risk of recurrence of BE
 - ↓ adverse effects
 - ↓ 30-/90-day mortality

Recommendation

- In patients with BE who require EET, treat them in a high-volume centre (strength of recommendation: conditional; quality of evidence: very low)

		Threshold
○ Process	– Rate of using second expert pathologist before starting EET	90%
	– Rate of tracking/documenting adverse events post-EET	
○ Outcome	– 18 mon rate of achieving	
	▪ Complete eradication of intestinal metaplasia (CE-IM)	70%
	▪ Complete eradication of neoplasia (CEN)	80%



- EET follow-up with continued endoscopic surveillance
 - Recurrence after complete elimination of intestinal mucosa (CE-IM) defined as "...1 or 2 surveillance endoscopies negative for visible BE [plus negative for] biopsies taken from the tubular esophagus [TE] and the gastroesophageal junction [GEJ]"
 - NDBE after CE-IM, 9-11%
 - Dysplastic IM, 2%
 - HGD/EHC, 1%
 - Do **not** stop surveillance after EET, because the risk of recurrent BE (+/- dysplasia) continues after EET and CE-IM
 - Site of recurrences
 - Tubular esophagus (TE), 25%
 - Non-visible in 20%
 - GEJ, 75%
 - Non-visible in 60%
 - Distal 5 cm of esophagus, 87%
 - Process
 - ER for visible lesions, ablation for residual flat BE
 - 90% of recurrences can be treated by endoscopy
 - Predictors of recurrence after CE-IM
 - Patient, older age
 - Long-segment BE
 - HGD/EAC before ablation
 - After CE-IM, perform endoscopic surveillance based upon worst pretreatment histopathology
 - LGD
 - 1 then 3 yr post-CE-IM, with EET then q2yr
 - HGD, intramucosal EAC
 - 3, 6, 12 mon post-CE-IM

Continue surveillance after CE-IM, unless stopping is dictated by the overall medical status of the patient

Recommendation

- In patients with BE who have been treated with successful EET, continue endoscopic surveillance long-term (strength of recommendation: strong; quality of evidence: moderate)



Barrett's Esophagus (BE): Endoscopic Eradication (Ablative) Therapy, Post-Ablation Surveillance and Treatment

Kahn A, et al. Am J Gastroenterol 2020; 115: 823-31.

➤ Indications

- BE with LGD/HGD (low- or high-grade dysplasia)
- Intramucosal esophageal adenocarcinoma (T1a EAC)

➤ Types of endoscopic eradication therapy (EET)

- Endoscopic resection
 - Endoscopic mucosal resection (EMR) +/- endoscopic submucosal dissection (ESD)
- Ablation: radiofrequency ablation (RFA)
 - Complications
 - Strictures, 6%
 - Bleeding, 1%
 - Perforation, 0.6%
- The above methods of treating BE plus LGD/HGD or T1a EAC are comparable in outcome with esophagectomy

➤ Definition

- Complete eradication of

	Success Rate
– Dysplasia (CE-D)	~90%
– Metaplasia, intestinal (CE-IM aka CRIM [complete remission of IM])	~80% (2 negative EGDs after EET, with no intestinal metaplasia of multiple biopsies (IM of tubular esophagus and gastroesophageal junction (GEJ, eradication of gastric cardia IM)
- Successful EET
 - No IM on EGD/histology
- Recurrence of BE after EET
 - IM, dysplasia, EAC in tubular esophagus (GEJ after endoscopic surveillance after successful EET (CE-IM or CRIM)

➤ Types

- Endoscopic
 - Equipment alert
 - “High-definition white light endoscopy [NHDWLE] should be considered as the standard of care for post-EET surveillance
- Histopathology
 - 4 quadrant biopsies q1cm
 - Through previous BE segment
 - Tubular esophagus plus GEJ

} Separate pathology sample bottles



- Note that targeted biopsies may be superior to this random biopsy protocol, but not yet adequate data to recommend for routine practice
- Alternate protocol
 - Target biopsies of visible abnormalities
 - 4-quadrant random biopsies
 - Top of gastric folds (in esophagus)
 - Every 1 cm of distal 2 cm of esophagus, plus remainder of pre-treatment BE segment if < 5cm
- When
 - Baseline biopsies (pre-EET)
 - HGD/EAC
 - q3mon x4 after CE-IM, then
 - q6mon x2, then
 - q1yr
 - LGD
 - q6mon x2, then
 - q1yr
 - Continue surveillance indefinitely

- Possible alternatives (based in statistical modeling: not yet evidence based)
 - At 3 mon, 6 mon, then q1yr
 - 1 yr then q3yr

➤ Treatment

• Endoscopy

- EGD appearance
 - Nodularity: endoscopic resection therapy (ERT)
 - Flat: ablation
- If seen only histopathologically (not on chromoendoscopy)
 - Most recurrences can be managed with EET, depending in part on pre-CE-IM treatment
 - Non-visible on EGD
 - Histologically non-dysplastic (IM) → EGD surveillance
 - Histologically dysplastic → volumetric laser endomicroscopy (VLE, based on optical coherence tomography with image depth of 2-3 mm for subsquamous imaging)
 - May have high false-positive rate for post-ablation subsquamous structures or focal ablation

Treatment Alert

- Confocal laser microscopy (CLM)
 - If no benefit when used with HDWLE
- Wide-area transepithelial sampling (WATS-3D)
 - Not yet validated for post-EET surveillance.
- Dysplastic recurrence after RFA CE-IM is seen more often in the GEJ in the cardia than in the tubular esophagus
 - This has been disputed, but until resolved, for purposes of patient safety, it is recommended "... to sample the GEJ/cardia during post-treatment surveillance"
- If post-treatment surveillance shows IM of GEJ/cardia, it is not known whether this is best to follow, or to treat.



- Reflux control
 - Objective
 - Control GERD symptoms
 - Eliminate esophagitis
 - If optimizing high dose of PPIs to control symptoms / achieve EGD-healing of esophagitis → consider surgical fundoplication
- Chromoprevention
 - The use of aspirin or statins “...has not been established in the post-ablation population

For “Horizon Watchers”

- Patients with dysplastic BE breath release ↑ volatile organic compounds, raising the speculation of breath test being used to determine the presence of dysplasia.

- Endoscopic eradication therapy (EET)
 - Indications
 - Barrett’s esophagus with low (LGD) / high grade dysplasia (HGD)
 - Intramucosal (T1a) esophageal adenocarcinoma (EAC)
 - Endpoints
 - Endoscopic/histological complete eradication
 - Dysplasia (CE-D)
 - Intestinal metaplasia (CE-IM)
 - Procedure
 - Endoscopic resection (ER)
 - Endoscopic mucosal resection (EMR)
 - Endoscopic submucosal dissection (ESD)
 - Ablation
 - Radiofrequency ablation
 - Adverse effects
 - Strictures, 6%
 - Bleeding, 1%
 - Perforation, 0.6%
 - Cryotherapy
- Endoscopic Surveillance after eradication (CE-D, CE-IM)
 - Definition of “successful GET”
 - No IM on surveillance histology after BE segment is visibly eradicated on either 1 or 2 endoscopic biopsy sessions
 - 2-EGD plus biopsy is preferable, since it is associated with a lower rate of recurrence (possibly due to sampling error with 1 set of biopsies from 1 EGD detected fewer lesions [i.e., missed])
 - Use 4-quadrant biopsies from both tubular esophagus plus the gastroesophageal junction (GEJ) / cardia



- Recurrence after EET
 - Definition
 - "... the presence of IM, dysplasia [LGD, HGD] or EAC in the tubular esophagus or GEJ in patients undergoing endoscopic surveillance after EET [1 or 2 EGDs] as defined by [absent] CE-IM"
 - Types of recurrence
 - Visible (by EGD)
 - Histopathological
 - Recurrence rates per yr
 - IM, 8-10%
 - LGD/HGD, 2-3%
 - Detection of recurrence (standard of care)
 - High-definition white light endoscopy (HDWLE)
 - Remove foam with simethicone
 - Remove mucus with N-acetyl cysteine
 - Soft, transparent plastic cap to provide en-face positioning for NEPA-focus examination / photodocumentation
 - Retroflexion to examine gastric cardia
 - Location of recurrence
 - Take targeted biopsies if possible
 - 4-quadrant biopsy has low yield (1% for any recurrence, 2% for dysplasia)
 - GEJ, 75% (within 2 cm of GEJ)
 - Tubular esophagus, 25%
 - Recurrences > 5 cm proximal to GEJ, 16%
 - Subsquamous BE after successful RFA, 0.9%
 - High risk for recurrence
 - ↑ age
 - ↑ length of BE
 - Baseline / initial HGD / IMCa (intramucosal cancer)
 - Proposed new protocol for endoscopic surveillance after EET for CE-IM
 - 4-quadrant biopsies
 - Top of gastric folds
 - Distal 2 cm of esophagus
 - Area 3-5 cm above the GEJ EGD/biopsy surveillance
 - Surveillance intervals: baseline findings
 - CE-IM q3mon x4, q6mon, then q1yr
 - LGD q6mon x2, then q1yr, or at 1 and 3 yr
 - HGD/IMCa 3, 6, 12 mon, then q1yr

- "Most of the dysplastic recurrences and occur at or below the grade of the baseline histology"
 - Only 6% recur at a greater than the pretreatment histology

} Continue long-term

❖ Treatment of recurrence

- Endoscopy
 - Type of endoscopic treatment depends upon the previous treatment, but generally
 - Pre-CE-IM treatment of lesions
 - Nodular, resect
 - Flat, ablation
 - Non-visualized (biopsy demonstrated)
 - Non-dysplastic: EGA/biopsy surveillance
 - Dysplastic: if lesion not identified by volumetric laser endomicroscopy (VLE) perform focal ablation



- Advanced imaging
 - Virtual chromoendoscopy
 - “Not currently advocated”
 - Confocal laser endomicroscopy (CLE)
 - Volumetric laser endomicroscopy (VLE)
 - Negative predictive value of 100% for recurrent disease
 - Wide-area transepithelial sampling
 - Abrasive brush samples entire BE or post-treatment segment
 - Non-endoscopic esophageal tissue sampling (e.g., Cytosponge)
 - “Breath biopsy”
 - Measure of exhaled volatile organic compounds (AUC, 0.79)
 - The technique “holds promise”
 - For untreated patients with BE, high- vs. low-dose PPI reduces
 - AI-cause mortality
 - HGD/EAC
 - Goal of retreatment
 - CE-IM
- Medical
 - PPIs to control symptoms and to heal erosive esophagitis
 - Use PPI adjustment or fundoplication” with “aggressive” control of acid reflux, in those achieving CE-IM, reflux control was associated with 3 yr recurrence in 6%
 - Chemoprevention
 - No role for ASA, NSAIDs, statins

Abbreviations: BE, Barrett’s esophagus; BMI, body mass index; CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; CLM, confocal laser microscopy; CRIM, complete eradication of intestinal metaplasia; ECA, esophageal cancer; EET, endoscopic eradication therapy; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; GEJ, gastroesophageal junction; HDWLE, high definition while light endoscopy; HGD, high grade dysplasia; IM, intestinal metaplasia; LGD, low grade dysplasia; mon, month; RFA, radiofrequency ablation; VLE, volumetric laser endomicroscopy; WATs, wide area transepithelial sampling; yr, year



Quality indicators for endoscopic eradication therapies in patients with Barrett's Esophagus (BE): The Treatment with Reception an Endoscopy Ablation Technique for Barrett's Esophagus (TREAT-BE) Consortium (2017)

Wani S, et al. Am J Gastroenterol 2017; 112: 1032-48.

➤ Background

- Barrett's esophagus is a precursor to dysplasia (low- and high-grade [LGD and HGD], respectively) and to esophageal adenocarcinoma (EAC).
- Quality indicators pre- and post-endoscopy are postulated to ↑ delivery of high quality best practice medicine becoming the basics for remuneration, rather than the current payment per unit of source of undefined quality.
- In time, these standards will be incorporated as benchmark targets for the curriculum of gastroenterology training programs.

➤ Methods (RAND/University of California, Los Angeles appropriateness method)

- The RAND/University of California, Los Angeles appropriateness methodology (RAM) was used to develop quality indicators for EET in patients with BE-related neoplasia.
 - In the RAM, the concept of appropriateness refers to the relative weight of the benefits and harm of an intervention.
 - An appropriate indicator is one of which the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin exclusive of costs.
 - This is modified Delphi method that unlike the original Delphi, provides panelists with the opportunity to discuss their judgment between rating rounds in the face of face meeting to discuss their answers, similar to this method of the National Institute of Health Consensus Conferences.

➤ Recommendations

- For patients in whom the diagnosis of dysplasia has been made, the rate at which the reading is made by a GI pathologist or confirmed by a second pathologist before EET is begun.
 - Type of measure: Process
 - Performance target: 90%
- The centre where EET is performed should have available high-definition white light endoscopy (HD-LED), and expertise in mucosal ablation as well as EMR techniques
 - Type of measure: Process
 - Performance target: N/A
- The rate at which documentation of a discussion of the risks, benefits, and alternatives to EET is obtained from the patient before course of treatment is begun.
 - Type of measure: Process
 - Performance target: > 98%



❖ Intra-procedure

- The rate at which landmarks and length of BE is documented by using the Prague criteria in patients with BE before EET.
 - Type of measure: Process
 - Performance target: 90%
- The reliable coefficient for a segment of BE are high when ≥ 1 cm, but low for BE segments < 1 cm.
 - Not all columnar lined areas of mucosa are continuous
 - Because these “islands” are not taken into account with the Prague C + M classification criteria, and because these criteria.... have not been established by formal investigation, and patients with any extent of intestinal in metaplasia currently and manage similarly, the Paris classification may be used together with the Prague classification.
- The rate at which the presence or absence of visible lesion is reported in patients with BE referred for ET.
 - Type of measure: Process
 - Performance target: 90%
 - Protruded I p (pedunculated)
 I s (sessile)
 - Flat II a (superficial elevated)
 II b (flat)
 II c (superficial depressed)
 - Excavated III, likely to contain invasive cancer
- High-definition white light endoscopy (HD-WLE) is more sensitive than standard definition WLE to detect BE related neoplasia.
- The rate at which the BE segment is inspected by using HD-WLE.
 - Type of measure: Process
 - Performance target: 95%
- Endoscopic mucosa resection (EMR, en bloc resection or proximal) is recommended to
 - Change diagnosis in 30% of patients with BE with early dysplasia
 - $\uparrow$ interobserver kappa value ($\downarrow$ variability of diagnosis)
- The rate at which endoscopic resection (define as en bloc or piecemeal resection) is performed in patients with BE with visible lesion.
 - Type of measure: Process
 - Performance target: 90%
- Use EMR in all patients with nodular BE segment
 - Determined T-stage +/- grade of dysplasia (LGD, HGD)
- Among patients undergoing EET who have not yet achieved CE-IM, the rate at which a defined interval of subsequently EET is documented.
 - Type of measure: Process
 - Performance target: 90%



- The rate at which complete eradication of neoplasia is achieved by 18 mon in patients with BE related dysplasia or intramucosal cancer referred for EET.
 - Type of measure: Outcome
 - Performance target: 80%
- The rate at which CE-IM is achieved by 18 mon in patients with BE related dysplasia and intramucosal cancer referred for EET
 - Type of measure: Outcome
 - Performance target: 70%
- Among patients who achieve CE-IM, the rate at which the recommendation is documented for endoscopic surveillance at a defined interval.
 - Type of measure: Process
 - Threshold: 90%
- Endoscopic mucosal resection (EMR) misses up to 30% of patients with metachronous metaplasia, and radiofrequency ablation (RFA) is superior for endoscopic eradication therapy.
 - RFA ↓ risk of progression of
 - BE → HGD/EAC by 25%
 - BE → EAC by 7%
- Durability limit even with eradication therapy of both RFA plus EMR
 - Recurrence of
 - Metaplasia, 0% to 15%
 - Dysplasia, 5% to 40%
- Endoscopic EGD must be continued after RFA or EMR.
 - Perform initial post-therapy EGD at 3-6 mon after complete eradication of BE (intestinal metaplasia), then repeat EGD surveillance at intervals based on pre-treatment histology.
- During endoscopic surveillance after EET, state the rate at which biopsies of any visible mucosal abnormalities are performed.
 - Type of measure: Process
 - Threshold: 95%

- EGD is essential after endoscopic eradication therapy for BE.

- Use the Seattle biopsy protocol for the EGD-based biopsy surveillance, including attention to taking targeted biopsies from visible mucosal abnormalities.
- The rate at which an anti-reflux regimen is recommended after EET.
 - Type of measure: Process
 - Threshold: 90%
- “Uncontrolled gastroesophageal acid reflux (GER) is associated with persistence of intestinal metaplasia (IM) after RFA.
 - Even if symptoms of GER are treated adequately with PPIs, the GER may continue.
 - This risk of developing post-treatment BE with HGD or EAC is associated with uncontrolled reflux.



- Continue PPI (most guidelines suggest PPI) until
 - GER symptoms < once per wk
 - No esophagitis on EGD.
- The rate at which adverse events are being tracked and documented in individuals post EET.
 - Type of measure: Process
 - Threshold: 90%
- Adverse events (AEs) are frequent with endoscopic eradication therapy.
 - Pooled rate, 9%
 - Stricture, 6%
 - Perforation, 0.6%
 - Combination therapy → ↑ AEs
 - RFA + EMR AEs ↑4.4x vs RFA alone

Abbreviations: BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EGD, esophago-gastroduodenoscopy, EMR, endoscopic mucosal resection; GER, gastroesophageal reflux; HGD, high-grade dysplasia; LGD, low-grade dysplasia; RFA, radiofrequency ablation



DYSPHAGIA

Uninvestigated Esophageal Dysphagia: CAG (2018)

Liu LWC, et al. J Can Ass Gastroenterol 2018; 1: 5-19.

➤ Methods

- The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to evaluate the quality of supporting evidence, with the GRADE process of evaluating quality Supporting evidence conducted by formally trained GRADE methodologist. The quality of the evidence is created from high to very low.
 - “High” quality evidence indicates that further research is unlikely to change confidence in the estimate of effect and that the true effect lies close to this estimate.
 - Moderate quality evidence is associated with moderate confidence in the effect estimate, although further research could affect the confidence of this estimate.
 - “Low” quality evidence indicates that further study is likely to have an important impact on the confidence in effect estimate and would likely change the estimate.
 - “Very low” quality evidence indicates very little confidence in effect estimate, the true effect is likely to be substantially different than the estimate of effect.
- A strong recommendation is made when the benefits clearly outweigh the negatives and the results of no action.
- Conditional is used when some uncertainty remains about the balance of benefits potential harm. Key concept are statements that are not amenable to the GRADE process, either because of the structure of the street statement or because of the available evidence.
- In some stances, key concepts are based on extrapolation of evidence and/or expert opinion.

➤ Definitions

- Dysphagia
 - “...the sensation that food and or liquids are being obstructed or hindered in the in the passage from the mouth to the stomach”.
- Oropharyngeal dysphagia
 - “...difficulty initiating a swallow or passing food through the region of the mouth or throat”.
- Esophageal dysphagia
 - difficulty in transferring material down the esophagus in the retrosternal area”.
- Mixed
 - Oropharyngeal or esophageal dysphagia may occur together, especially when due to
 - Neurological diseases
 - Collagen vascular disorders
 - Infection



➤ Clinical

- Dysphagia for solids is usually associated with structural/mechanical causes
 - In time, solid food dysphagia may progress to dysphagia for solids plus liquids.
 - Site of dysphagia
 - % of patients localizing correctly the site of obstruction
 - Correct in, 22%
 - +/- 2 cm, 52%
 - +/- 4 cm, 74%
- } Message: the patient's localization of an obstruction is not a good indicator of the site of the causative pathology
- Position of localized symptoms.
 - False positive localization by patient.
 - Site of pathology
 - Proximal: distally, 5%
 - Distal: proximally, 15%
 - Odynophagia and suspected infection of esophageal mucosa
 - Candida Albicans
 - Cytomegalovirus (CMV)
 - Herpes simplex (HSV)

Recommendation

- Use the patient's history/physical of their presenting symptoms to establish whether the dysphagia is oropharyngeal or esophageal.
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 78%
 - Agree with minor reservation, 11%
 - Agree with major reservation, 11%
- Make this distinction to help identify persons who have high risk of aspiration.
 - GRADE: Strong recommendation, low-quality of evidence
 - Vote: Agree strongly, 100%
- Give examples of clinical assessment tools to distinguish oropharyngeal or esophageal dysphagia / persons with high risk of aspiration, and indicate which of these tools or scoring systems have acceptable performance characteristics (sensitivity ≥ 70%, specificity ≥ 60%).
 - Adequate
 - Cough test
 - TOR BSST (Toronto bedside swallowing screening test)
 - V-VST (volume viscosity swallowing test)
 - WST (3 oz water swallow test)
 - Not adequate
 - EAT (eating assessment tool)
 - SWOL QOL (dysphagia-related swallowing quality of the scale)
 - WVQ (wet voice quality)



- Risk of complications based upon patient's symptoms

	Pneumonia	Aspiration	Community Commonly Acquired Pneumonia
- Dysphagia in stroke patient	RR, 3.12; 95% CI, 2.07-4.87	RR, 11.56; 95% CI, 3.36-39.77	
- Oropharyngeal dysphagia in the elderly			OR, 11.9; 95% CI, 3.03-46.9

Recommendation

- For the patient with oropharyngeal dysphagia
 - Consult a speech language specialist
 - Arrange for VFSS (videofluoroscopy swallowing study)
- Use the patient's history of physical examination to distinguish between structural/motility disorders of the esophagus.
 - GRADE: Strong recommendation, moderate-quality of evidence
 - Vote:
 - Agree strongly, 56%
 - Agree with minor reservation, 33%
 - Disagree with minor reservation 11%

Dysphagia	Structural	Motility
- Rapid progression	+	-
- Regular	+	-
- Short duration	+	-
- Solids	+	-
	(early and late)	(late)

- If the symptoms suggest a structural cause of dysphagia
 - Features which suggests a esophageal cancer
 - Age $\geq$ 50 yr old
 - Bleeding/anemia (4%)
 - Vomiting (15%)
 - $\downarrow$ weight (unintentionally)

Clinical Diamond

- The strongest predictor of solid food dysphagia due to esophageal cancer is a short (< 8 wk) rather than > 8 wk duration of this symptom (OR, 11.2' 95% CI, 4.90-24.80; $p < 0.0001$).



- Conditions commonly associated with a motility cause of dysphagia
 - Heart ▪ Non-cardiac chest pain (NCCP)
 - Lung ▪ Reactive airway disease
 - GI ▪ Food bolus impaction
 - Endocrine ▪ Diabetes mellitus
 - MSK ▪ Connective tissue disease
 - Skin ▪ Atopic skin disease
 - Raynaud syndrome
 - Calcinosis/telangiectasia

Recommendation

- The distinction of the patient's dysphasia being from a likely structural vs. motility cause, and the appreciation for the importance of alarm features which help to achieve early consultation and ideally investigation within 2 wk.
 - GRADE: Strong recommendation, low-quality of evidence
 - Vote:
 - Agree strongly, 78%
 - Agree with major reservation, 22%
- “Persons with severe/rapidly progressive dysphasia, or high likelihood of cancer should be assessed within 2 wk (Canadian Consensus Guideline, Peterson WG et al. Canadian J Gastroenterol 2006; 20: 411-23)

❖ Investigation

- The first-choice investigation for esophageal dysphagia is urgent EGD rather than barium swallow.
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 78%
 - Agree with minor reservation, 22%
- A barium swallow may be appropriately performed first if there is limited/delayed access to EGD.
- Results from the barium study would accelerate early consultation with a specialist.
- The endoscopist for possible findings, wishes to know the characteristics of the lesion (e.g., to better prepare the patient and to obtain consent before insert an esophageal stent or feeding tube).
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 78%
 - Agree with minor reservation, 11%
 - Agree with major reservation, 11%



- An esophageal motility (manometry) study is the preferred first investigation if the patient with esophageal dysphagia is suspected of having a motility abnormality.
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 67%
 - Agree with minor reservation, 33%

A Reality Check

- It should be appreciated that in the reality of clinical practice, essentially all patients will require an EGD
 - To exclude eosinophilic esophagitis
 - To exclude adenocarcinoma of the gastric cardia, which may mimic the presentation of symptoms / diagnostic imaging suggestive of achalasia.
 - The appreciation of generally long wait time (> 6 mon) for esophageal manometry study, the relatively few centres in Canada, and often very long distance to travel to these few centres.
 - Chicago 3 classification esophagogastric outflow obstruction

Read the Test!

- Although the recommendations and statements imply the possible secondary nature of EGD or barium swallow in persons with a suspected motility cause of their dysphagia, and the presentation of a number of circumstances where both barium study or EGD be done as well as the manometry, it will be understood that for an EGD has sufficient sensitivity to
 - Determine subtle changes of esophageal inflammation
 - Obtain biopsies of areas of infection/inflammation, and
 - Biopsies for suspected Barrett's esophagus or eosinophilic esophagitis
 - Read the text for the complete story! "The consensus group agreed that, once structural and inflammatory abnormalities have been ruled out with EGD or barium esophagogram, esophageal manometry should be used to assess suspected motility disorders
- Take home message, "every patient with esophageal dysphagia needs EGD"

❖ Dysphagia in association with gastroesophageal reflux disease (GERD) symptoms

- Guidelines have changed over the years
 - First, the suggestion that dyspepsia in persons with dysphagia was an alarm symptom, necessitating EGD to exclude esophageal cancer.
 - Then guidelines suggesting that the presence of dysphagia in a patient with dyspepsia from likely GERD, should not represent a "red flag".



- In this guideline, it is recommended that in patients under 50 yr old presenting with esophageal dysphagia and reflux symptoms (GERD) and no [other] alarm features to suggest malignancy, further testing should to be performed if dysphagia does not resolve completely after a 4-wk trial of oral proton pump inhibitor (PPI) given twice daily”.
- GRADE: Strong recommendation, very low-quality of evidence
- Vote:
 - Agree strongly, 44%
 - Agree with minor reservation, 66%
- Part of the confusion to do EGD in persons with dyspepsia plus dysphagia comes from differences in the definition of “dyspepsia”
 - US definitions differentiate between dyspepsia and GERD
 - Canadian definitions include GERD as part of the definition of dyspepsia
- The authors of this guideline recommendation, indicate that “No study has directly compared the safety and efficacy of an empiric PPI trial first with EGD for those who do **not** respond completely to prompt EGD for all patients with optimal PPI while waiting for the EGD”.
- This editor agrees with the recommendation made in the text, approaching the patient with GERD symptoms plus dysphagia as needing an urgent EGD.
- For an inpatient with persistent dysphagia, perform EGD as the initial test during the hospitalization.
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 78%
 - Agree with minor reservation, 22%

❖ Esophageal mucosal biopsies

- Even if esophageal mucosa appears normal on EGD, multiple esophageal biopsies are required to diagnose several causes of esophageal dysphagia.
 - Eosinophilic (55 to 75% have dysphagia)
 - Lymphocytic
 - Infectious especially tuberculosis)
 - Esophageal lichen planus
 - Linitis plastica adenocarcinoma
- In patients having EGD for esophageal dysphagia, take multiple mucosal biopsies, unless they are clear features of erosive esophagitis.
 - GRADE: Strong recommendation, low-quality of evidence
 - Vote:
 - Agree strongly, 78%
 - Agree with minor reservation, 11%
 - Agree with major reservation, 11%
- Number of biopsies suggested
 - 2 to 4 biopsies from ≥ 2 sites distal and mid esophagus)
 - The diagnostic sensitivity for biopsies approaches 100% with 6 to 9 biopsies taken.



- Caution
 - In the presence of esophagitis (LA classification $\geq$ B), it may be difficult to diagnose
 - Barrett's esophagus (BE)
 - Eosinophilic esophagitis (EoE)
- } Treat the erosive esophagitis for $\geq$ 8 wk and then rebiopsy esophagus
- ❖ Manometry and suspected esophageal motility disorders
- Esophageal manometry is the “gold standard” for diagnosing esophageal motility disorders.
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 89%
 - Agree with minor reservation, 11%
 - In patients with persistent esophageal dysphagia, exclude structural/inflammatory causes, then perform esophageal manometry.
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 100%
 - There is a good concordance between esophageal manometry and a barium esophagogram, although diagnostic imaging may have lower sensitivity.
 - Manometry has its greatest clinical utility when performed in patients with dysphagia and previous non-diagnostic EGD +/- barium esophagus.
 - Manometry provided
 - Normal results, 80%
 - Non-information, 90%
 - Change in diagnosis, ~50%
 - Altered management, ~70%
 - When the decision is made for esophageal manometry
 - Perform high-resolution esophageal manometry (HREM), rather than conventional manometry.
 - GRADE: Strong recommendation, very low-quality of evidence
 - Vote:
 - Agree strongly, 56%
 - Agree with minor reservation, 33%
 - Agree with major reservation, 11%
 - Recordings should....”be interpreted by trained and experienced clinicians.... it is inadequate to rely solely on computer interpretation to ensure diagnostic accuracy”.

Abbreviations: BE, Barrett's esophagus; CI, confidence interval; CMV, cytomegalovirus; EAT, eating assessment test; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; HSV, herpes simplex virus; NCCP, non-cardiac chest pain; PPI, proton pump inhibitor; SWOL-QOL, dysphagia-related swallowing quality of life scale; TOR-BSST, Toronto bedside swallowing screening test; V-VST, volume viscosity volume test; WST, water swallow test; WVQ, wet voice quality



Food Impaction

❖ Non-endoscopic pharmacological management of esophageal soft food bolus impaction

Conservative management of esophageal soft food bolus impaction (Hardman J, et al. Cochrane Database Syst Rev 2020;5(5):CD007352. doi: 10.1002/14651858.CD007352.pub3)

- Definitive management is with endoscopic intervention, recommended within 24 h.
- Prior to endoscopy, many patients undergo a period of observation, awaiting spontaneous disimpaction, or may undergo enteral or parenteral treatments to attempt to dislodge the bolus.
- There is little consensus as to which of these conservative strategies is safe and effective to be used in the initial period, before resorting to definitive endoscopic management for persistent impaction.
- Intravenous (IV) diazepam followed by glucagon was compared with IV placebo on rates of disimpaction intervention.
 - The rates of disimpaction were small and insufficient, 38% vs. 32% (RR, 1.19; 95%CI, 0.51 to 2.75, P = 0.69)
- There is currently inadequate data to recommend the use of any enteral or parenteral treatments in the management of acute esophageal soft food bolus impaction,
 - There is also inadequate data regarding potential adverse events from the use of these treatments, or from potential delays in definitive endoscopic management.
 - Caution should be exercised when using any conservative management strategies in these patients.

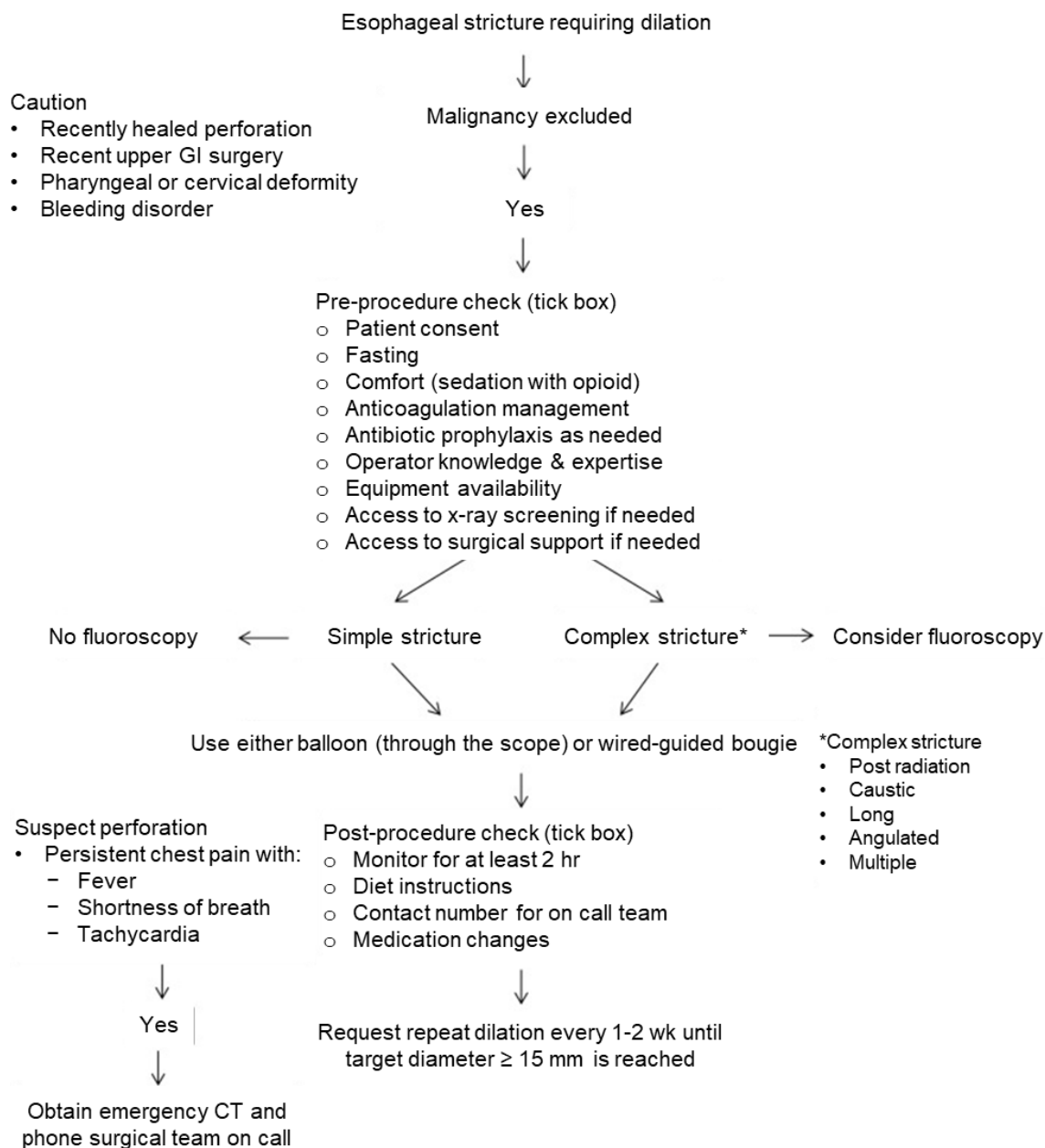


STRICTURES

Esophageal Dilation: British Society of Gastroenterology BSG Guidelines (2018)

Sami SS, et al. Gut 2018; ;67(6):1000-1023.

Stricture Dilatation Procedure Checklist



Printed with permission: Sami SS, et al. Gut 2018; ;67(6):1000-1023 (Figure 1)



➤ Patient preparation

- Predilation investigation

- Have a diagnosis of lesion before dilation
 - Biopsies can be taken safely before a benign lesion, but if the structure of the lesion may be malignant wait until the biopsies are reported before doing the dilation.

Recommendations

- GRADE evidence: Moderate
- Strength recommendation: Strong
- If endoscopic image or clinical features suggest that the structure is suspicious for being a malignant lesion
 - Repeat biopsies with ultrasound or with CT imagine
 - EUS
 - More sensitive than CT, but more difficult to obtain successful passage
- In young patients with dysphagia or clinical features suggestive eosinophilic esophagitis (EoE) obtain esophageal mucosa biopsies using accepted protocols.
 - GRADE evidence: Moderate
 - Strength recommendation: Strong
- In persons with suspected complex strictures (e.g., post-radiation, lye ingestion), first perform barium swallow to characterize the structure (location, length diameter, number) or to exclude possible esophageal diverticulum or large hiatus hernia.
 - GRADE evidence: Low
 - Strength recommendation: Strong
- Do **not** do esophageal dilations which are contraindicated active/incompletely healed esophageal perforation
 - GRADE of evidence: low
 - Strength of recommendation: strong
- Safe to perform cautiously
 - Healed / previous perforation, healed upper GI surgery, recent deformity of pharyngeal or cervical bleeding disorder
 - GRADE of evidence: low
 - Strength of recommendation: strong
- Informed Consent
 - Personalize the consent for the risk (complications) and benefits based on the patients esophageal condition, comorbidities.
 - Counsel all patients about the benefits and risks of dilatation and the likely need for multiple sessions before symptom resolution can be achieved.
 - GRADE of evidence: low
 - Strength of recommendation: strong
 - Tailor information to the individual patient's risk profile, based on the underlying cause, location, length and diameter of the stricture and coexistent adverse health problems
 - GRADE of evidence: low
 - Strength of recommendation: strong



- Provide information on alternate management approaches
 - GRADE of evidence: low
 - Strength of recommendation: strong
 - Provide written information, including risk and consequences of perforation
 - If possible: have a relative/caregiver present
 - Make an easy-to-understand diagram of the patients esophagus and pathology
- Depending upon National/Regional considerations, used published standards (e.g., British Society of Gastroenterology [BSG], Sheperd H and Hewett D. 2008/ print 20 June 2016)
- Include an outline of appropriate risks of serious/common complications
 - Perforation rates

Lesions	Perforation	Death	Type of Dilator
Benign	1.1%	0.5%	Savary-Gilliard (Wire guided (or balloon dilators (including through the scope [TTS] balloons) safer than non-wire guided Maloney dilators
Malignant	6.4%	2.3%	
Achalasia	< 8% 2% to 4%	0-1% 0-1%	

- The perforation rate is low in “experienced hands” and using a graded approach of dilation size (“start low, go slow”)
 - Physicians having previously not performed < 500 EGDs have an esophageal perforation 4x increased risk.
- Fasting
 - Fast for 6 h, or longer based upon the judgment of the clinician (such as in patient with untreated achalasia)
 - Advise patients to fast for ≥ 6 h before the procedure in order to ensure emptying of the oesophagus and stomach.
 - Patients with achalasia are likely to have esophageal stasis, and are therefore required to fast for a longer time based on the clinician’s judgement (GRADE of evidence: low; strength of recommendation: strong).
 - Medication
 - Anticoagulants, antiplatelet drugs
 - Follow appropriate guidelines
 - Preprocedure sedation
 - Make patient aware that the dilation may be uncomfortable without sedation
 - GRADE of evidence: low
 - Strength of recommendation: strong
 - Use benzodiazepine or propofol
 - Offer patients intravenous sedation with a benzodiazepine and an opioid analgesic as a minimum.
 - Propofol sedation (delivered by a suitably qualified person), or a general anaesthetic are valid alternatives based on the clinician’s and patient’s preference, procedure complexity, as well as local availability and expertise (GRADE of evidence: low; strength of recommendation: strong).



❖ The Dilation Procedure

- The procedure should be performed by, or under the direct supervision of “...an experienced operator who performs sufficient numbers [of esophageal dilations] to maintain their skill” plus one requested nurse plus one more in the endoscopy/radiology room.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - Consider exclusion of eosinophilic esophagitis by distal, mid and proximal oesophageal biopsies in patients with symptomatic Schatzki’s ring (GRADE of evidence: moderate; strength of recommendation: strong).
- National regulations vary for consideration of competence for performing esophageal dilations
 - For example, previously having performed ≥ 300 diagnostic EGDs (esophagogastroduodenoscopies) under direct supervision
- The dilation should be performed in
 - Fully equipped endoscopy room with access to x-ray screening and surgical support, or a similarly equipped radiological suite (GRADE of evidence: moderate; strength of recommendation: strong).
 - There must be an agreed protocol in endoscopy units to follow in case of a perforation, with clear identification of a qualified surgeon (on or off site) to manage this complication in cases where luminal treatment, such as a covered stent, is not feasible or appropriate (GRADE of evidence: low; strength of recommendation: strong).

❖ Esophageal Dilators

• Push (bougie) dilators

- Wired-guided
 - Metal olives
 - Celectin-type
 - Polyvinyl bougies
- Non-wire guided
 - Tungsten-filled weighted rubber bougies (Maloney dilators)
 - Use 5 to 20 mm diameter

• Balloon dilators (Endoscopically controlled)

- Through the [endo]scope (TTS) balloon dilators (single use)
- Wire-guided, single use, polyethylene balloon dilators with rubber-opaque markers to be used under radiographic guidance)
- Use balloon or wire guided dilators to perform esophageal dilation
 - GRADE of evidence: moderate
 - Strength of recommendation: strong).
- Do **not** use weighted (Maloney) bougies with blind insertion, because safer dilators are available
 - GRADE of evidence: high
 - Strength of recommendation: strong



- Consider using no more than three successively larger diameter increments in a single session for both bougie and balloon dilators; the precise restriction of 3×1 mm diameter increments is **not** evidence based.
 - GRADE of evidence: low
 - Strength of recommendation: low

- Types of Strictures

Characteristics	Simple	Complex
- Length	< 2 cm	≥ 2 cm
- Connect concentric	+	-
- Straight	+	-
- Easy passage of normal EGD	+	-
- Number of dilations needed	< 5	> 5
- Refractory, recurrence	-	+
- Size of initial dilation	10-12 mm (30 to 36F)	≤ 9 mm (filiform)
▪ GRADE of evidence: very low		
▪ Strength of recommendation: weak		

- Radiographic screening
 - Considerations for radiographic screening
 - Suspected diverticulum, large hiatus hernia
 - Resistance to pass guidewire
 - Inability to pass guidewire distal to structure
- Protocol for suspected esophageal perforation
 - Only perform post-procedure imaging if patient develops
 - Persistent chest pain
 - Dyspnea
 - Fever
 - Tachycardia

}
 - Suspect perforation →
Perform CT scan with oral contrast

Recommendations

- Do **not** perform imaging and contrast studies routinely after the procedure, unless patients, during recovery, develop persistent chest pain, fever, breathlessness or tachycardia.
 - GRADE of evidence: very low
 - Strength of recommendation: weak
- Suspect perforation when patients develop pain, breathlessness, fever or tachycardia.
 - Transient chest pain is not uncommon following dilatation but persistent pain should prompt a CT scan with oral contrast to look for perforation.
 - GRADE of evidence: low
 - Strength of recommendation: strong
- Ensure patients are well and can drink water before discharge from the endoscopy unit
 - GRADE of evidence: low
 - Strength of recommendation: strong



- Repeat EGD in endoscopy room if perforation is suspected.
- Consider corticosteroid injection at the resection site or oral prednisolone therapy in patients at high risk after large EMR or ESD to reduce stricture formation (GRADE of evidence: moderate; strength of recommendation: weak).
- When esophageal perforation is suspected
 - Performed immediate CT scan with oral contrast
 - Injection of contrast
 - GRADE of evidence: low
 - Strength of recommendation: strong
 - EGD guided insertion of a fully covered self expandable metal stent
 - GRADE of evidence: low
 - Strength of recommendation: strong
- Offer dilatation along with other forms of disease modification including diet modification, topical corticosteroids or other drugs (GRADE of evidence: moderate; strength of recommendation: strong).
- Inform patients that symptom response after dilatation usually lasts up to 1 yr
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Use CO₂ insufflation to ↓ luminal distention to ↓ post-procedure pain
 - GRADE of evidence: high
 - Strength of recommendation: strong
- Start other treatments for eosinophilic oesophagitis (EoE) before dilatation if possible, these treatments may be continued afterwards to prevent or delay recurrence of symptoms (GRADE of evidence: moderate; strength of recommendation: strong).
- Give the differential diagnosis of findings on CT scan with oral contrast performed after the development of symptoms associated with abnormal oesophageal perforation arising from an esophageal dilation procedure.
 - Air
 - Pneumothorax
 - Pneumomediastinum, pneumopericardium, air under a hemidiaphragm, pneumoperitoneum
 - Fluid
 - Pleural effusion
 - No abnormalities
 - A normal CT scan after esophageal dilation of a patient with post-dilation symptoms does not necessarily exclude an iatrogenic perforation
 - Upper esophageal sphincter (UES) disorders and dysphagia (dilation or radiofrequency ablation [RFA])
 - UES disordered opening
 - Cricopharyngeal bar +/- Zenker diverticulum
 - GRADE of evidence: moderate
 - Strength of recommendation: strong



❖ Post-procedure care

• Immediate

- Observe patient in recovery room for 2 h post-dilation.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Give patients a discharge note with instructions regarding intake of fluids, food and medications, as well as contact information for team/persons on call after hours.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Provide patients with contact information for the on-call team should they experience chest pain, breathlessness or become unwell
 - GRADE of evidence: low
 - Strength of recommendation: strong).

• Follow-up

- Multiple dilations may be necessary.
- At each session, use these progressive size increments of the dilation.
 - Once the 15 mm (45 F) dilation has been passed, 98% of patients achieve clinical response over a mean follow-up of ~19 mon, but
 - The shorter/smaller the patient, the shorter/narrow the esophagus
 - If the patient can pass a 12 mm barium pill after the dilations are complete, they will require significantly fewer dilation sessions than when the dilation program is stopped because of loss of symptoms.
- Perform weekly or two-weekly dilatation sessions until easy passage of a ≥ 15 mm dilator is achieved along with symptomatic improvement.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong

❖ Specific Types/Causes of Strictures Requiring Dilation

• Achalasia pneumatic dilation

- Contraindications
 - PD may cause esophageal perforation.
 - Sometimes perforation may be treated with an endoscopically inserted expandable stent or with a clipping
 - Sometimes perforation may require surgical repair.
 - Thus, do **not** perform PD in persons who could not withstand surgery (e.g., comorbidities, cardiopulmonary disease, frailty)
- Only used balloon dilators (pneumatic dilation [PD]), starting at 30 cm.
 - GRADE of evidence: high
 - Strength of recommendation: strong
 - Then second PD 2-28 d later, using 35 mm.
 - GRADE of evidence: high
 - Strength of recommendation: strong



- If symptoms or Eckardt score > 3 used 35 mm, and repeat PD in future, as needed.
 - GRADE of evidence: high
 - Strength of recommendation: strong
 - Use endoscopic or fluoroscopic control
 - GRADE of evidence: moderate
 - Strength of recommendation: strong).
 - Outcome
 - Effective on symptoms after
 - 1 yr 90%
 - 2 yr 86%
 - 5 yr 66%
 - If repeat PD necessary, results are very good, with remission rates
 - 5 yr 97%
 - 10 yr 93%
 - Post dilation symptoms of gastroesophageal reflux +/- erosive esophagitis (10% to 40%) heal with PPIs.
 - GRADE of evidence: high
 - Strength of recommendation: strong
 - Not necessary to routinely perform post-PD diagnostic imaging (e.g., water-soluble contrast swallow)
 - GRADE of evidence: moderate
 - Strength of recommendation: weak
 - If necessary, may do
 - Myotomy after PD
 - PD after myotomy
- Peptic Strictures
 - These short/straight strictures occur in ~2% of persons with GER-associated esophagitis.
 - ~80% of patients require only one esophageal dilation
 - Peptic strictures may be associated with esophagitis
 - Repeat dilation is more common with a long/tight (↓ diameter) peptic stricture.
 - Use PPIs to treat patients with GER-associated esophagitis/dysphagia (↓ need for dilation)
 - Peptic strictures (↓rate of recurrence of peptic strictures, and then ↓need for repeat dilation)
 - In this setting, use PPIs, not H2RAs (histamine 2 receptor antagonist).
 - GRADE of evidence: high
 - Strength of recommendation: strong



- Schatzki ring (SR)

- Definition

- "...an annular a constriction at the gastroesophageal mucosal junction, covered on its proximal side by squamous epithelium and distal side by gastric mucosa"
- Consider performing upper GI endoscopy, manometry, pH studies and barium swallow first in patients with post-fundoplication dysphagia, to understand the mechanism of dysphagia, before dilatation or repeat surgery.
 - GRADE of evidence: low
 - Strength of recommendation: weak

- Clinical

- SR may be a symptomatic, cause intermittet dysphagia for solids, or obstruction of a food bolus.
 - Dysphagia usually occurs when the aperture in the ring is small, ≤ 13 mm diameter
- Associated with
 - Gastroesophageal reflux disease (GERD)
 - Eosinophilic esophagitis (EoE): consider taking 4-quadrant lower, mid, upper esophageal mucosal biopsies.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - Offer a single dilatation session using graded dilatation to a relatively large diameter (16–20 mm) to treat dysphagia related to Schatzki's ring (GRADE of evidence: moderate; strength of recommendation: strong).

- Treatment

Recommendations

- PPI for associated GER-associated the esophagitis/EoE
 - If symptoms persist
 - Single dilation to 16-20 mm
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - SR may recur after dilation
 - Use PPIs to ↓ recurrence after dilation
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - ↓
 - Electrosurgical excision or
 - GRADE of evidence: high
 - Strength of recommendation: strong
 - Endoscopic obliteration of SR using jumbo biopsy forceps (4 longitudinal incisions with needle-knife papillotome plus 5 mm cutting wire), or
 - Endoscopic submucosal dissection (ESD) needle knife at experienced centres
 - GRADE of evidence: very low
 - Strength of recommendation: weak



- Do **not** treat an asymptomatic and incidentally discovered SR.
 - GRADE of evidence: low
 - Strength of recommendation: strong
- Take distal, mid and proximal esophageal mucosal biopsies to exclude EoE.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Treat symptomatic SR with three progressive increments in size of dilation, with repeated sessions until reaching 16-20 mm diameter.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Give PPI after dilation of SR
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Electrosurgical incision may also be used to treat SR.
 - GRADE of evidence: high
 - Strength of recommendation: strong

❖ Post-endoscopic Therapy Strictures

- Post-endoscopic mucosal resection (PEMR) or post endoscopic submucosal dissection (PESD)

➤ Treatment

Recommendations

- Inform patients when obtaining consent to have either EMR/ESD that there is a 50% chance of developing asymptomatic stricture if
 - Size of respected site > 75% of circumference of the esophagus
 - Length of resection > 40 mm
 - GRADE of evidence: high
 - Strength of recommendation: strong
- These post mucosal resection strictures may be treated by dilation
 - Savary/balloon dilation
 - Median number of dilations required: 33% required 5 endoscopic dilations, placement of stent, or incision therapy
 - Inform patients of 1.1% risk of perforation
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - Endoscopic balloon dilation
 - Treatment success rate, 90%
 - May be used to ↓ risk of stricture formation (prophylactic/preventive): after the endoscopic resection, repeat dilation q1wk until the mucosal defect has healed.
 - Prophylactic dilation
 - ↓ median number of strictures from 92% to 59%
 - ↓ number of days for structure to resolve, from 48 d to 29 d
 - ↓ sensitivity of stricture



- Offer dilation for the management of post mucosal resection strictures
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Inform patients having a post-endoscopic stricture dilation that the rate of perforation is up to approximately 1%.
- Offer fully covered self-expanding metal stents (SEMS) in carefully selected patients for the dilation of strictures after endoscopic resection (ER).
 - GRADE of evidence: low
 - Strength of recommendation: weak
- Prevention of post-ER stricture
 - To ↓ risk of development of post-ER stricture
 - Consider using
 - PPIs
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - Corticosteroids po or at injection site after large EMR or ESD
 - GRADE of evidence: moderate
 - Strength of recommendation: weak
 - Benefit of corticosteroids
 - ↓ number of required dilation sessions
 - Endoscopic intralesional injections of steroids are applied based on the concept that inflammation and fibrosis after esophageal ER are inhibited by the direct administration of steroids to the resection site.
 - Fully covered metal stents self-expandable stents (SEMS)
 - Offer fully covered SEMS in carefully selected patients for the prevention of refractory strictures after ESD of large lesion placing the stent at the same time as the first stricture dilation.
 - GRADE of evidence: moderate
 - Strength of recommendation: weak
 - There is a possible benefit of placing sheets impregnated with polyglycolic acid (PGA) in the area of ESD to promote tissue repair/healing.
- Post Ablative Therapy
 - Photodynamic therapy (PDT)
 - No longer advocated, because of ↑ risk of photosensitivity
 - Strictures
 - Inform patients that stricture formation requiring dilatation is significantly higher in the following situations.
 - After photodynamic therapy (PDT) (36%) compared with other forms of ablation
 - Where ER has preceded ablation (12% vs 6%)
 - With use of higher doses of energy with RFA for Barrett's esophagus (BE); and
 - After RFA for early squamous cell neoplasia (14–23%).
 - GRADE of evidence: moderate
 - Strength of recommendation: strong



Recommendations

- Give PPI after RFA to ↓ risk of stricture
 - GRADE of evidence: low
 - Strength of recommendation: strong).
- Radiofrequency ablation (RFA)
 - Adjunctive therapy for Barrett's esophagus (BE)
 - Endoscopic resection plus RFA
 - Ablation depth is 500 µm → ↓ strictures
- Inform patient when treatment causes ↑ rates of esophageal strictures
 - PDT, 36%
 - ER before RFA 12% to 6%
 - ↑ doses of every use of RFA for BE → ↑ risk of strictures
 - After RFA for each SCC, 14-23%
 - GRADE of evidence: low
 - Strength of recommendation: weak
- Dilate strictures from RFA (even if ER before RFA)
 - GRADE of evidence: moderate
 - Strength of recommendation: strong

❖ Eosinophilic Esophagitis (EoE)

➤ Demography

- Commonest cause of
 - Esophageal obstruction
 - Spontaneous perforation
- Second most common cause of benign disease of the esophagus

➤ Treatment

Recommendations

- Treatment includes
 - Topical corticosteroids (CS)
 - Elimination diet
 - Esophageal dilation
 - Offer dilatation along with other forms of disease modification using diet, topical CS or other drugs (GRADE of evidence: moderate; strength of recommendation: strong).
 - Start CS/diet therapy before dilation
 - Start other treatments for eosinophilic oesophagitis (EoE) before dilatation if possible.
 - Those may be continued afterwards to prevent or delay recurrence of symptoms
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - The most cost effective (US) is topical corticosteroids (CS), followed by dilation
 - GRADE of evidence: moderate
 - Strength of recommendation: strong



- Show caution when the EoE-associated structure is < 7 mm calibre
- Use dilation initially before CS or diet therapy for acute symptoms such as food bolus obstruction and daily dysphagia.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Offer dilatation to patients with established tight stricture, narrow calibre esophagus and those who do **not** respond to diet or drugs
 - GRADE of evidence: high
 - Strength of recommendation: strong
- Use intralesional steroid therapy combined with dilatation in refractory strictures with evidence of inflammation (macro- or microscopically) on the assumption that anti-reflux therapy has been maximised previously with no benefit
 - GRADE of evidence: high
 - Strength of recommendation: strong).
- Food bolus obstruction
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
- Tight/ narrow stricture esophagus
- Inform patients having esophageal dilation
 - Mucosal tear, perforation, and bleeding are no more common than with other causes of benign strictures.
 - Reassure patients that dilatation of EoE is no more dangerous than dilatation for other esophageal diseases, and the perforation rates are similar
 - GRADE of evidence: high
 - Strength of recommendation: strong
 - Chest pain is common after dilation for EoE and may last for up to 48 h
 - GRADE of evidence: high
 - Strength of recommendation: strong
- Perform dilations cautiously, “start low, go slow”: q3-4wk, gradually ↑size of dilation until reaching 16-18 mm.
 - Symptom response after initial dilations usually lasts ~ 1 yr
 - GRADE of evidence: moderate
 - Strength of recommendation: strong)
 - Repeat dilation as needed
 - GRADE of evidence: high
 - Strength of recommendation: strong
 - Maintain dilation q6-12wk
- EGD is only 25% sensitive to detect narrowing of the esophagus to ≤ 15 mm
 - It would be helpful in the treatment of EoE to be able to better target esophageal compliance.
 - This can be attempted using
 - Balloon pull-through
 - Endoscopic Functional Luminal Imaging Probe (EndoFLIP) where available
 - GRADE of evidence: low
 - Strength of recommendation: weak
 - These measures of length and tightness are also useful to optimize fundoplication



- Post-operative strictures

- Common causes of post-operative dysphagia/strictures:

- Cancer
 - Esophagus, stomach
 - Esophagectomy plus esophagogastrostomy, 4% to 66%
- GERD
 - Fundoplication 5% to 45%

- Imaging

- Patients with post-operative dysphagia, consideration for dilation or repeat surgery
 - Barium swallow
 - EGD
 - pH study
 - Manometry
 - Consider performing upper GI endoscopy, manometry, pH studies and barium swallow first in patients with post-fundoplication dysphagia, to understand the mechanism of dysphagia before dilatation or repeat surgery (GRADE of evidence: low; strength of recommendation: weak).
- Choices of methods

- Bougienage - Balloon dilation	}	▪ visualization by EGD and fluoroscopy	→ requires dilation to 30-40 mm
- First dilation
 - Benefit in ~45%
 - Repeat dilation may be required, and be successful in ~ 66%
 - Patient resistant to adequate/repeated dilation 30-40 mm may require surgical treatment for associated slower gastric emptying, for example using pyloroplasty or pyloromyotomy
 - Consider treatment of concurrent delayed gastric emptying in order to reduce the need for redilations.
 - GRADE of evidence: low
 - Strength of recommendation: weak
- In patients with post-Nissen plication, use balloon dilation up to 30-40 mm Hg.
 - GRADE of evidence: low
 - Strength of recommendation: weak

- Supplementary methods of treating postoperative strictures

- Injection of corticosteroids not proven to be useful in this setting, but is a guideline recommendation
 - GRADE of evidence: moderate
 - Strength of recommendation: weak
- Alternative to steroid injection is endoscopic needle knife incision (ENKI)

	Maintenance of luminal potency at 12 mon
- Endoscopic needle knife incision (ENKI)	62%
- Endoscopic balloon dilation (EBD)	20%



- Post-radiation strictures

- Tumour risk factors
 - ↑ invasion (T score)
 - ↑ circumference
 - ↑ doses of radiation
- Ischemia, fibrosis/stenosis of esophagus and alterations in mediastinum
- Endoscopic CARD (combined antegrade and retrograde dilation, under general anesthesia if esophagus obstructed)

Recommendations

- Consider a combined antegrade and retrograde dilatation (CARD) or rendezvous approach under general anaesthetic [using guidance under fluoroscopic control] as an alternative to surgery in treatment of the completely obstructed oesophagus, where local expertise is available (GRADE of evidence: moderate; strength of recommendation: weak).
- Use a guidewire to navigate through the obstruction when using the CARD approach to re-establish luminal patency (GRADE of evidence: low; strength of recommendation: strong).
 - After gaining luminal patency using the CARD procedure, perform subsequent dilatation using either balloon or bougie (GRADE of evidence: moderate; strength of recommendation: strong).
- Perforation rate 0.4% to 32%
 - Dilatation may be necessary, but preferably do after 3 wk, and at intervals between dilations of < 2 wk
 - Consider avoiding dilatation within 3 wk of initial caustic ingestion.
 - GRADE of evidence: low
 - Strength of recommendation: weak
 - Consider a time interval between dilatations of < 2 wk
 - GRADE of evidence: very low
 - Strength of recommendation: weak
- Caustic strictures
 - Perform EGD with CO₂ insufflation within 12-48 h after CT scan.
 - GRADE of evidence: moderate
 - Strength of recommendation: strong
 - Do **not** do EGD with known or suspected caustic stricture to assess damage or need for treatment, if suspected
 - Burn to supraglottic, or
 - Perforation of esophagus
 - Perform upper GI endoscopy, manometry, pH studies and barium swallow first in patients with post-fundoplication dysphagia, to understand the mechanism of dysphagia before dilatation or repeat surgery.
 - GRADE of evidence: low
 - Strength of recommendation: weak



- Refractory strictures
- Definition
 - A stricture is refractory if an “...inability to maintain a luminal diameter of ≥ 14 mm after five sequential dilation sessions 1-2 wk apart or maintain the target diameter for 4 wk once it has been reached”.
- Common causes
 - Complex structures
 - Long, > 2 cm
 - Very narrow
 - Irregular, angulated
- Stents
 - 40% of refractory strictures respond to the insertion of self-expanding metal stents (SEMS), with the intention to remove stents within 4 to 8 wk
 - Offer temporary placement of fully covered self-expanding removable stents in patients where previous methods have been unsuccessful in maintaining adequate oesophageal patency.
 - GRADE of evidence: low
 - Strength of recommendation: weak
 - The optimum duration of stent placement is usually between 4 to 8 wk, but may vary depending on stricture aetiology and length, and type of stent
 - GRADE of evidence: very low
 - Strength of recommendation: weak
 - Do **not** leave stent for longer than 4 to 8 wk
 - GRADE of evidence: very low
 - Strength of recommendation: weak
 - After the beneficial response of refractory structures to the first stenting, $\sim 70\%$ recur, especially for long strictures.
 - Stent migration occurs in 30%, and the other complications in 20%, such as
 - Aspiration
 - Bleeding
 - Perforation
 - Pneumonia
 - Metal stents have fewer complications than do plastic stents.
 - Do **not** use partially/uncovered metal stents ($\uparrow$ risk of becoming embedded in the wall of the esophagus).
 - Placement of biodegradable stems may be useful short-term in patients with refractory strictures $\rightarrow \downarrow$ frequency of required dilations.
 - GRADE of evidence: low
 - Strength of recommendation: weak



- Selected, trained patients may benefit with self-dilation of short, proximal strictures.
 - GRADE of evidence: very low
 - Strength of recommendation: weak
- When all else fails, consider the benefits of the surgical approach.
 - GRADE of evidence: low
 - Strength of recommendation: weak
- Quality control: suggested audit of effectiveness
 - Use a standard scoring system in > 90% of patients
 - Fully completed consent forms (BSG guidelines Shepherd H and Hewwette D, 2016)
 - Symptom relief/comfort
 - Complications, readmissions, mortality
 - Follow-up dilations within 2 wk
 - Perforation ratio of strictures
 - Benign <1%
 - Malignant 1-2%

Abbreviations: AGREE, Appraisal of Guidelines for Research and Evaluation; BE, Barrett's esophagus; BSG, British Society of Gastroenterology; CARD, combined antegrade and retrograde dilation; CI, confidence interval; CO₂, carbon dioxide; CR, computed tomography; CS, corticosteroids; CT, computed tomography; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ENKI, endoscopic needle knife incision; EoE, eosinophilic esophagus; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; F, French; GDG, Guideline Development Group; GRADE, Grading of Recommendations Assessment Development and Evaluation; H2RA, histamine-2 receptor antagonist; h, hour; LES, lower esophageal sphincter; mon, month; NICE, National Institute for Health and Care Excellence; PD, pneumatic dilation; PDT, photodynamic therapy; PEMR, post-endoscopic mucosal resection; PESD, post-endoscopic submucosal dissection; PPI, proton pump inhibitor; RFA, radiofrequency ablation; SCC, squamous cell cancer; SR, Schatzki ring; TTS, through the scope; UES, upper esophageal sphincter; US, United States; wk, week; yr, year



DISORDERS OF ESOPHAGEAL MOTILITY

Achalasia: ACG Guidelines (2020)

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

- Demography
 - Incidence, $\sim 1/10^5$ persons per yr
 - Prevalence, $\sim 10/10^5$ persons
 - Peak incidence, 30 to 60 yr
- Pathophysiology
 - Idiopathic, but likely immune-mediated disorder of the lower esophagus and sphincter (LES) → loss of inhibitory neurons in the myenteric plexus (inhibitory > excitatory) / ↓VIP, ↓NO → unopposed activity of excitatory neurons releasing Ach → neuronal imbalance of excitatory neuronal activity >> inhibitory neuronal activity → failure to relaxation of LES.
- Clinical
 - Dysphagia
 - Heartburn ($\sim 30\%$), regurgitation
 - Non-cardiac chest pain (NCCP) / chest discomfort
 - ↓ body weight / nutritional deficiencies
 - Because a high proportion of persons who have achalasia have heartburn and are initially misdiagnosed as having GERD, the guidelines suggest that "...persons who are initially suspected of having GERD but do **not** respond to acid-suppressive therapy should be evaluated for achalasia (GRADE quality very low, recommendations strength strong).
 - Achalasia must be suspected in those with dysphagia to liquids or to solids, and in those with regurgitation unresponsive to an adequate trial of proton pump inhibitor (PPI) therapy (strong recommendation, low-quality evidence).



- Diagnostic imaging
 - Barium swallow
 - “Bird peak” lower esophagus (gastroesophageal area, failure of relaxation of LES → distortion of shape)
 - Retained barium in proximal body of esophagus
 - The diagnosis of achalasia is supported by barium esophagram findings, including
 - Dilation of esophagus
 - Retention of food/fluids
 - A narrow esophagogastric junction with “bird beak” appearance
 - Aperistalsis, and
 - Poor emptying of barium

(Strong recommendation, moderate quality evidence).
 - Barium esophagram is recommended to assess esophageal emptying and esophagogastric junction morphology in those with equivocal motility testing (strong recommendation, low quality evidence).
 - Dilation of esophagus
 - Timed barium esophagram
 - ↑ time for esophageal emptying of barium, or ↑ height of barium column at a fixed time after intake of barium
 - May be useful to use one of these parameters to assess adequacy of treatment

Abbreviations: Ach, acetylcholine; EGD, esophagogastroduodenoscopy; LES, lower esophageal pressure; NCCP, non-cardiac chest pain; NO, nitric oxide; POEM, peroral endoscopic myotomy; VIP, vasoactive intestinal peptide

- Endoscopy
 - Assessment of gastroesophageal junction (GEJ, aka esophagogastric junction [EGJ]) and gastric cardia is recommended in all patients with achalasia to rule out pseudoachalasia (strong recommendation, moderate quality evidence)
 - The commonest cause of pseudoachalasia is adenocarcinoma of the gastric cardia / GEJ, which is best visualized by EGD and retroflexion of the endoscope, with biopsies as necessary
 - Retained saliva
 - Puckering of EGJ



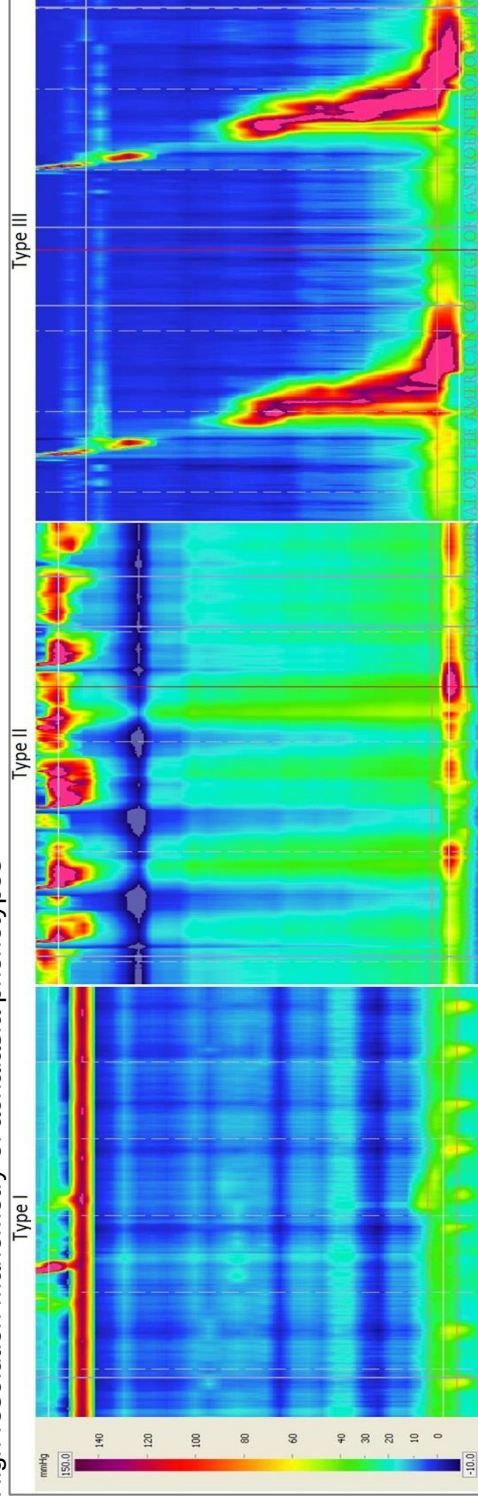
❖ High Resolution Systems

• High-resolution esophageal manometry (HREM)

- Compared with the now outdated conventional manometry of the esophagus
 - ↑ accuracy / ↑ reproducibility to diagnose achalasia
 - Possibility to classify subtypes of achalasia, which helps to guide therapy, and to predict response
 - Better description of esophageal pressure contractile pattern.



High resolution manometry of achalasia phenotypes



Type I-absent pressurization (left)
 Type II-pan pressurization (middle), and
 Type III-spastic contractions (right).

Lower esophageal sphincter relaxation is impaired for all subtypes.

Printed with permission: Vaezi, MF, et al. Am J Gastroenterol 2020;115(9):1393-1411. (Figure 2)

- All patients with suspected achalasia who do **not** have evidence of a mechanical obstruction on endoscopy or esophagram should undergo esophageal motility testing before a diagnosis of achalasia can be confirmed (strong recommendation, low-quality evidence).



➤ Diagnosis

- In patient with suspected achalasia, perform barium swallow (esophagram) or esophago-gastroduodenoscopy (EGD) to exclude a mechanical cause of esophageal obstruction.
- If there is no evidence of a mechanical cause of esophageal obstruction, perform an esophageal motility study.
- Esophagram findings suggestive of achalasia
 - Body
 - Aperistalsis
 - Dilation
 - Retention of food/liquid
 - Esophagogastric junction (EGJ)
 - Narrowing (“bird-beak appearance”)
 - Slow emptying of barium from the esophagus / ↑ height of barium column in esophagus
 - Retained food
 - May be especially useful in patients with equivocal motility testing
- Esophagogastroduodenoscopy (EGD)
 - Essential to carefully to inspect GEJ / gastric cardia for a cancer which may cause “pseudoachalasia”
- Use high resolution manometry (HRM) rather than conventional manometry to diagnose achalasia, because of
 - ↑ accuracy and reproducibility
 - Better description of esophageal pressurization and contractile patterns, and
 - Capability to subclassify the subtypes of achalasia, and thereby to help guide therapy and to predict progression prognosis.
- High-resolution impedance system (functional lumen imaging probe [FLIP]) to assess
 - Assesses cross-sectional area
 - Pressure (distensibility)
 - Benefits to
 - Assesses opening dynamics of EGJ
 - FLIP is performed at EGD in sedated patient.
 - Allows calculation of EGJ distensibility index (prognostic indicator of poor EGJ opening when > 0.3 mm / mm Hg)
 - High agreement with conventional manometry, but also may help diagnose achalasia when classical manometry (CM) is equivocal.

➤ Classification

- ↓ relaxation of LES plus
 - Aperistalsis (100% failed peristalsis),
 - No panesophageal pressurization (< 30 mm Hg)
 - Panesophageal pressurization (> 30 mm Hg)
 - Splastic contractions
- | | |
|----------|------|
| Type I | 30% |
| Type II | ~65% |
| Type III | < 5% |



- Type II achalasia, the most common subtype, has good short and longer outcomes, regardless of the type of treatment used.
- Surgery is superior to other forms of therapy (e.g., pneumatic dilation or pharmacotherapy) for achalasia type I and III.
 - Type III achalasia has a high response rate to POEM (more extensive myotomy) (98%) compared to Heller myotomy (80%)

➤ Treatment

• Pharmacotherapy

- Mode of action
 - Relaxation of smooth muscle of esophagus, especially area of EGJ → relaxation of the non-relaxed LES
- Oral
 - Nifedipine (calcium channel blocker [CCB]), 10 to 30 mg sublingual (SL) before meals (AC) → ↓ Ca^{2+}_i (intracellular calcium)
 - Isosorbide dinitrate 5 mg SL AC → Nitric oxide (NO)
 - Also use
 - Anticholinergics (atropine)
 - B-adrenergic agonist (terbutaline)
 - Bronchodilator (theophylline)
 - Phosphodiesterase inhibitor (Sildenafil)

Relaxation of smooth muscle of esophagus, especially area of EGJ and produces relaxation of the non-relaxed LES

Abbreviations: AC, before meals; Ca^{2+}_i , intracellular calcium; CCB calcium channel blocker; NO, nitric oxide; PBD, pneumatic balloon dilation; SL, sublingual

- Endoscopic botulinum toxin injection (EBTI is presynaptic inhibitor of release of Ach from excitatory nerve endings on the myenteric complex of distal esophagus and LES) →
 - Cleaves SNAP-25 protein →
 - ↓ Ach-containing presynaptic vesicles coming into contact with membrane of neuron → ↓ LES pressure ~50%
 - No direct effect on smooth muscle of LES.
 - Response, mon

3	70%	} ▪ Additional botulinum injections required in ~45%
6	~50%	
12	~40%	
 - Botulinum toxin causes scarring at injection site
 - ↓ benefit over time

Therapeutic Tip

- Previous use of botulinum toxin injections does **not** “...significantly affect performance and outcome of myotomy”, or to ↑ rate of complications from surgery.



- For patients who are not fit for surgical therapy for achalasia, and therefore also those who would not be suitable for pneumatic dilation and the risk of perforation of the esophagus for which the patient might not be sufficiently fit to undergo surgical repair of the perforation
 - Botulinum toxin injection would be useful.

❖ Pneumatic Balloon Dilation (PBD)

Therapeutic Tips

- All patients considered for PBD must be possible candidates for surgery in the event of esophageal perforation needing repairs” (which is reported in ~2%)
- Balloon dilators
 - Polyethylene balloons size 3.0, 3.5 and 4.0 are used in graded fashion and are distended to 10 to 15 psi (pounds per square inch) of air for 15 to 60 sec (reassess at 4 to 6 wk after initial dilation).

- Cumulative benefit (good to excellent symptom relief) at follow-up of ~1.6 yr.

Dilator diameter, cm	Benefits
3.5	86%
4.0	90%

- Predictors of good response to pneumatic balloon dilation (PBD)
 - Patient
 - Females
 - Age, > 45 yr
 - Esophagus
 - Non dilated
 - LES pressure after PBD < 10 mm Hg
- It is recommended that young men (< 45 yr) should start PBD with pneumatic balloon size 3.5 cm (rather than 3.0 cm for all other patient profiles including young women), ... in addition to laparoscopic Heller myotomy (LHM) or per oral endoscopic myotomy [POEM]”.
- Complications
 - Perforation 2%
 - Failure to sustain success of treatment
 - Because of ↓ LES pressure with PBD → ↑ risk of GERD → peptic strictures
- Despite of ↑ risk of esophageal perforation (~2%) with PBD, there is “...minimal data to support the routine post-PBD performance of a gastrografin esophagram
 - Of course, it is appropriate to investigate a suspected PBD esophageal perforation.



- Myotomy

- Division of inner circular muscle fibers in LES
- Surgical myotomy

	Good Outcome
– Transthoracic, open	83%
– Transabdominal, open	85%
– Laparoscopic Heller myotomy (LHM)	6 mon, 89% 6 yr, 57% Best for Type I, 80% Type II, 92% Less for III, 71%

- Post-myotomy fundoplication

- Every post-surgical myotomy associated GERD

	With Fundoplication	
	No	Yes
▪ Thoracotomy	29%	14%
▪ Laparostomy	28%	8%
▪ Thoracoscopy	28%	
▪ Laparoscopy	31%	9%
– Risk		
▪ Abnormal acid exposure	47%	9%
▪ ↑ distal H ⁺ exposure		
▪ POEM laparoscopic myotomy plus fundoplication	39%	~11%

- When myotomy is performed for achalasia, a fundoplication should be performed at the same time to ↓ abnormal acid exposure post-myotomy, thus ↓ risk of GERD-associated complications such as peptic strictures.
 - Both the Dor anterior and the Toupet posterior fundoplications are appropriate and equivalent in terms of ↓ acid exposure, ↓ development of dysphagia, the need for reintervention/hospitalization LOS, and patient quality of life.

➤ Treatment

- The choice of initial therapy should be guided by the patients' age, sex, preference, and local institutional expertise (weak recommendation, low-quality evidence).
- Initial therapy
 - Good surgical candidates, high-volume centre of excellence
 - Laparoscopic surgery myotomy (Heller procedure), plus partial fundoplication, or
 - Graded pneumatic dilation
 - If not a candidate for definitive therapy, as mentioned above, consider
 - EGD guided repeated injection of botulinum
 - Pharmacotherapy
 - Calcium channel blocker, long-acting nitrate



- Follow up
 - Symptom assessment
 - Consider esophagram (time to empty esophagus of a fixed amount of barium, or measured height of esophageal luminal column of barium)
 - Surveillance EGD for known ↑ risk of esophageal cancer (ECA)
 - Not recommended
- Peroral Endoscopic Myotomy (POEM)
 - Procedure
 - Natural orifice transmural endoscopic surgery (NOTES) used to perform the myotomy submucosal plane, circular muscle fibers → myotomy, using endoscopic submucosal dissection before the muscle cut ≥ 6 cm into esophagus plus 2 cm below squamocolumnar junction (SCJ).
 - Benefit
 - “...improvement in symptoms and requirement of additional or surgical treatment > 90% best for achalasia (type I, II, and III, which does not respond as well to surgery, such as laparoscopic Heller myotomy (LHM) or PBD.
 - Type III
 - Benefit
 - LHM, 71%
 - POEM, 93%
 - RR, 3.5, 95% CI, 1.39-8.77, P = 0.001
 - Clinical response, 98% vs. 80%
 - Weighted clinical success, 92%
 - Adverse events 11%
 - But more GERD, and
 - ↑ esophageal acid exposure, 39% vs. 17%
- Post POEM GERD
 - Use tailored POEM or LHM for type III achalasia “...as a more efficacious disruptive therapy for LES compared with pneumatic dilation (PD).”
 - Editor's note
 - Given the strength of the evidence for POEM for type III rather than LHM, it is surprising that this recommendation was not made.
 - Note that the above recommendations do **not** necessarily apply to end stage achalasia (please see following section).



- POEM is associated with less development of GERD as compared with LHM plus fundoplication or PBD.
 - Editors note
 - The following was surprisingly not in the guideline as a recommendation with regards to GERD after POEM, but was not stated.
 - “It may be prudent to screen [by EGD] patients who undergo POEM for erosive esophagitis or Barrett’s esophagus....” or
 - “...patients who are contemplating POEM should be advised that lifelong acid suppression with PPI may potentially be needed.”
- Esophagostomy
 - May be indicated for end-stage achalasia
 - Megaesophagus
 - Tortuous “sigmoid-shaped” esophagus

}

↑ risk of

 - Aspiration
 - Pneumonia
 - Malnutrition
 - Periprocedure complications
 - Esophagectomy is associated with ↑ risk of respiratory complications (10%) as well as mortality rate of 2% “... [even] at highly specialized surgical centres”.
 - Esophagectomy is recommended in “....surgically fit patients with megaesophagus who have failed other interventions”.
- Self-expanding Metallic Stents (SEMS)
 - SEMS have better 5-yr clinical response vs. botulinum toxin injection (~50% vs. 4%), but is associated with more chest pain and regurgitation.
 - SEMS is considered to be only “a temporary measure”, and is **not** recommended for the management of long-term dysphagia in patients with achalasia.”

Recommendations

- Initial treatment in patients fit willing to have surgery, pneumatic dilation (PD), or laparoscopic surgical myotomy (LSM).
 - Either graded pneumatic dilation (PD) or LSM with a partial fundoplication are recommended as initial therapy for the treatment of achalasia in those who are fit and willing to undergo surgery (strong recommendation, moderate quality evidence).
- Perform PD or LSM only in centres of excellence.
 - PD and surgical myotomy should be performed in high volume centres of excellence (strong recommendation, low quality evidence).
- Decide between PD versus LSM on the basis of patient age, gender, preference, hospital expertise.
 - The choice of initial therapy should be guided by the patients’ age, sex, preference, and local institutional expertise (weak recommendation, low quality evidence).



- For patients who are not candidates for PD or LSM, use
 - Botulinum toxin injection (BTI)
 - BTI is recommended in patients who are not good candidates for more definitive therapy with PD or surgical myotomy (strong recommendation, moderate quality evidence).
 - If not candidates for PD or LSM, and who have failed BTI,
 - Give pharmacological therapy
 - Pharmacologic therapy for achalasia is recommended for patients who are unwilling or cannot undergo definitive treatment with either PD or surgical myotomy, and who have failed botulinum toxin (strong recommendation, low quality evidence).
- Provide follow-up for patient response to treatment
 - Symptom relief
 - ↑ esophageal emptying
 - Barium pill test
 - Follow up after therapy may include assessment of both symptom relief and esophageal emptying by barium esophagram (strong recommendation, low quality evidence).
- Surveillance endoscopy for esophageal cancer is not recommended (strong recommendation, low quality evidence).

➤ Comparison of therapeutic modalities

- Taking into account the wishes of the patient, their surgical risk, the subtype of possible presence of end-stage achalasia, and the costs, the following is an approximation of the results of comparative studies.

Surgery (POEM = LHM) = PBD > EBTI > Rx

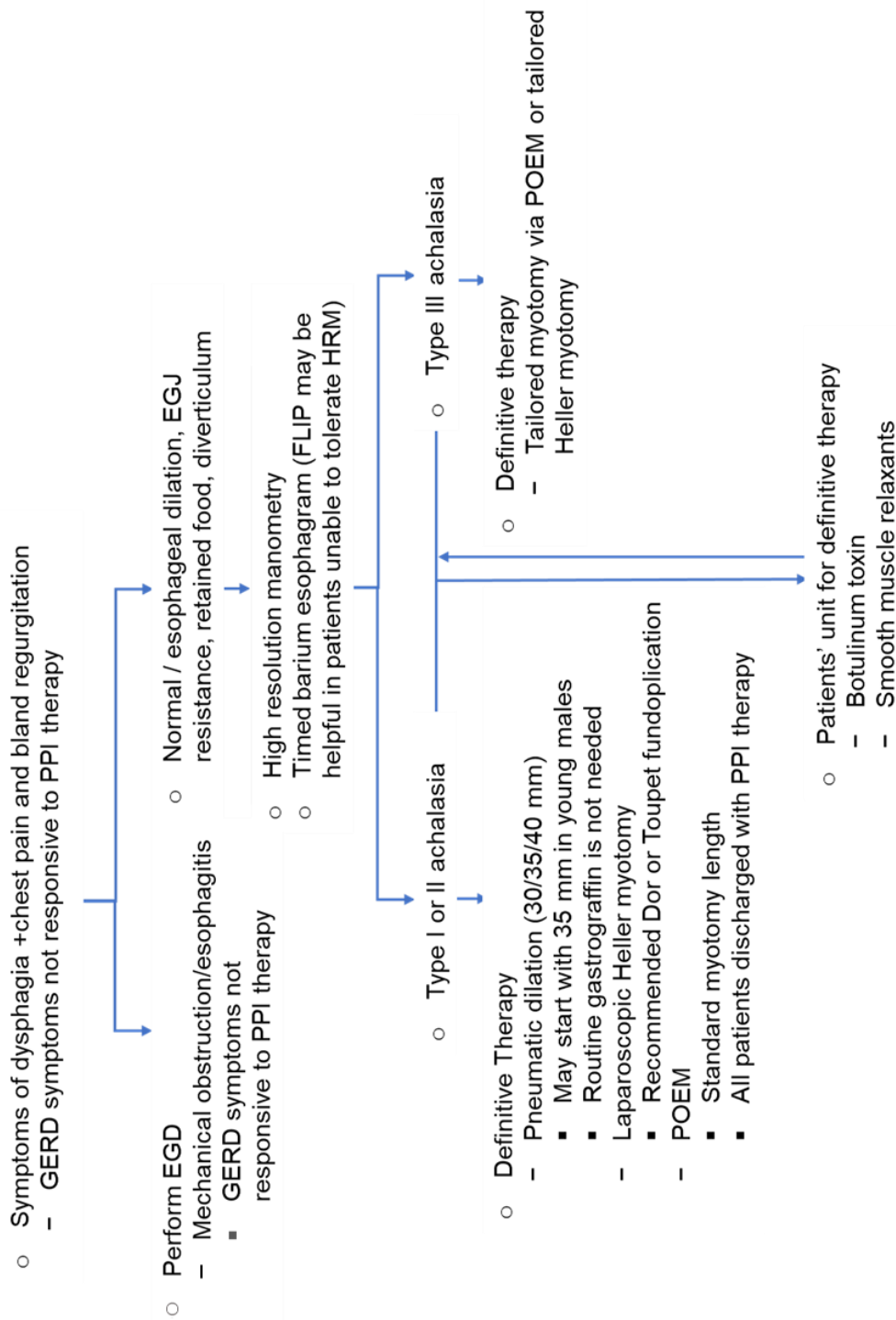
- Recall that botulinum toxin injection (EBTI) can be performed if patient is not a surgical risk, and is not suitable for LHM, POEM, or PBD.
 - EGD may be necessary to determine if symptoms relate in part to associated GERD esophagitis, and therefore the need for PPI therapy.

Abbreviations: EBTI, endoscopic botulinum toxin injection; FLIP, functional limited image probe; LHM, laparoscopic Heller myotomy; PBD, pneumatic balloon dilation; POEM, peroral endoscopic myotomy; Rx, pharmacotherapy





Diagnostic and Treatment Algorithm for Patients with Suspected Achalasia.



Abbreviations: FLIP, functional lumen imaging probe; GERD, gastroesophageal reflux disease; HRM, high resolution manometry; PPI, proton pump inhibitor.

Printed with permission: Vaezi, MF, et al. Am J Gastroenterol 2020;115(9):1393-1411. (Figure 8)



- Post-therapy Assessment
 - Symptoms
 - Eckardt score (ES)
 - Focus on patient's dysphagia, chest pain, regurgitation, weight loss
 - Not sufficient to follow treatment success or to define failures
 - Patient reported outcome (PRO)
 - Encouraged by FDA to be developed and used in this setting
 - High resolution manometry
 - Good to assess
 - The completeness of myotomy (to determine if spastic contractions persist)
 - Does not adequately assess
 - Bolus retention (esophageal clearance)
 - Presence of post-treatment GERD
 - Timed barium esophagram (TBE; fluid plus tablet)
 - Good therapeutic outcome after treatment (surgery, PBD) of achalasia
 - Normally, complete emptying of esophagus at 1 min post-ingestion.
 - To evaluate post-therapy (surgery, PBD) of achalasia with continued/recurrent symptoms, use TBE, and not ES or HRM alone.
- Treatment of continued/recurrent symptoms (failed therapy or recurrent disease)
- Failed LHM/POEM → PBD
 - Rate of surgical failure (LHM, POEM) at ≥ 10 yr, 5% to 30%
 - Success rate of PBD after failed LHM, POEM, 89%.
- Failed POEM/PBD → LHM (especially if myotomy was complete)
 - If failed POEM/PBD, attempt LHM before referred for esophagectomy
 - Before referral for esophagectomy, perform barium esophagram, EGD, manometry/FLIP.
- Failed PBD/LHM → POEM
 - If failed LHM
 - POEM gives clinical response of 80% at median follow-up time of 8.5 mon, and 96% at median follow-up time of 28 mon.
- EGD surveillance for esophageal cancer
 - Risk of
 - Squamous cell cancer (SCC), 310/10⁵ patient years at risk (with ↑ risk with ↑age, and need for retreatment)
 - Adenocarcinoma (ACA), 21/10⁵
 - Patients with achalasia may develop metaplasia (Barrett's esophagus)
 - However, do **not** do routine endoscopic surveillance (EGD) for possible esophageal cancer in patients with achalasia, unless there are symptoms to suggest such as complication
 - Note that: "...many experts are in focus of some form of endoscopic or radiographic surveillance in patients with achalasia at an interval of every 3 yr if the disease has been present for more than 10-15 yr".



High Resolution Esophageal Manometry (HREM) and Achalasia Syndromes

Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688.

➤ Demography

- With the use of greater sensitivity of high resolution esophageal manometry (HREM) versus standard manometry, the incidence of achalasia is thought to be $\sim 3/10^5$, with a prevalence of $\sim 30/10^5$
 - Mean age of diagnosis, 56 yr

➤ Treatment

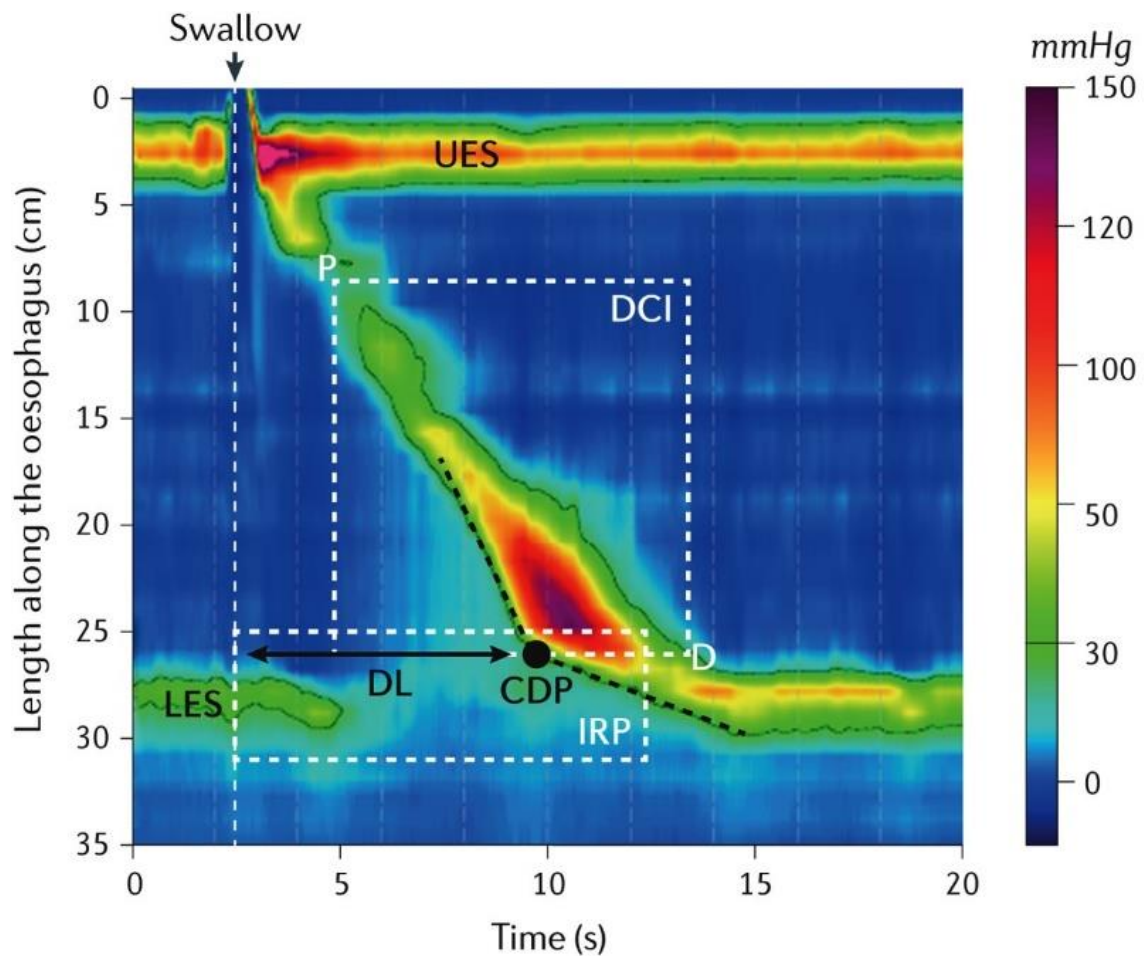
- Give the advantages of per-oral endoscopic myotomy (POEM) for the surgical treatment of achalasia.
 - ↓ morbidity
 - ↑ customization
 - Enables a calibrated intervention that is customized [personalized] to patient-specific physiology

High Resolution Esophageal Manometry (HREM)

➤ Analysis metrics

- “P” is the nadir pressure value (sometimes called the transition zone), separating the first two contractile segments.
- D is the pressure minimum that separates the second two segments, both of which reside in the smooth muscle esophagus, from the lower esophageal sphincter (LES).
- The distal contractile integral (DCI) is a summation of the contractile amplitude in the span from P to D in units of mmHg·s·cm (1,476 mmHg·s·cm in this example, normal value, 450-8000 mmHg·s·cm).
- The contractile deceleration point (CDP) indicating the transition from peristalsis to ampullary emptying that is localized in the distal esophagus by the intersection of the two black dotted tangent lines.
- Distal latency (DL) is measured from upper sphincter relaxation (vertical white dotted line) to the CDP (7.5 s this examples; normal value, > 4.5 sec).
- Esophagogastric junction relaxation is summarized by the integrated relaxation pressure (IRP), which is calculated within the 10 s IRP window beginning with upper sphincter relaxation as the average eSleeve pressure during the 4 s of greatest relaxation (7.8 mmHg in this example; normal value, < 15.0 mmHg; IRP > 15 mmHg indicates EGJ outflow obstruction)
 - The eSleeve is a 'virtual sleeve' placed at the esophogastric junction.





Source: Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688. (Figure 2)

- LES pressure has 3 components
 - EGJ pressure
 - Anatomic crural diaphragm pressure
 - Intrabolus pressure (pressurization as bolus passes through EGJ)
- The metric of EGJ relaxation is the “integrated relaxation pressure” (IRP)
 - IRP > 15 mm Hg defines EGJ outflow obstruction
- HREM measures
 - Esophagogastric junction (EGJ) relaxation
 - HREM does not measure lower esophageal sphincter [LES] relaxation



- Peristalsis

- Distal contractile integral (DCI)

- “DCI integrates the length, vigor and persistence of there the distal esophageal contraction from the pressure minima at the transition zone to the EGJ”
 - This is thought of as 3-dimensions space composed of time in seconds (s), multiplied by the length (cm) of the distal esophageal segment, multiplied by the height of the solid pressure (mmHg.s.cm)
 - Examples of DCI

mm.Hg.cm	Swallows/Peristalsis
> 8000	▪ Hypercontractile
< 450	▪ Weak
< 100	▪ Failed

- Distal latency (DL)

- Premature contractions
 - The interval from upper esophageal sphincter (UES) relaxation to the contractor deceleration point (CDP), the inflection point in the wavefront velocity just proximal to the EGJ.
 - Propagation velocity shows at the CDP
 - $DL < 4.5$ sec defines premature contractions
 - These premature contractions arise from dysfunction of the inhibitory neurons of the esophageal myenteric plexus
 - These premature contractions are the defining characteristics of
 - Distal (diffuse) esophageal spasm (DES)
 - Type III achalasia (Chicago classification)

- Contractile Deceleration Point

SO YOU WANT TO BE A GASTROENTEROLOGIST!

The contractile deceleration point (CDP) is firstly defined as the inflection point in the wavefront velocity just proximal to the EGJ.

- Give the additional components of the definition of the CDP.
 - The CDP must be localized to within 3 cm of the LES, plus
 - If there is compartmentalized pressurization [of the esophagus], the CDP needs to be localized along an isobaric contour time of greater magnitude than the compartmentalized intrabolus pressure.



Management of Esophageal motility disorders: Achalasia Syndromes

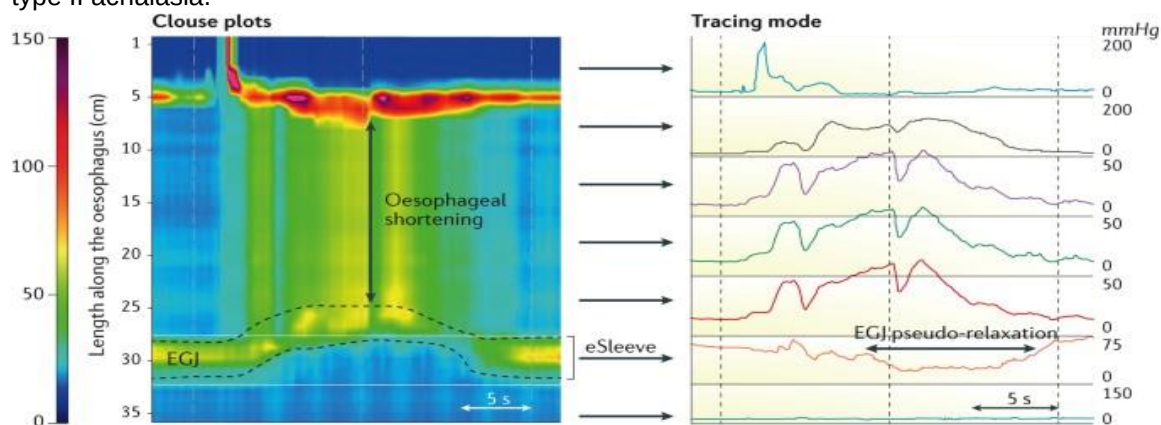
Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688

➤ Definition

- The defining features of achalasia requires both
 - ↓ EGJ relaxation
 - Absent peristalsis
- Give the exceptions
 - Some patients with achalasia have an IRP < 15 mmHg
 - Sometimes there is peristalsis in achalasia
- Note that “absent peristalsis” does not exclude pressurization or contractility (non-peristaltic contractility)
- Absent peristalsis but 3 types of contractility/pressurization
 - No pressurisation
 - Type I (classical achalasia)
 - Panesophageal (uniform pressurization in esophagus from UES to LES, resulting from non-occluding contraction)
 - Type II (most common subtype)
 - Premature spastic contraction in the distal esophagus (↓ intensity; fragments of peristalsis)
 - Type III (spastic)

➤ HREM Subtypes

Pseudorelaxation as a consequence of esophageal shortening after a swallow in a patient with type II achalasia.



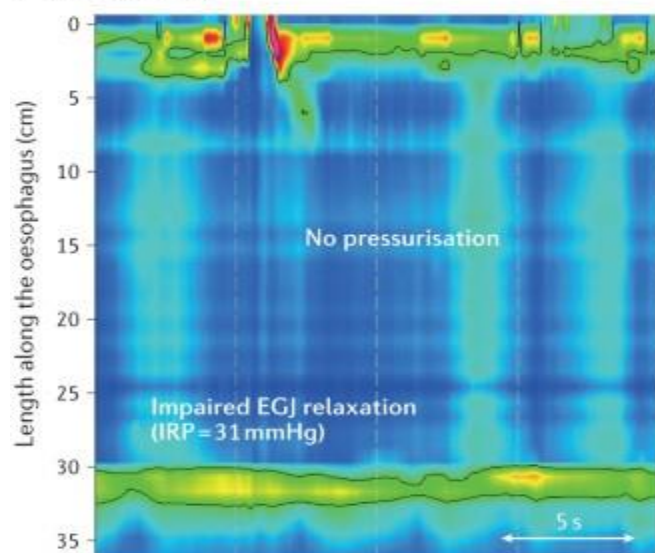
- The dotted lines on the high-resolution manometry (HRM) plot depict the path of the lower esophageal sphincter
 - This takes it above the span of the eSleeve (a 'virtual sleeve' placed at the esophogastric junction) and thereby
 - Simulates relaxation (tracing panel)

Source: Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688. (Figure 1)



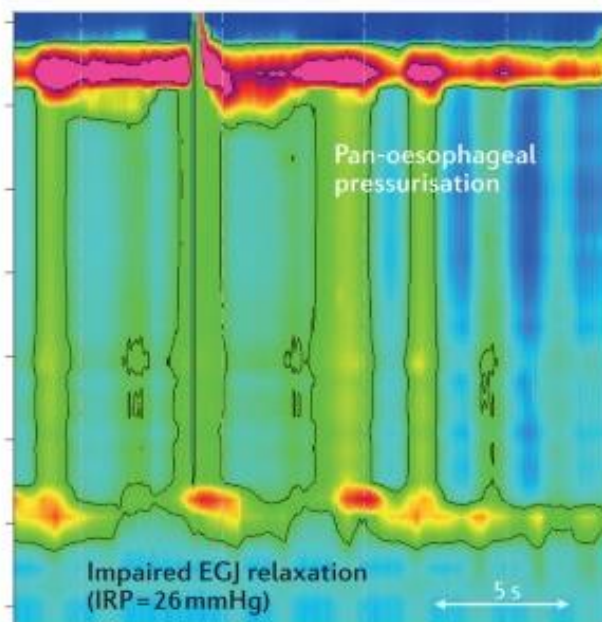
High-resolution manometry of achalasia subtypes (Chicago Classification v 3.0)

a Type I achalasia



- Classic achalasia (type I achalasia)
 - Integrated relaxation pressure (IRP) ≥ 15 mmHg and absent peristalsis without marked pressurization or contractions.

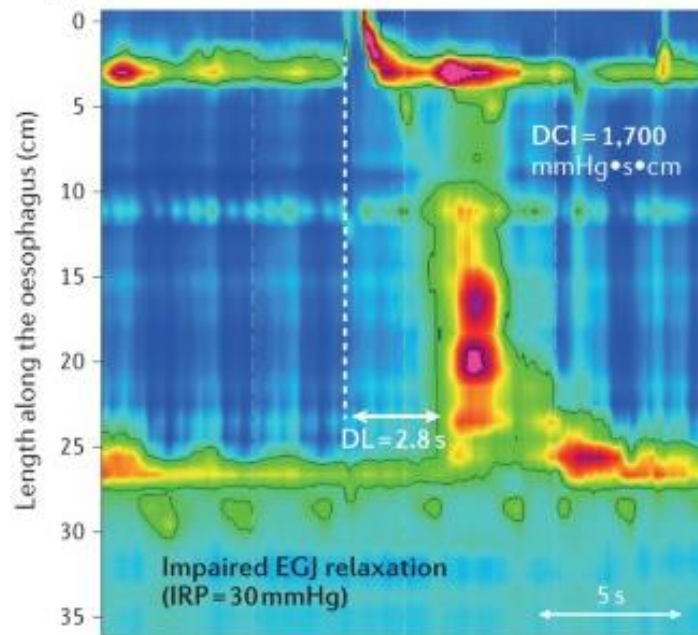
b Type II achalasia



- Achalasia with esophageal pressurization (type II achalasia)
 - IRP ≥ 15 mmHg
 - $\geq 20\%$ of swallows associated with pan-esophageal pressurization to >30 mmHg.

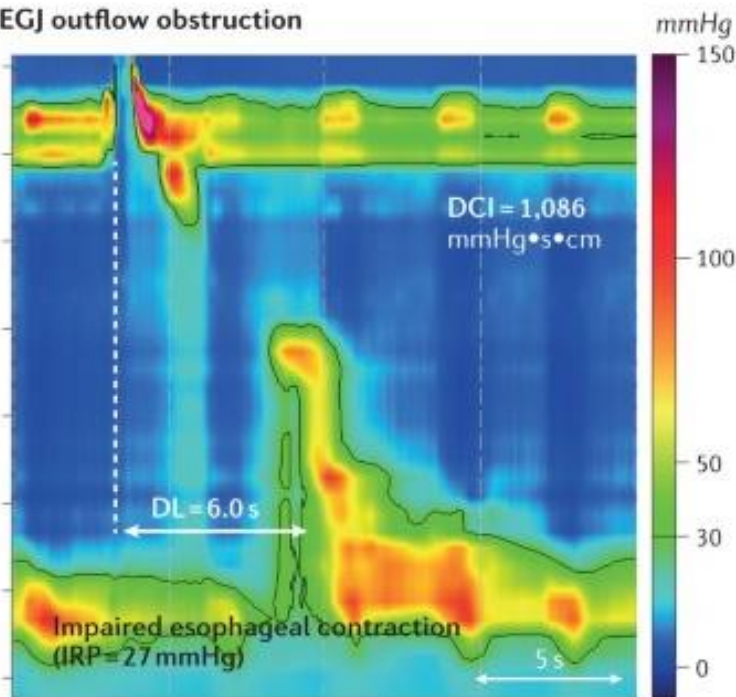


c Type III achalasia



- Spastic achalasia (type III achalasia)
 - IRP ≥ 15 mmHg and
 - A spastic contraction with $\geq 20\%$ of test swallows

d EGJ outflow obstruction



- Esophagogastric junction (EGJ) outflow obstruction treated as achalasia but not meeting diagnostic criteria for achalasia because of preserved fragments of peristalsis. Dashed white lines represent initial upper oesophageal sphincter relaxation DL, distal latency.

Source: Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688. (Figure 3)



SO YOU WANT TO BE A ESOPHAGOLOGIST!

- Give why type II achalasia is commonly known diagnosed/misdiagnosed with conventional manometry.
 - Panesophageal pressurization may be misdiagnosed as spastic contraction
 - Presence of LES pseudo-relaxation during the panesophageal pressurization.
 - ↑ volume, LES moves upwards from contraction of the longitudinal muscles of the esophagus → shortness the length of the esophagus.
 - A sensor placed at the LES at rest may become distal to LES after swallowing, and thereby appear to be relaxed, and causing pseudo-relaxation.

Clinical achalasia syndromes within the Chicago Classification (CC, v3.0)

Subtype	Esophageal contractility	Added criteria
○ Type I	– Absent contractility	-
○ Type II	– Absent peristalsis	Pan-oesophageal pressurization with $\geq 20\%$ of swallows
○ Type III	– Absent peristalsis – Premature contractions with $\geq 20\%$ of swallows	-

Abbreviations: IRP, integrated relaxation pressure; ULN, upper limit of normal

Source: Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688. (Table 1)



❖ Other achalasia syndromes (beyond the CC v3.0)

CC v3.0 diagnosis	IRP > ULN?	Esophageal contractility	Notes
○ Esophagogastric junction (EGJ) outflow obstruction	Yes	– Sufficient peristalsis to exclude type I, II or III achalasia	• Heterogeneous group • Early or incomplete achalasia • Can resolve spontaneously • Recording artefacts
○ Opioid effect (not in CC)	Yes	– Normal, hypercontractile or premature	• Can mimic EGJOO, type III achalasia, DES or jackhammer
○ Mechanical obstruction (not in CC)	Yes	– Absent, normal or hypercontractile	• EUS, CT or MRI of the EGJ might clarify the aetiology
○ Absent contractility	No	– Absent contractility	• Can be achalasia • Abnormal FLIP distensibility index supports achalasia • Oesophageal pressurization with swallows or MRS supports achalasia
○ Distal esophageal spasm	Yes/no	≥20% premature contractions (DL <4.5 sec)	} • Might be confused with spastic achalasia
○ Jackhammer esophagus (JE)	Yes/no	≥20% of swallows with DCI >8,000 mmHg.s.cm	

Source: Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688. (Table 2)

- Normal IRP achalasia
 - Some patients with achalasia do **not** have the definition-required IRP > 15 mmHg
- Give the explanation why IRP is not normally low in some persons with achalasia.
 - When there is no esophageal pressurization, the magnitude of IRP depends only on the contractability of the EGJ.
 - Some patients with achalasia have ↓ pressure of LES, rather than the normal / ↑ LES pressure sometimes seen in a achalasia.



- However, the LES dysfunction in the patients with IRP > 15 mmHg may be demonstrated by
 - Barium swallow, slow transit of pill, rapid drinking EGJ, high resolution impedance manometry
 - Functional luminal image probe (FLIP)
 - Abnormal distensibility index EGJ opening diameter/intraluminal distensile pressure.
- Achalasia with preserved peristalsis
 - Type III achalasia has fragments of peristalsis / premature spastic contractions for $\geq 20\%$ of swallows on HREM.
- Peristalsis recovery after treatment
 - There may be a time-dependent progression of pathological steps in the development of achalasia, and the steps in the recovery of function after myotomy.
 - The subtypes of achalasia may also reflect differences in the underlying pathology
 - Postulated spectrum:
 Inflammation of myenteric plexus $\rightarrow$ ↓ ganglion cells $\rightarrow$ neurofibrosis
 [Type II] [Type III achalasia]
- Esophagogastric junction outflow obstruction (EGJOO)
 - IRP > 15 mmHg, but enough peristalsis in body of esophagus that the criteria for diagnosis of achalasia type I, II, or III are not met
- Further investigation of patients with HREM demonstrated EGJOO required to establish etiology
 - Provocative/adjunctive measures
 - Rapid drink challenge (RDC)
 - Solid test meal (STM)
 - Computed tomography (CT)
 - Functional lumen impedance probe (FLIP)
 - Endoscopic ultrasound (EUS)
- Differential diagnosis
 - Esophagus
 - Early achalasia
 - Infiltration/cancer ($\uparrow$ stiffness)
 - Vascular obstruction
 - Hiatus hernia (sliding, para-esophageal)
 - Peptic stricture
 - Abdominal
 - Obesity
 - Drugs
 - Opiates
 - Anti-reflux medication
 - Surgery
 - Bariatric



➤ Treatment

Preferred treatments for achalasia subtypes and achalasia syndromes as defined by CC v3.0

Condition	Preferred treatment	Comment
○ <i>CC v3.0 achalasia subtypes</i>		
– Type I achalasia	PD, LHM, POEM	• All treatments efficacious • Expect more reflux after POEM, especially in patients with hiatal hernia
– Type II achalasia	PD	• All treatments are highly efficacious, PD has least morbidity and lowest cost
– Type III achalasia	POEM	• Can calibrate the myotomy to the spastic segment
○ <i>Achalasia syndromes beyond CC v3.0</i>		
– Esophagogastric junction outflow obstruction	• 1st choice: observation • 2nd choice: calcium channel blockers • 3rd choice: botulinum toxin type A	• Many cases resolve spontaneously • If achalasia therapies are applied, 1st choice PD, 2nd choice POEM
– Absent contractility deemed to be achalasia	PD, LHM, POEM	• Treat as type I achalasia
– DES deemed to be achalasia	POEM	• Treat as type III achalasia
– Opioid effect	• 1st choice: discontinue opioid • 2nd choice: botulinum toxin type A • 3rd choice: PD • 4th choice: POEM	• Time course of reversal with opioid cessation is not known
– Obstruction	• Conventional dilation • Operative reversal if relevant • Directed medical therapy irrelevant	• Many entities mimic achalasia, (sometimes termed 'pseudoachalasia'); eosinophilic esophagitis, cancer, reflux stricture

Abbreviations: LHM, laparoscopic Heller myotomy PD, pneumatic dilation; POEM, peroral endoscopic myotomy;

Source: Kahrilas PJ, et al. Nat Rev Gastroenterol Hepatol 2017; 14: 677-688. (Table 4)



- POEM
 - Mid-esophageal endoscopic insertion through submucosal to gastric cardia, followed by myotomy of circular muscle of esophagus (mean length, 17 cm) over variable length of lower esophagus
 - Effective in
 - Achalasia type I/III
 - Absent contractility, thought to be achalasia
 - DES, thought to be achalasia
 - DES/Jackhammer esophagus
 - Opioid effect on esophagus (fourth choice after stopping opioids, botulinum toxin type A, pneumatic dilation (PD))
 - Short-term good outcome > 90%
 - ↑ risk of post-procedure gastroesophageal reflux (GER)
- Pharmacological
 - Botulinum toxin type A, calcium channel blockers (CCBs), long-acting nitrites, phosphodiesterase type 5 inhibitors
 - Excellent (90%) response rate, but 5 yr benefit ~50% (not durable)
 - Retreat with drugs may be effective
 - Useful in patients who are not candidates for LHM/PD, all while awaiting one of these more optimal treatments

Abbreviations: CDP, contractile deceleration point; CT computed tomography; DCI, distal contractile integral; DL, distal latency; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outlet obstruction; EoE, eosinophilic esophagitis; EUS endoscopic ultrasound; FLIP, functional luminal image probe; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; PD, pneumatic dilation; POEM, per-oral endoscopic myotomy; RDC, rapid drink challenge; s, seconds; STM, solid test meal; UES upper esophageal sphincter



HYPERCONTRACTILE ESOPHAGUS (HE)

Proceedings of the Pisa Symposium

deBortoli N, et al. am J Gastroenterol 2021; 116: 263-273.

➤ Physiology of swallowing

- In order to understand the pathophysiology of HE, HE with esophagogastric junction outlet obstruction (EGJOO) and achalasia, several points are important in the consideration of key events which occur with normal swallowing.
- Primary (voluntary swallowing) / secondary (distention of body of esophagus) peristalsis
 - Immediate activation of all inhibitory nerves of esophagus (deglutitive inhibition), then
 - Excitation of excitatory neurons → peristalsis contractions of muscles
 - Contraction of longitudinal muscle → stretch/activated mechanosensitive motor neurons → release of nitric oxide (NO) → inhibition of motor neurons / alteration in speed/strength of peristalsis

➤ Definition of HE

- DCI > 8000 mmHg/sec/cm plus
 - ≥ 20% of hypercontractile swallows on the supine 10 swallow HRM protocol
- “....a primary motor disorder of the esophageal body where an excess of excitatory cholinergic drive, associated with temporal asynchrony of circular and longitudinal muscle contraction leads to exaggerated smooth muscle contraction”.
- Because of heterogeneity of hypercontractile esophageal disorder an “umbrella term” is proposed to include traditional HE.
 - DCI > 8000 mmHg/sec/cm
 - DL, IRP normal
 - Abnormal inhibition during multiple rapid swallows (MRS)
 - May be associated pattern during rapid drink challenge, i.e., only present on provocative testing with MRS

➤ Pathophysiology

- Similar in HE, HE plus EGJOO and achalasia
- ↑ excitatory cholinergic drive
- Temporary asynchrony of contractions of circular and longitudinal smooth muscle → ↑ smooth muscle contraction
- May be associated with
 - Jackhammer esophagus, a subtype of HE.
 - Esophagogastric junction outflow obstruction (EGJOO)
 - Abnormal inhibition of esophagus (please see above “physiology of swallowing”)
 - Histopathological changes similar to those seen in patients with achalasia
 - ↓ ganglion cells in myenteric plexus (MP)
 - Interstitial cells of Cajal (ICCs)
 - ↑ lymphocytic/eosinophilic inflammation in MP



➤ Manometry

- HRM shows three contraction segments in the body of the esophagus.
 - Proximal skeletal muscle segment
 - Two distal smooth muscle contraction segments
- HRM software determines three components of an esophageal motility abnormalities (Chicago classification)
 - Integrated relaxation pressure (IRP)
 - LES relaxation
 - Distal latency (DL)
 - Timing of peristalsis
 - Distal contractile integral (DCI)
 - Strength of peristalsis (Hg per cm per sec)
- The manometric pressure profile of esophageal peristalsis has one phase before and are after the point of highest contraction amplitude (overall contraction vigor)
 - Pre-peak
 - Post-peak
 - Post- > pre-

➤ Subtypes

- Esophageal body, +/-
- Lower esophageal sphincter (LES)
- HE with EGJOO
 - DCI > 8000 mmHg/cm/sec, plus ↑ IRP (reflecting ↑ EGJOO because of ↑LES pressure)

MCQ GEM

- HE plus EGJOO may be asymptomatic
 - Symptoms more common with ↑DCI / ↑IRP
 - These patients are more likely to require endoscopic or surgical therapy.

- Only the LES (rare)
- Jackhammer esophagus
- Nutcracker (hypertension contractions)
- Abnormalities produced by provocative testing during HRM



➤ Causes

- Esophagogastric outlet obstruction (EGJOO)
- Gastroesophageal reflux disease (GERD)
- Opioid use
- Inflated gastric lap-bands (bariatric surgery)
 - Progression to achalasia type III in ~25% in 2 yr, especially those patients with HE plus HE EGJOO
 - ↓ lower esophageal sphincter relaxation (LESR)
 - ↓ distal latency (DL)
 - ↑ amplitude of esophageal contraction

MCQ PEARL

- Give how HREM distinguishes, HE, DES, EGJOO and achalasia type III ($\geq 20\%$ spasm, $DL < 4.5$ sec) in the patient who abuses opioids.
 - Diagnosis best made
 - On opioids ■ EGJOO and achalasia
 - On/off opioids ■ HE, DES

➤ Diagnosis

- EGD
- Barium diagnostic
- Manometry (HRM, Chicago Classification 3.0 metres)
 - Traditional HE
 - IRP – LES relaxation is normal
 - DL – Peristalsis timing is normal
 - DCI – Peristalsis ↑ (> 8000 mmHg/s/cm plus other metrics, such as
 - Abnormal opening of EGJ
 - ↓ deglutitive inhibition during multiple rapid swallow (MRS)
 - Heterogeneity in contraction
 - Strength
 - Progression
 - DCI pre-/post-peak
- Provocating testing
 - Rapid drink challenge (RDC): rapidly drinking 100-200 mL of water while standing up (upright position)
 - RDC
 - Normal: RDC → hypopressive (↓ LES), then peristalsis wave in ~50%
 - Abnormal:
 - HE → hyperpressive (brief) (↑ LES)
 - Achalasia hyperpressive, (prolonged)



- Distinguishing normal from abnormal RDC: one of the following
 - > 2 pressurizations at 20 mmHg
 - > 8% of time > 20 mmHg
 - EGJ gradient > 4 mmHg
 - Sensitivity, 80%
 - Specificity, 93%
- Structural changes
 - Rings, webs, strictures
 - Diverticula
 - Tumour
- Retained column of barium
- Corkscrew pattern may be seen on DES
 - Neither sensitive nor specific
- HE with EGJOO
 - DCI > 8000 mmHg/sec/cm, plus ↑IRP (reflecting ↑ EGJOO because of ↑LES pressure)
 - Pathophysiology
 - ↓ abnormal inhibition
 - Compliance of esophageal wall abnormal
 - Mechanical obstruction of EGJ → ↑contraction of body of esophagus
- Corkscrew esophagus
 - Suggestive of distal esophageal spasm
- Jackhammer esophagus
 - HE (DCI > 8000 Hg/sec/cm) with “chaotic and repetitive esophageal contraction”, and normal DL (timing of peristalsis)
- Functional lumen Image Probe (FLIP): Panometry
 - Gut-to-be validated in HE
 - Measures “....lumen diameter across a space time domain along the distal esophagus and through the EGJ”.
 - Metrics
 - Normal
 - Repetitive antigrade contractions
 - Abnormal
 - No contractility
 - ↑ lift of LES
 - No contractility
 - Occluding contractions, sustained along distal esophagus
 - EGJOO → repetitive hypercontractile pattern



➤ Clinical

- Usual symptoms
 - Dysphagia (~50%)
 - Chest pain, heartburn (~40%)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the use of rapid drink challenge (RDC) to identify patients with HE plus EGJOO who are more likely to develop severe dysphagia, as seen in ~50% of patients.
 - Shortening
 - Pressurization
 - Changes in HRM of esophagus in HRM using RDC
→ likely more severe dysphagia
 - Early panesophageal pressurizing with RDC suggests
 - ↑ muscle thickening of muscle in HE → ↓ muscle compliance → early panesophageal pressurization

- Multiple rapid swallows (MRS):

- In health, 5 swallows of 2 mL of water every 2-3 sec, repeated 3 times
- MRS
 - Inhibition (complete) in 85%
 - ↑ contraction vigour in 80% (contraction reserve)

SO YOU STILL WANT TO BE A GASTROENTEROLOGIST!

- Give three HRM abnormal features which are common in HE plus EGJOO, and in achalasia type III
 - Inhibition, complete
 - ↑excitatory (contraction vigour)
 - Loss of contraction reserve
 - Independent of changes in LES function

➤ Treatment

- Medical

- Associated conditions
 - Gastroesophageal reflux disease
 - Eosinophilic esophagitis
 - Visceral hypersensitivity
 - Psychiatric comorbidities
- Pain
 - Trazodone, 25-50 mg po qhs
 - Tricyclic antidepressants (TCAs)
 - Selective serotonin receptor reuptake inhibitors (SSRIs)
- Proton pump inhibitors (PPIs)
- PPIs, topical corticosteroids, dietary changes



- Dysphagia
 - Anticholinergics, e.g., atropine
 - May correct a synchronizing between contraction of circular and smooth muscle
 - Calcium channel blocker
 - Nitrates
 - Phosphodiesterase-5 inhibitors (↓ degradation of nitric oxide)

- ↓ contraction vigour
- ↓ LES pressure

MCQ GEM

- Patients with HE plus normal DL are more likely to respond to anti-cholinergics or to phosphodiesterase-5 inhibitors

- Endoscopic
 - Botox injection (100 IU) lasts 6-12 mon, and may then benefit the need to be repeated
 - Pneumatic balloon dilation
- Surgery
 - Myotomy, including per-oral endoscopic myotomy (POEM, 16 cm myotomy) and laparoscopic Heller myotomy (extending 5 cm into distal esophagus, and 2 cm into the stomach)
 - Benefit of POEM
 - All spastic esophageal disorders, ~95%
 - HE, ~70%
 - Symptomatic HE with ↑DCI / demand IRP more likely to need endoscopic or surgical therapy (i.e., more likely to fail medical therapy)

Abbreviations: DCI, distal contraction integral; EGJ, esophageal gastric junction; EGJOO, esophagogastric junction outflow obstruction; FLIP, functional lumen image probe; GERD, gastroesophageal reflux disease; HE, hypertensive esophagus; HRM, high resolution manometry; ICCs, interstitial cells of Cajal; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LESR, lower esophageal sphincter resistance; mon, month; MP, myenteric plexus; MRS, multiple rapid swallows; NO, nitric oxide; POEM, per oral endoscopic myotomy; PPIs, proton pump inhibitor; qhs, at every bedtime; RDC, rapid drink challenge; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants



EOSINOPHILIC ESOPHAGITIS (EOE): INTERNATIONAL CONSENSUS (2018)

Dellon ES, et al. Gastroenterology 2018; 155: 1022-1033)

➤ Definition

- Eosinophilic esophagitis (EoE) is a clinicopathological condition that is immune or antigen driven and is characterized clinically by symptoms of esophageal dysfunction and histologically by ≥ 15 eosinophils per high power fields (eos/hpf).

➤ Reason for updated diagnostic criteria

- Proton pump inhibitors (PPIs) $\downarrow$ eosinophils in the esophagus
 - PPI are better classified as treatment for esophageal eosinophilia (EE), rather than as a diagnostic criteria.
- An updated diagnostic algorithm was developed for eosinophilic esophagitis (EoE), with the removal of the requirement for a PPI trial.
- EoE and GERD are not mutually exclusive, and may coexist
 - EoE may cause GERD
 - GERD may cause EoE
- EoE and PPI-responsive esophageal eosinophilia (PPI-REE) may be different stages of the same process, with EoE and PPI-REE sharing “similar clinical, endoscopic, histologic, immunologic, and molecular features before PPI treatment.”
 - PPI-REE may simply be a subtype of EoE

Suggested Additional Reading:

Lucends AJ, et al. United European Gastroenterol J 2017; 5: 335-358.

Freesberg DE. Gastroenterology 2017; 152: 706-715.

• Updated EoE Diagnostic Algorithm

❖ Chronic symptoms which suggest EoE

- GI - Heartburn, regurgitation
 - Dysphagia, odynophagia
 - Food impaction/refusal
 - Chest/abdominal pain
 - Vomiting
- Associations
 - Asthma
 - Atopic dermatitis
 - Allergies to food (immediate type)
 - Family history of EoE



❖ Endoscopy (EGD)

- Normal
- Rings/strictures/narrowing
- Furrows, longitudinal
- Edema, exudates
- Erythema (apparent inflammation)
- Microabscesses
- Crepe-paper mucosa

} - EoE Endoscopic Reference Score
(Hirano I, et al. Gut 2013; 62: 489-495)



❖ Esophageal histopathology

- ≥ 15 eos/hpf (~ 60 eos/mm²)
- Biopsy from ≥ 2 sites in esophagus (lower, middle), as well as any areas of apparent inflammation from esophagus, stomach, duodenum
 - "Eosinophil infiltration should be limited to the esophagus"



❖ Exclude other conditions which may be associated with esophageal eosinophilia ≥ 15 eos/hpf (eosinophilia esophagitis [EoE] versus non-EoE disorders)

- Esophagus
 - Eosinophilic gastritis, enteritis, or colitis with involvement of esophagus
 - GERD
 - Pill esophagitis
 - Esophageal dysmotility (including achalasia)
 - Infection
 - Viruses
 - Fungi
 - Inflammation
 - Crohn disease affecting esophagus
 - Connective tissue disorders
 - Ischemia
 - Vasculitis
- Extraesophageal
 - Hypereosinophilic syndrome
 - Hyper IgE syndrome
 - Drug hypersensitivity reactions
 - Graft-versus host disease
 - Severe atopy metabolic wasting syndrome
 - Dermatologic conditions, esophageal (e.g., pemphigus)



- Confirmed eosinophilic esophagitis ←

- Symptoms of esophageal dysfunction
- ≥ 15 eos/hpf (~ 60 eos/mm²) on biopsy
- No significant other causes of symptoms and/or esophageal eosinophilia



❖ Treatment

- Dietary elimination/restriction (6 food diet)
- Proton pump inhibitors (PPIs)
- Topically acting corticosteroids

Challenges to Current Clinical Practices

- Once an adenomatous is identified, the patient is recommended to have a follow-up colonoscopy earlier than the person who had no adenoma (repeat colonoscopy in 10 yr).
- The timing of the earlier colonoscopy is determined by the size , number, and histopathology of the original (index) adenoma

		Relative risk of developing CRC	
- Advanced adenoma	20 (95% CI 15.3-24.7)	RR, 1.2 (95% CI 0.8-1.7, p=0.30)	RR, 2.7 (1.9-3.7, p < 0.001)
- Non-advanced adenoma	9.1 (6.7-11.5)		
- No adenoma	7.5 (5.8-9.7)		

- Conclusion

		Relative risk of dying from CRC	
- "identification of non-advanced adenoma may not be associated with increased colon cancer risk "... over a median of 13 yr of follow-up"	RR, 1.2 (0.5-2.7, p = 0.68)		RR, 2.6 (95% CI 1.2-5.7, p = 0.001)
- Based on this study, the follow-up of persons with a non-advanced adenomatous colonic polyp on index colonoscopy should be at the same 10 yr interval as persons whose index colonoscopy did not show adenomatous polyps			

Adapted from: Click B, et al. JAMA 2018; 319: 2021-2031



STOMACH

Alajmi, Abdulaziz

Almudaires, Abdulaziz

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GASTRIC PRE-CANCER / CANCER

Management of Gastric Intestinal Metaplasia (GIM): AGA Guidelines (2019)

Gupta S, et al. Gastroenterol 2019; 158: 693-702; Gawron AJ, et al. Gastroenterology 2020;158(3):705-31; Altayar O, et al. Gastroenterol 2020;158(3):732-44.

- Helicobacter pylori infection (HPI)
 - Causative in ~90% of non-cardia gastric cancers (GCA) around the world.
 - HPI causes a spectrum of histopathological changes, including gastric intestinal metaplasia (GIM) and GCA.
 - Eradicating HPI → GCA
 - 32% ↓ risk of GCA (RR, 0.62; 95% CI: 0.48 – 0.96), and
 - 33% ↓ risk of mortality from GCA (RR, 0.67; 95% CI: 0.38 – 1.17)
 - Eradication of HPI in patients with GIM → 24% ↓ risk of GCA (RR, 0.76; 95% CI: 0.36 – 1.61)

Recommendation

- In persons who are incidentally found to have gastric intestinal metaplasia (GIM), test for H. pylori infection (HPI) and if positive, treat and confirm eradication (Strong recommendation, moderate quality evidence)
- Routine endoscopic surveillance
 - Prevalence of GIM in gastric biopsies overall ~5%
 - Risk of progression of GIM to dysplasia – 15% at
 - 3 yr (95% CI: 13% - 17%); vs. 5 yr (95% CI: 12% - 19%)
 - Risk of GIM progressing to GCA not influenced by race/ethnicity of patient (very low quality evidence), but in the USA, “....racial/ethnic minorities have much higher risk for incident and fatal gastric cancer than non-Hispanic whites”
 - Persons with
 - Average risk of GCA with
 - GIM in gastric (antrum +/- incisura)
 - Incomplete GIM (partial / all colonic type)
 - Risk of GCA ~0.16% in 1 yr, 1.6% in 10 yr
 - ↑ risk of GCA
 - GIM in gastric body plus antrum +/- incisura (2.1x ↑RR) 95% CI: 0.97 – 4.42)
 - Complete (small intestinal type) intestinal metaplasia (3.3x ↑RR)
 - Family history of GCA (4.5x ↑RR of GCA); 95% CI 1.33 – 15.46)
 - Risk of incomplete GIM progressing to GCA, ↑RR 3x (RR, 3.33; 95% CI: 1.96 – 5.64)
 - Without direct evidence, if shared decision-making (patient and physician) is for endoscopic surveillance, this should be done q3-5 d

Recommendation

- In persons who are incidentally found to have GIM, and who are otherwise of low-risk for GCA, do **not** perform endoscopic surveillance.



- In patients with GIM who are at higher risk of GCA, surveillance may be provided for GCA for persons – “who put a high value on potential but uncertain reduction in gastric cancer → mortality, and who put a low value on potential risks of surveillance endoscopies
- These high-risk factors include
 - Patient (family history of GCA)
 - Immigrants from high incidence regions (e.g., East Asia, South America)
 - Racial/ethnic minorities
 - GIM: Incomplete vs complete and Extensive vs limited
 (Conditional recommendation, very low quality of evidence)
- Repeat endoscopy (EGD)
 - The risk of GCA being missed at the time of the first EGD and found at repeat EGD 1 yr later is 0.5% (95% CI: 0.4% - 0.6%)

Recommendation

- In patient with GIM, do **not** repeat the EGD for the purpose of risk stratification
(Conditional recommendation, very low quality of evidence)
- Comment
 - “based on shared decision-making, patients with
 - GIM and high-risk stigmata
 - Concerns about completeness of baseline endoscopy, and/or
 - Overall increased risk of gastric cancer.....may reasonably elect for repeat endoscopy within 1 yr for risk stratification

➤ Comparison

In patients with GIM	AGA, 2019	ASGE, 2015	ESGE, 2019
○ Test and treat for HPI	+		+
○ Do not do routine EGD surveillance	+	+	+
– Except possibly for high-risk (SDM)	+	+	
○ Do not repeat EGD for risk surveillance	+		-
– Except possibly for high risk (SDM)	+		-
– Supported			
▪ Repeated EGD 3 yr from baseline			
– Severe gastric atrophy			
– GIM in both antrum plus body			
– Based on OLGA/OLGIM			
▪ Repeat EGD in 1-2 yr			
– Family history plus above risk features			

Abbreviations: AGA, American Gastrointestinal Association; ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; EGD, esophagogastroduodenoscopy; ESGE, European Society for Gastrointestinal Endoscopy; GCA, gastric cancer; GIM, gastric intestinal metaplasia; OLGA, Operative Link on Gastritis Assessment; OLGIM, Operative Link on Gastritis Assessment Intestinal Metaplasia; RR, relative risk; SDM, shared decision making; USA, United States of America



Gastric Cellular Plasticity and Reprogramming in Gastric Repair and in the Development of Gastric Cancer

Sáenz JB and Mills JC. Nat Rev Gastroenterol and Hepatol 2018; 15: 257-72.

- Appreciation for the importance of the sequence of chronic gastritis, metaplasia, dysplasia and gastric adenocarcinoma (GAC) requires a basic understanding of gastric repair process.
- Functional organization of the stomach
 - Proximal
 - Cardia, fundus, body
 - Oxyntic glands (parietal cells → HCl, intrinsic factor)
 - Chief cells (digestive enzymes, e.g., pepsinogens)
 - Target cells (unknown function)
 - Distal
 - Antrum
 - Deep mucous cells
 - mucus (e.g., MUC6)
 - Zymogenic proteins
 - No parietal or chief cells
 - Both body and antrum
 - GI peptide secretory cells
 - Pit (foveolar) cells → mucus

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the bactericidal capacity of human gastric HCl secretion.
 - Gastric acid secretion in a non-hypersecretion can destroy every hour 10^9 (10 billion) microorganisms.
- The anatomic and glandular organization of the human stomach
 - The human stomach can be divided into two anatomic regions, the corpus and the antrum.
 - These regions are characterized by the cellular composition of their glands, with corpus units (purple inset) defined by acid-producing parietal cells and zymogenic chief cells.
 - The antrum unit is largely devoid of parietal cells and chief cells and instead comprises mucous cells (green) that extend down to the gland base.
 - Both corpus and antrum units contain an isthmus region, made up of proliferative stem cells, and a surface/pit region, with pit cells extending up from the isthmus to the luminal surface.
 - Pre-parietal, pre-pit, and pre-mucous cells are also shown.



➤ Response to gastric injury

❖ Superficial/mucosal response

• Viscous gel matrix

- Replaces the pit cell lineage through “cellular death, restitution, and proliferation by exposure of pit region (“foveolar hyperplasia”)”
 - Mucin (MUC5AC) glycoproteins
 - Buffers (HCO_3^- , non HCO_3^-)
 - Trefoil factors
- } - Secreted by surface/pit cells
- Regulated by acetylcholine, gastrin, histamine, epithelial growth factors (EGF), hepatocyte growth factors (HGF), prostaglandins (PGs)

• Lipid-protein gastric membrane and tight junction proteins

• Give the basic mechanism of secretion of prostaglandin and the process if adaptive cytoprotection (in the stomach).

- COX enzymes
 - 1, constitutive
 - 2, inducible
 - EP receptor subtypes
 - EP1 → mucus secretion
 - EP3 → ↓ histamine (ECL cell), ↓ HCl (parietal cells)
 - EP 4 → HCO_3^- secretion
- } ▪ Prostaglandin E2 (PEG2) → binds to EP receptors

• Local blood flow

- Angiogenic factors
 - Vascular endothelial growth factors A1 B (VEGF A1 B)
- Vasodilator
 - Nitric oxide (NO) → ↑ mucosal / ↓ H^+

• Adaptive/regeneration

- Adaptation (patients from endogenous HCl damage)
 - Surface/pit cells
 - Restitution (fast, in minutes)
 - Restores cell junctions / mucosal integrity by migration of cells
 - Proliferation
 - New surface epithelial cells
- Proliferation
 - Progenitor cells (stem cells in isthmus between gastric pits and deeper gastric glands become new surface cells in days)
 - Enhanced by mesenchymal/mitogenic factors
 - EGF
 - Heparin-binding: EGF-like growth factor
 - $\text{TGF}\alpha$
 - Amphiregulation



- ❖ Glandular response, corpus glandular response and SPEM
 - Adaptation (when HCl production ↓/lost)
 - ↓ parietal chief cells “corpus glandular differentiation” metaplastic cells → SPEM new parietal/chief cells (hybrid phenotype)
 - Corpus glandular differentiation is known as “SPEM”, spasmolytic polypeptide-expressing metaplasia, aka TFF2
 - Death/destruction of parietal cells → SPEM → metaplastic change leading to new parietal/chief cells
 - Factors which assist SPEM and the metaplastic state
 - Epithelial
 - Neurogenic locus Notch homologous protein 1 (NOTCH 1/2)
 - Gastrin
 - Sonic hedgehog protein (SHO)
 - Mesenchymal
 - Bone morphogenetic protein 4 (BMP4)
 - Noggin
 - Immune factors
 - IFN γ , IL-1 β , IL-13, IL-33
- The superficial and glandular responses in the gastric corpus
 - The corpus unit responds to gastric injury through two main mechanisms
 - The superficial response, and
 - The glandular response
 - The surface epithelium consists of pit cells (purple) that produce a viscous mucus barrier that protects against endogenous (e.g., acid, denoted by H⁺) and exogenous (not shown) injury.
 - Breaches in the surface epithelium resulting from acid oversecretion, decreased mucus production, and/or ischemia can lead to ulcers and/or bleeding.
 - The superficial injury response restores the protective barrier of the surface epithelium by increasing mucus production, restoring local blood flow, and re-establishing epithelial integrity through restitution and cellular proliferation.
 - The glandular injury response correlates with the loss of acid-producing parietal cells and a replacement of the deeper glandular epithelium with metaplastic cells that co-express markers of mucous neck cells and chief cells. This metaplastic response (middle) is often termed Spasmolytic Polypeptide-Expressing Metaplasia (SPEM) and represents a transient response to re-establish homeostasis.
 - The superficial and glandular responses are not mutually exclusive and can occur simultaneously within the same corpus unit.



- Theories for cellular origins of SPEM
 - Possible mechanisms for the initiation of SPEM and the replacement of depleted glandular epithelium.
 - Isthmal stem cell (white) to serves as the unique cell of origin for SPEM
 - All of the glandular cells - parietal cells, chief cells mucous neck cells
 - Must die and be replaced with cells derived from a proliferative, isthmal stem cell that has trans-differentiated to become a stem cell for metaplastic cells.
 - Others, have hypothesized that SPEM arises from the trans-differentiation of chief cells into metaplastic cells following the loss of parietal cells.
 - These basal metaplastic cells repopulate the corpus unit from the base up, while isthmal proliferation results only in an expansion of pit cells, a process known as foveolar hyperplasia.
 - Another hybrid model can also be envisioned wherein both the isthmal stem cells and chief cells can contribute to SPEM
 - In this scenario, two foci of proliferation may be dedicated to generating different cells along the gland axis, with the isthmal stem cell giving rise to pit cell precursors and/or mucous neck cell precursors, and the chief cells giving rise to metaplastic cells. Bacteria represent Helicobacter pylori.
- The expansion of SPEM and the Cyclical Hit model
 - The topographic expansion of SPEM during sustained glandular injury results in the “antralization” of the corpus, such that corpus units become metaplastic and morphologically resemble antral units.
 - The antralization of the corpus likely emerges from an initial focus of metaplasia at the transition between corpus and antrum and expands proximally along the lesser curvature before spreading to the greater curvature.
 - The transition zone represents a dynamic, hybrid region that progresses along the leading edge of antralization.
 - The earliest sites of antralization will have the longest history of metaplasia with associated dedifferentiation-redifferentiation cycles, increased risk of accumulation of mutations, and an increased likelihood that those mutations will seed dysplasia/neoplasia.
 - As post-mitotic chief cells become metaplastic and re-enter the cell cycle to proliferate and fuel metaplasia, they can accumulate genetic mutations through replicative stress.
 - Chief cells within the initial focus of metaplasia, a region that would have sustained the longest duration of glandular injury, harbor genetic mutations that can become unmasked and prevent re-differentiation, either leading to apoptosis or potentially serving as a cell of origin for dysplasia.



Diagnosis and Management of Patients at a Risk of Gastric Adenocarcinoma (GAC): BSG Guidelines (2019)

Banks M, et al. Gut 2019; 68: 1545-75.

➤ Terminology

- Chronic atrophic gastritis (CAG) includes
 - Gastric atrophy (GA), and
 - Gastric intestinal metaplasia (GIM)
- Correa cascade of progression to intestinal-type gastric cancer (GCA)

➤ Spectrum of chronic gastritis: Correa cascade

Chronic gastritis (non-atrophic)



Gastric atrophy (GA)

- ↓ glands
- Fibrosis of lamina propria
- Replacement of gastric glands by metaplastic / pseudopyloric glands



Gastric intestinal metaplasia (GIM)



Gastric dysplasia (GD)



Intestinal-type gastric cancer (GCA)

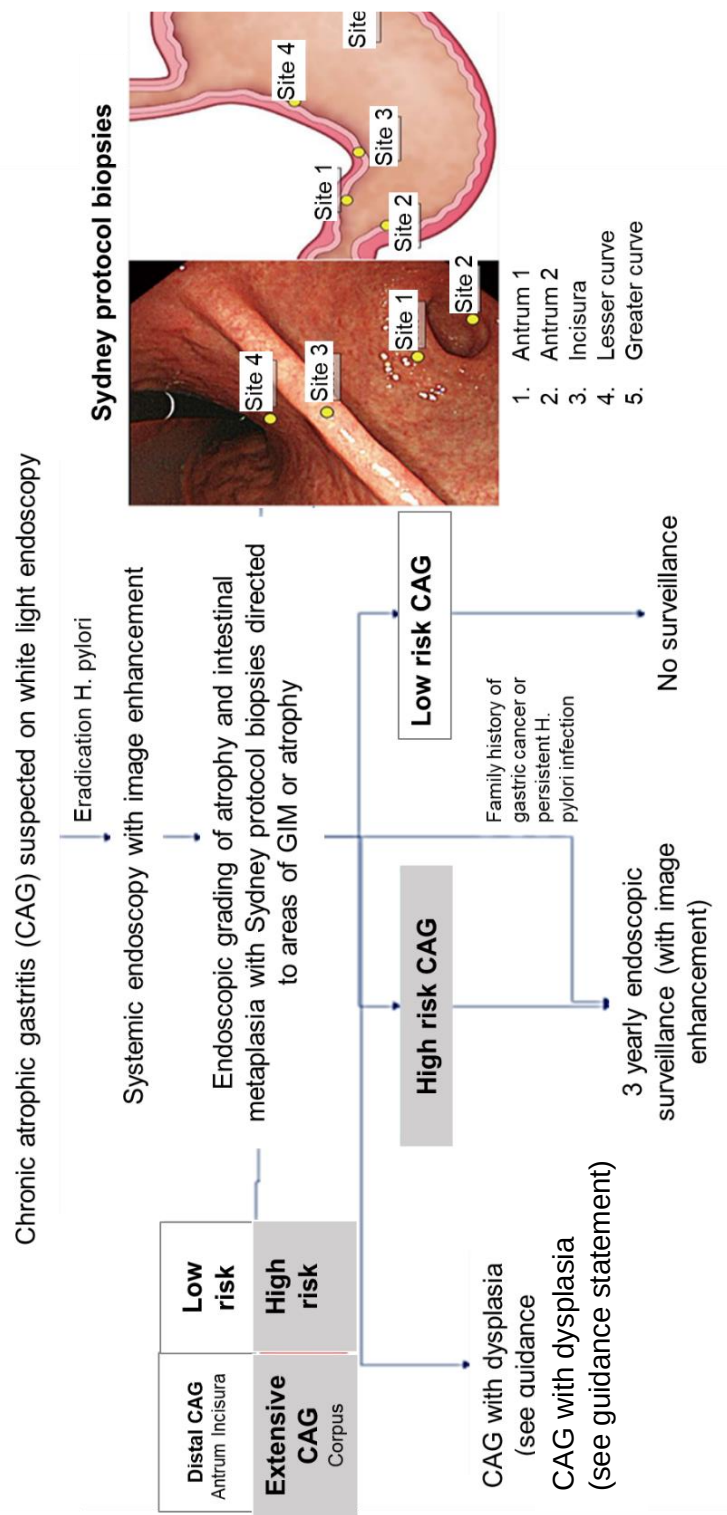
Risk of Progression to GCA

Histopathology	Annual incidence of GCA	
GA	0.1%	○ Endoscopy (EGD) – GCA, 1.9% – GIM, severe, 10%
GIM	0.25%	
LGD	0.6%	
HGD	6%	

• Gastric Atrophy

- Histopathology
 - ↑ chronic inflammatory cells lymphocytes / plasma cells in lamina propria (LP)
 - ↓ pre-existing gastric glands
- “....the interobserver and intra-observer agreement of endoscopic severity assessment, in experienced hands, is moderate to excellent....[but there is a “....low inter-observer agreement by histopathologists when staging GA using the OLGA (Operative Link on Gastritis Assessment) staging system, based on biopsies taken using the Sydney protocol”.





Printed with permission: Banks M, et al. Gut 2019; 68: 1545-75 (Figure 1A)



- Gastric Intestinal Metaplasia (GIM)

- Causes/associations

- Older age
- H. pylori infection
- Smoking
- Persons with a first-degree relative with GCA

- Demography (Europe)

	<u>Prevalence of GIM on EGD</u>
○ H. pylori infection	
– Negative	15%
– Positive	30%
○ Gastric ulcer	55%
○ GCA	100%

- Risk of developing GCA

- Annual incidence of GIM → GCA 0.25% at 5 yr
 - Varies with
 - Type
 - Type I (intestinal) “complete IM”
 - Type II, III (colonic) “incomplete IM”
 - Extent
 - Focal
 - Scattered foci
 - Lesser curve/incisura
 - Antrum
 - Predominant
 - Antrum/incisura
 - Magenstrasse
 - Cardia to pylorus along lesser curve, plus
 - Greater curve of prepyloric antrum
 - Diffuse
 - All gastric mucosa, except fundus

} Similar risk of GCA, ~7%

} Usually “complete IM”

} Usually “incomplete IM”

- Risk of GIM progression to GCA greatest for
 - Magenstrasse
 - ↑ risk ~6x
 - Diffuse
 - ↑ risk ~12x

	<u>Cumulative 5-yr risk of GCA</u>
– No GIM	5.3%
– GIM in antrum	9.8%

- The Operative Link on Gastric Intestinal Metaplasia (OLGIM) staging system is a “reproducible” marker of risk [of progression to GCA], with high interobserver agreement.



➤ Criteria for referring to genetic services

- Suspected familial gastric cancer
 - Gastric cancer in one family member before age 40 yr, or
 - Gastric cancer in two first-degree/second-degree relatives, with one diagnosis before age 50 yr*, or
 - Gastric cancer in three first-degree/second-degree relatives, independent of age*.

*In order to account for significant family history, the affected relatives need to be within the same side of the family (maternal or paternal).

- Suspected hereditary diffuse gastric cancer (HDGC)
 - One case of diffuse gastric cancer before age 40 yr, or
 - Two cases of gastric cancer, regardless of age, in two first-degree/second-degree relatives, at least one confirmed diffuse gastric cancer, or
 - Personal and family history of diffuse gastric and lobular breast cancers, with one diagnosis before age 50 yr.
 - A personal or family history of cleft lip/palate in a patient with diffuse gastric cancer.
 - In situ signet ring cells or pagetoid spread on gastric biopsies.
- Ethnicity (may be influenced by prevalence of *H. pylori*)
 - Risk of GCA
 - Black/Hispanic-Latino 1.7x ↑risk
 - Asian 2.1 x ↑risk
 - Chinese OR 4.79 (95% CI, 4.54 to 5.01)
 - Korean OR 7.39 (95% CI, 7.06 to 7.73)
- Pernicious Anemia (PA)
 - Pooled incidence of GCA in persons with PA ~0.3% per yr, of 6.8 or
 - GCA; RR, 2.18 (95% CI, 1.94 to 2.45)
 - Gastric neuroendocrine tumour 11.4 (95% CI, 8.9 to 14.7)
- Gastric surgery
 - The risk of GCA in the gastric stomach increases 30 yr after gastric surgery, after this interval, the standardized incidence ratio is 2.29 (95% CI, 1.38 to 3.57)
- *H. pylori* and Risk of Gastric Cancer (GCA)
 - There is “compelling evidence” that the eradication of infection with *H. pylori* reduces the subsequent risk of GCA.
 - In geographical regions of low risk for GCA, it is not cost-effective to test and treat *H. pylori*.
 - Some groups of persons in Canada have ↑ risk of *H. pylori* infection / GCA, such as
 - Indigenous Canadians
 - “New” Canadians who have immigrated from high-risk areas



- It may be important to treat *H. pylori* infection, depending on the histological changes associated with the *H. pylori* infection (chronic gastritis, gastric atrophy, gastric intestinal metaplasia, dysplasia, early GCA)
 - This concept is referred to as the “point of no return”, i.e., treatment at or beyond a particular histopathological grade may no longer be beneficial to prevent subsequent regression to GCA.
 - Evidence supports treatment/eradication of persons with *H. pylori* infection plus
 - Non-atrophic/atrophic changes, but not those who have progressed to GIM/GA
 - HGD/intramucosal (“early”) GCA → development of GCA in *H. pylori*
 - Treated 13.4%
 - Not-treated 7.9%
- } P = 0.03
- Biomarkers to identify

- Biochemistry
 - Pepsinogen I ▪ Secreted by chief / mucous neck cells in fundic mucosa
 - Pepsinogen II ▪ Secreted by pyloric / Brunner glands
 - Inflammation ▪ ↑ serum pepsinogen I and II
 - Gastric atrophy ▪ ↓↓ PG I, ↓ PG II
 - ↓ ratio of PG I/II

	<u>Cut-off Values (ng/mL)</u>
PG I	< 70
PG II	≤ 3

- Performance characteristics of PG I/II for diagnosing GCA/CAG (CA, GIM)

	GCA	CAG	GA	Follow-up of positive test GCA
▪ Sensitivity	69%	69%	65%	57%
▪ Specificity	73%	88%	80%	76%

- Positive pepsinogen test, negative serology for *H. pylori* → ↑ risk of extensive GA
 - PG I plus PG II, plus *H. pylori* serology plus gastrin-17
 - Sensitivity for GCA 75%
 - Specificity 96%
 - NPV 91%
 - PPV 86%
 - Performing biochemical testing to target persons for EGD to diagnose GA/GIM/GD and to thereby ↓ risk of GCA are “not yet ready for prime time”.
 - Extensive GCA can be suspected by measuring
 - Serum pepsinogen I
 - Serum pepsinogen I plus II
 - to obtain ratio of I/II
- } +/-
-
- (Evidence level: low quality; grade of recommendation weak; level of agreement 93%)



Recommendation

- Do **not** use biomarkers to predict the presence of GCA in geographical areas where the risk of GCA is low (such as in United Kingdom, but not necessarily in all population groups in Canada)
(Evidence level: low quality; grade of recommendation, weak: level of agreement: 100%)
- Endoscopic evaluation
 - It is important to make an endoscopic diagnosis of GCA, in order to target biopsies of the gastric mucosa
 - Rate of missed GCA, ~10%
 - Quality principle of EGD
 - Clean mucosa
 - Good distention (air insufflation)
 - Thorough mapping of stomach and mucosal cleansing technique
 - BSG Position Statement: Use combination of air insufflation, and fluid aspiration
- Give the reasons why duration of EGD for diagnosis of GCA should be > 7 min.
 - ↑ detection (2x) of high-risk lesions (GA, GM)
 - ↑ detection (3x) of GD, GCA
- Recommendations for photography plus biopsies (European Society of Gastrointestinal Endoscopies [ESGE]) for systematic screening protocol
 - Taking ≥ 4 photography → ↑ detection of pathology
 - Antrograde
 - Antrum
 - Lower body
 - Middle-upper body
 - Retrograde
 - Fundus-cardia
 - Middle-upper body
 - Incisura

Quality improvement

- This type of vigorous systematic screening protocol ↑ rate of detection of early gastric cancer (EGCA) from 0.2% to 2.3%

Recommendations

- Persons at ↑risk of GCA (including those with GCA and GIM) should have a
 - A full systematic EGD protocol of the stomach
 - Clear photographic documentation of gastric regions and pathology
 - Minimum examination time of 7 min

(Evidence level: moderate quality; rate of recommendation: strong; level of agreement: 100%)



- All gastric dysplasia and early gastric adenocarcinoma should be resected en bloc
 - An endoscopic mucosal resection (EMR) technique can achieve en bloc excision for lesions ≤ 10 mm in size.
 - But, only an endoscopic submucosal dissection (ESD) technique can ensure en bloc excision for lesions > 10 mm in size (evidence level: high quality; grade of recommendation: strong; level of agreement: 100%).
 - Complete (R0) endoscopic resection of gastric dysplasia and early gastric adenocarcinoma with the following features should be considered as potentially curative:
 - Low grade dysplasia (LGD)
 - High grade dysplasia (HGD)
 - Well or moderately differentiated intramucosal adenocarcinoma
 - Irrespective of size, if not ulcerated
 - < 3.0 cm in size if ulcerated
 - < 3.0 cm in size, with superficial submucosal invasion (Sm1; < 500 μ m submucosal invasion as measured in a straight line from the deepest fibre of the muscularis mucosae).
 - Poorly differentiated intramucosal adenocarcinoma, ≤ 2.0 cm in size (evidence level: moderate quality; grade of recommendation: strong; level of agreement: 93%).
 - The histopathological features of early gastric adenocarcinoma associated with a higher risk of lymph node metastasis (LNM) after endoscopic resection include the following:
 - Poorly differentiated submucosal cancer, irrespective of invasion depth below muscularis mucosae.
 - Signet ring cancer
 - Lymphovascular invasion
 - Depth of submucosal invasion $\geq 500\mu$ m as measured in a straight line from the deepest fibre of the muscularis mucosae (evidence level: moderate quality; grade of recommendation: strong; level of agreement: 93%).
- eCura System Weighted scores to stratify curability for early gastric cancer

Risk Factors		Points	
○	Lymphatic invasion	3	
○	Lesion size >30 mm	1	
○	Positive vertical margin	1	
○	Venous invasion	1	
○	Submucosal invasion ≥ 500 μ m	1	

Lymph Node Metastasis (LNM) Risk Groups	Points	Risk of LNM (%)	Cancer-specific 5-yr survival (%)
– Low	0–1	2.5	99.6
– Intermediate	2–4	6.7	96.0
– High	5–7	22.7	90.1



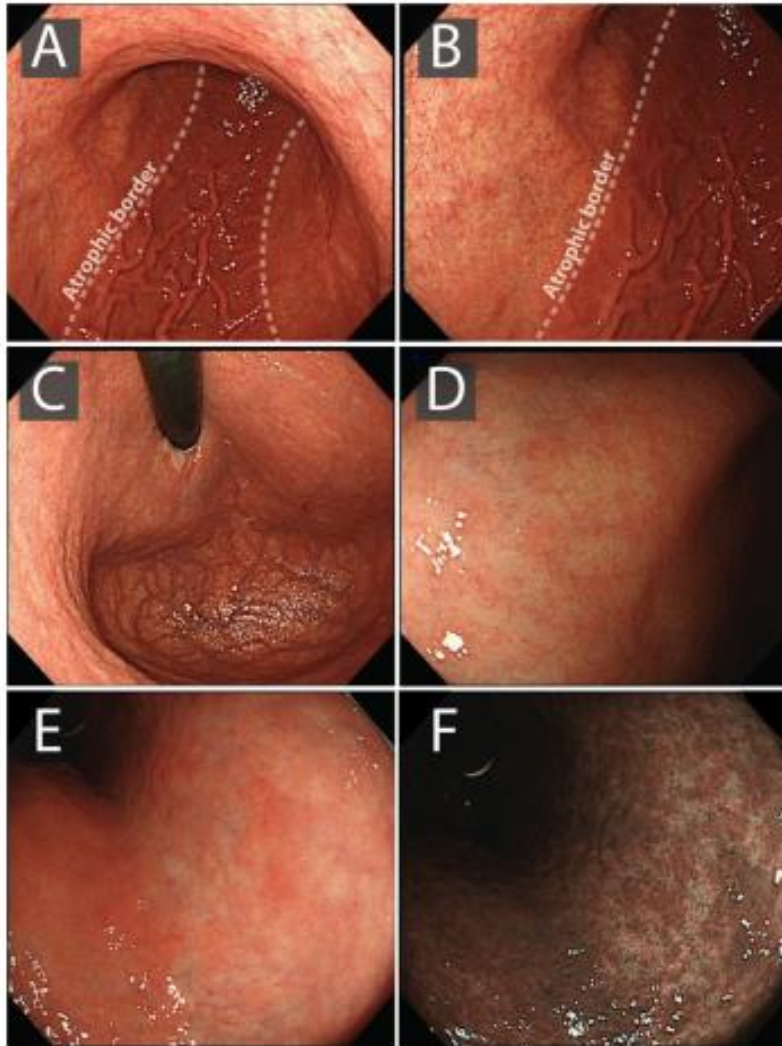
- Pharmacological
 - Do **not** use NSAIDs or COX-2 inhibitors to ↓ risk of progression of premalignant lesions of the stomach (evidence level: moderate; grade of recommendation: strong; level of agreement: 100%).
 - Do **not** use of antioxidants to ↓ prevalence of premalignant gastric lesions (evidence level: moderate; grade of recommendation: strong; level of agreement: 100%).
- White Light Endoscopy (WLE)
 - WLE diagnosis of GA, GIM, GD is not optimal
 - Use magnification and enhanced endoscopy.
 - Because WLE may be the only imaging available, the diagnostic features from the dated methodology will be described below
 - In the normal gastric body, WLE shows
 - Collecting venules (no H. pylori infection; sensitivity 93%, specificity 48%)
 - Pit pattern
 - In body, round
 - In antrum, elongated
- Magnifying endoscopy
 - Body
 - Straight tubular dark brown crypt opening
 - Round pits surrounded by light margined crypts epithelium (MCE)
 - Light area surrounded by dark circular subepithelial capillaries
 - In NBI
 - Regular vessels with normal histology
 - Accuracy, 83% (95% CI, 75% to 90%)
 - Antrum
 - Glands are oblique, branched, grooved, dark “pit openings”
 - Light, ridged/villiform MEE surrounds dark coiled subsequent capillary network (groove-type pattern”)
 - Histopathological E it looks like a papillary surface structure

Foveolar type pattern



- White Light Endoscopy (WLE)

Chronic atrophic gastritis (CAG) and the atrophic border on white light and image enhanced endoscopy.

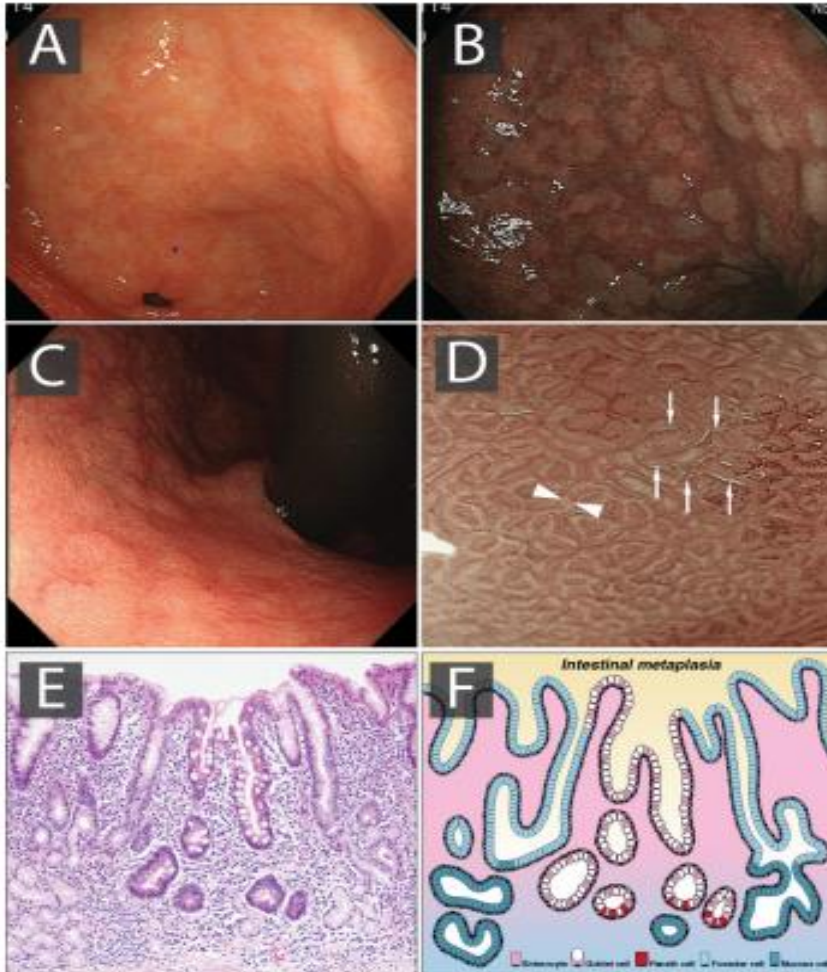


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- There are four principle endoscopic features of CAG:
 - Palour (A, B, C, D and E)
 - Loss of gastric folds (A, B, C, D and E)
 - Prominence of the vessels (A, B, C and D) and
 - Atrophic border (A and B).
- The paler areas of atrophy are also clear on image enhancement (F).



Gastric intestinal metaplasia under white light, image enhanced and magnification endoscopy.



- Intestinal metaplasia typically appears as small grey white slightly elevated plaques surrounded by mixed patchy pink and pale areas of mucosa causing an irregular uneven surface.

(A). These appearances are more evident with image enhancement (B). Corpus GIM can be distinguished from the normal straight/tubular glands of the corpus by a 'groove type pattern' similar to that of the antrum or villiform pattern of the intestine and may be appreciated with higher resolution technology on white light endoscopy (C). GIM in the antrum is more difficult to characterize as the normal glands are oblique. Additional features of GIM to aid diagnosis in the antrum include the light blue crest (LBC) and the marginal turbid band (MTB) (D). The LBC is a fine, blue-white line on the crest of the epithelial surface seen with NBI enhancement (Fine arrows in D). The MTD can be seen between the broad arrows. The numerous goblet cells characterise GIM (E & F)

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- White Light Endoscopy

	Chronic Atrophic Gastritis (CAG)	Gastric Atrophy (GA)	Gastric Intestinal Metaplasia (GIM)
○ Colour	Reddish	Pale	- Lipid droplets (white plaque material in subepithelial capillaries) - Margined turbid band (MTB) on mucosal surface (early GIM) - Light blue crest (LBC) (NBI) – highly specific sign for GIM – several late GIM
○ Folds	Enlarged/thickened	↓ folds (Sn, 67%; Sp, 88%)	- Surrounding patchy pale or pink areas
○ Vessels	- ↓ collecting venules - Capillary vascular structure - Mucous sticking - Gastric juice turbid - Xanthomas	Prominent collecting venules visible (Sn ~ 50%, Sp 87%)	- Raised irregular surface - Straight/tubular glands → groove-type pattern
○ Margin	- Nodularity of antrum	Atrophic border	

- ❖ Performance characteristics

WLE	Sn	Sp
○ Histological diagnosis		
- GA antrum	62%	58%
- Body	47%	76%

- Narrow Band Imaging (NBI), no magnification

- Turbulovillous mucosal pattern indicating GIM on histopathology – accuracy 84%
- Irregular vessels, mucosal pattern indicating GIM on histopathology – accuracy 84%
- Irregular vesicle, mucosal pattern indicating GA – accuracy, 95%
- LBG, GIM: Sn 63%; Sp 94%
- White opaque substance (WOS): Sn 50%; SP 100%
- LBC plus WOS: Sn 87%; Sp 94%

- Audit Targets
 - GIM +/- GA – 10%



- Sensitivity

	WLE	WLE plus NBI
- GIM	53%	87%
- GD, body	74%	92%
- GA, antrum	62%	58%

- Summary “.....WLE alone was not sufficient accurate to reliable diagnose GA or GIM, and enhanced optical techniques should be used for diagnosis and staging”.

- ❖ Gastrodysplasia (GD), early gastric cancer (EGCA)

- WLE signs

- Colour
 - ↑ redness, or palour
 - Enhanced detection with
 - Chromoendoscopy
 - NBI
 - Blue laser
 - Flexible spectral image colour enhancement (FICE)
- Vessels
 - ↓ vascularity
- Stage
 - Slight elevation or depression
- Consistency
 - Nodularity
- Folds
 - Conveyance, abnormal
 - Flattery

- Histopathological

- Classification
 - Adenomatous (intestinal)
 - Adenomatous dysplasia
 - Body, lesser curve
 - Foveolar (gastric)
 - More commonly
 - Associated with HGD
 - Antrum, incisura
 - Red, flat/depressed
 - Mixed (hybrid)
 - Superficial neoplastic lesions
 - Paris classification 0-Is, 0-IIa, 0-IIc



Recommendations

- Do **not** diagnose/stratify GA/GIM by using just white light endoscopy
 - Use high resolution IEE and magnification endoscopy
 - IEE is the best imaging modality for the purpose
 - Document for location/extent of GA/GIM by photography
 - Grading risk
 - Low
 - Distal
 - Antrum
 - Incisura
 - Proximal
 - Body +/- antrum and incisura
 - If WLE shows
 - Colour
 - ↑ redness, or palour
 - Vessels
 - ↓ vascularity
 - Shape
 - Slight elevation or depression
 - Consistency
 - Nodularity
 - Folds
 - Convergence, abnormal
 - Flattening
- Suggests GD/EGCA →

- Perform IEE, and

- Magnification endoscopy
- IEE is the best imaging modality to diagnosis GD/EGCA

❖ Protocol for Gastric Mucosal biopsies

- Recommendation
 - Gastric mucosal biopsies are taken when in the endoscopic findings suggest GIM (endoscopic-led staging), and are directed at sites within the Sydney protocol and the modified Kimura staging system.
 - Use separate containers for the sites and label are having been directed or random biopsies
- The Integrated and Modified Kimura & Sydney Biopsy System.
 - The modified Kimura staging system divides the extent of atrophy into
 - Antrum only (antral)
 - Antrum to incisura (antral dominant)
 - Antrum to lesser curve (corpus dominant), and
 - Antrum, lesser curve and greater curve (pan-atrophy)
 - This Sydney protocol biopsies which should be taken from
 - The antrum (site 1 and 2)
 - Incisura (site 3)
 - Lesser curve (site 4), and
 - Greater curve (site 5)



- Pathology of gastric cancer
 - Adenocarcinoma
 - Intestinal, diffuse, mixed
 - Staging: American Joint Committee on Cancer (AJCC) T, N, M stages
 - T Depth of penetration
 - N Number of enlarge nodes with malignant features
 - M Presence of metastases
- 5-yr survival rates
 - Stage I 57%
 - Surgery is curative: all others require
 - Surgery plus adjuvant chemotherapy/chemoradiotherapy, or
 - Perioperative chemotherapy
 - Stage IV 5%
- Palliation
 - Please see Tey JCS, et al. Cochrane Database of Systemic Reviews 2019, Issue 10. Art No: CD013450
- Radiotherapy
 - Indication
 - Bleeding pain, obstruction (tolerates solids,
 - Bleeding
 - Mechanism
 - Response rate, 50% to ~90%
 - Pain
 - Response rate, 46% to 86%
 - Obstruction
 - Response rate, 53% to ~80%
- Gastrectomy
 - Indications
 - Bleeding, pain, obstruction
 - Other procedures
 - Palliative gastrojejunostomy (gastric outlet obstruction)
 - Stent
 - Self-expandable metal shunt (SEMS)
 - Plastic



❖ Surveillance

• CAG (CA, GIM)

- ↑ risk of progression (CAG, GA, CIM, GD, EGCA, GCA)
 - Extent of GA/GIM
 - Family history
 1. First-degree relative
 2. Second-degree relative

Histologically proven GCA



Cumulative 5-yr incidence of GCA, 10%

- Surveillance of GA/GIM is controversial, but the following is recommended

Recommendations

- For GA/GIM affecting antrum and body, perform endoscopic surveillance q3yr
 - Perform endoscopic surveillance q3yr should be offered to patients diagnosed with extensive GA or GIM, defined as that affecting the antrum and body (evidence level: low quality; grade of recommendation: strong; level of agreement: 100%).
 - For GA/GIM limited to antrum, plus additional risk factors (strong family history persistent chronic H. pylori infection and chronic active gastritis) – perform EGD q3yr
 - Do **not** do surveillance in patients with GA or GIM limited just to the gastric antrum; unless
 - There are additional risk factors such as a strong family history of gastric cancer or persistent H. pylori infection (then 3-yearly surveillance)Evidence level: low quality; grade of recommendation: strong; level of agreement: 93%
- Patient with non-visible dysplasia should have immediate second EGD plus enhanced imaging plus full biopsy protocol
 - Persistent non-visible LGD → repeat EGD plus biopsies q1yr
 - Patients with non-visible LGD have immediate second endoscopy with enhanced imaging and extensive biopsy sampling, repeat EGD within 1 year, if no visible neoplasia is detected.
 - If there is persistent, non-visible LGD, EGD should be repeated annually thereafter.
- Evidence level: low quality; grade of recommendation: strong; level of agreement: 100%
 - Persistent non-visible HGD → repeat EGD plus biopsies q6mon, and discuss at multidisciplinary meeting
 - Patients with non-visible HGD have immediate second endoscopy with enhanced imaging and extensive biopsy sampling.



- Do ongoing surveillance at 6-monthly intervals for persistent, non-visible HGD.
 - Discuss HGD at the regional upper GI cancer MDT and referred to a clinician with the appropriate expertise
- Evidence level: low quality; grade of recommendation: strong; level of agreement: 100%

- HGD

- Risk of progression of HGD found on random biopsy to GCA is 6% per yr
 - Detectable dysplastic lesion in 80%
 - Synchronous GCA in 30%
- Histological diagnosis may underestimate severity of lesion
 - Initial diagnosis of
 - LGD upgraded to $\geq$ HGD in 25%
 - Indefinite for dysplasia upgraded to $\geq$ GD in 25%

Recommendation

- Persons whose gastric mucosal biopsies are reported as being indefinite for GD should be "... reviewed by an expert pathologist and undergo a repeat procedure with image enhancement."
- Perform endoscopic resection (ER) for visible LGD/HGD
 - Perform surveillance rather than ER
 - ER not possible, not appropriate, or not preferred by patient
 - Dysplasia not visible
 - Surveillance, HGD
 - Repeat EGD plus biopsy q6mon
- Surveillance after endoscopic mucosal resection (EMR) / endoscopic submucosal dissection for GD/ECA
 - After EMR/ESR
 - Risk of recurrence
 - Synchronous lesions
 - Metachronous

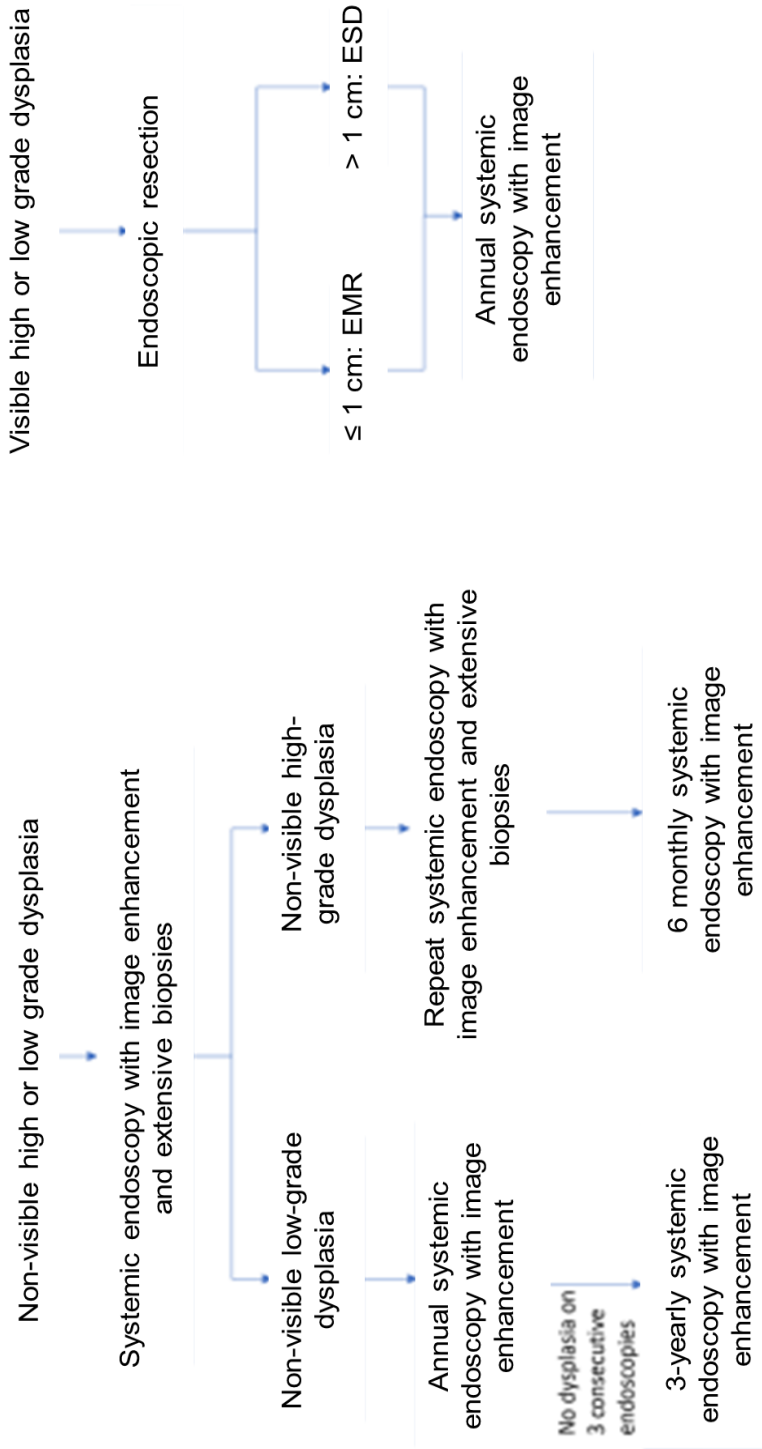
} 10% to 20%





- ❖ Treatment
- Endoscopic therapy

BSG Guidelines for the Endoscopic Management of Gastric Dysplasia



Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NVHGD, non-visible high-grade dysplasia; NVLGD, non-visible low-grade dysplasia;

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- Options
 - Stents
 - Endoscopic laser therapy (neodymium-yttrium-aluminium-garnet (YAG))
 - Successful relief of dysphagia in ~70%, but procedure may need to be repeated, and perforation rate is 5%
 - Argon plasma coagulopathy for bleeding of tumour
- The intestinal-type adenocarcinoma has a better prognosis than the diffuse-type, and the following recommendations refer to the intestinal type of GCA.
 - The prognosis depends upon the LNM classification (but the diffuse-type does not).
- Superficial intestinal adenocarcinoma lesions have a low risk of LNM, and the cancer-specific survival can be predicted from the LNM risk groups.

Recommendations

- For intestinal-type adenomatous lesions of GD/EGCA, perform
 - EMR for complete endoscopic/resection (R0) en bloc of lesions ≤ 10 mm, and
 - ESR for lesions > 10 mm (risk of LNM in the following low risk superficial lesion is $< 1\%$, with 5-yr disease-free survival of rates of 99%)
- These lesions include
 - Dysplasia
 - LGD/HGD
 - Well/moderately differentiated
 - Intramucosal adenocarcinoma
 - No ulceration, any size
 - Ulceration, < 3 cm
 - Submucosal adenocarcinoma
 - < 3 cm
 - SM, < 500 μ m submucosal invasion
 - Poorly differentiated
 - Intramucosal adenocarcinoma, ≤ 2 cm
- Do **not** perform EMR/ESR for lesions with high risk for LNM involvement
 - Histological features of high risk of LNM after EMR/ESR
 - Submucosal cancer
 - Poorly differentiated (regardless of extent of invasion below muscularis mucosa)
 - Well differentiated, ≥ 500 μ m invasion below muscularis mucosa
 - Signet ring cells
 - Lymphovascular invasion



- The eCura system may be used to predict the risk of LMN, and therefore the cancer-specific 5-yr survival

Risk factor	Points	Risk Assessment	Risk of LNM	Cancer-specific 5-yr Survival
- Lesion				
▪ Size > 3 cm	1	0-1	~3% (low)	99.6%
▪ Vertical margin	1	2-4	~7% (intermediate)	
- Invasion				
▪ Submucosal ≥ 500 µm	1	5-7	~23% (high)	90%
▪ Venous	1			
▪ Lymphatic	3			

- Pharmacological treatment

- Aspirin (ASA)
 - ↓ risk of GCA (cardia, non-cardia)
 - OR 0.7 (95% CI, 0.6 to 1.0)
- ASA or NSAIDs
 - ↓ risk of GCA
 - ASA, 0.7 (95% CI, 0.62 to 0.82)
 - NSAIDs, 0.86 (95% CI, 0.80 to 0.94)
- Further studies are required before the use of ASA, NSAIDs, COXIBs or antioxidants can be recommended for prophylaxis of these premalignant conditions.

Recommendations

- Do **not** use NSAIDs common COXIBs to ↓ risk of progression of premalignant conditions of the stomach.

➤ Palliation

Palliative gastric radiotherapy with or without chemotherapy versus non-radiotherapy approached for locally advanced or metastasis (or both) gastric cancer (Tey JCS, et al, Cochrane Database of Systemic Reviews 2019, issue 10. Art No: CD013450. DOI: 10.1002/14651858.CD013450

- Radiotherapy

- Indication
 - Bleeding, pain, obstruction (tolerates solids, or liquids, or require parenteral nutrition)
- Bleeding
 - Mechanism
 - Vascular endothelial injury-formation of thrombosis
 - Response rate, 50% to ~90%



- Pain
 - Response rate, 46% to 86%
- Obstruction
 - Response rate, 53% to ~80%
- Gastrectomy
 - Indications
 - Bleeding, pain, obstruction
 - Other procedures
 - Palliative gastrojejunostomy (gastric outlet obstruction)
 - Stent
 - Self-expandable metal shunt (SEMS)
 - Plastic
- ❖ Endoscopic Screening of GCA
 - In populations with a low risk of GCA, do **not** perform EGD screening or surveillance.
 - In persons ≥ 50 yr of age plus multiple other risk factors (male, smokers, personal history of pernicious anemia, or family history of first-degree with relative with GCA)
 - Consider EGD screening
 - If initially EGD is normal
 - Do **not** repeat (i.e., do **not** do surveillance)
 - If initial EGD shows GA/GIM
 - Follow the above guidelines
- ❖ Epithelial Gastric Polyps
 - Types
 - Adenomatous
 - Hyperplastic
 - Fundic gland
 - These guidelines do **not** apply to non-epithelial polyps, e.g., neuroendocrine tumours (NETs) or gastrointestinal stromal tumours
 - Fundic Gland Polyps (FGPs)
 - Common, multiple (most common type of gastric polyp)
 - < 1 cm, smooth, shiny, light
 - Larger (> 1 cm)
 - $\uparrow$ risk of GD/GCA (2%)
 - Tiny gray dots on surface (seen best within enhanced imaging)



- In fundus/body
 - Same or lighter colour, NPV for FGP ~95%
 - Lacy vessels, isolated or homogenous absence of vascular pattern, NPV for GA/GCA, 100%
 - Same or light in colour, homogenous absence of surface pattern, FGPs ~ 95%
- Associations
 - Idiopathic
 - Use in PPIs
 - Familial adenomatous polyposis (FAP)

- Optical enhancement EGD
 - Small round pits, homogenous microvascular pattern
 - Sensitivity, 95%; Specificity, 97%
 - Same or light colour, no vessels/isolated lacy vessels are FGPs
 - Sensitivity, ~65%; specificity, ~95%

- Suspect association with FAP
 - Patient < 40 yr
 - Family history of FAP
 - Polyp
 - > 1 cm, > 20 in number
 - GD (abnormal surface and vascular pattern)
 - Present in duodenum (usually in gastric fundus/body)
 - When these risk characteristics are present → screen colonoscopy.
 - Surveillance gastroscopy
 - Only with FAP association
 - Use Spiegelman scoring system to assess risk/need for surgical resection of duodenum
- Hyperplastic polyps (HP)
 - Second most common type of gastric polyp
 - Associated with gastric
 - Ulcers
 - Stomas
 - Gastrectomy site
 - Usually, < 1.5 cm
 - Surface erosions



- Associated with CAG / H. pylori infection
 - In the post gastrectomy stomach / > 1 cm more
 - GD ~10%
 - GCA 2%
 - Surrounding synchronous GCA, 6%
 - Dysplastic HP
 - Test, treat for H. pylori infection, and prove eradication
 - Resect if
 - Pedunculated
 - > 1 cm
 - Bleeding, obstruction
 - Preferably use enhanced endoscopic imaging (EEI)
 - For certain use EEI if WLE does not give certain diagnosis
 - Hyperplastic Foveolar Polyps (HPFP)
 - Small, flat plaques in fundus (MWFL, multiple white flat lesions)
 - Endoscopy
 - Foveolar pit pattern
 - Histopathology
 - Hyperplasia of foveolar epithelium
 - MWFL
 - Fundic gland protrusions of parietal cells
 - Oxyntic gland protrusions
- Optical enhancement EGD

 - Long / villous pits, dense vascular pattern
 - Sensitivity, ~95%; specificity, 92%
- Treatment
 - Exclude associated GD, synchronous GCA, H. pylori infection
 - Treat for H. pylori if positive, and confirm eradication
 - Resect large, pedunculated or symptomatic HP
 - If GA, GD, CIM → enter into appropriate surveillance program
 - Adenomatous Polyps (AP)
 - Least common gastric polyp, ~10%
 - Small (< 2 cm), single (80%)
 - Antrum, incisura
 - Pink, lobulated
 - Sessile/pedunculated



- Audit Targets
 - GIM +/- GA, 10%

- Highly premalignant
 - Associated GA, GIM
 - > 2 cm, GCA in 50%
 - Synchronous GCA, 30%
- Resection
 - EMR, unless > 1.5 cm → ESD
 - Repeat EGD in 6 to 12 mon, then q1yr (interval depends upon AP number/size and GD)

Recommendations

- Documents
 - Photographic documentation
 - Do photographic documentation for all polyps or representative polyps, if numerous

(Evidence level: low quality; grade of recommendation: strong; level of agreement: 100%).

- Location, number of polyps, and
- Size of largest polyp
 - Document
 - The number of gastric polyps (or estimated number)
 - Location
 - Size

(Evidence level: low quality; grade of recommendation: strong; level of agreement: 100%).

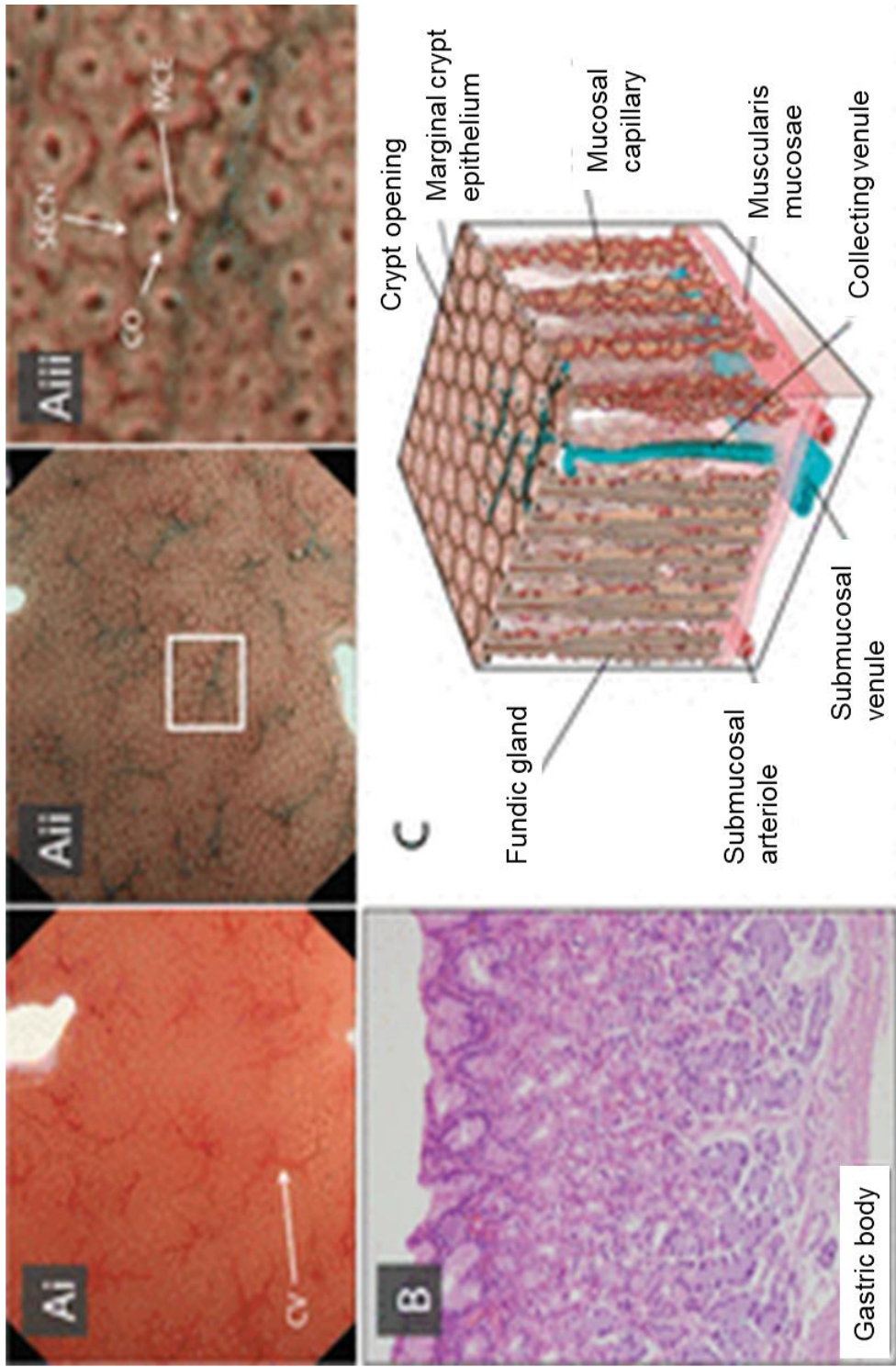
- Histological examination for all
 - Hyperplastic (HP) and adenomatous polyps (AP)
- Biopsy
 - Gastric polyps other than FGPs should be biopsied for histopathological assessment (Evidence level: low quality; grade of recommendation: strong; level of agreement: 100%).
 - Assess background for GA, GIM, H. pylori infection, synchronous neoplasia,
 - Fundic gland polyps (FGPs)
 - Colour
 - Lighter or same as background > 1 cm
 - Dark
 - Brown surrounded by white colour

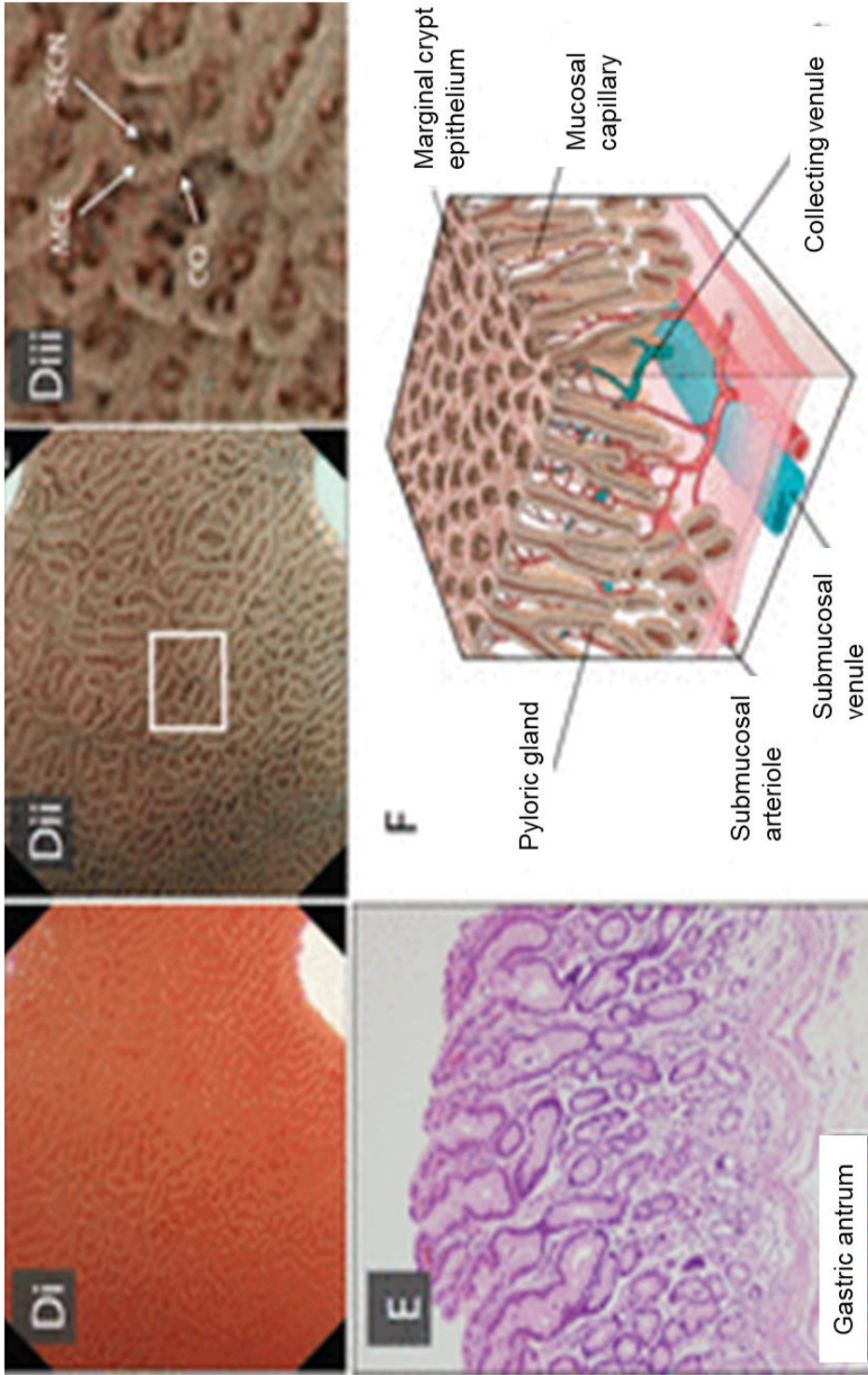


Abbreviations: AP, adenomatous polyp; ASA, aspirin; BSG, British Society of Gastroenterology; CAG, chronic atrophic gastritis; cm, centimetres; CS, Cowden syndrome; EGCA, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESR, endoscopic submucosal resection; FAP, familial adenomatous polyposis; FGP, fundic gland polyp; FICE, flexible spectral imaging colour enhancement; GCA, intestinal-type gastric cancer; GD, gastric dysplasia; GIM, gastric intestinal metaplasia; GIST, gastrointestinal stromal tumour; GRADE, Grading of Recommendation Assessment Development and Evaluation (system); H. pylori, *Helicobacter pylori* (infection); HDGCA, hereditary diffuse gastric cancer; HGF, high grade dysplasia; HNPCC, hereditary non-polyposis colon cancer; HP, hyperplastic polyp; HPFP, hyperplastic foveolar polyp; IEE, imaging enhancement endoscopy; JPS, Juvenile polyposis syndrome; LBC, light blue crest; LGD, low grade dysplasia; LNM, Lymph node metastasis; LP, lamina propria; mon, month; MTB, marginal turbid band; MWFLs, multiple white flat lesions; NBI, narrow band imaging; NET, neuroendocrine tumour; NPV, negative predictive value; NSAID, non-steroidal anti-inflammatory drug; OLGA, operative link on gastritis assessment (staging system); OLGIM, operative link on gastric intestinal metaplasia (staging system); OR, odds ratio; PA, pernicious anemia; PG, pepsinogen; PICO, Patients, Interventions, Controls, and Outcomes (system); PJS, Peutz-Jeghers syndrome; PPIs, proton pump inhibitors; PPV, positive predictive value; PTHS, PTEN tumor syndrome; Sn, sensitivity; Sp, specificity; yrs, years



Normal gastric corpus and antrum mucosal surface pattern with white light, enhanced and magnification endoscopy.





Printed with permission: Banks M, et al. Gut 2019; 68: 1545-75. (Figure 3)



- The round 'pit patterns' of the corpus (Ai) and elongated 'pit patterns' of the antrum (Di) can be seen without magnification or enhancement.
 - In the corpus (Ai), the red collecting venules (CV) are evident as well as the round dark red crypt openings (CO).
- The vascular anatomy becomes more pronounced with NBI (Aii & Dii).
 - The visible anatomical components seen on magnification NBI include the dark brown 'crypt openings' (CO), the dark brown sub-epithelial capillary network (SECN), and the light brown marginal crypt epithelia (MCE).
- The corpus mucosa has dark round 'crypt openings', surrounded by the lighter MCE, followed by the darker circular SECN (Aii & Aiii).
 - In contrast, the dark, oblique 'crypt openings' in the antrum are grooved so the light coloured ridged or villiform epithelium (MCE) surrounds the dark SECN, termed the 'groove type pattern' (Dii & Diii).
- The corresponding histopathological architecture can be seen in the corpus (B and C) and in the antrum (E and F).

- The risk of cancer for patients with gastric atrophy and intestinal metaplasia

	Annual incidence (%)	5-Year incidence of gastric cancer (%)
○ All GA	1.9	0.1–0.5
– Mild GA	0.7	
– Severe GA	10	
○ All GIM		0.15–0.4
		0.25
– Antral GIM	5.3	
– Antral and corpus GIM	9.8	
	Interval of 4-48 mon	
○ Low-grade dysplasia	0–23	0.6
– High-grade dysplasia	60–85	6

Abbreviations: GA, gastric atrophy; GIM, gastric intestinal metaplasia.

Printed with permission: Banks M, et al. Gut 2019; 68: 1545-75. (Table 3)

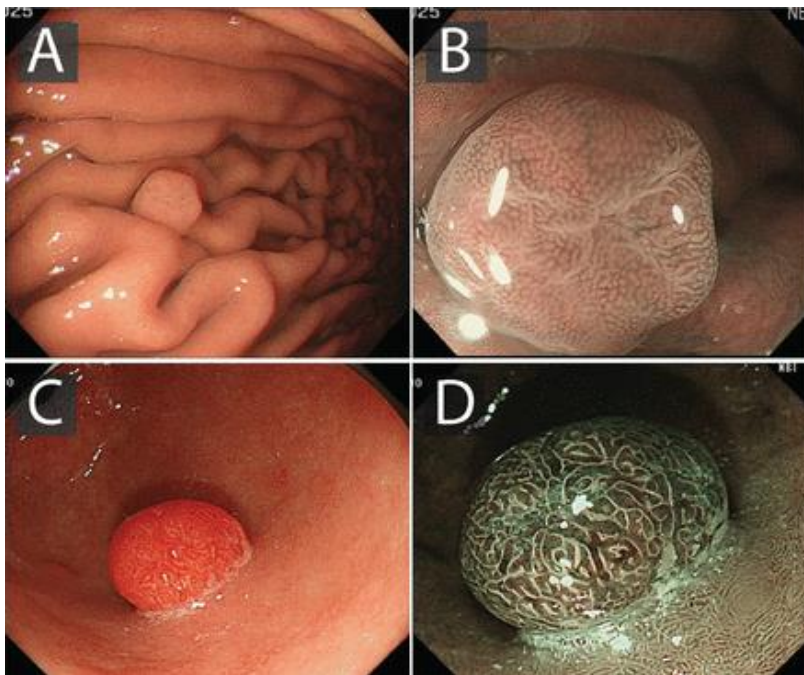
- Criteria for referring to genetic services
 - Suspected familial gastric cancer
 - Gastric cancer in one family member before age 40.
 - Gastric cancer in two first-degree/second-degree relatives with one diagnosis before age 50*, or
 - Gastric cancer in three first-degree/second-degree relatives, independent of age*.



- Suspected hereditary diffuse gastric cancer
 - One case of diffuse gastric cancer age < 40, or
 - Two cases of gastric cancer regardless of age in two first-degree/second-degree relatives, at least one confirmed diffuse gastric cancer*, or
 - Personal and family history of diffuse gastric and lobular breast cancers, with one diagnosis before age 50.
 - A personal or family history of cleft lip/palate in a patient with diffuse gastric cancer.
 - In situ signet ring cells or pagetoid spread on gastric biopsies.

*In order to account for significant family history, the affected relatives need to be within the same side of the family (maternal or paternal).

Fundic Glandular and Hyperplastic Polyps



- Fundic glandular polyps seen in the corpus and body. They are either lighter or the same colour as the surrounding mucosa.
- On near view, with image enhancement, lacy blood vessels are seen through the translucent surface and the surface shows a pattern of fine grey dots.
- Hyperplastic polyps are smooth, red, buttered with whitish exudates (fibrin) and are dome shaped.
- The surface vascular pattern is more prominent on image enhancement (D).

Printed with permission: Banks M, et al. Gut 2019; 68: 1545-75. (Figure 7)



- Relative to the background mucosa, polyps are divided in two groups:
 - Lighter or same colour
 - Further subdivided according to their vascular network
 - Darker
 - a) Isolated vessels
 - b) No vessels
 - c) Brown vessels surrounding white structures
- Hereditary Gastric Cancer (HDGC)
 - Clinical suspicion
 - Associated with lobular breast cancer as well as colon cancer
 - Require surveillance of stomach, colon, and breasts
 - Genetic testing if
 - Personal history
 - Diffuse gastric cancer age < 40 yr
 - Family history
 - ≥ 3 family members with documented diffuse gastric cancer in first or second degree relatives of any age
 - ≥ 2 family members if diffuse gastric cancer, with ≥ 1 diagnosed when < 50 yr
 - Surveillance
 - Stomach
 - Diffuse gastric cancer age < 40 yr
 - Colon
 - Colonoscopy after 40 yr if family member with CRC
 - Breast
 - Age 35 clinical examination (q6mon, mammography q1yr and MRI q6mon (Conditional recommendation, low quality evidence)



Gastric Cancer Therapy

❖ Stomach

Palliative gastric radiotherapy with or without chemotherapy versus non-radiotherapy approached for locally advanced or metastasis (or both) gastric cancer (Tey JCS, et al. Cochrane Database of Systematic Reviews 2019, Issue 10. Art. No.: CD013450. DOI: 10.1002/14651858.CD013450)

➤ Pathology

- Adenocarcinoma
 - Intestinal, diffuse, mixed
- Staging: American Joint Committee on Cancer (AJCC) T, N, M stages
 - T Depth of penetration
 - N Number of enlarged nodes with malignant features
 - M Presence of metastases

➤ 5-yr survival rates

- Stage 1 57%
 - Surgery is curative: all others require
 - Surgery plus adjuvant chemotherapy/chemoradiotherapy, or
 - Perioperative chemotherapy
- Stage IV 5%

➤ Palliation

• Radiotherapy

- Indication
 - Bleeding, pain, obstruction (tolerates solids, or liquids, or require parenteral nutrition)
- Bleeding
 - Mechanism
 - Vascular endothelial injury-formation of thrombosis in/near bleeding vessels
 - Response rate, 50% to ~90%
- Pain
 - Response rate, 46% to 86%
- Obstruction
 - Response rate, 53% to ~80%



- Gastrectomy
 - Indications
 - Bleeding, pain, obstruction
 - Other procedures
 - Palliative gastrojejunostomy (gastric outlet obstruction)
 - Stent
 - Self-expandable metal shunt (SEMS)
 - Plastic
- ❖ Endoscopic therapy
 - Options
 - Stents
 - Endoscopic laser therapy (neodymium-yttrium-aluminium-garnet (YAG))
 - Successful relief of dysphagia in ~70%, but procedure may need to be repeated, and perforation rate is 5%
 - Argon plasma coagulopathy for bleeding of tumor



SUBEPITHELIAL LESIONS

Diagnosis and Management of Gastrointestinal Subepithelial Lesions: ACG Clinical Guideline (2023)

Jacobson BC, et al. Am J Gastroenterol 2023;118(1):46-58

➤ Terminology

- The term subepithelial lesion (SEL) used to describe mass or mass-like structure that projects into the GI lumen
 - Arises from a non-mucosal layer within the GI tract wall
 - Structures adjacent to the GI tract can lead to extrinsic compression that mimic SEL
- Historically, SELs were called “submucosal” lesions
 - Because of they originated below the mucosa
 - With EUS, you see all the layers
 - Since the “submucosa” is a layer on its own, it could be confused for a lesion originating from that layer alone

➤ Pathology

- SELs are most commonly seen during endoscopy although sometimes picked up on CT scans
- The potential for SEL to be neoplastic is broken down into lesions which are
 - Non-neoplastic lesions
 - Neoplastic but benign
 - Neoplastic with malignant potential
 - Malignant

➤ Clinical

- Usually asymptomatic but
 - If they are large enough → dysphagia, overt/occult GI bleeding and chronic anemia
- Their location under the mucosa makes it difficult to diagnose from simple biopsy during endoscopy
 - Especially heterotopic pancreas, and lipoma
 - Malignant potential
 - NET
 - GIST
 - Granular cell, heterotopic pancreas (rare)

➤ Differential Diagnosis

- Extrinsic compression
 - ~1/3 of SEL are extrinsic compression
 - Esophagus ← Spine, bronchogenic cyst
 - Stomach
 - Fundus ← xepheid process
 - Antrum ← gallbladder
 - Duodenal bulb ← gallbladder



- Layer of bowel wall
 - Location
 - Muscularis mucosa (MM)
 - Esophagus - LEIO, GCT
 - Stomach - GIST, HP
 - Submucosa (SM)
 - Stomach - NET, HP, SCH
 - Colon - LIP
 - Rectum - NET
 - Muscularis propria (MP)
 - Esophagus - LEIO
 - Stomach - NET, GIST, HP, SCH
 - Duodenum - NET
 - Small bowel - LYM
 - Rectum - NET
 - All layers, all sites
 - Metastases
- Along the GI tract
 - Esophagus - LEIO, GCT
 - Stomach - NET, HP, SCH
 - Small bowel - LYM
 - Colon - LIP
 - Rectum - NET

➤ Diagnosis

Recommendation

- Perform Endoscopic Ultrasound (EUS) preferentially endoscopy or contrast-enhanced cross-sectional imaging for the diagnosis of non-lipomatous SEL (conditional recommendation; very low quality of evidence).
- SELs diagnosis is based on endoscopic appearance and radiographic (except for lipomas)
- Lipomas
 - Present anywhere in the GI Tract
- Endoscopy (EGD, colonoscopy)
 - Does **not** differentiate from extramural lesion
 - Slight yellow appearance
 - Positive pillow sign (where lipoma is easily deformed when pressed with a closed biopsy forceps akin to one's head indenting a pillow)
 - Specificity, 99%
 - Sensitivity, 40%
 - Lipomas will have the same Hounsfield units as fat
- EUS correctly differentiates an intramural from extramural lesion with white light endoscopy compared to EUS
 - Sensitivity, 87%
 - Specificity, 29%



- CT does **not** detect smaller (< 3 cm) SEL would miss many neuroendocrine tumours
 - CT scanning only good for diagnosis, **not** for tissue acquisition
- No recommendation of using forward viewing vs oblique viewing echoendoscope when evaluating SEL (strong recommendation; low quality of evidence).
- Forward viewing echoendoscope may be more helpful in
 - Cases of post-surgical anatomy
 - Multiple randomized studies have compared forward-viewing echoendoscopes with standard oblique-viewing linear echoendoscopes
 - Otherwise, no significant differences in diagnostic yield for SEL using forward-US oblique-side echoendoscope
 - 6 min shorter procedure time with forward viewing echoendoscope

Recommendation

- Do **not** take bite-on-bite biopsies in the evaluation of SEL before EUS (conditional recommendation; very low quality of evidence).
- Standard biopsy forceps are **not** recommended for diagnosis of SELs
 - They fail to sample deeper than the mucosal layer of the GI Tract – leading to inadequate sampling
- Use jumbo biopsy of crypts for “bite-on-bite biopsies” (BBB) to remove the mucosa above the SEL
 - Then perform repeat biopsies within the mucosal defect
 - EUS, then BBB
 - Diagnostic tissue in 92% (66 of 72) of patients, with no complications
- Only 1 prospective study was done in 2011 at RUSH medical Centre, comparing
 - 93 patients, first had EUS and then Bite on bite. 72 underwent bite on bite biopsy technique
 - In EUS, then FNA only 58% were amendable to EUS-FNA (lesion too small or too mobile)
 - Of those that had FNA, only 42 out of 93 had sufficient material to render a diagnosis
 - This suggests that bite on bite is better at obtaining tissue for diagnostic yield, but all bite on bite were done after EUS, which confirmed non vascular lesion or confirmed it was not extrinsic compression.
 - Therefore, guidelines do suggest that bite on bite biopsy with jumbo forceps be considered if
 - EUS with FNA/FNB with ROSE (rapid on-site evaluation) is not feasible, and
 - If vascular lesions are excluded based on the clinical scenario and endosonographic appearance
- Use EUS plus tissue acquisition to improve diagnostic accuracy in the identification of solid non-lipomatous SEL (conditional recommendation; very low quality of evidence).
- EUS imaging alone is **not** inadequate to diagnose solid non lipomatous SEL
 - Diagnostic yield of type of SEL on first EUS is 43-50%
 - Differentiating benign from malignant SEL
 - Sensitivity, 64-80%
 - Specificity, 77-80%



- Some EUS findings associated suggest malignancy (especially for GIST)
 - Heterogenous echotexture
 - Large size (>3 cm in some studies, >5 cm in others)
 - Irregular margins
 - Echogenic foci, and
 - Cystic spaces
- ≥ 2 of irregular border, echogenic foci, and cystic spaces, sensitivity for malignancy in a GIST, 80% to 100%
 - Absence of all EUS findings, chance of malignancy
- Thus, EUS findings can be helpful but not perfect in SELs
 - Even better for only 0-11% GIST (which EUS is the best for)
- Interobserver variability of interpreting EUS, argues against EUS without tissue acquisition
 - EUS is good-to-excellent for cysts and lipomas, but
 - Poor-to-fair for other SELs such as leiomyomas and vascular lesions
- Fine needle aspiration (FNA) or fine needle biopsy (FNB) has been consistently shown to ↑ diagnostic accuracy compared to EUS alone
 - ↑ diagnostic accuracy with tissue acquisition from a range of 30%–50%, to a range of 73%–84%
- Note
 - Tissue diagnosis is **not** always possible for small or mobile lesions
 - For these small / mobile lesions
 - Homogenous appearing SEL which lack worrisome features of malignancy (mentioned above) can be followed safely as they have a low risk for developing malignancy
- It is **not** known for what the number of SEL we are unable to attain FNA/FNB
 - “In the absence of a tissue diagnosis and/or resection of an SEL, the patient should be enrolled in some form of surveillance plan unless there is a high degree of confidence that the SEL has no malignant potential”
- Perform EUS-FNB alone / EUS-FNA plus ROSE sampling
- For solid non-lipomatous SEL compared with EUS-FNA without ROSE (conditional recommendation; low quality of evidence).
- For mostly SELs > 2 cm, 10 total studies (6 randomized trials) compared EUS-FNA with FNB of SEL
- FNB of SEL gives
 - ↑ rates of adequate samples
 - ↑ histologic cores
 - ↑ diagnostic accuracy, and
 - Requires ↓ numbers of needle passes vs. FNA
- However, FNA plus ROSE gives better results, with
 - No significant differences between FNA and FNB
- Biomarker staining and quantification of mitotic figures yield (needed for GIST) yield better immunohistochemical



- Lesions < 2cm
 - Often amenable to sampling (depends on location)
 - There is no fixed cutoff in size below which FNA/FNB may not be attempted
 - Very small lesions can be resected completely and assessed for pathology
- Use an unroofing technique when a pre-resection definitive diagnosis of an SEL is necessary and when EUS-FNA or FNB is nondiagnostic (conditional recommendation; low quality of evidence).
- “Unroofing” is the use of endoscopic submucosal dissection (ESD) to obtain a sample when EUS methods have failed to provide a diagnosis
 - Use some form of mucosal incision (e.g., free hand needle knife) to exposure the submucosa for
 - Direct biopsy of the SEL or
 - To permit a tunneled approach to reach the SEL (“Mucosal incision-assisted biopsy [MIAB]”)
 - The mucosal defect is usually closed with clips post biopsy
- Prospective randomized and non-randomized studies suggest that
 - Overall, unroofing technique/MIAB provide a higher diagnostic yield and are safe for those with the specific training, but
 - Still clinical equipoise regarding whether these are more superior than FNA/FNB
 - Limitation of the unroofing techniques
 - Submucosal dissection → local fibrosis which can hinder future attempts at endoscopic resection
 - When EUS-FNA/FNB is non-diagnostic, and when pre-resection diagnosis is required
- With small SEL confined to the deep mucosa or submucosa)
 - Primary endoscopic resection may be the preferred strategy for both diagnosis and treatment

➤ Treatment

- Asymptomatic benign SEL do **not** require resection
 - Consider risk of malignant transformation (e.g., size of lesion) resection risk, patients overall health)
 - Inadequate evidence to make definitive recommendations regarding surveillance intervals
- Endoscopic resection
- Performed to treat some SELs

• EMRs

- Elevate the lesion away from the muscularis propria before snare resection
 - Injection of fluid into submucosa, flooding GI lumen with water, or use of banding device
 - Elevating the lesion
 - Helps with tissue capture
 - Limits thermal injury to deeper layers (↓ risk of complications)



- ESD
 - Inject fluid into the submucosa (create an incision around the perimeter of the lesion)
 - Carefully dissect the lesion from the deeper layers
 - Allows for precise control of both lateral and deep margin dissection with electrocautery knives
- STER: Submucosal tunneling endoscopic resection
 - Similar to per oral endoscopic myotomy (POEM) to form a submucosal tunnel which
 - Allows for access to, and removal of, tumors arising from the muscularis propria (MP) layer
 - Keeps the integrity of the mucosa intact, avoiding a full thickness defect/perforation

Recommendation: Treatment

- Use STER or surgical resection for the management of SEL originating from the muscularis propria (MP) layer of the esophagus / gastroesophageal junction (GEJ) when resection is necessary (conditional recommendation; very low quality of evidence).
- SELs coming from the muscularis propria (MP) of the esophagus or GEJ are almost always GIST or leiomyomas
 - Leiomyomas do **not** have malignant potential
 - Some GISTs need to be removed
 - Overall, endoscopic or surgical removal is required for
 - Symptomatic lesions and for a subset of GIST
- Traditionally in the past, these lesions that required removal were done with surgically with thoroscopic Enucleation, but now some endoscopic techniques are used:
 - STER is ESD
 - Potential advantages of STER over traditional ESD is
 - Preserve the integrity of the mucosal layer (theoretically ↓ chance of leaks / infectious complications)
- STER vs Surgery – limited evidence (1 retrospective trial and one small prospective randomized trial)
 - Rate of successful en bloc resection and adverse events were similar
 - But procedure time (50 less mins) and hospital length of stay (2.5 days shorter) favoured STER
- “Because both STER and surgical resection are feasible techniques with comparable out- comes, the resection method may be driven by available local expertise”

Recommendation: Surveillance vs. Resection

- There is insufficient evidence to recommend surveillance vs resection of gastric GIST <2 cm in size.
 - Resection is suggested for gastric GIST >2 cm and all non-gastric GIST owing to their malignant potential (conditional recommendation; very low quality of evidence).



- The management of incidentally found GIST < 2cm is controversial
 - The incidence of metastasis in lesions this size approaches 0% regardless of mitotic rate
 - If there are no high-risk features for a <2cm gastric GIST (irregular borders, cystic spaces, ulceration, echogenic foci, or heterogeneity), then endoscopic or radiographic surveillance is reasonable (The National Comprehensive Cancer Network guidelines)
 - If high risk features, then surgical resection is recommended
- For GIST <2 cm, if the clinical decision is to resect, endoscopic methods may be considered as acceptable alternative therapies compared with surgery
 - Insufficient data to suggest any 1 endoscopic method over another
- GIST > 2cm
 - Have a high rate of metastatic spread (which increases with the size of the lesion)
 - Lesions > 10 cm plus a high mitotic rate
 - Risk of metastases, 86%
- Resect these lesions
 - ESD vs Surgery
 - ↓ procedure time, ↓ blood loss, and ↓ length of hospital stay
 - No significant difference in tumour recurrence
 - However overall, all of the studies showed that the surgery group had larger lesions

Recommendation

- Perform EMR or ESD for the resection of type 1 gastric neuroendocrine tumours (gNETs) (conditional recommendation; very low quality of evidence).
- Gastric NETs are classified into type 1, type 2 and type 3

➤ Types

Characteristic	gNET Type 1	gNET Type 2	gNET Type 3
Relative frequency	70-80%	5%	10-15%
Cell of origin	Enterochromaffin-like cells (ECL)		
Size/Number	Small and Multiple	>2cm, solitary (aggressive)	
Location	Fundus and Body		Any area
Serum Gastrin	↑ atrophic gastritis	↑ (tumours MEN-1)	Normal (aggressive)
Gastric Acid Secretion	Low	High	Normal
Risk of Mets	2-5%	10-20%	>50%

Qayed E. Gastroenterology Clinical Focus (Pocket Edition). 2022.

- ESD and EMR have been compared in small retrospective studies and have shown similar negative margin resection rate (ESD has favoured towards being better but not statistically significant)



Recommendation

- Perform ESD rather than EMR for the resection of low-grade, small, type 3 gNET without radiologic or EUS evidence of lymphadenopathy that do **not** undergo surgical resection (conditional recommendation; very low quality of evidence).
- Perform endoscopic resection
 - Superficial low grade, small tumours (< 1cm) with
 - No evidence of regional lymphadenopathy on EUS or other imaging
 - Only one retrospective study that looked at ESD vs EMR for type 3 gNETs
 - 50 patients with 41 in the EMR group and 9 in the ESD group
 - Positive margins were seen in 14.6% of EMR group and 11.1% (1 out of 9) in ESD group
 - When you combine this with the Type 1 gNET data for ESD vs EMR which showed higher R0 resection rates – makes more sense to suggest ESD over EMR for a more aggressive tumour
- There is no one type of endoscopic therapy (EMR vs ESD) for the resection of small (< 1 cm), low-grade rectal NET (conditional recommendation; very low quality of evidence).
- From all NET, rectal NET are thought to have the best prognosis
- The decision on how to resect them depends mainly on size of the lesion
 - < 1 cm – risk of metastasis was 3%
 - 1.1-1.9 cm – risk is 66%
 - >2cm – risk was 73%
- Consider endoscopic resection when the rectal NET are < 1 cm
- Data for EMR vs ESD
 - Mixed for small rectal NET (some show ESD has higher R0 resection while others show band ligation EMR does).
 - Most recent study showed similar rates of margin free resection
- Therefore, use either EMR or ESD can be used for small (< 1 cm) rectal NET

Abbreviations: EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection; FNA, fine-needle aspiration; FNB, fine-needle biopsy; GCT, granular cell tumour; GIST, gastrointestinal stromal tumors; HP, heterotopic pancreas; LEIO, leiomyomas; LIP, lipoma; LYM, lymphadenopathy; MIAB, mucosal incision–assisted biopsy; MM, muscularis mucosa; MP, muscularis propria; NET, neuroendocrine tumors; ROSE, rapid on-site evaluation; SCH, Schwannoma; SEL, subepithelial lesion; SM, submucosa; STER, submucosal tunneling endoscopic resection



GASTRODUODENAL OBSTRUCTION AND GASTROPARESIS

Endoscopic Management of Duodenal Obstruction

Ichkhanian Y and Khashab MA. Am J Gastroenterol 2019; 114: 1566-68

- Benign
 - Balloon dilations may be required
- Malignant
 - Usually palliative management
 - Attempt to avoid surgical gastrojejunostomy (mean survival time of these patients 12-16 wk)
- Treatment choices
 - Nasogastric decompression
 - Endoscopic
 - Enteral stenting (ES):
 - Uncovered self-expandable metal stents
 - High rate of recurrence from tumour ingrowth/overgrowth, ~30%
 - Median potency of ES 55 days
 - Endoscopic ultrasonography (EUS)
 - Guided gastroenterostomy (EUS-GE)
 - Transgastric approach and cautery-assisted lumen apposing metallic stent (LAMS)
 - Types
 - Direct
 - Balloon-assisted
 - Success rate
 - Technical, 93%
 - Clinical, 90%
 - Adverse events (AEs)
 - abdominal pain
 - Hemoperitoneum
 - Food impaction / occlusion of stent
 - Recurrence/need for re-intensifiers < 5%
 - Adverse events may be more severe than with ES



- Enteral Stenting and EU-GE in the management of gastric outlet obstruction: Clinical and Technical Consideration

Enteral Stenting (ES)	EUS-guided Gastro-enterostomy (EUS-GE)	Comments
○ Requires a self-expandable metal stent (SEMS) ○ Technical challenge – Less ○ Rate of stent occlusion in reintervention – Higher ○ The ability to pass the guide wire through the obstruction is prerequisite for ES. ○ Must ensure the absence of downstream stenosis ○ Contraindications – Intervening perigastric varices – Ascites: No – Extensive peritoneal adhesions: No	– Lumen-apposing metal stent (LAMS) – Technical challenge ▪ More – Rate of stent occlusion in reintervention ▪ Lower – Requires the small bowel lumen to be within 1-2 cm from the gastric wall. – Must ensure the absence of downstream stenosis – Intervening perigastric varices – Should be avoided in patients with large (↑ risk of peritonitis, leakage, and dehiscence) – Yes (↑ risk of delayed stent migration and leakage)	▪ An electrocautery-enhanced LAMS is required for direct EUS-GE ▪ EUS-GE requires training in advanced therapeutic endoscopy and EUS ▪ Stent occlusion is considered the major drawback of ES. ▪ Distance > 2 cm may result in – Incomplete apposition of the stomach and small bowel lumens, resulting in ↑ risk of leakage, stent migration, and perforation. ▪ Multiple sentences of obstruction may occur in patients with territorial carcinoma sources an extensive little Friday ▪ Patients with pancreaticobiliary tumour or thrombosis of portal vasculature ▪ No risk of developing perigastric varices ▪ Physical assessment and review of abnormal imaging are helpful in deciding the best approach ▪ Pulling the jejunum toward the stomach an maintaining it in that position using the lumen-opposing forces of the stent may not be possible during EUS-GE / ↑ risk delayed stent migration and leakage)

Abbreviations: AEs, adverse events; ES, enteral stent; EUS, endoscopic ultrasound; EUS-GE, endoscopic ultrasound gastroendoscopy; LAMS, lumen opposing metal stent; SEMS, self-expandable metal stent

Printed with permission: Ichkhanian Y and Khashab MA. Am J Gastroenterol 2019; 114: 1566-8



Gastroparesis: Narrative Review of the Work of the Gastroparesis Clinical Research Consortium (GpCRC) (2022)

Pasricha PJ, et al. Gastroenterol 2023; 20: 2684-2695

- Demography
 - Idiopathic gastroparesis, female > male (90% vs. 10%)
- Subtype
 - Idiopathic (ID)
 - Diabetic (DE), type I, II
- Severity
 - About 75% of patients have
 - ↓ gastric emptying (GE)
 - 2 h, 95%
 - 4 h, 32%
 - ↓ GE more common in DMT1
 - Severity
 - Mild, 17%
 - Moderate
 - Orally consumed (“compensated” nutrition), 61%
 - Severe
 - Non-oral nutrition support, 22%
 - ↑ nausea / ↑ hospitalization in “Blacks”, compared to other races (please see Pathophysiology, Genetics)
 - Hospitalization
 - 1.8 /yr
 - Total parenteral nutrition (TPN), 7%
 - Gastric electrical stimulator installed, 6%
 - A greater proportion of women than men has severe symptoms, but a lower proportion of women hospitalize

Adapted from Pasricha PA, et al. Clin Gastroenterol and Hepatol 2022; 20: 2684-2695 (Table 1)



Symptoms	Prevalence	↑ symptoms	Prediction for severe symptoms
○ Nausea	> 95% (IG = DG) (severe in ~60%)	– Food, ~66% – No food, ~25% – Motion, ~25%	– Positive ▪ Satiety/failures score, OR 2.83 – Negative ▪ Age, OR 0.194 ▪ SF-36 mental, 0.94; physical, 0.96
○ Abdominal pain	90% (IG = DG) (severe in ~33%)	– Food, 50% (↓ symptoms with food in 25%)	– Positive ▪ GCSI; OR, 2.1 ▪ Beck Depression Inventory Score; OR, 10 – Negative ▪ Age, every 5 yr; OR, 0.9 ▪ White race; OR, 0.4
○ Vomiting	IG, 57%; DG, 80% (severe in ~33%)	– Food, 75%	– Positive ▪ Satiety scores; OR, 2.14; ▪ GERD score, OR, 1.77 – Negative ▪ White race; OR, 0.2 ▪ Bloating score; OR, 0.62
○ Bloating	75% (severe in ~40%)		– Positive ▪ Constipation; OR, 1.15 ▪ Lower abdominal pain score; OR, 1.37 ▪ BMI; OR, 1.61 ▪ Female gender; OR, 2.81 – Negative ▪ PAGI-QoL scores; OR, 0.39
○ Early satiety fullness	66% (severe in 50-60%)	– Non-GI ▪ Depression/anxiety, > 50% ▪ Migraine, 41% ▪ Gallbladder disease, 35% ▪ Endometriosis, 16%	Early satiety – Positive ▪ Bloating; OR, 1.98 ▪ Upper abdominal pain score; OR, 1.55 ▪ Gastric retention at 4 h; OR, 1.03 ▪ Female gender; OR, 2.81 – Negative ▪ BMI; OR, 0.91 ▪ Female gender; OR, 0.29 Fullness – Positive ▪ Stomach seen to be larger; OR, 1.62 ▪ Upper abdominal pain score; OR, 1.68 – Negative ▪ BMI; OR, 0.95 ▪ Ritchey scorer; OR, 0.52



	Overall	Main Symptom
○ Associated disorders		
- GI		
▪ GERD	25%	10%
▪ IBS	66% (IBS-M in 50%) constipation, severe 60%	5%

Adapted from Pasricha PA, et al. Clin Gastroenterol and Hepatol 2022; 20: 2684-2695.

- Malnutrition
 - ↓ intake of calories (deficient), vitamins, correlate with symptoms of constipation and bloating, not pain or vomiting
 - Despite this, only 10% were BMI < 18.5, and 40% were overweight or obese
 - ~30% gained weight over a year of follow-up
 - Unexpectedly, these patients who gained weight had more gastric retention and constipation

Abbreviations: BMI, body mass index; DG, diabetic gastroparesis; IG, idiopathic gastroparesis; OR, odd ratio; GERD, gastroesophageal reflux disease; GCSI, Gastroparesis Cardinal Symptom Index; PAGI-QoL, Patient Assessment of Gastrointestinal Disorders Quality of Life; SF-36, Medical Outcomes Study Short-form



Prokinetics (PK)

Gudsoorkar, V; Quigley, EMM. Am J Gastroenterol 2020; 115: 5-8.

- Dopamine receptor antagonists
 - D2 receptors antagonists in
 - Central nervous system (CNS)
 - Central antiemetic effects
 - Enteric nervous system (ENS)
 - Metoclopramide also has
 - 5-hydroxy tryptamine (5-HT4)
 - Indications
 - Esophagus
 - GERD
 - Functional dyspepsia
 - Stomach
 - Nausea/vomiting
 - Gastroparesis
 - Serotonergic receptor agonists
 - Cisapride acts on esophagus, stomach and colon – limited use
 - ↑ LES
 - ↑ gastric emptying
 - ↑ colonic transit
 - Motilin receptor agonists
 - Erythromycin
 - Motilin receptor agonist
 - Cholinergic
 - Bethanechol
 - Acetylcholinesterase inhibitors
- Indications
- D2 antagonists
 - Esophagus
 - GERD
 - Domperidone
 - Levosulpiride
 - Itopride
 - Functional dyspepsia
 - Domperidone
 - Levosulpiride
 - Itopride



- Stomach
 - Nausea/vomiting ■ Domperidone
 - Gastroparesis ■ Domperidone
- Serotonin antagonists
 - Esophagus
 - Functional dyspepsia ■ Mosapride
 - GERD ■ Mosapride
 - Stomach
 - Gastroparesis ■ Velusetrag
 - Renzapride
 - Naronapride
 - Colon
 - Chronic idiopathic constipation (CIC) ■ Prucalopride
 - Velusetrag
 - Relenopride
 - IBS-C ■ Tegaserod
 - Renzapride

➤ Adverse effects

Practice Alert

- CVS
 - All classes of changes used as prokinetics except cholinergic itopride, a dopamine → prolongation of QT interval
 - Consider use of alternate to PK especially in patients with cardiovascular disease
 - Perform periodic monitoring with ECG
 - Bradycardia with cholinergic, especially parietal neostigmine
- CNS
 - Extrapyramidal reaction with some dopaminergic (metoclopramide > domperidone)
 - Headache with serotonergic agents
- GI
 - Pain, diarrhea with serotonergic

Abbreviations: 5-HT4, 5-hydroxytryptamine; CIC, chronic idiopathic constipation; CNS, central nervous system; CVS, cardiovascular system; ECG, electrocardiogram; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBS-C, irritable bowel syndrome, constipation predominant; LES, lower esophageal sphincter



UPPER GASTROINTESTINAL BLEEDING (UGIB)

Upper Gastrointestinal and Ulcer Bleeding: ACG Clinical Guideline (2021)

Laine L, et al. Am J Gastroenterol 2021; 116: 899-917

- Stratification

Risk factor at admission	Factor score
○ Symptoms	
– Melena	1
– Syncope	2
– Hepatic disease*	2
– Cardiac failure	2
○ Signs	
– Systolic blood pressure (mm Hg)	
▪ 100-109	1
▪ 90-99	2
▪ <90	3
– Heart rate (beat per minute)	
▪ ≥ 100	1
○ Laboratory	
– Blood urea nitrogen (mg/dL)	
▪ 18.2 to < 22.4	2
▪ 22.4 to < 28.0	3
▪ 28.0 to < 70.0	4
▪ ≥ 70	6
– Hemoglobin (g/dL)	
▪ 12.0 to < 13.0 (men); 10.0 to < 12.0 (women)	1
▪ 10.0 to < 12.0 (men)	3
▪ < 10.0	6

* Hepatic disease and cardiac failure were not defined in the original report of the Glasgow-Blatchford score. One more recent study defined hepatic disease as known history, or clinical and laboratory evidence, of chronic or acute liver disease and cardiac failure as known history, or clinical and echocardiographic evidence of cardiac failure

Printed with permission: Laine L, et al. Am J Gastroenterol 2021; 116: 899-917 (Table 3)



➤ Initial management of patients presenting with overt upper gastrointestinal bleeding.



Initial risk stratification and triage

- Very-low Clinical Risk
 - Risk score indicates 0-1% false negative for transfusion, hemostatic intervention, or death
 - Glasgow-Blatchford Score 0-1
 - Not Very-low Clinical Risk
 - Risk score indicates >1% false negative for transfusion, hemostatic intervention, or death
 - Glasgow-Blatchford Score ≥ 2
- ↓
- Discharge from emergency department with outpatient management if no other reason for hospitalization
 - Admit to hospital or observation unit

Pre-endoscopic management

- Resuscitation, attention to active comorbidities
- RBC transfusion if hemoglobin < 7 g/dL
- Suggest erythromycin 250 mg infusion 30-90 min before upper endoscopy
- No recommendation for or against proton pump inhibitors (other guidelines recommend PPI IV/PO)

Endoscopy

- Upper endoscopy within 24 hr of presentation
- ↓
- Low-risk endoscopic findings
 - E.g., clean-based ulcer, non-bleeding Mallory-Weiss tear, erosions
 Discharge patient if stable vital signs and hemoglobin, and no reason for hospitalization
 - Non low-risk endoscopic findings
 - E.g., ulcer with stigmata of hemorrhage, varices, neoplasm, Dieulafoy lesion
 Patient remains in hospital

- Future risk assessment tools may be used if score
 - Discriminates risk of transfusion
 - Hemostatic intervention, or
 - Death with 99–100% sensitivity (0%–1% false negatives)

Printed with permission: Laine L, et al. Am J Gastroenterol 2021; 116: 899-917. (Figure 2)



Recommendation

- Use the Glasgow-Blatchford score (GBS) to identify a subgroup of patients with upper GI bleeding (UGIB) (~25%) who may be safely discharged from the Emergency Room (ER) for early outpatient follow-up.
- GBS of 0 to 1
 - Sensitivity, 99%
 - A false negative of 1% was considered to be acceptable
 - Specificity, 19-24%

(Conditional recommendation, very-low-quality evidence).

• Red Blood Cell Transfusion (RBCT)

Recommendation

- Restrictive policy of red blood cell (RBC) transfusion with a threshold for transfusion at a hemoglobin of 7 g/dL for patients with UGIB (conditional recommendation, low-quality evidence).
- Threshold to initiate RBCT (excluding patients with restrictive exsanguinating UGIB)
 - Stable patients with UGIB, including critical care patients 7 g/dL
 - Cardiovascular disease, cardiac/orthopedic surgery, acute coronary syndrome 8 g/dL
- Benefit of restrictive transfusion
 - "...no evidence of an impact on clinically important outcomes
 - 43% ↓ number of patients requiring RBCT
 - ↓ mortality, 5% vs. 9% (for liberal use of RBCT)
 - ↓ rebleeding, 10% vs. 16%, aHR 0.68; 95%CI: 0.47-0.98)
 - ↓ RBCT reactions, 3% vs. 9%, P = 0.001
 - ↓ cardiac complications, 11% vs. 16%, P = 0.004

• Pre-EGD Prokinetic, erythromycin

Recommendation

- Give an infusion of erythromycin before endoscopy in patients with UGIB (conditional recommendation, very-low-quality evidence).
- Give erythromycin 250 mg IV, usually over 5-30 min, wait 20-90 min and do EGD
- Be aware of rare
 - Ventricular tachyarrhythmias e.g., torsade de pointes
 - Assess before IV erythromycin
 - History of cardiac / hepatic disease
 - Concurrent anti arrhythmia therapy
 - Metabolized by CYP3A4
 - Drugs which ↑ QT interval plus
 - Baseline ECG showing ↑ QT



❖ Pro-EGD

- Prokinetics, erythromycin
 - Give erythromycin 250 mg IV, usually over 5-30 min, wait 20-90 min and do EGD.
 - Be away of rare
 - Ventricular tachyarrhythmias e.g., torsade de pointes
 - Assess before IV erythromycin
 - History of cardiac/hepatic disease
 - Concurrent antiarrhythmics therapy

Recommendation

- Give erythromycin IV before endoscopy in patients with UGIB (conditional recommendation, very-low-quality evidence).
- PPI recommendation
 - No recommendation for/against pre-endoscopic PPI therapy for patients with UGIB.
 - Some guidelines recommend PPI IV before EGD, then to continue IV PPI for 3 d if high risk lesion
 - Evidence is variable/imprecise, even on meta-analysis of RCTs
 - Metabolized by CYP3A4
 - Drugs which ↑QT interval plus
 - Baseline ECG showing ↑QT
 - Electrolyte disturbance

• Time of EGD

Recommendation

- Patients admitted to/under observation in hospital for UGIB should undergo endoscopy within 24 h of presentation (conditional recommendation, very-low-quality evidence)
 - Measure time of EGD from time of patient presentation of in ER, and ideal time of EGD as within 24 h provides covers ideal time for both stable as well as non-stable patients.
 - A trend to lower in-hospital mortality for perform EGD in patient with UGIB and hemodynamically
 - Stable 12-36 h
 - Unstable 6-24 h
- } Selecting 24 h provides adequate time to obtain hemodynamic stability and to address the treatment of comorbidities
- Even in high-risk patients (GBS ≥ 12) had
 - ↓ rebleeding 1% vs 8%
 - ↓ mortality 9% vs 7%
- } Comparing EGD within 6 h versus within 6-24 h



- PPI therapy (80 mg IV bolus, 8 mg/h for 72 h, or 40 mg b.i.d. to q.i.d. po/IV)

Recommendation

- Use high-dose PPI therapy given continuously or intermittently for 3 days after successful endoscopic hemostatic therapy of a bleeding ulcer (strong recommendation, moderate- to high-quality evidence).
- High-risk patients with UGIB due to ulcers who received endoscopic hemostatic therapy followed by short-term (3 d) high-dose PPI therapy in hospital continue on twice-daily PPI therapy until 2 wk after index endoscopy (conditional recommendation, low-quality evidence).
- Mechanisms of action of PPI
 - $\downarrow H^+ \rightarrow \downarrow$ pepsin activity $\rightarrow \downarrow$ clot lysis
 - $\uparrow$ platelet/clot stability
- Continuous/intermittent PPI IV
 - $\downarrow$ rebleeding
 - RR: 0.43, 95% CI: 0.33-0.56
 - $\downarrow$ mortality
 - RR: 0.41; 95% CI: 0.22-0.79
 - $\downarrow$ surgery
 - RR: 0.42; 95% CI: 0.25-0.71
- After 3 d of IV continuous/intermittent / po intermittent PPI 40 mg b.i.d. to q.i.d.
 - High risk lesion (Forrest I a, b; II a, b) PPI b.i.d. for ~ 2 wk (duration will depend upon underlying cause)
 - Low risk lesion (Forrest IIc, III) PP PPI od

- Endoscopy for UGIB

Recommendation

- Patients admitted to or under observation in hospital for UGIB undergo endoscopy within 24 hours of presentation (conditional recommendation, very-low-quality evidence).
 - Measure time of EGD from time of patient presentation with GIB, and ideal time of EGD is within 24 h provides covers ideal time for both stable as well as non-stable patients.
 - A trend to lower in-hospital mortality for perform EGD in patient with UGIB and hemodynamically
 - Stable, 12-36 h
 - Unstable
- } Lasting 24 h provides adequate time to obtain hemodynamic stability and to treat comorbidities



- Even in high risk patient (GBS ≥ 12)
 - ↓ rebleeding, 1% vs. 8%
 - ↓ mortality, 9% vs. 7%
- } Company EGD within 6 h vs. within 6-24 h

Clinical Consideration

- Patients who die from an UGIB usually do so as a result of their comorbidities
- Use the rule of “EGD within 24 h” to optimize the management of the GI bleed, plus the comorbidities.

• Endoscopic Hemostatic Therapy (EHT)

Recommendation

- Endoscopic therapy in patients with UGIB due to ulcers with active spurting, active oozing, and nonbleeding visible vessels (strong recommendation, moderate-quality evidence).
- Removal of adherent clot

Recommendation

- We could not reach a recommendation for or against endoscopic therapy in patients with UGIB due to ulcers with adherent clot resistant to vigorous irrigation.
- There are several ways to attempt to remove a clot: vigorous lavage, mechanical manipulation using hemostatic probe, cold snare guideline.
- Presently it is suggested that “...Guidelines should provide a recommended action...”, and so now the terminology that is used is as above, “we could not reach a recommendation for or against”
- Available equipment for EHT

Recommendation

- Endoscopic hemostatic therapy with bipolar electrocoagulation, heater probe, or injection of absolute ethanol for patients with UGIB due to ulcers (strong recommendation, moderate-quality evidence).
- Endoscopic hemostatic therapy with clips, argon plasma coagulation, or soft monopolar electrocoagulation for patients with UGIB due to ulcers (conditional recommendation, very-low- to low-quality evidence).



- Epinephrine injection not be used alone for patients with UGIB due to ulcers but rather in combination with another hemostatic modality (strong recommendation, very-low- to moderate-quality evidence).
- Endoscopic hemostatic therapy with hemostatic powder spray TC-325 for patients with actively bleeding ulcers (conditional recommendation, very-low-quality evidence).
- Over-the-scope clips as a hemostatic therapy for patients who develop recurrent bleeding due to ulcers after previous successful endoscopic hemostasis (conditional recommendation, low-quality evidence).
- Most robust evidence
- Low-to-very-low quality evidence
- Use epinephrine injection only with a second modality
- Most robust evidence
 - Bipolar electrocoagulation / heater probe
 - Ingestion of absolute alcohol
- Low-to-very low-quality evidence
 - APC, CLIPS, soft monopolar electrocoagulation
 - 1:10,000 dilution, 0.5 to 2.0 mL aliquots
- Use epinephrine injection only with a second modality
- Antisecretory therapy after endoscopic hemostatic therapy for bleeding ulcers

Recommendation

- High-dose PPI therapy given continuously or intermittently for 3 days after successful endoscopic hemostatic therapy of a bleeding ulcer (strong recommendation, moderate- to high-quality evidence).
- Mechanism of action of PPI
 - $\downarrow H^+ \rightarrow \downarrow$ pepsin activity $\rightarrow \downarrow$ clot lysis
 - $\uparrow$ platelet / clot stability
- Continuous//intermittent PPI IV
 - $\downarrow$ rebleeding
 - RR: 0.43; 95% CI: 0.33-0.56
 - $\downarrow$ mortality
 - RR: 0.41; 95%CI: 0.22-0.79
 - $\downarrow$ surgery
 - RR: 0.42; 95%CI: 0.25-0.71
- After 3 d of IV continuous / IV intermittent / po intermittent PPI 40 mg b.i.d. to q.i.d.
 - High risk lesion (Forrest Ia,b; II a, b), PPI b.i.d. for ~2 wk
 - Low risk lesion (Forrest IIc, III), PPI od



- Recurrent ulcer/bleeding after successful EHT

Recommendation

- Patients with recurrent bleeding after endoscopic therapy for a bleeding ulcer undergo repeat endoscopy and endoscopic therapy rather than undergo surgery or transcatheter arterial embolization (conditional recommendation, low-quality evidence for comparison with surgery, very-low-quality evidence for comparison with transcatheter arterial embolization).
- Rebleeding after EHT treated by EHT or surgery
 - ↑ rebleeding with repeat EHT vs. surgery 23% vs. 7%
 - No difference in mortality 11% vs. 48%
 - Second EHT group
 - Surgery required in 27%
 - Surgery group
 - Second surgery required in 9%
 - ↑ complications with surgery vs. repeat EHT
 - Second EHT vs. surgery 18% vs. 36%
- Complications of repeat EHT ↑ perforation
 - If second first EHT was with thermal method, use different modality for second EHT
- Failure of EHT (persistent/recurrent bleeding)

Recommendation

- We suggest patients with bleeding ulcers who have failed endoscopic therapy next be treated with transcatheter arterial embolization (conditional recommendation, very-low-quality evidence).
- Further ↑ rebleeding more common with TAE is surgery
 - OR, 2.44; 95%CI; 1.77-3.26; aHR 2.48; 95%CI: 1.33 to 4.62
- ↑ major complications with surgery than with TAE
 - OR, 0.4; 95% CI; 0.30-0.67
 - 8 vs. 16 d, adjusted acceleration factor = 0.59; 95% CI: 0.45-0.77
- ↓ length of hospital (LOS) stay TAE vs. surgery
- No difference in mortality rate between TAE and surgery



Glasgow-Blatchford Score Point

- Clinical
 - Melena, 1
 - Syncope, 2
 - Acute/chronic liver disease, 2
 - Heart failures, 2

 - Heart rate ≥ 100 bpm, 1
 - Systolic blood pressure, mmHg
 - < 90 , 3
 - 90-99, 2
 - 100-109, 1
- Laboratory
 - Hemoglobin, g/dL
 - < 10 , 6
 - 10-12 men, 1
 - 12-13 women, 1
 - Blood urea nitrogen, mg/dL
 - ≥ 70 , 6
 - 28-70, 4
 - 22.4-28.3 to 18.2-22.4, 2

❖ Risk stratification

Recommendations

- Patients who present to the emergency department with UGIB who are very low risk (risk assessment score with $\leq 1\%$ false negative rate for the outcome of hospital-based intervention or death, e.g., Glasgow-Blatchford score = 0–1), may be discharged with outpatient follow-up rather than admitted to hospital (conditional recommendation, very-low-quality evidence).
- Use the Glasgow-Blatchford score (GBS) to identify a subgroup have patients with upper GI bleeding (UGIB) (~25%) who may be safely discharged from the emergency room (ER) for early outpatient follow up.
- GBS of 0 to 1
 - Sensitivity 99%
 - A false negative of 1% was considered to be acceptable
 - Specificity 19% to 24%



❖ Red Blood Cell Transfusion (RBCT)

Recommendation

- Use restrictive policy of red blood cell (RBC) transfusion threshold for transfusion at a hemoglobin of 7 g/dL for patients with UGIB (conditional recommendation, low-quality evidence).
- Threshold to restrictive RBCT (excluding patients with exsanguinating UGIB)
 - Stable patients with UGIB including critical care patients, cardiovascular disease, orthopedic surgery, coronary syndrome 8 g/dL.
 - “...no evidence of an impact on clinically important outcome
 - 43% of patients require RBCT
 - ↓ mortality
 - 5% vs 9% (for liberal use of RBCT)
 - ↓ rebleeding
 - 10% vs 16%, aHR 0.68, 95% CI, 0.47-0.98
 - ↓ RBCT reactions
 - 3% vs 9%, p=0.001
 - ↓ cardiac complications
 - 11% vs 16%, p=0.04

❖ Endoscopic Hemostatic Therapy (EHT)

Recommendation

- Perform endoscopic hemostatic therapy (EHT) in patients with UGIB due to ulcers with active spurting, active oozing, and nonbleeding visible vessels (strong recommendation, moderate-quality evidence).

❖ Removal of Adherent Clot

Recommendation

- No recommendation for or against endoscopic therapy in patients with UGIB due to ulcers with adherent clot resistant to vigorous irrigation.
- There are several ways to attempt to remove a clot: vigorous lavage, mechanical manipulation using hemostatic probe, cold snare guillotine.
- The ASG guideline of 2012 suggests that EHT may be considered in the patient with an adherent clot.
- Presently it is suggested that “...Guidelines should provide a recommended action...”, and so now the terminology that is used as above “we could not each recommendation. for or against...”
 - Practical consideration
 - If clot is removed, it will reveal either a high risk visible vessel, or a low risk “dot-like” lesion



- “Should a clot be treated? It depends what is underneath, a visible vessel which must be treated with EHT, versus a reddish dot, which is not treated”
- If a high-risk lesion
 - Use PPI for 3 d, then switch to PPI po
 - Perform EHT
- If a low-risk lesion
 - Use PPI po for 3 d
 - No EHT performed

❖ Available equipment for EHT

Recommendations

- For patients with UGIB due to ulcers
 - Use EHT or injection of absolute ethanol (strong recommendation, moderate-quality evidence)
 - With clips, argon plasma coagulation, or soft monopolar electrocoagulation (conditional recommendation, very-low- to low-quality evidence)
 - Epinephrine injection not be used alone for patients with UGIB due to ulcers but rather in combination with another hemostatic modality (strong recommendation, very-low- to moderate-quality evidence).
 - Hemostatic powder spray TC-325 for patients with actively bleeding ulcers (conditional recommendation, very-low-quality evidence).
 - In patients who develop recurrent bleeding due to ulcers after previous successful endoscopic hemostasis (conditional recommendation, low-quality evidence)
 - Use over-the-scope clips as hemostatic therapy (↓ rebleeding, ↓ mortality)
 - EHT better than no EHT
 - EHT (thermal contact with bipolar electrocoagulation or heater probe vs. injection of absolute alcohol
 - Epinephrine (epi injection) or argon plasma coagulation plus second mortality vs. first modality.
- Most robust evidence
 - Bipolar electrocoagulation/heater probe
 - Injection of absolute alcohol
- Low to very low-quality evidence
 - APC, CLI PS, soft monopolar electrocoagulation
 - 1:10,000 dilution, 0.5 to 2.0 mL aliquots
- Use epinephrine injection only with a second modality.
- Recurrent bleeding after previous successful EHT
 - Over the scope clips
- Active bleeding hemostatic powder spray TC-325 x-is a temporizing measure to be followed by second look EGD.



❖ Recurrent ulcer / bleeding after successful EHT

Recommendation

- Patients with recurrent bleeding after EHT for a bleeding ulcer
 - Perform repeat endoscopy and endoscopic therapy
 - Do **not** undergo surgery or transcatheter arterial embolization (conditional recommendation, low-quality evidence for comparison with surgery, very-low-quality evidence for comparison with transcatheter arterial embolization).
- After treated by EHT or surgery
 - Second EHT surgery required in 27%
 - ↑ perforations from second EGD
 - Surgery second, repeat surgery required in 9%
 - ↑ rebleeding with repeat EHT vs surgery 23% vs 7%
 - No difference in mortality 11% vs 18%
 - ↓ complications with surgery vs repeat EHT second EHT vs surgery 18% vs 36% before
- Complications of repeat EHT
 - ↑ perforations
 - If first EHT was with thermal method, use different modality for second EHT

❖ Failure of EHT (persistent/recurrent bleeding)

Recommendation

- Patients with bleeding ulcers who have failed endoscopic therapy
 - Treat with transcatheter arterial embolization (TAE; conditional recommendation, very-low-quality evidence).
- ↑ rebleeding more common with TAE vs surgery
 - OR, 2.44; 95% CI: 1.77-3.35
- ↑ major complications with surgery than with TAE
 - OR, 0.45; 95% CI: 0.30-0.67
- ↓ LOS (length of hospital stay) TAE vs surgery 8 vs 16 d adjusted acceleration factors 0.59; 95% CI: 0.45-0.77
- No difference in mortality rate between TAE and surgery

Abbreviations; ACG, American College of gastroenterology; aHR, adjusted hazard rates; APC, Argon plasma coagulation; b.i.d., twice a day; CI, confidence interval; ECG, electrocardiogram; EGD, esophagogastroduodenoscopy; EHT, endoscopic hemostatic therapy; ER, emergency room; GPS, Glasgow Blatchford score; h, hour; H⁺, hydrogen ion; IV, intravenous; LOS, length of (hospital) stay; NV UGIB, non-variceal upper GI bleeding; OD, once a day; PICO, population, intervention, comparator and outcome; PPI, proton pump inhibitor; RBCT, red blood cell transfusion; RR, relative risk; UGIB, upper GI bleeding



Management of Anticoagulants and Antiplatelets During Acute Gastrointestinal Bleeding and the Periendoscopic Period: ACG/CAG Guidelines (2022)

Abraham NS, et al. Am J Gastroenterol 2022; 117: 542-558

Please Note: Where recommendations could be made, the recommendations were all conditional, and the certainty of evidence was very low.

➤ Classes of Drugs of Interest

○ VKA	- Vitamin K antagonists	} Antithrombotic
○ DOAC	- Direct oral anticoagulants	
○ P ₂ Y ₁₂ RI	- P ₂ Y ₁₂ receptor inhibitors	
○ ASA	- Acetylsalicylic acid	

❖ Setting of Elective Endoscopy

❖ Setting of Acute Upper/Lower GI Bleeding

• Warfarin reversal

- Fresh frozen plasma (FFP) does not necessarily correct INR (anticoagulation continues)
 - Use of FFP in the setting → ↑ risk of thrombotic events (OR: 4.22; 95%CI, 1.25-14.3)
- Do **not** use FFP to correct ↑ INR in patient on warfarin
 - **No** recommendation made re use of prothrombin complex concentrate (PCC)
 - However, exceptions to above: consider use of PCC if
 - ↑↑ supratherapeutic INR
 - Massive blood transfusion not desirable because of "...its effect on coagulopathy or dilution of blood products"
- Use PCC rather than FFP for patients with GI bleed, on warfarin, and in ER/hospital
- Do **not** use vitamin K for patients on GI bleed, on warfarin, in ER/hospital
 - Exceptions
 - If ↑↑ INR, and correction planned over 2-4 wk
 - If plan is to stop warfarin



Recommendations

- Reversal agents
 - Direct thrombin inhibitor (DTI) reversal (dabigatran, apixaban, rivaroxaban)
 - Do **not** give drugs to reverse DTI in patient in ER/hospital
However, “selective use may be appropriate in patients with a life-threatening GI bleed who have taken dabigatran in the past 24 h
 - Normal agents
 - Dabigatran: idarucizumab
 - Rivaroxaban, apixaban, andexanet alpha
 - Do **not** give PCC to reverse DTI, as noted above for DTI reversal
 - Do **not** give platelet transfusions to the patient taking ASA, or the thienopyridine P2Y12 receptor inhibitor clopidogrel, prasugrel or ticagrelor (↑ CNS defects, ↑ death)

Continue ASA

- Endoscopic diagnosis of the cause of upper GI bleed (UGIB) should be made within 24 h, and within 24-36 h for lower GI bleed (LGIB).

Recommendations

- Do **not** withhold ASA used for secondary cardiovascular prevention in patients with GI bleeding
- If for some reason the ASA was stopped, perform endoscopic hemostatic successful therapy and then restart ASA (Conditional recommendation, very low certainty of evidence)
- High risk procedures (major bleeding within 30 d of endoscopy)
- Esophagus
 - BE
 - EMR, ESD, RFA
 - EVBL
 - Esophageal variceal band ligation
 - Stricture/spasm
 - Balloon / pancreatic dilation
- Stomach
 - Feeding (PEG/PEJ)
 - Cysts gastrostomy
 - GU
 - Injection, burning, clipping
 - Laser



- Small bowel
 - Enterostomy, balloon
 - Assisted, therapeutic
- Duodenum
 - DU
 - Injection, burning, clipping
- Colon
 - Polypectomy
- Biliary
 - ERCP, sphincterotomy
 - EUS plus FNA
 - Resection of ampulla

Abbreviations: BE, Barrett's esophagus; EMR, endoscopic mucosal resection; ESR, endoscopic submucosal dissection; EVBL, esophageal variceal band ligation; FNA, fine needle aspirate; GU/DU, gastric/duodenal ulcer; PEG/J, percutaneous endoscopic gastrostomy/jejunostomy; POEM, peroral endoscopic myotomy

➤ High, Moderate and Low Risk of Periendoscopic Thrombosis/Embolism in Patients on Anticoagulant Therapy

• High risk	○ Heart Valve replacement – Mitral valve – Aortic valve, caged-ball or tilted disk – CVA/TIA within past 3 mon	Atrial fibrillation (AF) – Rheumatic valvular heart disease – CHADS2 5/6 ▪ CHADS2 VaSc ≥ 7 – CVA/TIA within 3 mon
• Medium risk	– Aortic valve, leaflet, plus – ≥ 1 of the following ▪ > 75 yr ▪ AF ▪ CVA/TIA ▪ Hypertension ▪ Heart failure ▪ Diabetes mellitus	▪ CHADS2, 2-4 ▪ CHADS2 VaSc 5/6



Recommendation

- Warfarin
 - Continue warfarin for patients having an elective (planned) GI endoscopic procedure
 - Exception: Stop warfarin for 5 d if the patient is having a high-risk procedure (please see above) for procedure bleeding
 - If a patient does stop warfarin in the periprocedural period, do **not** use bridging anticoagulation (conditional recommendation, low certainty of evidence) (associated with ↓ risk of periprocedural CVA/thromboembolism)
 - Exception: may use bridging heparin 3 d before and 3-5 d after procedure if patient has
 - Atrial fibrillation, CHADS2 score > 5
 - Previous thromboembolism when VKPs stopped
 - High risk surgery bridging heparin, carotid endarterectomy, heart valve replacement, vascular surgery (major)
- DOACs
 - Temporarily stop DOACs in patient having elective (planned) GI endoscopic procedures
- Antiplatelet therapy
 - Dual ASA plus P2Y12 inhibition for secondary cardiovascular prevention
 - Continue ASA, temporarily stop P2Y12 inhibitor (conditional recommendation, very low certainty)
 - Only P2Y12 inhibition (no recommendation made)
 - Only ASA
 - Do **not** stop (conditional recommendation, very low certainty of evidence)
- ❖ When to Restart Anticoagulation After Endoscopy
 - Warfarin / DOAC, P2Y12 inhibitor
 - No recommended time of same day vs. 7 d



NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING (NV UGIB)

Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations from the International Consensus Group

Barkun AN, et al. Ann Int Med 2019; 171: 805-22.

❖ Resuscitation, Risk assessment, Pre-endoscopy (EGD) Care

Recommendations

- Resuscitation
 - Achieve hemodynamic stability with infusion of colloid or crystalloid solutions (Designated a good practice statement)
 - Border reduction in 90-day mortality using colloid (RR; 0.92, 95% CI, 0.86-0.99)
- Risk assessment
 - Use the Glasgow Blatchford score (GBS) to assess risk for bleeding
 - GPS < 1
 - Low risk, patient may be managed as an outpatient
 - Prognostic scales are recommended for early stratification of patients into low- and high-risk categories for rebleeding and mortality (Agree, 97% [Vote: a, 56%; b, 35%; c, 6%; d, 3%]. Grade: Low, 1c)
 - No recommendation made regarding use of pre-endoscopic Rockall prognostic scale (RPS) to assess risk as high or low for rebleeding.
 - A Glasgow Blatchford score ≤ 1 signifies with high sensitivity (99%) and low risk of rebleeding or mortality "...and thus may not require hospitalization or inpatient endoscopy" (Grade: conditional recommendation, low quality evidence)
 - No recommendation regarding pre-endoscopy Rockall prognostic score (Grade: for PICO: very low-quality evidence)
 - Do **not** use the AIMS65 prognostic score (Grade: conditional recommendation, low quality evidence)
 - Sensitivity for detecting high risk patients with UGIB

	Sensitivity	Misclassification
▪ GBS	0.99	≤ 1%
▪ RPS	0.93 – 0.96	4% - 7%
A65	0.78 – 0.82	~20%
 - Stratify patient risk (low or high) for rebleeding and mortality
 - Target RBC transfusion to maintain hemoglobin (Hg) concentration ≥ 70 g/L
 - This target may need to be raised for patient with
 - Inadequate oxygenation at that Hg level
 - Patients with ischemic heart disease



- Target hemoglobin (Hg) concentration for blood transfusion (“restrictive” transfusion)
 - No cardiovascular disease < 80 g/L
 - Benefits
 - ↓ rebleeding (RR, 0.58 [99% CI, 0.40-0.84])
 - ↓ all cause of mortality (RR, 0.65 [99% CI, 0.45-0.97])
 - ↓ need for, and number of blood units required
 - Other analyses have also suggested a target of Hg of 70 g/L
 - With cardiovascular disease
 - Target an Hg > 80g/L but no specific cut-off was identified but
 - It was suggested ‘...giving blood transfusion at a higher hemoglobin threshold than in those without cardiovascular disease’.
 - In patients receiving anticoagulants, correction of coagulopathy is recommended but
 - Should not delay endoscopy. (Agree, 97% [Vote: a, 38%; b, 44%; c, 15%; d, 3%]. Grade: Low, 2c, “probably do it”)

Clinical Alert

- These statements about restrictive transfusion target “...do not apply to patients with exsanguinating bleeding, who may require more liberal transfusion”
- NG tube
 - Consider use of nasogastric tube in selected patients “...because the findings may have prognostic value”.
- Feeding
 - Low-risk patients / low-risk of for bleeding feed within 24 h
- H. pylori infection
 - Test and treat all persons with NVUGIB with peptic ulcers.
 - Use 14 day triple or quadruple first line therapy
 - Prove eradication of H. pylori infection
- Endoscopic management (acute UGIB, high risk for rebleeding/mortality “high risk stigmata”)
 - Have in place a team for multidisciplinary care, plus institution-specific protocols for persons with NVUGIB
 - Endoscopy
 - Do **not** delay EGD in persons with UGIB who are taking vitamin K antagonist (VKA) or direct oral anticoagulants (DOACs)
 - Threat the iatrogenic coagulopathy as needed (but so not delay EGD)
 - Reassurance
 - Periendoscopic
 - Reversal agent → ↑ risk of thromboembolism
 - Non-reversal agent → no change in risk of thromboembolism or rebleeding



- Patients already on anticoagulants
 - Proceed with EGD even before correction of therapeutic coagulopathy (if medically safe)
 - In patients who receive low-dose ASA and develop acute ulcer bleeding, ASA therapy should be restarted as soon as the risk for cardiovascular complication is thought to outweigh the risk for bleeding. (Agree, 100% [Vote: a, 70%; b, 30%]. Grade: Moderate, 1b)
 - In patients with previous ulcer bleeding who require cardiovascular prophylaxis, it should be recognized that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI. (Agree, 100% [Vote: a, 70%; b, 24%; c, 6%]. Grade: Moderate, 1b [adding PPI to ASA])
- Promotility agents to improve EGD examination yield
 - Not recommended
 - Note: other new guidelines support use of pre-EGD erythromycin
- Give pre-endoscopy PPI (IV bolus, then infusion)
 - Duration of IV PPI made on basis of EGD diagnosis of “high-risk stigmata”
 - Administration of PPI should not delay EGD

❖ EGD management

- Timing
 - For most patients, within 24 h of UGIB
- Patients at low risk of rebleeding or mortality, endoscopy should be performed within 24 h of patient's presentation (Grade: conditional recommendation, very low quality evidence)
- In patients with high risk for rebleeding or mortality, whether high-risk patients would benefit EGD within 12 h rather within 24 h “remains unanswered”, and recommendation could be made for or against performing EGD within 24 h after presentation (Grade for PICO: very low quality evidence)
 - (Lau JY, et al. N Eng J Med 2020; 382: 1299-1308) have reported that in high risk persons (rebleeding, death), there is no difference in 30-day mortality rate if EGD was performed within 6 h or between 6 to 24 h after consultation.
- If a clot found on ulcer (Forrest IIb) remove the clot (washing/snare to remove) and manage visible lesion (visible vessel → endoscopic hemostatic therapy [EHT] (Forrest IIa); red dot (Forrest IIc, no EHT)
- EHT (Forrest Ia, b; IIa)
 - Use 2 methods
 - Epinephrine injection
 - Thermocoagulation
 - Clips
 - Epinephrine injection alone provides suboptimal efficacy and should be used in combination with another method. (Agree, 100% [Vote: a, 71%; b, 24%; c, 6%]. Grade: Moderate, 1b, “don't do it”)
 - Clips, thermocoagulation, or sclerosant injection should be used in patients with high-risk lesions, alone or in combination with epinephrine injection. (Agree, 97% [Vote: a, 50%; b, 35%; c, 12%; d, 3%]. Grade: High, 1a, “do it”)



- Routine second-look endoscopy is not recommended. (Agree, 91% [Vote: a, 50%; b, 21%; c, 21%; d, 3%; e, 3%; f, 3%]. Grade: Moderate, 2b, “probably don't do it”)
- Endoscopic hemostatic therapy (EHT) for active UGIB from ulcers with high-risk stigmata (Forrest classification I, IIa)
 - Use thermocoagulation or sclerosant injection
 - Or use through the scope clips
 - Clips, thermocoagulation, or sclerosant injection should be used in patients with high-risk lesions, alone or in combination with epinephrine injection. (Agree, 97% [Vote: a, 50%; b, 35%; c, 12%; d, 3%]. Grade: High, 1a, “do it”)
 - Some data does not show significant differences for the above three therapies, including combination therapies
 - Other data suggest that hemoclips may be superior to epinephrine injection; other data suggests that combination therapy may be optimal.
 - Do **not** use TC-325 hemostatic powder spray as a single therapy.
 - TC-325 may be used if standard EHT fails, or a not available (i.e., “temporizing therapy to stop bleeding when conventional endoscopic therapies are not available”).
 - Do **not** use for low-risk lesions
 - Routine second-look endoscopy is not recommended. (Agree, 91% [Vote: a, 50%; b, 21%; c, 21%; d, 3%; e, 3%; f, 3%]. Grade: Moderate, 2b, “probably don't do it”)
 - There was no recommendation regarding the use of a Doppler endoscopic probe (DEP) to assess the adequacy of hemostasis.
 - While it would have been speculated that DEP would be most beneficial for assessment of high-risk lesions, this was not demonstrated:
 - DEP → ↓ rebleeding for high- and low-risk lesions (RR, 0.42; 95% CI, 0.2-0.9), but
 - No ↓ bleeding for just high-risk lesions (RR, 0.50 [CI, 0.24 to 1.08])
- Biopsy of gastric ulcer for possible malignancy and gastric mucosa from antrum and body for possible H. pylori infection not covered in guideline
- PPI for Forrest
 - Ia,b; IIa PPI IV for 72 h then PPI po
 - IIc; III Stop PPI IV, switch to po
- Forrest III lesion
 - Test and treat for H. pylori infection in persons with bleeding ulcer [including persons taking ASA, NSAIDs, COX-2 inhibitor]
 - If biopsies were taken at the time of EGD and in the presence of fresh blood, and the biopsies were reported to be negative for H. pylori
 - The presence of blood may give a false negative result
 - Repeat H. pylori testing at a later time (serology, urea breath test, feces, repeat EGD with biopsies)
 - In patients with an H. pylori infection, they must be retested after appropriate therapy to prove eradication of the H. pylori.



- In patients with previous ulcer bleeding who require an NSAID
 - Gastroprotective therapy with PPI, or switching to a COX-2 inhibitor plus PPI reduces the risk of recurrent bleed
 - Advise the patient that even when taking PPI with ASA, NSAID or COX-2 inhibitor
 - There remains a clinical important risk for recurrent bleeding (~50%).
 - In the patient on long-term ASA, NSAID and COX-2 inhibitors who have had an UGIB from an ulcer, they must also be tested and treated for H. pylori infection, with repeat testing after treatment to prove eradication.
- Resuscitation
 - Upper GI bleed, patient with hemodynamic instability
 - Resuscitate with adequate colloids or crystalloids to “...restore end-organ perfusion and tissue oxygenation while steps are taken to control bleeding” (Designated a good practice statement)
 - Repeat EGD (second-look EGD) not recommended routinely

Recommendations

- Perform EGD within 24 h of patient presenting with UGIB
 - The role of endoscopic therapy for ulcers with adherent clots is controversial. Endoscopic therapy may be considered, although intensive PPI therapy alone may be sufficient. (Agree, 86% [Vote: a, 24%; b, 50%; c, 12%; d, 9%; e, 3%; f, 3%]. Grade: Moderate, 2b, “probably do it”)
 - The finding of a clot in an ulcer bed warrants targeted irrigation in an attempt at dislodgement, with appropriate treatment of the underlying lesion. (Agree, 97% [Vote: a, 59%; b, 29%; c, 9%; d, 0%; f, 3%]. Grade: Moderate, 2b, “probably do it”)
 - Active rebleeding plus urgent EGD is associated with ↑ morbidity/mortality
 - This may be the cause of the risk of EGD in the patient who is hemodynamically unstable.
 - Take home message: stabilize the patient and perform EGD within 24 h.
 - No recommendation could be made to perform EGD within 12 h of patient with high-risk ulcer lesion.
 - Early endoscopy (within 24 hours of presentation) is recommended for most patients with acute upper gastrointestinal bleeding. (Agree, 100% [Vote: a, 85%; b, 12%; c, 3%]. Grade: Moderate, 1b, “do it”)

Clinical Alert

- If the patient is suspected as having chronic liver disease / portal hypertension, the UGIB might be from esophagogastric varices → stabilize and perform EGD within 12 h
- Garcia-Tsao G, et al. Am J Gastroenterol 2007; 102: 2086-102.

- Do **not** use prokinetic agents before EGD in the hope of ↑ visibility (controversial).
- Give PPI before EGD to “.... downstage the endoscopic lesion and to decrease the need for endoscopic hemostatic therapy), but should not delay endoscopy.



❖ Pharmacological management

• Proton pump inhibitor (PPI)

- UGIB patients, high-risk stigmata, successful EHT
 - Non high dose PPI
 - No recommendation for or against (Grade for PICO: very low-quality evidence)
 - High dose PPI (80 mg IV bolus, followed by 72 h of continuous ≤ 8 mg/h infusion →
↓ rebleeding, ↓ mortality

Note: H2RA or octreotide/somatostatin, are not recommended for patients with acute NVUGIB.

- “The consensus group concluded that the evidence supports a strong recommendation for high dose PPI for patients with bleeding ulcers with high risk stigmata (active [arterial or venous] bleeding or visible vessel) who have had successful endoscopic therapy”.
 - Target to determine what is underneath
 - Visible vessel
 - EHT plus PPI IV
 - Pigmented dot, use PPI po

Call the surgeon or therapeutic radiologist (for percutaneous embolization)

- If EHT plus PPIs fail.

Recommendations

- After the 72 h of high dose IV PPI, the patient with high risk stigmata should receive PPI po b.i.d. for 14 days, then od (Grade: Conditional recommendation, very low quality evidence)
- Use PPI bolus plus infusion for bleeding ulcers with high-risk stigmata.
 - An intravenous bolus followed by continuous-infusion PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy. (Agree, 94% [Vote: a, 65%; b, 24%; c, 6%; d, 3%; e, 0%; f, 3%]. Grade: High, 1a, “do it”)
 - No recommendation could be made about non-high dose PPI, H2RA or no treatment in persons with previous successful EHT.
- Most patients who have undergone endoscopic hemostasis for high-risk stigmata should be hospitalized for at least 72 h. (Agree, 100% [Vote: a, 68%; b, 24%; c, 9%]. Grade: Low, 1c)



- Percutaneous embolization can be considered as an alternative to surgery for patients for whom endoscopic therapy has failed. (Agree, 100% [Vote: a, 62%; b, 32%; c, 6%]. Grade: Low, 2c, “probably do it”)
- Patients with bleeding peptic ulcers should be tested for *H. pylori* and receive eradication therapy if it is present, with confirmation of eradication. (Agree, 94% [Vote: a, 82%; b, 12%; c, 0%; d, 3%; e, 3%]. Grade: High, 1a, “do it”)
 - Negative *H. pylori* diagnostic tests obtained in the acute setting should be repeated. (Agree, 94% [Vote: a, 68%; b, 21%; c, 6%; d, 3%; e, 3%]. Grade: Moderate, 1b, “do it”)
- After 3 d of high-dose IV PPI, continue with PPI po b.i.d. to complete 2 wk of PPI therapy (3 d IV, 11 d po)
 - Patients should be discharged with a prescription for a single daily-dose oral PPI for a duration as dictated by the underlying etiology. (Agree, 94% [Vote: a, 56%; b, 32%; c, 6%; d, 3%; e, 3%]. Grade: Low, 1c, “do it”)
- Previous ulcer bleeding, patient already receiving single anti-platelet therapy or dual antiplatelet therapy (DAPT)
 - Use PPI therapy as well as testing treating and confirming *H. pylori* eradication of each pair reinfection 2 prevent rebuilding for duration consistent with the ongoing need for antiplatelet therapy.
 - In patients with previous ulcer bleeding who require cardiovascular prophylaxis, note that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI. (Agree, 100% [Vote: a, 70%; b, 24%; c, 6%]. Grade: Moderate, 1b, “do it” [adding PPI to ASA])
 - The same holding time for patients with previous ulcer bleeding also require continued cardiovascular prophylaxis with VKAs/DOACs.
 - Do **not** use H2RA, or octreotide/somatostatin routinely for patients with acute UGIB.
 - An intravenous bolus followed by continuous-infusion PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy. (Agree, 94% [Vote: a, 65%; b, 24%; c, 6%; d, 3%; e, 0%; f, 3%]. Grade: High, 1a, “do it”)
- Hemostatic Spray (TC-325)
 - Hemostatic powder spray (TC-325) may be used as a “temporizing therapy” when the above “conventional therapies are not available or fail”, but should not be used as monotherapy (Grade: Conditional recommendation, very low-quality evidence)
 - Initial hemostatic rate 90-97%, but 1 wk rebleeding rate 22-27%
 - May be of possible benefit when given before or after EHT
 - Do **not** use for low-risk lesions.
- Doppler endoscopic probe (DEP)
 - No recommendation could be made for the use of DEP after EHT to “assess the need for further endoscopic therapy.” (Grade for PICO: very low quality evidence)
 - DEP ↓ rebleeding of all lesions (RR, 0.42; 95% CI, 0.2 – 0.9), but not for high-risk lesions (RR, 0.50; 95% CI, 0.24 – 1.05)



- Upon discharge
 - Make arrangements for testing/treating *H. pylori* infection if not already done.
 - Dispense a prescription "...for a single daily dose and PPI for duration as dictated by the underlying cause" (duodenal ulcer ~4 wk, depending upon *H. pylori* status; gastric ulcer, 8-12 wk to confirm ulcer healing, and to obtain biopsies for proof of *H. pylori* eradication, if not already achieved by another non-serological method.
 - The patient with a gastric ulcer on first EGD and negative biopsies for gastric cancer must have repeat EGD to prove complete healing of the GU.
 - If the GU is not completely healed, repeat biopsies consider EUS – directed biopsies, continue b.i.d. doses of PPI, confirm eradication of *H. pylori* infection, and repeat EGD with biopsies to exclude non-biopsy and continued suspicion of GCA.
- For the Forrest IIb lesion / clot in the bed of an ulcer
 - Use targeted investigation of clot to determine if this is a IIa lesion which requires EHT, plus PPI IV or a IIc lesion which does not.

Abbreviations: A65, AMS 65 prognostic score; ASA, aspirin; b.i.d., twice a day; CI, confidence interval; DAPT, dual anti-platelet therapy; DEP, Doppler endoscopic probe; DOAC, direct oral anti-coagulant; EGD, esophagogastroduodenoscopy; EHT, endoscopic hemostatic therapy; GBS, Glasgow Blatchford score; Hg, hemoglobin; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug; od, once a day; po, by mouth; PPI, proton pump inhibitor; RPS, Rockall prognostic score; RR, relative risk; UGIB, upper GI bleeding; VKA, vitamin K antagonist

- Cardiovascular prophylaxis (previous UGIB, patient require continuation cardiovascular prophylaxis therapy)

Recommendations

- Use PPI prophylaxis therapy (Grade: Conditional recommendation, high quality evidence).
- "The evidence consistently supports a benefit with PPI therapy in patients with previous ulcer bleeding who continue single or dual antiplatelet therapy and suggests that PPI therapy is superior to clopidogrel alone in patients receiving ASA".
 - Other guidelines suggest testing and treating *H. pylori* infection in persons on long term ASA/NSAIDs to ↓risk of ulcer bleeding.

Clinical Caution

- Test for active *H. pylori* may be falsely negative if performed while there is blood in the stomach.
- Negative *H. pylori* diagnostic tests obtained in the active setting should be repeated.

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; EGD, esophagogastroduodenoscopy; EHT, Endoscopic hemostatic therapy; GBS, Glasgow Blatchford score; IV, intravenous; NVUGIB, non-variceal upper GI bleeding; po, by mouth; PPIs, proton pump inhibitors; UGIB, upper GI bleeding



GASTROESOPHAGEAL VARICES

Portal Hypertensive (Esophageal) Bleeding in Patients with Cirrhosis: AASLD Guidelines (2017)

Garcia-Tsao G, et al. Hepatology 2017; 65; 310-335

➤ Definition

- Portal hypertension (PH) is defined as a hepatic venous pressure gradient (HVPG) > 12 mmHg
 - Varices develop at the rate of 10% to 15% per year
 - At any time, about 50% of persons with cirrhosis have varices

➤ Classification of cirrhosis

Terminology	HVPG, mmHg	Clinical Decompensation*	Histological Cirrhosis
○ Compensated cirrhosis (CC)	> 5, < 10	-	-
– Clinically significant portal hypertension; (CSPH)	> 10	+	+
▪ Without GEV** (60%)		-	+
▪ With GEV* (40%)	> 10	+/-	+
○ Decompensated cirrhosis * (GEV in 85%)		+	

*ascites, VH, HE, post-surgical decompensation, HCC

** Note the distinction between the pressure of GEV (gastroesophageal varices versus VH, variceal hemorrhage: GEV appear in 40% of patients in compensated cirrhosis, but with bleeding from GEV (VH), the portal pressure (PP) will be > 10 mm Hg, the patient by having VH is now classified as having decompensated cirrhosis.

Prognosis of terminology	Cirrhosis, yr
– Stage	
▪ Compensated	> 12
▪ Decompensated	~ 1.8
Variceal Hemorrhage (VH)	5 yr mortality rate
– Isolated	20%
– Associated with other clinical features of decompensation	80%

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BRTO, balloon-occluded retrograde transvenous obliteration; CACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh classification; GEV, gastroesophageal varices; HCC, hepatocellular cancer; HE, hepatic encephalopathy; LS, liver stiffness; NIT, non-invasive test; NSBB, non-specific beta blocker; PP, portal pressure; SWE, shear wave elastography; TE, transient elastography; TIPS, transjugular intrahepatic portal hypertension; VH, variceal hemorrhage; VP; vasopressin



- GEV will be present overall in
 - CC, 60% (CC, GEV+)
 - CC, GEV → CC GEV+, 8% per year
 - Decompensated cirrhosis 85% have GEV
 - DC + GEV → VH, 15% per yr
 - VH, initial bleed, 6 wk mortality rate, 15% - 25%
 - Recurrent bleed (untreated GEV), 60% in 1-2 yr
 - Prognosis of EGV depends on progression to large GEV (10% per yr)
 - Rate depends on
 - Severity of liver disease
 - Size of GEV
 - Red wale
 - HVPg > 20 mmHg marks

➤ Pathophysiology

- Fibrosis of tissue
 - Vessel
 - Distortion from regenerative nodules
 - Microthrombi
 - ↓ endothelial no bioavailability
- ↓
- ↑ vascular tone
- ↓
- ↑ PP
- ↓
- ↑ no production
- ↓
- Splanchnic vasodilation
- ↓
- ↑ collateral circulation
- ↓
- ↑ gut blood flow
- ↓
- GEV
- } ▪ ↑ intrahepatic resistance to portal flow → ↑ portal pressure (PP)
- The pathogenesis of portal hypertension includes
 - ↑ intrahepatic vascular resistance as the result of changes in intrahepatic morphology
 - ↑ blood flow in splanchnic circulation as the result of
 - Imbalance of vasoactive agents, angiotensin II, antidiuretic hormone, endothelin, norepinephrine, nitric oxide
 - Neogenesis
 - Development of collateral veins as the result of neoangiogenesis as
 - Dilation of portosplenic collateral veins
 - Targets for pharmacotherapies
 - Structural
 - Anti-fibrotics
 - Anti-coagulants



- Functional (vasodilation) plus splanchnic vasodilation
 - α -adrenergic antagonists
 - Angiotensin-2 blockers
 - Nitrates
 - Statins
 - Diuretics / Na^+ restriction
- Splanchnic vasoconstriction
 - Non-selective beta blockers (NSBB)
 - Vasopressin (VP)
 - Somatostatin/ octreotide
- Procedural therapies
 - Esophageal variceal ligation (EVL, aka esophageal band ligation)
 - Injection
 - Sclerosants/sclerotherapy
 - Balloon occluded retrograde transmission (BRTO, L. renal vein $\rightarrow$ gastro- / splenorenal collateral)
 - Transjugular intrahepatic portosystemic shunt (TIPS)
 - Hemostatic powders
 - Endoscopic ultrasound-guided injection of varices
- Types of surgical shunts
 - Selective: divert all portal blood
 - Non-selective: divert some portal blood
 - Portocaval shunts (PV to IVC)
 - Mesocaval shunts (SMV to NC)
 - Proximal splenorenal shunt PSV to LRV
 - H-graft polytetrafluoroethylene ≥ 16 mm grafts
 - Target diameter TIPS
- Distal splenorenal shunt (distal splenic vein flow into left renal vein)
- H-graft poly tetra fluoroethylene reinforced grafts (8 m, 10 mm 1D, correcting SMV/PV $\rightarrow$ IVC)
- Small diameter TIPS
 - Risk of hepatic encephalopathy from shunts
 - Selective 10% to 20%
 - Non-selective, 40% to 80%

Procedure	HE	Variceal Rebleeding
○ Surgical shunt		
- Non-selective	40% to 80%	
- Selective	10% to 80%	
○ TIPS		
- 10 mm	40%	13% to 17%
- 8 mm*	18% to 27%	7% to 16%

* required more re-interventions



- First/repeat acute esophageal variceal bleeding
- PRBC transfusion target to initiate PRBCs and to maintain hemoglobin (Hb) concentration to 7 d/dL
- Vasoactive drugs
 - Octreotide/somatostatin, or
 - Vasopressin / terlipressin

} For 2-5 d

Drug	Recommended Dose	Duration
○ Octreotide (SMT analogue)	- Initial IV bolus of 50 µg (can be repeated in first hour if ongoing bleeding) - continuous IV infusion of 50 µg/hr	2-5 d
○ Vasopressin (VP)	- Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min, plus - IV nitroglycerin at a starting dose of 40 µg/min (can be increased to maximum of 400 µg/min, adjusted to maintain a systolic blood pressure 90 mm Hg)	24 h
○ Somatostatin (SMT)	- Initial IV bolus 250 µg (can be repeated in the first hour if ongoing bleeding) - Continuous IV infusion of 250-500 µg/hr	2-5 d
○ Terlipressin (VP analogue)	- Initial 48 h: 2 mg IV every 4 h until control of bleeding - Maintenance: 1 mg IV q4h to prevent rebleeding	2-5 d

Abbreviations: IV, intravenous; SMT, somatostatin; VP, vasopressin

Source: Garcia-Tsao G, et al. Hepatology 2017; 65: 310-335

- Ceftriaxone 1 g / 24 h IV for 7 d, or when blood stops / vasoactive drug is stopped
- EGD when patient is stable, and within 12 h
 - EBL for EVB
- TIPS procedure within 72 h of EGD for EVB/EVL for following indications, as long as no contraindications
 - Failure of EBL
 - High risk of rebleeding cirrhosis
 - Child-Pugh class C, or
 - Class B with active bleeding on EGD
 - Once TIPS is successful placed, stop IV vasoactive drugs
- Secondary prophylaxis (after recovery from acute EVB)
 - Maintenance
 - NSBB or EVL
 - NSBB or EVL failure (recurrent EVB) → TIPS
 - If TIPS placed, no NSBB/EVL required



- Secondary prevention (prevention of rebleeding)
 - Continue
 - NSBB
 - Continue nadolol or propranolol (but not carvedilol) at dose and durations as suggested in table of treatment of primary prophylaxis
 - Continue EGD plus EBL q1-4wk to obliterate RV
 - Then after EV obliterate, then repeat EGD + EVL at 3 to 6 mon, then q6-12mon
 - If TIPS performed, no NSBB + EVL required
 - Variceal bleeding
 - Acute bleeding
 - Risk of acute rebleeding ~70%
 - Effectiveness of pharmacological and endoscopic methods to stop variceal bleeding ~80%
 - For those who continue to bleed / have rebleeding
 - Decompressive shunts between hypertensive portal and normotensive systemic veins

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Diagnostic Imaging
 - Abdominal ultrasound (US) of the liver is recommended for persons with cirrhosis, and even some without cirrhosis (e.g., chronic HBV infection in persons with unique characteristics) to detect early HCC.
 - During this US procedure, changes from in portal pressure may be observed.
- Give the features on diagnostic imaging which suggest the presence of portal hypertension (PHT).
 - Portal collateral circulation (100% specific for CSPH)
 - Umbilical vein recanalized
 - Spontaneous splenorenal circulation
 - Left/short gastric vein dilation
 - Reversal of flow in portal system
 - Portal (congestion)
 - Dilation
 - ↓ velocity of flow

Clinical Tip

- The absence of physical signs associated with chronic liver disease (such as palmar erythema, spider nevi, caput medusa (visible abdominal portosystemic collaterals) does not exclude the presence of clinically significant portal hypertension (CSPH; HVPG ≥ 10 mmHg).



MCQ Trick

- Give the values of HVPg (mmHg) at which the following occur.
 - GEV 10
 - Risk of VH ≥ 12
 - $\uparrow$ mortality rate ≥ 16
 - Failure to control bleeding/death (during acute VH) early rebleeding ≥ 20
 - $\downarrow$ risk of complications < 12 , or 20% $\downarrow$ from baseline
 - Recent VH
 - HE
 - Ascites
 - Death
 - $\uparrow$ (3%) in mortality rate (over 19 mon), in patients awaiting liver transplantation $\uparrow$ of 1
 - The HVPg is correlated with Child-Pugh score / MELD score (Model for end-stage liver disease)
 - These are predictions of risk of
 - Rebleeding
 - Death
- Give the “backbone” of non-invasive [diagnostic tests] of portal hypertension (PH).
 - MR elastography
 - To assess liver stiffness (LS)
 - Transient elastography (TE; FibroScan®)
 - LS/TE ≥ 21 kPa and HVPg ≥ 10 mmHg are equally effective in predicting decompensation”

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give non-invasive tools (NITs) in addition to TE to predict the value of CSPH, the changes in HVPg, or the absence of $\uparrow$ HVPg ($< 150,000/\text{mm}^3$).
 - Value of CSPH
 - Shear wave elastography (SWE)
 - Two dimensional real-time SWE
 - Magnetic resonance elastography (MRE)
 - LSxSS/platelet count
 - Spleen stiffness (SS) > 54 kPa in the presence splenomegaly
 - $\downarrow$ platelet count plus another unrelated NITs



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the pharmacodynamic properties of statins which support their benefit to treat patients with cirrhosis (all stages).
 - Stellate cells
 - ↓ hepatic fibrogenesis
 - Endothelium
 - ↓ intrahepatic endothelial dysfunction
 - ↓ portal pressure
 - ↑ hepatic perfusion
 - ↑ hepatic function

❖ NSBBs and primary/secondary prevention of VH

- Some authors suggest that the “optimal [therapeutic] response” to NSBBs is
 - Pulse rate
 - ↓ 50-55 bpm
 - ↓ 20% from baseline
 - The problem is “...that changes in heart rate do **not** correlate with changes in HVPG, and that non-invasive tolls (NITs) are not useful in assessing changes in HVPG”.
- Problems with use of NSBBs
 - Contraindications 15%
 - Dose ↓ / discontinuation 15%

} Carvedilol 3.125 mg b.i.d. → max 6.25 mg b.i.d.

➤ Treatment

It is generally believed that small esophageal varices (EV) have a low risk for VH.

- Give the exceptions, when small EV have a high risk of VH.
 - Red wale marks, signaling thinning of venous wall.
 - Any size of EV in a patient who is CTP-C stage.
 - The value of the INR is “.... Not a reliable indicator of coagulation status in [patients with] cirrhosis”.
 - It is recommended to
 - Attempt to correct the ↑ INR value by giving fresh frozen plasma (FFP) or factor VIIa
 - “No recommendation can be given regarding platelet transfusion in patients with VH”.
 - Give Ceftriaxone 1 g / 24 h for maximum of 7 d in patients with VH in order to
 - ↓ infection (e.g., spontaneous bacterial peritonitis [SBP])
 - ↓ recurrent VH
 - ↓ death
 - The commonest cause of upper GI bleeding (UGIB) in patients with cirrhosis is peptic ulcer disease.



- Give how to be certain that a patient with cirrhosis and UGIB and VH has in fact bleed from the varices.
 - Visualize the active bleeding from varix
 - Red wale sign
 - White nipple sign
 - When varices are the only lesion seen on EGD, and blood is in the stomach on EGD.
 - EGD performed > 24 h after UGIB, and there is no active bleeding, and just varices are seen on EGD.
 - Non-cirrhotic prehepatic pH occurs in adults in some parts of the world and may be associated with varices.
- Management of Esophageal Varices in Patients with Cirrhosis

Findings	Management
○ No varices	- EGD q3yr, unless decompensation develops
○ Varices - Small varices < 5 mm ▪ With red wale marks (erythematous raised areas) - Large varices (> 5 mm) - Varices in patients unable to tolerate β blockers - Bleeding varices	- EGD q3yr, unless decompensation develops - Non-selective β-blocker therapy (NSBBs): (propranolol, nadolol, or carvedilol) - Start NSBB or endoscopic variceal band ligation (EVBL) - EVBL - EVBL

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H. PYLORI INFECTION

Treatment of *Helicobacter pylori* Infection (ACG) (2017)

Chey WD, et al. Am J Gastroenterol 2017;112(2):212-239.

➤ Demography

- *H. pylori* infection is chronic and is usually acquired in childhood.
 - The exact means of acquisition is not always clear. The incidence and prevalence of *H. pylori* infection are generally higher among people born outside North America / Europe than among people born here.
 - Within North America, the prevalence of the infection is higher in certain racial and ethnic groups, the socially disadvantaged, and people who have immigrated to North America (factual statement, low quality of evidence), as well as Indigenous Canadians.

➤ Indications

- All patients with a positive test of active *H. pylori* infection should be offered treatment (Strong recommendation, quality of evidence: not applicable),
- Which patients should be tested for the infection
 - All *H. pylori* infected persons with active peptic ulcer disease (PUD)
 - Past history of PUD (unless previous cure of *H. pylori* infection has been documented)
 - Low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or a history of endoscopic resection of early gastric cancer (EGC).
- For testing, treating and proof of eradication
 - Peptic ulcer disease
 - Active
 - Previous
 - Not tested or treated for *H. pylori* infection
 - Not proven to have been eradicated
 - Uninvestigated dyspepsia, no clinically significant alarm symptoms, < 60 yr old and without alarm features, non-endoscopic testing for *H. pylori* infection is a consideration.
 - Those who test positive should be offered eradication therapy (conditional recommendation, quality of evidence: high for efficacy, low for the age threshold).
 - Mucosa-associated lymphoid tissue (MALT) lymphoma
 - Early gastric cancer, treated with endoscopic resection
 - Mucosa-associated biopsy proven chronic active gastritis, atrophic gastritis, intestinal metaplasia



➤ Treatment

- Indications for treatment
 - A positive non-serological test (i.e., patient has active infection)
 - The critical issue is which patients should be tested for *H. pylori* infection, because a positive test for active *H. pylori* (urea breath test, stool antigen, endoscopy-based test)

A = Amoxicillin; B = Bismuth; C = Clarithromycin; F = Fluoroquinolone; M = Metronidazole; N = Nitroimidazole; P = Proton pump inhibitor; T = Tetracycline

- First-line

- Take into account the patients with previous exposure to antibiotics, and local results of sensitivity testing of the *H. pylori* to the choice of antibiotics (Conditional recommendation, moderate quality of evidence).
- Triples
 - PAC/M, when C resistance < 15%, and
 - No previous macrolide
 - Clarithromycin triple therapy (consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 d) is recommended treatment option in regions
 - Where *H. pylori* clarithromycin resistance is known to be <15% and
 - In patients with no previous history of macrolide exposure for any reason (conditional recommendation, low quality of evidence (for duration: moderate quality of evidence)
- PAL
 - Levofloxacin triple therapy (consisting of a PPI, levofloxacin, and amoxicillin for 10–14 d) (conditional recommendation, low quality of evidence (for duration: very low quality of evidence)
- Quadruples
 - BPTN
 - Bismuth quadruple therapy (consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10–14 d) is recommended first-line treatment option.
 - Especially, bismuth quadruple therapy in patients with any previous macrolide exposure or who are allergic to penicillin (strong recommendation, low quality of evidence).
 - PACN
 - Concomitant therapy (a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10–14 d) (Strong recommendation, low quality of evidence (for duration: very low quality of evidence)



- Sequential
 - PA for 5-7 d, then PCN for 5-7 d
 - Sequential therapy (a PPI and amoxicillin for 5–7 d followed by a PPI, clarithromycin, and a nitroimidazole for 5–7 d is a suggested first-line treatment option (conditional recommendation, low quality of evidence (for duration: very low quality of evidence).
 - PA for 5-7 d then PFQN for 5-7 d
 - Fluoroquinolone sequential therapy (a PPI and amoxicillin for 5–7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5–7 d) (conditional recommendation, low quality of evidence (for suggested duration: very low quality of evidence).
- Hybrid
 - Hybrid therapy (PPI and amoxicillin for 7 d followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 d) (conditional recommendation, low quality of evidence (for duration: very low quality of evidence).
- Salvage
 - Try to avoid antibiotics used for previous attempts to eradicate *H. pylori*
- Prior treatment failure
 - Avoid previously used antibiotics that have been taken by the patient (strong recommendation, moderate quality of evidence).
 - PBMT or PAL if patient's first-line failed therapy contained clarithromycin
 - Selection of the best salvage regimen should be directed by local antimicrobial resistance data, and the patient's previous exposure to antibiotics.
 - Clarithromycin or levofloxacin-containing regimens of patients first-line failed therapy contained bismuth.
 - Bismuth quadruple therapy for 14 days is a recommended salvage regimen (strong recommendation, low quality of evidence)
 - Recommended salvage regimens PBMT, PAL, PAMC, PAR (conditional recommendation, moderate quality of evidence (for duration: very low quality of evidence).
 - Do **not** use clarithromycin triple regimen for “salvage” (conditional recommendation, low quality of evidence)

Abbreviations: A, amoxycillin; B, bismuth; C, clarithromycin; d, day; FQ, fluoroquinolone; M, metronidazole; N, nitroimidazole; P, proton pump inhibitor; R, rifabutin; T, tetracycline



❖ Prediction of eradication success

- Depends upon
 - The choice of regimen used
 - The patient's adherence to a multi-drug regimen with frequent side-effects, and
 - The sensitivity of the H. pylori strain to the combination of antibiotics administered (Factual statement, moderate quality of evidence).
- Patient
 - Adherence
 - Indication not diagnosed / used for functional dyspepsia
- Drug
 - Correct dose, duration, combination
 - Local rates of antibody resistance

❖ Proof of eradication

- Fecal antigen, urea breath, biopsy testing
 - ≥ 4 wk after antibiotic therapy completed
 - 1-2 wk of no PPI intake(strong recommendation; low quality of evidence; for the choice of methods to test for eradication: moderate quality of evidence).

❖ Antibody resistance

- Establish local rates of antibody resistance for H. pylori
 - Organized efforts are needed to document local, regional and national patterns of resistance in order to guide the appropriate selection of H. pylori therapy (strong recommendation; low quality of evidence).
- Recently reported antimicrobial resistance rates by H. pylori (Howden CW and Graham DY. Am J Gastroenterol 2020; 116: 1-2)

	<u>Ranges, %</u>
– Amoxicillin	< 2 -6
– Clarithromycin	17-43
– Levofloxacin	31-69
– Metronidazole	20-44
– Tetracycline	< 2



Randomized Clinical Trial of Vonoprazan Triple vs. Lansoprazole Dual Therapy for *Helicobacter pylori*

Chey WD, et al. *Gastroenterol* 2022; 163: 608-619

- Randomized, controlled, phase 3 trial of 14 d treatment-naïve adults with *H. pylori* infection
- Medications
 - V-dual ▪ Vonoprazan (V) 20 mg po b.i.d., amoxicillin 1 g b.i.d. (A)
 - V-triple ▪ V 20 mg b.i.d., plus A 1 g b.i.d., plus clarithromycin 500 mg b.i.d.
 - L-triple ▪ Lansoprazole 30 mg b.i.d., plus eradication rates clarithromycin

	Non-resistant		Resistant		All Patients	
V-double	79%	Non-inferior (P = 0.007)	66%	Superior P < 0.001	72%	Superior P < 0.001
V-triple	85%		68%		81%	
L-triple	79%		32%		69%	

Similar rate of adverse events in each group

- Eradication rates with PPI-based triple therapy, < 80% (clarithromycin resistance)
 - *H. pylori* susceptibility to antibiotics is influenced by intragastric pH
 - The potassium competitive acid blocker (PCAB) Vonoprazan vs. Lansoprazole has
 - ↑ T_{1/2}, 7.9 h vs. 2.5 h
 - ↑ 12-24 h
 - pH > 4, 88% vs. 42%
 - pH > 6, 33% vs. 7%

Laine L, et al. *Am J Gastroenterol* 2022; 118: 1158-1161

- *H. pylori* strains
 - Not resistant to clarithromycin
 - Vonoprazan-based triple and dual regimens are non-inferior to lansoprazole-based triple therapy for eradication of *H. pylori*
 - Resistant to clarithromycin
 - Significantly higher eradication rates about 15% of US isolates for *H. pylori* are clarithromycin-resistant, and clarithromycin-containing regimens are not recommended (Shah SC, et al. *AGA Clinical Practice Update Gastroenterology* 2021; 160: 1831-1841)
- The best current regimen is a 14-day bismuth quadruple therapy with tetracycline, with a cure rate of 87%.

Recommendation

- “PPI-clarithromycin-based triple regimens should be used only in patients without prior macrolide use who live in regions where clarithromycin resistance is known to be < 15%
- “Clarithromycin triple therapy is no longer a reasonable first-line empiric therapy in the United States” (Ho JJC, et al. *Am J Gastroenterol* 2022; 117: 1221-1230).



- Antibiotic resistance of *H. pylori* (US)
 - Metronidazole, 43%
 - Levofloxacin, 38%
 - Clarithromycin, 32%
 - Amoxicillin, 3%
 - Tetracycline, 0.9%
 - Rifabutin, 0.2%

Recommendation

- “The decision to use an optimized regimen empirically should be based on knowledge of the local susceptibility patterns and include monitoring treatment outcomes to ensure the regimen remains highly effective locally (Graham DY and Moss SF. *Am J Gastroenterol* 2022; 117: 524-528)

Compare and Contrast the Metabolism, Pharmacokinetics (PK) and Pharmacodynamics (PD) of the Proton Pump Inhibitor (PPI) Lansoprazole and the Potassium-competitive Acid Blocker (PCAB, Vonoprazan)

Adapted from Laine L, et al. *Am J Gastroenterol* 2022; 117: 1158-61

Feature	Lansoprazole	Vonoprazan
○ Metabolism	Proton Pump Inhibitors (PPIs)	Potassium competitive acid blockers (PCABs)
– Prodrugs	+	-
– Converted to sulfonamide	+	-
– Stored in vesicles inactive state	+	-
– Require acidic pH for activation in extracytoplasmic secretory vesicle in apical membrane of parietal cell	+	-
– Binding to		
▪ Active pumps (vesicles)	+	+
▪ Inactive pumps (cytoplasm)	-	+
▪ Cysteine (irreversible competitive)	+	-
▪ Ionic (reversible competitive)	-	+
– Block		
▪ H ⁺ binding site	+	-
▪ K ⁺ binding site	-	+
○ Pharmacokinetics (PK)		
– T _{max} , h	2	2
– T _½ , h	1.4	7.9



Feature	Lansoprazole	Vonoprazan
○ Pharmacodynamics		
– Day 7		
▪ Mean intragastric pH		
0-2 h	2.1	2.2
12-24 h	2.5	4.6
▪ % 24 h		
pH > 4 (holiday)	42%	88%
pH > 6	7%	33%

Secondary outcomes efficacy assessments.

	Vonoprazan		Lansoprazole
○ Eradication rate	Dual	Triple	Triple
– All patients	77%	81%	69%
– Clarithromycin-resistant strains	70%	66%	30%

Currently available and effective *H. pylori* therapies in the United States.

- Empiric Therapies

- Bismuth quadruple therapy
 - Bismuth subsalicylate q.i.d. 14 d
- Bismuth (e.g., PeptoBismol®) 2 tablets or 2 capsules q.i.d. 30 min before meals
 - Tetracycline HCl 500 mg and
 - Metronidazole 500 mg 30 min after meals q.i.d. (plus a PPI, 30 min b.i.d. before breakfast and with the evening meal [see PPI recommendations below])
- Pylera®. 3-in1 formulation of bismuth quadruple therapy with bismuth citrate) metronidazole and tetracycline 14-days
- Give combination tablets 4 times daily (with meals and at bedtime) plus a PPI 30 min before breakfast [please see PPI recommendations below]
- Rifabutin triple therapy. 14-days
- Rifabutin 150 mg b.i.d. 30 after breakfast and the evening meal, amoxicillin 1 gram t.i.d. 30 after breakfast, the evening meal, and bedtime plus 40 mg of esomeprazole or rabeprazole 30 min before breakfast and the evening meal. (see PPI recommendations below).
- Talicia® 3-in 1 formulation of rifabutin/amoxicillin/omeprazole triple therapy, 14-d
- 4 capsules t.id., as directed by the package insert



- Therapies only effective as susceptibility-based therapy. Do not use empirically unless proven to cure >90% locally
 - Clarithromycin triple therapy, 14-d
 - Clarithromycin 500 mg b.i.d.,
 - Amoxicillin 1 g b.i.d. 30 min after meal (plus a PPI b.i.d. 30 min before breakfast and the evening meal)
 - Metronidazole triple therapy, 14-d
 - Metronidazole 500 mg b.i.d., amoxicillin 1 g b.i.d., 30 min after meal (plus a PPI b.i.d. 30 minutes before breakfast and the evening meal)
 - Levofloxacin triple therapy, 14-d
 - Levofloxacin 500 mg in a.m., amoxicillin 1 g b.i.d., 30 min after meal (plus a PPI b.i.d. 30 min before breakfast and the evening meal)

PPI recommendations

- PPI should preferably be a PPI which is minimally affected by CYP2C19 metabolism (i.e., rabeprazole or esomeprazole) and at least 20 mg per dose (preferably 40 mg) of rabeprazole or esomeprazole b.i.d.
- Therapies containing unnecessary antibiotics that should not be used
 - Regimens that include at least one antibiotic that offers no therapeutic benefit and serve to increase global antimicrobial resistance include
 - Concomitant, hybrid, reverse hybrid, sequential therapies and vonoprazan clarithromycin and amoxicillin triple therapy

Abbreviations: a.m., in the morning; b.i.d., two time daily; HCl, hydrochloride; mg, milligram; PPI, proton pump inhibitor; q.i.d., 4 times daily; t.i.d., three times daily;

*The FDA recommends fluoroquinolones be used as a last choice because of the risk of serious side effects.



EATING DISORDERS (ED)

Werlang ME, et al. Am J Gastroenterol 2021; 116: 68-76.

➤ Demography

- The commonest eating disorders which a gastroenterologist/hepatologist may see are anorexia nervosa (AN) avoidant/restrictive food intake disorders (ARFID), bulimia nervosa (BN), and binge eating disorder
 - Patients with ED may present with GI-related symptoms/signs, or persons with GI issues may concurrently be suspected with an ED (bidirectional)
 - Important for the gastroenterologist to be capable of having basic knowledge for the possibility of having a clinical suspicion to not miss this important consideration.
- Prevalence of ED in various GI distortions
 - Chronic idiopathic constipation (CIC)
 - 20%
 - In AN CIC improved with weight gain
 - IBD
 - 24%
 - Poor prognosis / severe IBD
 - ↓ use / adherence to medications
 - IBS
 - 24%
 - SN/BN in ~66%
- Gender
 - Overall
 - 3:1 (25% male)
 - BEDS, 2:1 (33% male)
- Age
 - Girls < 20 yr, ED in 13%
 - Women > 50 yr, ED in 13%
- ↑ mortality/morbidity with ED, so important to diagnose even when subclinical, or when associated with other medical conditions.
- Eating disorders are estimated to have a prevalence of 24% in gastroenterology practice.
 - Anxiety, depression and somatization disorders are common in patients with GI disorders, as also are they common in ED

➤ Pathophysiology

- EDs
 - Inherited-genetic predisposition
 - Environmental
 - Weight stigma/teasing
 - Neurophysiological dysregulation
 - Hypothalamic-pituitary-adrenal axis
 - Catecholamine balance
 - Insular cortex
 - Reward pathways



- Secondary effects

- Once ED is present, there are secondary changes in
 - Central nervous system (CNS)
 - Autonomic nervous system (ANS)
 - Enteric nervous system (ENS)
 - Microbiome dysregulation

➤ Clinical

- Associations

- GI
 - Nausea, early satiety, fullness
 - ↓ gastric fundus accommodation
 - ↓ gastric emptying rate (gastroparesis)
- Other systems
 - CNS
 - Poor sleep
 - Head and neck
 - Parotid gland enlargement
 - Mouth
 - Dental caries
 - Esophagus
 - GERD/regurgitation
 - Stomach
 - Delayed gastric emptying
 - Colon
 - Constipation
 - ↓ weight
 - Rectal prolapse
 - Metabolic/nutrition
 - Electrolyte disturbances
 - ↓ intake of calories
 - Malnutrition/↓BMI
- Psychological features
 - Anxiety /depression
 - Body dissatisfaction
 - Emotional dysregulation
 - Harm avoidance
 - Somatization
 - Temperamental
- Diet
 - Diseases associated with diet-related treatment are associated with ↑ risk of ED
 - Celiac disease
 - IBD
 - Cystic fibrosis
 - Diabetes mellitus



- Physical examination
 - ↓ BMI
 - Eyes
 - Periorbital edema
 - Heart
 - Bradycardia
 - Hypotension
 - Ankle edema
 - Mital valve prolapse murmur
 - GI
 - V bowel sounds
 - Skin
 - Hypothermia
 - Yellow palms
 - Self-injuries, non-suicidal (BN)
 - Signs of nutritional deficiencies
 - Hair
 - Lanugo hair
- Laboratory
 - Liver
 - Abnormal LEs, LFTs, including ↑INR
 - Biochemistry
 - Hypo-albuminemia
 - Phosphatemia
 - Metabolic alkalosis
 - QTc prolongation
- Diagnostic imaging
 - ↓ BMD (bone mineral density) on DEXA scan

Abbreviations: AN, anorexia nervosa; ANS, autonomic nervous system; ARFID, avoidant/restrictive food intake disorder; BED, binge eating disorder; BMD, bone mineral density; BN, bulimia nervosa; BW, body weight; CIC, chronic idiopathic constipation; CNS, central nervous system; ED, eating disorder; ENS, enteric nervous system; GI, gastrointestinal; GU, genitourinary; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; INR, International Normalized Ratio; LEs, liver enzymes; LFTs, liver function tests



- Treatment
 - Suspect, diagnose
 - Multidisciplinary approach, especially psychiatrists specialized in ED
 - Management of
 - Nutritional deficiencies
 - Electrolyte/metabolic disorders
 - Associated conditions, e.g.,
 - IBD
 - Diet-treated conditions (celiac disease)
 - Gastroparesis
 - Chronic constipation
- ❖ EDs from the Psychological (DSM-5) perspective
- Demography
 - Affects persons of all weight categories
 - Up to 24% of adults
- Anorexia nervosa (AN)
- Definition
 - Persistent energy intake restriction leading to weight loss or failure to make expected gains in body weight
 - Accompanied by fear of gaining weight / becoming obese
 - Continued behaviour which interferes with weight gain
 - “...low weight must be assessed in the context of one’s biological [historic weight and growth history] as opposed to absolute BMI”
 - Often associated with amenorrhea



- Avoidant/restrictive food intake disorder (ARFID)
 - Demography
 - ~20% of persons with functional GI disorders
 - More common in persons with Crohn disease / ulcerative colitis (~25%)
 - Definition
 - Restriction of dietary intake due to concerns regarding the adverse consequences of eating, with significant
 - ↓ weight
 - Nutritional deficiency
 - Need for oral nutritional supplements (including enteral feeding)
 - Interference with psychological functioning
 - No distorted body image +/-
 - No concern about body weight / function
- Bulimia Nervosa (BN)
 - Definition
 - “Recurrent episodes [once per wk for 3 mon] of binge eating”, with feeding of less of control during the binge eating episodes
 - Associated with
 - Self-induced vomiting
 - Laxative/diuretic/medication abuse
 - Excessive exercise/fasting
- Binge Eating Disorder (BED)
 - Definition
 - “Recurrent episodes [once per wk for 3 mon] of binge eating”, with feeding of less of control during the binge eating episodes
 - Associated with feelings of
 - Body dissatisfaction
 - Disgust/shame
 - Guilt/embarrassment

} Distress



Obesity and the Gastroenterologist

Jirapinyo P and Thompson C. Am J Gastroenterol 2021; 116: 918-34

➤ Approach to the patient with obesity

❖ Stages of change in the Health Behavior

- Precontemplation
 - Unaware, resistant: motivational techniques
- Contemplation
 - Aware, prepared to change
 - 5As" ask, advice, assess, assist, arrange
- Preparation
 - Willingness to change within 6 mon
 - OARS: open-minded questions, affirmations, reflections, summaries
- Action
- Maintenance

❖ Clinical examinations

- Weight
 - Body mass index (BMI)
 - Waist circumference
 - Waist-hip ratio
 - % body fat
- Weight-associated medical conditions
 - Neck/axilla
 - Hyperpigmentation
 - ↑ circumference M > 17", F > 16"
 - Acanthosis nigrans / insulin resistance
 - ↑ risk of sleep apnea possible
 - Cushing disease (polycystic ovarian syndrome [PCO])
- Skin
 - Thin atrophic
 - Hirsutism

❖ Psychological

- Activity disorders
 - Anorexia nervosa (AN)
 - Avoidant / restrictive food intake disorder (ARFID)
 - Bulimia nervosa (BN)
 - Night eating syndrome (NES)
 - Bing eating disorder
 - Purging disorder

❖ Diet/Eating Habits

- Diet
 - Recall, 24 h



- Food
 - Log
 - Frequency questionnaire
- Patterns
- Frequency
- Duration of frequency
- ❖ Lifestyle
 - Sedentary
 - Exercise
 - Duration
 - Frequency
 - Type
 - Amount
 - 30 min per day, most days of the week
 - Maintenance, 200-300 min per h
- Suggestions
 - Food log
 - Meal planning
 - Cognitive restricting / behavioural therapy
 - Relapse prevention
 - Join a group if you think and the patient feel that it will help!
- ❖ Energy Expenditure
 - Total energy expenditure (TEE) calories burned per day
 - Resting energy expenditure (RER) (60% to 75%)
 - Heart beating, breathing, body temperature
 - Thermic effect of meals (TEM) (10%)
 - Energy for assimilation of food
 - Energy expenditure from physical activity (EEPA; exercise plus non-exercise thermogenesis [NEAT], 15% to 30%)
- ❖ Medical contributing the weight gain
 - Anti
 - Contraception
 - Convulsion
 - Depression
 - Diabetes
 - Histamines
 - Hypertension
 - Inflammatory/corticosteroids
 - Psychotic



Medications associated with weight gain, weight neutrality and weight loss

Medical type	Weight gain	Weight neutral	Weight loss
○ Anticonvulsants	– Carbamazepine – Gabapentin – Pregabalin – Valproic acid	– Lamotrigine – Levetiracetam – Phenytoin	– Topiramate – Zonisamide
○ Antidepressants	– MAOIs – SSRI ▪ Mirtazapine ▪ Citalopram	– SSRIs ▪ Fluoxetine ▪ Sertraline	– Bupropion
○ Antidiabetics	– Insulin, meglitinides, Sulfonylureas – Thiazolidinediones	– Alpha-glucosidase inhibitors, Bromocriptine – Colesevelam, DPP-4 inhibitors	– GLP-1 agonists, Metformin – Pramlintide, SGLT2 inhibitors
○ Antihistamines	– First generation antihistamine ▪ Diphenhydramine ▪ Hydroxyzine ▪ Meclizine	– Second generation antihistamines ▪ Cetirizine ▪ Loratadine – Third generation antihistamine ▪ Fexofenadine – Alternative class of medication ▪ Decongestants	
○ Antihypertensive	– Alpha-blockers ▪ Prazosin ▪ Doxazosin ▪ Terazosin – Beta-blockers ▪ Atenolol ▪ Metoprolol ▪ Nadolol ▪ Propranolol	– ACE inhibitors, ARBs – Beta blockers ▪ Carvedilol ▪ Nebivolol – Calcium channel blockers ▪ Thiazides	
○ Antipsychotics	– Clozapine – Lithium Olanzapine – Quetiapine – Risperidone	– Aripiprazole – Lurasidone – Ziprasidone	
○ Contraceptives	– Progestin	– Barrier methods, Intrauterine device – Surgical sterilization	
○ Steroids	– Glucocorticoids	– Inhaled steroids – Topical steroids – NSAIDs – DMARDs	



Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; DMARD, disease-modifying anti-rheumatic drugs; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide; MAOI, n=monoamine oxidase inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; SGLT2, sodium-glucose co-transporter 2; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants

Adapted from: Jirapinyo P and Thompson C. Am J Gastroenterol 2021; 116: 918-34 (Table 2)

❖ Associated Medical Conditions/Complications

➤ Gastrointestinal Conditions associated with obesity

Gastrointestinal Organ	Gastrointestinal Conditions Associated with Obesity
○ Esophagus	- Abnormal esophageal peristalsis - Isolated hypertensive lower esophageal sphincter (LES) pressure ▪ Gastroesophageal reflux disease (GERD) ▪ Erosive esophagitis ▪ Barrett's esophagus ▪ Esophageal adenocarcinoma
○ Stomach	- Dyspepsia - Erosive gastritis - Gastric ulcer - Gastric cancer - Fasting gastric volume - Gastroparesis
○ Small intestine	- Duodenal ulcer - Small intestinal bacterial overgrowth (SIBO) - Diarrhea (related to change in bile acids) ▪ ↑ colonic transit and ↑ mucosal permeability) - ↑ absorption of ▪ Glucose (related to increased SGLT-1 [sodium glucose linked transporter -1]) ▪ Protein (specifically whey hydrolysates) ▪ Long chain fatty acids (related to ↑ induction of lipid binding proteins)
○ Colon	- Diverticulitis - Diverticular bleeding - Recurrent diverticulitis - Clostridium difficile infection - Polyps ▪ Adenomatous ▪ Sessile serrated - Colorectal cancer - Dyssynergic defecation ▪ Incomplete rectal evacuation ▪ Fecal incontinence - Crohn disease (conflicting data) - Earlier loss of response to biologics in IBD patients



Gastrointestinal Organ	Gastrointestinal Conditions Associated with Obesity
○ Liver	– Non-alcoholic fatty liver disease (NAFLD) – Non-alcoholic steatohepatitis (NASH) – Cirrhosis – Hepatocellular carcinoma (HCC)
○ Biliary tree	– Cholelithiasis – Cholecystitis – Cholesterosis – Gallbladder cancer
○ Pancreas	– Acute pancreatitis – Pancreatic ductal cancer

Adapted from: Jirapinyo P and Thompson C. Am J Gastroenterol 2021; 116: 918-34 (Table 1)

➤ Laboratory

- Blood
 - CBC
 - Liver enzymes (ALT/AST, AP/GGT)
 - Electrolytes
 - Fasting blood glucose (FBG); HbA1C (hemoglobin A1C)
 - TSH
 - Lipids
 - Creatinine
 - Vitamin D
- Urine
 - Albumin

Abbreviations: AEs, adverse effects; ALT, alanine; AN, anorexia; ARFI, avoid and restrict food intake; ASGE, American Society for Gastrointestinal Endoscopy; AST, aspartate aminotransferase; BE, Barrett's esophagus; BMI, body mass index; BN, bulimia nervosa; CRC, colorectal cancer; EEPA, energy expenditure from physical activity; EGD, esophago-gastroduodenoscopy; EWL, excess weight loss; F, females; FBG, fasting blood glucose; GABA, gamma amino butyric acid; GERD, gastroesophageal reflux disease; GGT, gamma glutamyl transferase; GLP1, glucagon-like peptide 1; HbA1C, hemoglobin A1C; IBW, ideal body weight; M, males; NEAT, non-exercise thermogenesis; NES, night eating syndrome; POS, polycystic ovarian syndrome; POSE, primary obesity surgery endoluminal; REE, resting energy expenditure; RVGB, Roux-en-Y gastric bypass; SAEs, severe adverse effects; SG, sleeve gastrectomy; TEE, total energy expenditure; TEM, thermic effect of meals; TSH, thyroid stimulating hormone; TWL, total body weight; WC, waist circumference; yr, year



➤ Endoscopy

- Esophagogastroduodenostomy (EGD)
 - Preoperative
 - Recommended by International Federation for the Surgery of Obesity and Metabolic Disorders
 - Even for asymptomatic patients (~50% of patients coming to bariatric surgery may have an abnormality)
 - Post-operative, where appropriate, e.g.,
 - Surgical
 - Anastomosis strictures
 - Pouch size
 - Marginal ulceration
 - GERD (50%) /BE (12%, de novo)
 - Gastrogastric fistula
 - Sleeve stenosis / angulation
 - Surgery related complication
- If the patient is over age 45 yr
 - Remember to recommend colonoscopy for screening for colorectal cancer (CRC), especially with ↑ risk of CRC in persons with ↑ BMI
- Abdominal ultrasound
 - To determine presence of non-alcoholic fatty liver disease

➤ Medications

- Indication
 - No response to lifestyle +/- meds
 - No defecation to result in < 1.4% to 8.6% TWL, and
 - BMI ≥ 30 kg/m²,
 - BMI ≥ 27 kg/m² plus obesity-related comorbidities
- Review patient's indications, and where possible to those which are weight neutral, or are associated with ↓ body weight (please see table)
 - Targeted/effective response
 - ≥ 5% placebo-adjusted TWL at 3 mon, or placebo-adjusted
 - ≥ 35% of patients having ≥ 5% TWL, when TWL ≥ 2x placebo effect

Treatment Caution

- Do not use these medications during pregnancy

The New Medication on the Block

- Gelesis 100, a hydrogel capsule
 - TWL 6.4% at 6 mon, vs 4.4% for placebo
 - ≥ 5% TWL achieved in 59%

* added in press: the treatment of obesity has been changed in 2023 with the FDA approval of Ozempic and Wegovy (Novo Nordisk) injections (currently approved for diabetes mellitus).



Name	↑ NOR release	GABA receptor modulation	Opioid Antagonist	↓uptake of NOR / dopamine	GLP, agonist	Lipase Inhibitor	Glucose: ↓ gut absorption, ↓ liver prediction, ↑ peripheral uptake of glucose

-
- Phentermine +
 - Phentermine +
 - + topiramate
 - ER
 - Topiramate +
 - Naltrexone plus bupropion +
 - Bupropion +
 - Semaglutide +
 - Liraglutide +
 - Metformin +
 - Orlistat +
 - Orlistat results in ~25% ↓ fat calorie absorption; the remaining drugs act on the arcuate nucleus → ↑ activity of pro-opiomelanocortin neurons → satiety / ↓ intake

➤ Surgery (bariatric)

• Indications

- BMI
 - $\geq 40 \text{ kg/m}^2$, or
 - $\geq 35 \text{ kg/m}^2$ plus ≥ 1 comorbidity
- Use for patients with
 - GERD
 - Associated metabolic diseases
- Surgical steps
 - Divide stomach into small/large pouch
 - Transect jejunum
 - Pouch anastomosis
 - Gastrojejunal
 - Jejunojejunal

• Types

- Sleeve gastrectomy (SE)
 - Create a tubular structure along the lesser curve by removing fundus and gastric curve



➤ Bariatric Surgery

- Classify the types of bariatric surgery, and for ten of these give the complications.

❖ Early/postoperative

- Sleeve gastrectomy (SG)
 - Roux-en-Y gastric (RYGB)
- } Anastomotic leaks

❖ Late

- SG
 - Reflux +/- complications
- RYGB
 - GJA stenosis/dilation
 - Cholelithiasis
- Laparoscopic adjustable band ligation (LAGB)
 - Reflux +/- complications
 - Esophageal dilation
 - Band erosion/slippage

❖ Early or late

- SG
 - Stenosis
- RYGB
 - Anastomotic ulceration
 - Gastrogastric fistula
 - Intestinal obstruction

• Complication

Surgical Procedure

	SG	RYGB	LAGB
○ Esophagus			
- Reflux	+		+
- Dilation			+
○ Stomach			
- Band, erosion			+
- Surgical			
▪ Slippage			+
▪ Leaks		+	
- GJA			
▪ Stenosis		+	
▪ Dilation		+	
▪ Obstruction		+	
▪ Ulceration		+	
- Sleeve			
▪ Leaks	+		
▪ Stenosis	+		
- Gastrogastric fistula		+	
○ Small bowel			
- Obstruction		+	
○ Gallbladder			
- Cholelithiasis		+	



- Bariatric Surgery Outcomes

	↓ EWL 12 mon	↓ TWL 12 yr	SAE Death	Reoperation	AEs
○ SG	52%		0.6%	3%	9%
○ RYGB	63%	27%	1.1%	5%	12%

- Bariatric Endoscopy

- Stomach
 - ↓ weight from metabolic conditions
 - Balloon
 - 3 balloon, filled with N2 gas, each swallowed 4 wk apart
 - Remove balloons by EGD at 6 mon
 - Orbera®
 - 1 balloon, filled with fluid, placed by EGD
 - Remove balloon by EGD in 6 mon
 - Endoscopic sleeve gastroplasty (ESG) (overstitching endoscopic stitching system)
 - Primary Obesity Surgery Endoluminal (POSE) opposition of serosa to gastric fundus or body (POSE2) by plication
- Small bowel
 - ↓ weight from direct effects on metabolic conditions

- Outcomes

Bariatric Surgery Type	TWL at 1 yr	EWL at 1 yr	SAE	Re-op	Miscellaneous: bleeding, infection, leakage	Death
○ Sleeve Gastrectomy	23%	52%	13%	3%		0.6%
○ Roux-en-Y Gastric Bypass (RYGB)	32%	63%	18%	5%		1%
○ Adjustable Gastric Banding (AGB)	20%	34%	15%	7%		0.3%
○ Biliopancreatic Diversion with Duodenal Switch (BPD-DS)	45%	56%	9%			0.6%
○ One Anastomosis Gastric Bypass (OAGB)	35%	67%	9%	2%		0.1%
○ Single Anastomosis Duodenoileal Bypass with Sleeve Gastrectomy	3%	67%	3%			

Adapted from: Jirapinyo P and Thompson CC. Am J Gastroenterol 2021;116(5):918-34 (Figure 2)



Bariatric Endoscopy Type

	TWL at 1 yr	EWL at 1 yr	SAE	Re-op	Miscellaneous: Death bleeding, infection, leakage
○ Obera Gastric Balloon	12%		2%	All complications, including death	
○ Obalon Balloon System	10% at 6 mon		5%		5%
○ Primary Obesity Surgery Endoluminal (POSE)	13% (12-15 mon)				3%
○ Endoscopic sutured Sleeve Gastropasty (ESG)	16%				2%
○ Aspiration Therapy	18%				4%
○ Transpyloric shuttle	10%				3%

	Total Weight loss (TWL) at			Severe Adverse Effects		
	6 mon	12 mon	5 yr	Migration	Perforation	Death
○ Obalone		10%			0.15%	
○ Obera		11.3%		1.4%	0.1%	0.1%
○ E56	17%	16%	2.2% – Nausea, – Pain, Bleeding, – Perigastric leak, – Fluid collection			
○ POSE	12%	13%	3.2% – Fever, chest pain, bleeding, hepatic abscess			
○ POSE2	15%	18% (9 mon)				

Targets for Bariatric Endoscopy (ASGE/ASBMS) → ↓EWL (excess weight loss) ≥ 25% at 1 yr, with severe adverse effect rate ~5%



Bariatric/Gastric Surgery and Endoscopy

Barakat MT and Adler DG. Am J Gastroenterol 2021; 116: 657-665.

❖ Esophagectomy and Esophageal Reconstructions

- Resection of portion of esophagus (transthoracic or transhiatal) requires a conduit between remaining esophageal remnant and stomach.
 - The conduit can be from
 - Stomach (gastric pull-up, using greater tube – 1 anastomosis
 - Jejunum }
 - Colon } requires 2 anastomosis
- Anastomotic leaks in the cervical esophagus
 - Repair with endoscopy plus
 - Standard clips, or
 - Stents
 - Negative pressure / vacuum therapy
 - May be complicated by
 - Mediastinitis
 - Sepsis
- Thoracic therapy
 - Self-expanding metal stents (SEMS)
 - Leaks may continue
 - SEMS may migrate distally, but may require
 - OTSC placement, or
 - Suturing
- Anastomotic strictures
 - Often at an anastomosis which was previously included with an anastomotic leak
 - Treatment options
 - Balloon dilation
 - Corticosteroids injection plus repeated dilation
 - Stent through stricture
 - Covered esophageal self-expanding metal stent (SEMS), or
 - Lumen-opposing metal stent (LAMS)

❖ Gastrectomy and Gastric Reconstruction

Reconstructions after gastrectomy for patients with gastric cancer

- Billroth I reconstruction
 - Billroth reconstruction involves resection of gastric antrum, pylorus, and in usually, a portion of the proximal duodenum, with creation of a gastroduodenal anastomosis joining the proximal stomach and middle duodenum



- Resection of
 - Gastric antrum
 - Pylorus
 - Portion of proximal to duodenum plus
 - Gastroduodenal anastomosis
 - Common complication
 - Bile reflux (duodenogastric [DG] bile reflux)
 - Effect on endoscopy minimal for EGD, US, ERCP
- Billroth II reconstruction
 - Resection of
 - Gastric antrum
 - Inversion of duodenum stump
 - Mobilize loop of jejunum plus
 - End-to-side gastrojejunostomy
 - Shorter stomach
 - End-to-side gastrojejunal anastomosis
 - With 2 lumens
- ```

graph TD
 A[End-to-side gastrojejunal anastomosis] --> B[With 2 lumens]
 B --> C[Afferent pancreaticobiliary limb with duodenal stump plus inverted ampulla]
 B --> D[Efferent elementary limb]

```
- End-to-side gastrojejunostomy
  - Complication of DG bile reflux, as compared to Billroth I anastomosis
  - Effect on endoscopy-challenge to do ERCP
    - Consider assistance using dilation or balloon-enhanced endoscopy
    - If sphincterotomy required, consider sphincteroplasty (papillary balloon dilation)
  - For EUS visualization of pancreas/liver
    - Use forward-viewing echoendoscope into afferent limbs
  - Billroth II
 

|                |     |    |
|----------------|-----|----|
| - Gastroscopic | 85% | 5% |
| - Duodenoscopy | 85% | 5% |
- Roux-en-Y (RYGB) reconstruction
  - Billroth II reconstruction involves resection of the gastric antrum with maintenance of an intact inverted duodenum stump.
    - A mobilized loop of jejunum is then used to perform an end to side gastrojejunostomy
      - Resulting anatomy notable for a foreshortened stomach an end to side gastrojejunal anastomosis with 2 lumens – one leading to the pancreaticobiliary (afferent) limb and the other leading to the elementary efferent limb
  - Resection of
    - Portion of stomach
    - Transect jejunum ~40 cm distal to ligament of Treitz
    - End-to-side gastrojejunal anastomosis (between distal small bowel and gastric pouch)



- Side-to-side anastomosis
  - Anastomosis duodenum to other jejunal segment ~60 cm distal to the gastrojejunal anastomosis < 2 limbs
- Effect on endoscopy: use
  - Colonoscopy
  - Laparoscopy
  - EUS-directed transgastric ERCP (EDGE)
- Give the approximate endoscopic success rates of ERCP and rates of adverse effects of the endoscopic approaches for patients with Roux-en-Y gastric bypass, Billroth II and Whipple pancreaticoduodenectomy.

| Post-surgical Anatomy      | Endoscopic Approach   | Endoscopic Success | Adverse Events |
|----------------------------|-----------------------|--------------------|----------------|
| ○ Roux-en-Y gastric bypass | ○ Balloon-enteroscopy |                    |                |
|                            | - Single              | 80%                | 5%             |
|                            | - Double              | 85%                | 5%             |
|                            | - Spiral              | 77%                | 0              |
| ○ Directed                 | - EUS, transgastric   | 95%                | 15%            |
|                            | - Laparoscopy         | 80%                | 10%            |

#### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the approach to performing ERCP in the patient with gastrectomy and no excluded gastric remnant.
  - Gastrectomy after
    - Liver transplantation for PSC (no excluded gastric remnant)
    - Balloon/spiral enteroscopy-assisted ERCP
    - Colonoscopic-assisted ERCP
    - EUS-directed transgastric ERCP (EDGE) approach
      - Create a transluminal pathway (gastric pouch / proximal jejunal efferent limb to remnant stomach: ERCP with usual duodenoscope)
        - Cannulation risk, 96%
        - Complication rate, 15% - 30%
        - Migration of LAMS, 13%
        - Persistent fistula formation, 10%



❖ Bariatric reconstruction

- Sleeve gastrectomy

- Size of gastric sleeve for a 2 cm conduit for solids/liquids
  - Stenosis → gastric outlet obstruction

- Adjustable and vertical banded gastroplasty (VGB)

- Place a band across the proximal stomach →
  - Create extrinsic compression
  - Form a small gastric pouch → ↓ satiety → ↓ body weight
  - Inconsistent weight loss
- Complications
  - Slipped band
  - Band erosion

- Duodenal switch (DS) with biliopancreatic diversion reconstruction

- High morbidity/mortality
  - Sleeve gastrectomy
  - Divide the stomach at the pylorus
  - Divide the jejunum at the centre of the jejunal segment
  - Mobilize distal jejunum, create gastrojejunostomy
  - Construct Roux-en-Y configuration
  - Transect 40 cm distal to ligament of Treitz
  - Create end-to-side gastrojejunal anastomosis between distal small bowel and gastric pouch
- Effect on endoscopy
  - Laparoscopy-assisted transenteric ERCP
  - Percutaneous cholangioscopy through a percutaneous biliary drain tract (modified EDGE procedure with LAMS placement)

❖ Pancreatic reconstructions

- Pancreaticoduodenectomy (Whipple procedure)

- Removal of pancreatic lesion
  - Pancreaticojejunostomy, and
  - Hepatojejunostomy, and
  - Reconstruction
    - Billroth II, or
    - Roux-en-Y
- Effect on endoscopy
  - ERCP
    - Colonoscopy or balloon enteroscope for ERCP – high success rate
    - May require EUS to view the rest of pancreas/jejunal limbs



## ❖ Small Bowel Reconstruction

- Kasai portoenterostomy for biliary atresia
  - Resect all abnormal extrahepatic ducts to capsule of liver
  - Anastomose cut surface of the liver to jejunal Roux-en-Y limbs (bile flows from liver into jejunum (afferent pancreaticobiliary limb leads to hepaticojejunostomy)
  - Effect on endoscopy
    - Perform ERCP with colonoscope or balloon enteroscope into the Roux limbs of hepatojejunostomy
    - EUS may be necessary
- Choledochoduodenostomy and choledochojejunostomy
  - Living donor liver transplantation
  - Choledochal cyst resection

}

- Roux-en-Y
  - Join common hepatic duct
    - To duodenum (choledochoduodenostomy)
    - To jejunum (choledochojejunostomy, modified loop jejunostomy reconstruction)
- Small bowel transplantation
  - Indications
    - Inherited
      - Atresia
    - Injury
      - Trauma
      - Surgery
    - Immune
      - Necrotizing enterocolitis
    - Ischemia
      - Vascular embolization/thrombosis
  - Surgery resect distal to D3 (third part of the duodenum, leaving ampulla in place) leaving pancreas/liver
- Multivisceral transplantation
  - Transplantation of enbloc graft comprised of stomach, duodenum, small intestine, pancreas, liver
  - Effect on endoscopy
    - Usual methods for ERCP, EUS



## SMALL BOWEL

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Howarth, Nisha

Hudson, David

Iablokov, Vadim

Malhi, Gurpreet

Wilson, Aze



## DIARRHEA

### Chronic Diarrhea (BSG Guideline 2018)

Arasaradnam RP, et al. Gut 2018; 0: 1-20.

#### ➤ Clinical

- Importance of patient's personal history, e.g., family history of celiac disease, IBD including microscopic colitis and colorectal cancer
  - Establish if patient actually has fecal overflow, use clinical judgement rather than marker studies if overflow diarrhea suspected, investigate cause of possible colonic obstruction.
  - Fecal incontinence
    - History, physical including digital rectal examination
      - Anorectal manometry
      - Endoanal ultrasound (Grade of evidence level 3, Strength of Recommendation, strong)

#### ➤ Laboratory

- Blood
  - Complete blood counts (CBC) (Grade of evidence level 3, Strength of recommendation strong)
  - Tissue transglutaminase (tTG plus serum IgA) / endomysial antibody (EMA) (Grade of evidence level 1, Strength of recommendation strong)
  - Thyroid function
  - C reactive protein (CRP) reflects bowel inflammation, but ~10% of persons do **not** produce CRP (false negative test)
  - Sensitivity of biological tests for celiac disease
  - tTG IgA plus EMA IgG (endomysial antibody)
    - High-risk population, sensitivity and specificity each > 90%
    - Low risk populations, PPV ~80%
    - When histopathology is of small bowel biopsy does not show less atrophy, < 90%
  - In presence of IgA deficiency
    - tTG IgG plus EMA IgG
  - About 6% of patients with celiac disease are negative for these antibodies
  - If immunosuppression suspected, do HIV testing (Grade of evidence level 2, Strength of recommendation strong).
  - Serum electrolyte
  - Hemoglobin A1C, fasting blood sugar
  - If bile acid diarrhea (BAD) is suspected
    - Fasting serum C4 (Grade of evidence level 2, Strength of recommendation strong).
    - Do **not** do glucose or lactulose breath tests (Grade of evidence level 2, Strength of recommendation strong), or hydrogen plus methane breath tests (Grade of evidence level 4, Strength of recommendation strong).
    - Stool testing for laxatives [and stool electrolytes] if laxative abuse is suspected (Grade of evidence level 5, Strength of recommendation weak).





- Stool
    - Most likely causes of absence of diarrhea in persons who are immune competent
      - Protozoa                      Amebiasis  
                                         Giardia lamblia  
                                         C. difficile
      - Bacteria                      C. difficile
- } Sensitivity of fresh stool cultures, 60% to 90%
- Stool ELISA for giardiasis
    - Sensitivity, 92%
    - Specificity, 98%
  - Stool ELISA tests also available for amoeba
  - 48 h stool collection for fecal bile acids
  - Culture and sensitivity, ova and parasites
  - Fecal calprotectin
  - Fecal elastase if pancreatic dysfunction suspected
  - C. difficile infection (CDI)
    - Presence of organism glutamate dehydrogenase enzyme immunoassay / PCR
    - Toxin-producing EIA
  - Use fecal calprotectin cut off of 50 µg/g between functional (IBS) disease versus organic IBD
  - Fecal immune testing (FIT)
    - If the patient has lower gastrointestinal symptoms suspicious colorectal cancer (CRC) without rectal bleeding
    - Use fecal calprotectin in younger patients (under 40 years) with chronic diarrhea in whom inflammation is suspected, and not cancer (Grade of evidence level 1, Strength of recommendation strong).
    - Remember the ↑ predicts if there is a positive family history of CRC
      - For those with lower gastrointestinal symptoms suspicious of colon cancer (without rectal bleeding), do fecal immunological testing to rule out the need for referral or urgent investigations, either in primary or secondary care; (Grade of evidence level 2, Strength of recommendation weak)
  - If decision made to examine the colon
    - Colonoscopy plus ileoscopy plus biopsy is the preferred investigation (Grade of evidence level 1, Strength of recommendation strong), with mucosal biopsies for microscopic colitis (Grade of evidence level 1, Strength of recommendation strong).
  - If patients < 40 yrs and fecal calprotectin is normal
    - Perform sigmoidoscopy plus biopsies (Grade of evidence level 3, Strength of recommendation strong).
- Radionucleotide scanning
  - 75-SeHCAT (75 selenium homocholic acid taurine) retention
  - Best diagnostic yield / BAD in Crohn disease and IBS-D / functional diarrhea
    - A C4 assay is a recommended alternate
    - No recommendation re use of FGF19 assay
    - Do **not** use an empirical trial of sequestrants



- Predicts therapeutic response to cholestyramine

| 75 SeHCAT Retention | Respond to Cholestyramine (BAST) |
|---------------------|----------------------------------|
| < 5% (severe)       | 96%                              |
| < 10%               | 80%                              |
| < 15% (mild)        | 70%                              |

- There is a greater response to BAST in patients with severe vs mild BAD.
- Note the lack of response of diarrhea symptoms does **not** exclude the possibility of BAD (about 45% of persons with BAD do **not** respond to cholestyramine)
- Implications
  - Make a diagnosis of BAD by investigations, not from an empiric (therapeutic) trial
- If patient with suspected BAD fails to respond to cholestyramine →
  - For second-line therapy, use colevelam
- Examples of patients with disorders associated with BAD with positive SeHCAT scan
  - Cholecystectomy, ~50%
  - Resection of terminal ileum / R. colon,
    - Crohn disease, ~90% (as correlation between length of resection and SeHCAT retention)
    - Causes other than Crohn disease, ~75%
  - Radiotherapy, ~35%
    - With resection, ~75%
- If bile acid diarrhea (BAD) is suspected
  - Se HCAT (< 15% suggests BAD) (Grade of evidence level 2, Strength of recommendation strong) (please see guidelines on BAM, which follow)
- Outdated Urine and breath tests
  - <sup>13</sup>C triglyceride breath test
  - Stool chymotrypsin

#### Breath Tests

- H<sub>2</sub> is not produced by mammals,
  - The hydrogen present in the breath is derived from the intestinal microbe.
- Not all enteric bacteria produce H<sub>2</sub>, including
  - Enterococci spp.
  - Pseudomonas spp.
  - Staphylococcus



- The performance characteristics of breath tests are mediocre!

| Probe                      | Sensitivity  | Specificity | PPV   | NPV   |
|----------------------------|--------------|-------------|-------|-------|
| Glucose                    | < 50% to 62% |             | < 70% | < 70% |
| Lactulose                  | 17% - 62%    | 68%         |       |       |
| 75 SeHCAT with breath test | 39%          | 100%        |       |       |

#### ➤ Diagnostic imaging

#### Recommendations

- Small bowel
  - Barium studies
    - Both small bowel barium follow through and enterolysis have poor performance characteristics
  - MR enterography with diffusion-weighted imaging (MR-DWI) is superior to CTE and to barium studies.
  - Videocapsule endoscopy (VCE) may be better way to diagnose the cause of small intestinal bleeding.
    - Not recommended to make the diagnosis of celiac disease, but may prove useful in the celiac patient who is suspected of developing a small bowel tumour
  - Of limited use
    - Enteroscopy (±device assisted) has limited diagnostic value for the diagnosis of the cause of chronic diarrhea
      - Its role is mainly for targeting predefined lesions (Grade of evidence level 4, Strength of recommendation strong)
    - Videocapsule endoscopy (do either MR enterography or video capsule endoscopy (VCE) (depending on local availability) rather than CT as first-line investigation for diagnosing inflammation within the small bowel [Grade of evidence level 1, Strength of recommendation strong]), including if there is suspicion for celiac disease (Grade of evidence level 5, Strength of recommendation strong).
- Pancreas
  - CT, MRI, EUS may show subtle early changes in the parenchyma and ducts in persons with PEI, but 80% to 90% of pancreatic acinar cells must be lost before the changes become clinically significant.
  - MRCP with secretin (MRCP-S) has
    - Equivalent sensitivity as ERCP
    - Correlates with
      - Fecal elastin
      - Histopathology of pancreas



- MRCP (first choice) or CT
  - To demonstrate parenchymal / duct drainage if pancreatic insufficiency suspected
    - MRI (with MRCP protocol) is the recommended investigation of choice for diagnosing chronic pancreatitis. If unavailable, CT would be the next modality of choice (Grade of evidence level 2, Strength of recommendation strong).
  - Second-line investigations
    - Endoscopic ultrasound (EUS)
    - MRCP with secretion (Grade of evidence level 3, Strength of recommendation weak)
- EUS (endoscopic ultrasound) has equivalent sensitivity as direct (tube-based) pancreatic function tests
- ERCP correlates with secretin, cholecystokinin (CCK) and food-stimulated pancreatic function tests
- Do **not** do abdominal ultrasound as an initial investigation of chronic diarrhea
  - Ultrasonography of the small bowel, while attractive due to its non-invasive nature and absence of radiation exposure, has a limited diagnostic role hence cannot be recommended routinely (unless other modalities are unavailable) (Grade of evidence level 4, Strength of recommendation strong) (please see Guidelines on BAM, which follow)
- Suspected fistula
  - Cross-sectional imaging with contrast (Grade of evidence level 3, Strength of recommendation strong).
- Small intestine manometry
  - Only if there is clinical suspicion and failure to respond to therapy [or suspicion of small intestinal transit disorder] (investigate for intestinal transit with manometry only if there is clinical suspicion and failure to respond to therapy (Grade of evidence level 4, Strength of recommendation strong).
- Small intestinal bacterial overgrowth (SIBO) suspected
  - Empirical trial of antibiotics (Grade of evidence level 3, Strength of recommendation strong).
  - Small intestinal aspiration for culture is a research tool (Grade of evidence level 2, Strength of recommendation weak).
  - [Measure of stool total bile acids, or duodenal aspartate ratio of primary to secondary bile acids, or ratio of conjugated to unconjugated bile acids are also research tools]

Abbreviations: BAD, bile acid diarrhea; CBC, complete blood count; CDI, Clostridium difficile infection; EMA, endomysial antibody; EUS, endoscopic ultrasound; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; NET, neuroendocrine tumour; SIBO, small intestinal bacterial overgrowth; tTG, tissue transglutaminase



## ❖ Some Causes of Chronic Diarrhea

- Microscopic Colitis

- Demography

- Usually in middle-aged (mean age 60 yr) women with watery diarrhea (F>M)
- Prevalence
  - In persons with chronic diarrhea, ~10%
  - 50 to 200/10<sup>5</sup>
- Types
  - Lymphocytic, 77%
  - Collagenous, 68%
  - 25% occur age < 45
- Persons may have misdiagnosis of IBS-D (prevalence, ~10%)
- May be associated with use of
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Proton pump inhibitors (PPIs)

- Endoscopy

- Colonic mucosa on endoscopy appears normal
  - Essential to take multiple mucosal biopsies to diagnose lymphocytic/collagenous colitis

- Histopathology establishes diagnosis

- Lymphocytic colitis: ↑ intraepithelial and lamina propria lymphocytes > 20 per 100 cells
- Collagenous colitis: subepithelial collagen band > 10 µm
- Diagnostic yield of colonic mucosal biopsy
  - Right side > left

- Scoring system (Cotter)

- Excellent scoring system to exclude microscopic colitis (NPV 97%; Cotter TG, et al. J Clin Gastroenterol 2017; 51: 228-34)

- Maldigestion of FODMAP (fermentable oligo-, di-, mono-saccharides, and polyols)

- Fructose
  - Low capacity for enterocytes to absorb fructose → chronic diarrhea
  - 25 g fructose (soft drinks, corn syrup) → fructose intolerance in ~40% of persons
- Fructans
  - Wheat-associated diarrhea
- Sugar alcohols/polyols
  - Sorbitol, artificial sweeteners



- Lactose
  - Primary lactase deficiency → loss of 13910 C/C genotype in the promoter region of lactase enzymes → lactase deficiency → lactose maldigestion
  - Secondary lactase deficiency associated with disease is affecting brush border membrane in enterocytes (e.g., celiac disease)
- Post-radiation chronic diarrhea
  - Pelvic radiation, e.g., gynecological/prostate cancer therapy
- Rapid transit
  - Stomach
    - Vagotomy
    - Dumping syndrome
  - Small bowel
    - Resection
    - Loss of ileal “brake” (resection of ileocecal valve)
  - Metabolic disorder
    - Type 1 diabetes mellitus
    - Hyperthyroidism
- Crohn disease (CD)
  - Bile acid diarrhea (BAD) is common in patients with CD (~50%)
  - Bile acid sequestrant therapy (BAST) may be effective in
    - CD patient in remission as well as
    - CD after therapy for active disease
  - The overall rate of response to cholestyramine to cholestyramine is ~ 60% (2 g to 4 g per day, maximum 24 g/day)
    - In those failing cholestyramine as first-line therapy for BAD, ~50% will respond to colesevelam, also BAST

#### Clinical GEM

- Fecal incontinence may be mistaken for diarrhea, but
  - The patient with chronic diarrhea may have sufficient fluid loss that they overburden normal mechanisms for fecal continence, and are misdiagnosed as having fecal incontinence.

#### Therapeutic Caution

- In patients with ileal resection >100 cm with steatorrhea >20 g/day giving cholestyramine
  - ↑ steatorrhea (fatty diarrhea)
  - ↓ watery diarrhea



- Pancreatic Exocrine Insufficiency (PEI)

- Clinical

- Symptoms of PEI usually develop
  - 10-15 yr after other symptoms of chronic pancreatitis
  - After ↓ pancreatic exocrine insufficiency (PEI)
- Stool
  - 3 day collection for fat
    - 5 g to 7 g/day usually small bowel disease
    - > 13 g/day usually pancreatic exocrine insufficiency (PEI)
  - Single stool sample of 100 g
    - Elastase-1 (anionic protease of the serine protease)
    - Stool sample stable for 1 wk to measure elastase family

| Values          | Elastase µg/gm stool |
|-----------------|----------------------|
| – Normal        | 300 – 500            |
| – Insufficiency |                      |
| ▪ Mild/moderate | 100 – 200            |
| ▪ Severe        | < 100                |

- After ↓ pancreatic enzymes by 80% to 90%
  - Performance characteristics (severe PEI)
    - Sensitivity, 73% to 100%
    - Specificity, 80% to 100%
- } False positive in persons with diarrhea  
(dilation of stool elastase from ↑ H<sub>2</sub>O from diarrhea)
- Not useful for mild PEI, sensitivity < 60%
  - Superior to
    - Para-amino benzoic acid
    - Pancreolauryl test



## **Bile Acid Malabsorption (BAM) and Management of BA Diarrhea (BAD): CAG Guideline (2020)**

Camilleri M and Vijayvargiya P. Am J Gastroenterol 2020; 115: 1596-1603.

Sadowski DC, et al. J Can Assoc Gastroenterol 2020; 3: e10-e27.

- Demography
  - The prevalence depends upon the diagnostic tool used to make the diagnosis
- Metabolism of bile acids (BAs)
  - Cholic (CA) and chenich (chenodeoxycholic) acids (CDCA) are the primary BAs synthesized in the hepatocytes from cholesterol (Chol)
  - The conversion of Chol to BAs is by the rate-limiting enzyme 7 $\alpha$ -hydroxylase (cytochrome P450 7A1 and CYP7A1)
  - The BAs are conjugated with the amino acids, glycine and taurine, and excreted across the canalicular membrane of the hepatocytes by the carrier BSEP (bile salt export protein)
  - The bile salts are partially deconjugated and dehydrated by the microbiome into deoxycholic acid (DCA) and lithocholic acid (LCA), as well as small amounts of ursodeoxycholic acid (UDCA) and other tertiary BA.
  - 95% of the bile salts are actively reabsorbed by the brush border membrane of the ileocytes by the way of Na<sup>+</sup>-dependent in apical sodium BA transporter (ASBT).
  - Bile salts which are not absorbed in the ileum (5%) pass into the colon, and are lost in the feces.
  - In the cytosol of the ileocyte, the absorbed BAs
    - Stimulate nuclear FXR (farsenoid X receptor) to bind to BAs
    - Produce the enteroendocrine hormone FGF-19 (fibroblast growth factor 19)
  - FGF-19 is produced in proportion to the amount of BA to be exported from the ileocyte by the basolateral membrane by OST $\alpha$ / $\beta$
  - FGF-19 enters the hepatocyte through FGF-receptor 4 by way of
    - The second BA receptor is GPBAR1 (G-protein coupled BA receptor, aka T6R5 [Takeda G coupled receptor 5])
      - GPBAR is present in enterocytes, cholangiocytes as well as in smooth muscle, normal cells, brown adipose tissue, and immune cells
      - GPBAR1 stimulates motility and release of serotonin
  - The activity if 7 $\alpha$ -hydroxylase is modified by the FGF-19, with  $\uparrow$  hepatocyte synthesis of interaction with Klotho  $\beta$ , a surface protein, and induction of a small heterodimer protein which binds to 7 $\alpha$ -hydroxylase to modify hepatic BA synthesis from cholesterol (negative feedback inhibition)
    - Primary BAs produced from Chol in response to BA ileal absorption
    - The relationship between FXR, which reflects ileocyte BAs, and activity of hepatocyte 7 $\alpha$ -hydroxylase, is inverse:  $\downarrow$  ileal BA,  $\downarrow$  FGF-19,  $\uparrow$  7 $\alpha$ -hydroxylase,  $\uparrow$  BA synthesis





- The full name of the rate-limiting enzyme for conversion of Chol to BA is 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4)
  - C4 may be measured in serum, and when there is ↓ BA absorption, there is ↑ serum C4; thus BAM and BAD are associated with ↑ C4 in serum

➤ Pathophysiology

- Mechanisms of colonic diarrhea in BAM
  - ↓ ileal absorption of BA → ↑ spoilage of BA into colon
- ↑ BA in colon
  - ↑ Cl<sup>-</sup> / H<sub>2</sub>O secretion
    - ↑ cGMP
    - ↑ cAMP → ↑ CFTR
    - EGFR (epidermal growth factor receptor)
    - ↑ aquaporin channels 3/8 → ↑ H<sub>2</sub>O secretion
    - ↑ TGR5 → ↑ serotonin
- ↓ Na<sup>+</sup>/K<sup>+</sup> ATPase  $\alpha$ 1/ $\beta$ 1
- ↓ Na<sup>+</sup>/H<sub>2</sub>O absorption
- ↑ motility (↑ high amplitude propagating contractions of colon)
  - ↑ TGR5 → ↑ serotonin
- Microbiome
  - ↑ Clostridium scindens, Escherichia coli
  - ↓ Bifidobacterium

➤ Subtypes of BAM

- When BAM is diagnosed by the 75 SeHCAT retention test (please see laboratory, below)

|                 |                                     |                           |       | Prevalence<br>of BAM                  |                                                                          |
|-----------------|-------------------------------------|---------------------------|-------|---------------------------------------|--------------------------------------------------------------------------|
| – Type 1<br>BAM | ▪ Crohn<br>disease                  | – No ileal<br>resection   |       | 11% to 52%                            |                                                                          |
|                 |                                     | – With ileal<br>resection |       | 90%                                   |                                                                          |
|                 |                                     |                           |       | 75 SeHCAT<br>Retention                |                                                                          |
| – Type 2        | ▪ IBS-D /<br>functional<br>diarrhea | – Mild                    | < 15% | } ▪ Prevalence overall,<br>35% to 80% |                                                                          |
|                 |                                     | – Moderate                | < 10% |                                       | } ▪ Severity of BAM<br>predicts response to<br>bile acid<br>sequestrants |
|                 |                                     | – Severe                  | < 5%  |                                       |                                                                          |



|          |                        |                                          |  | Prevalence<br>of BAM |
|----------|------------------------|------------------------------------------|--|----------------------|
| - Type 3 | ▪ Post-cholecystectomy | - 1 wk,<br>- 3 mon                       |  | 25%<br>~5%           |
|          | ▪ Microscopic colitis  | - Lymphocytic<br>- Collagenous           |  | 60%<br>~25%          |
|          | ▪ Radiotherapy         | - No resection<br>- With resection       |  | 18%<br>~70%          |
|          | ▪ Right hemicolectomy  | - For Crohn disease (CD)<br>- Not for CD |  | 87-100%<br>71-76%    |

| Type |                                |                                                                                                                                                                                    |
|------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1    | ○ Ileal disease                | - Crohn disease, radiation, resection                                                                                                                                              |
| 2    | ○ Idiopathic                   | - Irritable bowel syndrome, diarrhea predominant (IBS-D), functional diarrhea<br>- This may be due to unexplained, ↓FXR, ↓FGF-19, ↓GPBAR produced by ileocytes, ↓ASBT in ileal BBM |
| 3    | ○ Maldigestion / malabsorption | - Pancreatic insufficiency, cholecystectomy, celiac disease                                                                                                                        |
| 4    | ○ Drug / metformin             | - Mechanism <ul style="list-style-type: none"> <li>▪ ↑ synthesis of BA</li> <li>▪ ↓ absorption / ↑ colonic loss of BA</li> </ul>                                                   |

- Give why a response to BA sequestering therapy (BAST) such as cholestyramine does not prove the presence of BAM.
  - Patients with symptoms of BAM respond to therapeutic doses of cholestyramine, but
    - Patients with similar symptoms but no BAM (normal 75 SeHCAT retention) may also respond.

#### ❖ Diagnosis of BAM/BAD

- Use risk factors for BAD to raise clinical suspicion of BAD
  - GRADE. Strong recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 60%; yes, 40%.
  - Do **not** use symptomatology to raise clinical suspicion of BAM
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: no, 100%.



➤ Laboratory

- 75 selenium homotaurocholic acid test (75 SeHCAT)
  - Retention of 75 Se HCAT in body 7 d after intake, as measured by the whole body scanning with a gamma camera
    - “gold standard” test for BAM
    - Retention is partially determined by the total daily number of enterohepatic circulations (EHCs)
    - This number is about 4 to 16 per day, and to correct for this potential source of error, the measurement must not be done at day 7 after intake of test dose
  - Initial laboratory testing for BAD should be 75 SeHCAT testing in patients (GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 80%) with
    - Crohn disease (no objective evidence of information)
      - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 80%
    - IBS-D / functional diarrhea
  - Testing serum C4
    - IBS-D / functional diarrhea
      - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 60%; neutral, 20%.
  - FGF-19 assay
    - **No** recommendation for or against
      - GRADE. NO recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; neutral, 80%.
  - Do **not** use empirical bile acid sequestrant therapy (BAST) to make the diagnosis of BAD.
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 20%; no, 40%; strongly no, 40%.
- Fasting serum 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4)
  - Measure C4 with C18 liquid chromatography-tandem mass spectrometer
  - ↑ C4 indicates BAM
  - Performance characteristics

| C4, ng/mL |               | Comparison of C4 to |     |
|-----------|---------------|---------------------|-----|
| > 48.4    | 75 Se HCAT    | 90%                 | 79% |
| > 52.5    | 48-h fecal BA | 29%                 | 83% |



- Fasting serum FGF-19
    - Do **not** use clinically because of poor performance characteristics (Sn, 29%; Sp, 78%)
    - 48-h stool collection for BA while on previous 100 g/d fat diet for 4 d before collection
      - Performance characteristics
        - Sensitivity, > 55%
        - Specificity, > 74%
- Use the following fecal measurements
- Total fecal BA;  $\geq 2,337 \mu\text{mol} / 48 \text{ h}$  collection, or
  - CA plus CDCA > 10% of total fecal BA, or
  - Total fecal BAs  $\geq 1,000 \mu\text{mol} / 48 \text{ h}$  collection plus CA plus CDCA > 4%

#### ➤ Treatment

- Bile Acid Sequestrant Therapy (BAST) Induction: Therapy
  - In patients with associated treatable conditions, treat the underlying condition, and the BAD.
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 80%; yes, 20%.
  - Use cholestyramine to treat BAD
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 60%; yes, 40%.
    - Use cholestyramine first, rather than other bile acid sequestrants
      - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%.
    - Use alternate BAST if cholestyramine not tolerated
      - GRADE. Conditional recommendation, low-certainty evidence. Vote on PICO question: strongly yes, 40%; yes, 60%.
  - While empiric use of BAST is **not** recommended to make the diagnosis of BAD, if cholestyramine is used empirically
    - Use "gradual daily dose titration....to minimize side effects.
    - Designated a good practice statement
  - In patients with Crohn disease (CD) plus "... extensive ileal involvement or resection", do **not** use BAST (when resection > 100 cm and steatorrhea > 20 g/d, because then cholestyramine actually  $\uparrow$  steatorrhea).
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question (should we use BAST?): yes, 20%; no, 80%.
  - Always review concurrent medications for possible drug-drug interactions with BAST
    - Designated a good practice statement
      - Recommend to patient using BAST to consult with their pharmacist about drug-drug interactions, and the optimal time to take BAST relative to their other medications.
  - No recommendation made for or against measuring fat soluble vitamins at start of BAST, and annually thereafter
    - GRADE. NO recommendation; very-low-certainty evidence. Vote on PICO question: yes, 20%; neutral, 80%.



- Low-fat diet, < 20% total calories per day
  - 2-4 g/d po, titrate dose to symptom response; maximum 4-24 g/d supplement fat soluble vitamins if patient at risk for deficiency (severe BAM)
  - Rational and evidence
    - Provides maximum efficiency of BA sequestrants
- Bile acid sequestrant therapy (BAST)
  - Choices
    - Cholestyramine
    - Colestipol
    - Colesevelam (625 mg tablets, 3 tablets po b.i.d., or 6 tablets od, or 3.75 g powder od)
  - Rational
    - ↓ BA in colon to ↓ colonic diarrhea (↑ sequestered BA)
  - Results
    - Serum C4 concentration predicts response to BA sequestrants
    - About 50% of patients with BAM have ↓ stool symptoms, as well as other GI symptoms, when give BAST
    - Long-term use of ~7 yr
      - Continued therapy, 38% good response continued
      - Poor tolerance and stopping therapy in 24%
- Obeticholic acid (6-ethyl CDCA)
  - FXR agonist:
    - ↑ FXR-19, ↓ C4 / ↓ stool BA → ↓ symptoms of BAM
    - Adverse effect
      - Pruritis
- Loperamide
  - May be used as needed to supplement BAST
- Maintenance therapy
  - If induction therapy for BAD successful with BAST
    - Attempt using intermittent, or on-demand dosing (rather than continuous BAST)
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%.
  - If BAST not tolerated for maintenance therapy
    - Use “alternative antidiarrheal agents”
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 100%.
  - When empiric BAST maintenance used for BAD, “...use the lowest dose needed to minimize symptoms”.
    - Designated a good practice statement
  - If patients with BAD are maintained on BAST but develop recurrent / worsening symptoms
    - Re-evaluate the diagnosis of BAD



## Bile Acid Diarrhea (BAD) CAG Guidelines (2020)

Sadowski DC, et al. J Can Assoc Gastroenterol 2020; 0: e10-e27

### ➤ Demography

- Chronic diarrhea
  - Prevalence in seniors, 5% to 10%
- Persons with chronic diarrhea, ~25%
- Do **not** use just presence of chronic diarrhea to suspect BAD (GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: no, 100%)
  - Exclude fecal incontinence, overflow diarrhea, IBS-D (irritable bowel syndrome, diarrhea predominant)
    - GRADE. Strong recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 60%; yes, 40%.

### ➤ Pathophysiology

- Bile acids are synthesized in the hepatocytes by the rate controlled liver enzymes CYP7A1 (7 $\alpha$ -hydroxylase), through the intermediate 7 $\alpha$ -hydroxy-4-cholesten-3-one.
  - Negative feedback regulatory proteins from ileocytes include nuclear farvesoid receptor (NFR) and fibroblast growth receptor (FGR)
- When there is a mild/modest amount of bile acids (BA) escaping ileal reabsorption, the  $\uparrow$ BA spilled into the colon stimulate cGMP-mediated colonic secretion of chloride (Cl<sup>-</sup>)  $\rightarrow$  watery diarrhea (bile acid-induced diarrhea, BAID)
- When there is loss of amounts of BA which exceed the ability of the liver to upregulated its production of BA, then insufficient BA enter the upper small intestine in bile.
  - When the bile acid concentration drops below the critical micellar concentration (CMC) to form micelles to solubilize the products of gastric- and pancreatic-mediated digestion of lipids in the lumen  $\rightarrow$  steatorrhea (fatty diarrhea)

### ➤ Clinical

- "...change in bowel habits is a poor guide to the prevalence of neoplasia, unless advanced to the point of malignancy

### ➤ Testing

- Blood
  - $\uparrow$  serum 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4) for BAD (metabolic intermediate in conversion of cholesterol to bile acids [BA], which represents  $\uparrow$ BA turnover)
  - Performance characteristics:
    - NPV (negative predictive value), 95%
    - PPV (positive predictive value), 74%
  - There is an inverse correlation between C4 ( $\uparrow$ ) and SeHCAT retention ( $\downarrow$ ) in persons with BAD



- ↑ fecal calprotectin in the presence intestinal inflammation is from degradation of neutrophils → release of calprotectin → fecal calprotectin > 250 µg/g feces correlation with endoscopic inflammatory.

#### ➤ Treatment

- Before starting BAST
  - Review patient's list of other medications for possible drug-drug interactions (GRADE. NO recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; neutral, 80%)
  - In patients with BAD, use cholestyramine rather than BASTs as initial therapy for induction of clinical response.
    - GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%.
- Use cholestyramine, including for types /3 BAD from remedial causes (e.g., Crohn disease, small intestinal bacterial overgrowth 7 [but not if the patient has extensive ileal disease/resection] (GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question (should we use BAST): yes, 20%; no, 80%)
  - When starting cholestyramine, patient tolerance may be better with a gradual ↑dose (Designated a good practice statement)
  - Some patients prefer intermittent on-demand drug (GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%)
  - If unable to tolerate cholestyramine
    - Use alternate BAST (GRADE. Conditional recommendation, low-certainty evidence. Vote on PICO question: strongly yes, 40%; yes, 60%), or
    - Use alternate antidiarrheal drugs (GRADE. Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 100%)
  - If patient taking cholestyramine as an empirical therapy for maintenance of reduction in chronic diarrhea – use lowest beneficial dose (Designated a good practice statement)
  - If the patient has a recurrence / ↑ severity of chronic diarrhea while on BAST.
    - Review the diagnosis (Designated a good practice statement)
  - Its unknown whether persons with BAD and/or are on BAST, whether they need monitoring/replacement supplementation of fat-soluble vitamins.
  - Toxin immunoassay (EIA) or PCR testing for active C. difficile toxin

#### ➤ Adverse effects of BAST

- Long term use of cholestyramine
  - ↓ absorption of
    - Fat (calories)
    - Fat soluble vitamins (ADCEK) → ↑INR from ↓ vitamin K absorption
    - Folic acid
  - Drug interactions
    - Consult pharmacist for advice regarding timing and dosing of other medications, such as warfarin and digoxin



## ❖ Post-surgical diarrhea

### ➤ Mechanism

- ↓ surface area of ileum
  - Extensive resection
- ↑ transit rate
  - Dumping syndrome / myotomy
- Small intestinal bacterial overgrowth (SIBO)
  - Stenosis/stricture
  - Fistula (colon to small intestine)
  - Loss of ileocecal valve
- Bile acid diarrhea (BAD)
- Unmasking of second condition
  - Celiac disease
  - Lactase deficiency
  - Small bowel diverticulae
  - Pancreatic insufficiency (PI)

### ➤ Treatment

- BAST (cholestyramine) may benefit persons with post cholecystectomy diarrhea, when taken intermittently or on-demand

## ❖ Factitious diarrhea

- Other young / middle-aged female health professionals
- Laboratory testing
  - Urine
    - Anthraquinones
    - Bisacodyl
    - Phenolphthalein
  - Stool
    - Magnesium
    - Phosphate
    - Electrolytes (to calculate osmolality, which may be increased with intake of poorly absorbed FODMAPs, e.g., fructose, sorbitol, lactulose)





## CELIAC DISEASE

### Celiac Disease (CD) and HLA Genetics: Clinician's Guide (2019)

Brown NK, et al. Am J Gastroenterol 2019; 114: 1587-92

#### ➤ Definition

- Celiac disease (CD) is a complex inherited immune-mediated disorder in which, “the diagnosis of CD relies in specific serological testing, histological evaluation of duodenal biopsies and improvement of a gluten-free diet”

#### ➤ Demography

- Prevalence
  - 1% to 2% of persons of “European descent” (particularly of Scandinavian areas)
  - Affected first-degree relatives ~10% (7.5% to 15%)
  - Twins
    - Monozygotic
    - Concordant, 50% to 80%
    - Dizygotic, 10%

#### ➤ Definition

- “Celiac disease is considered to be an immune disorder that is triggered by an environmental agent (gliadin) in genetically predisposed persons” leading to symptoms and nutrient deficiencies arising from an enteropathy, plus associated multiple intestinal and extraintestinal features.

#### ➤ Pathophysiology

- HLA-DQ2 and D8 are obligately permissive for the development of CD.
- HLA DQ2/DQ8 indicates personal risk for CD, not CD itself
  - Predictive value for potential to develop CD
    - DQ2.5 High  
DQ2.5, 2 copies high risk of severe disease/symptoms
    - DQ8 Medium
    - DQ2.2 Low
  - But the inheritance does not follow Mendelian inheritance (1/2 of a heterodimer which is permissive for CD can be inherited from each parent, with neither parent encoding the full heterodimer).
- The genes which encode for HLA molecules are on the major histocompatibility complex (MHC) on chromosome 6
  - These HLA molecules are class II on the DQ loci
  - Each DQ locus codes on  $\alpha$ - or  $\beta$ - chain protein, which forms heterodimers on the surface of the antigen presenting cells (APCS)
  - These bind to a cleft in the DQA I and DQB1 molecules
    - In turn these bind to deamidated dietary peptides (such as  $\alpha$ -gliadins) → CD4+ T-cell response → inflammation (protein complex found by two different proteins)



- 90% of patients with CD encode for HLA-DQ 2.5 heterodimer, and the rest encode for DQ 2.2 or DQ8
- Gluten passes into the enterocyte, and is deamidated by tissue transglutaminases 2 (tTG2) into  $\alpha$ -gliadins
  - $\alpha$ -gliadin contains a five amino acid complex which binds to the HLA, heteromeric DQ-2 or DQ-8, is presented to the CD4+ T cells, and leads to gluten-specific CD-4 T-cell response in the enterocytes.

#### ❖ Environmental Factors

##### • Gluten

- Wheat protein
  - Gluten
    - Glutenin
    - Prolamins (gliadins)
  - No-gluten proteins
    - Globulin
    - Albumin

} Toxic in persons with celiac disease inherited susceptibility (HLA DQ2 or 8)

- |             | Origin   | Name       |                               |
|-------------|----------|------------|-------------------------------|
| ○ Prolamins | – Wheat  | ▪ Gliadins | } Not toxic in celiac disease |
|             | – Rye    | ▪ Secalins |                               |
|             | – Barley | ▪ Hordeins |                               |
|             | – Oats   | ▪ Avenins  |                               |
|             | – Corn   | ▪ Zeins    |                               |

- Fractions (epitopes) of gliadin (single polypeptide chains ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\zeta$ ))
- $\alpha$ -gliadin epitope, AA 56 to 75 activates T cells in celiac disease (amino acid sequences QQQPF [glutamine, proline, phenylalanine]; prolamines of wheat, rye, barley are ~30% glutamine, ~15% prolamine)
- Intracellular tTG (transglutaminase) released in celiac patients → deamidated gluten proteins → ↑ T-cell response
- Adding oats to a gluten-free diet (GFD) of persons with celiac disease does not affect symptoms, serology or histology
- The timing of the introduction of gluten into a suckling infants diet, and the amount of gluten taken, may determine whether the gliadin will be toxic.
- Other possible environmental triggers
  - Infection
    - Rotavirus (↑ risk of CD)
    - Use of antibiotics
    - H. pylori infection (↓ risk of CD)
  - Caesarian section
  - Living in Northern latitude



## ❖ Genetic Factors

### • Terminology

- Allele
  - A particular genetic sequence polymorphic genes have more than 1 allele
- Haplotype
  - Genes that are inherited together on the chromosomal segment
  - Protein complex formed by 2 different proteins
  - Encoding 2 different alleles
  - Encoding 2 identical alleles
- Concordance twins
  - Monozygotic ~60%
  - Dizygotic ~10%

} develop CD
- HLA class II molecules
  - DQ2 90% of CD patients
  - DQ8 CD risk in homozygotes > heterozygotes
- Lamina propria antigen-presenting cells (dendritic cells) have "...heterodimer antigen-presenting grooves which deliver gliadin negatively charged glutamic acid residues".
- The T cells binding to gliadin stimulate
  - B lymphocytes to produce Ig's
  - Other T cells to secrete
    - IL-4, -5, -6, -10, -15
    - Interferon growth factor (TGF- $\beta$ )
  - C-deamidated epitope for the T-cell response is the deamidated glutamine residue Q65E of  $\alpha$ -gliadin
- Inflammatory cytokines
  - Enteropathy
  - Aberrant  $\uparrow$  HLA class II cell surface antigen
- There may be additional but unknown genes which provide genetic susceptibility.

### • HLA-DQ genetic and protein structure

- The genes encoding HLA molecules are found in the MHC complex on chromosome 6.
  - HLA molecules involved in celiac disease are encoded in a region known as class II at the DQ loci (other class II genes include DR and DP).
- HLA-DQA1 and DQB1 loci encode for  $\alpha$ - and  $\beta$ -chains, respectively, that associate as heterodimers on the surface of APC, forming a cleft that binds peptide antigens.
- DQ molecules encoded in cis and trans.
- DQ molecules encoded in cis form from alleles on the same chromosome, whereas those in trans form from alleles on opposite chromosomes.
  - Once a gene is translated to a protein, a cell cannot determine which chromosome the protein came from, so any compatible DQ chains will form functional heterodimers.

Abbreviations: APC, antigen-presenting cell; HLA, human leukocyte antigen; MHC, major histocompatibility complex



- HLA in celiac disease pathogenesis
  - Gluten is digested into  $\alpha$ -gliadin, which can mediate both adaptive (shown here) and innate (not shown) immune responses.
  - Gliadin transverse enterocytes and is deamidated to a negatively charged particle by TTG2.
  - Deamidated gliadin preferentially binds to HLA-DQ2 or DQ8 on APC and is presented to CD41 T cells. This, in turn, leads to a gluten-specific CD41 T-cell response.

Abbreviations: APC, antigen-presenting cell; HLA, human leukocyte antigen; TTG2, tissue transglutaminase 2

#### ❖ Immune Factors

- Tissue transglutaminase
    - In addition to tTG, there may be  $\uparrow$  other antibodies
      - Anti-gliadin (IgA)
      - Casein
      - Endomysium (IgA; target is the enzyme calcium-dependent intracellular tTG-2)
      - Lactoglobulin
      - Non-gluten wheat proteins
      - Ovalbumin
    - tTG2 deaminates gliadin peptides involving the conversion of glutamine into glutamic acid (more negatively charged)
      - $\uparrow$  cross-linking molecules of extracellular matrix with
      - $\uparrow$  Q65E deamidated glutamine of  $\alpha$ -gliadin, a dominant epitope for T-cell activity
    - The T-cells in the lamina propria in CD are CD8+ T-cells (not the usual CD4+ T cells)
      - Also present
        - Primed memory cells with  $\uparrow$  expression of CD45RO
      - $\uparrow$  6x expression of TCRs (usually  $\sim$ 90%  $\alpha/\beta$  TCR in health)
    - IL-15 may bridge the interplay cell-mediated immune responses and adaptive immunity by
      - $\uparrow$  function of dendritic cells
      - $\downarrow$  apoptosis of IELs (intraepithelial lymphocytes)
- Recognize

  - Non-peptide antigens
  - Unprocessed stress-related proteins



➤ Laboratory

- HLA DQ2/DQ8 are required to bind a gliadin and to cause the damaging inflammatory T-cell response, but the haplotype does not cause but rather facilitates the causation of CD, first as
  - tTG2 does not cause CD, rather deamidates gluten to  $\alpha$ -gliadin, but without the appropriate HLA type, there would be no binding to the APC, and CD4+ T-cell response
  - Ideally, serology (tTG2) and small bowel biopsy should be performed in a gluten-containing diet
- HLA testing is not performed routinely in persons with typical CD serology and compatible small bowel biopsy, but may be useful to
  - Rule out CD in a person on a gluten-free diet (if other methods fail; HLA status is not affected by a gluten-free diet)
  - Rule out CD in a person with equivocal serology and biopsy
  - Identify high-risk first-degree family members (HLA-negative rules out CD)
- The special issue of testing first-degree family members (FDFM)
  - FDFM
    - Serology+, biopsy+ → diagnose CD → gluten-free diet (GFD)
    - Serology
      - repeat serology in 10 yr or when symptoms develop
      - test for HLA-DQ2 / DQ8
        - if negative, CD excluded
        - if positive (low positive predictive value) CD still possible → repeat serology in 10 yr

Abbreviations: CD, celiac disease; FDFM, first degree family member; GFD, gluten-free diet; HLA, human leukocyte antigen; tTG, tissue transglutaminase

➤ Prognosis

- Enteropathy-associated T-cell Lymphoma (EATL)
  - Poor prognosis
    - 5-yr survival 44% EATCL transformation to enteropathy-associated T cell lymphoma
    - Better 5 yr prognosis survival 44%
    - Budesonide, or 5-ASA (small bowel release)
  - Severe malnutrition, sepsis, lymphoma
  - Treatments of EATCL
    - Chemotherapy
    - Surgery
    - Bone marrow transplantation (controversial)



## Non-Celiac Gluten Sensitivity (NCGS)

Aziz I, et al. Nat Rev Gastroenterol 2015; 12: 516-26

### ➤ Definition

- An intolerance or sensitivity to a food / food substance has no immune-mediated bases (with no CD serology / mucosal changes), and no IgE-mediated wheat allergy.
- A food allergy causes symptoms within minutes to hours, is mediated by specific skin prick test and by IgE-based serology.
  - Distinct from IgE-mediated wheat allergy

(Sapone A, et al. BMC Med 2012; 10: 13; Catassi C, et al. Nutrients 2013; 5: 3839-53)

- Note the existence of NCGS has been called into question with the demonstration of “...no specific or dose-dependent effects of gluten implicating the non-gluten components, specifically FODMAPs...Biesiekierski JR, et al. Gastroenterology 2013; 145: 320-8)

### ➤ Demography

- Predominantly in adults
  - Family history of CD in 5% to 24%

### ➤ Associations

- Irritable bowel syndrome (IBS), 48%
- Food intolerances (e.g., lactose), 35%
- IgG-mediated allergies, 22%

### ➤ Immunogenesis

|                                                  | NCGS | CD |
|--------------------------------------------------|------|----|
| ○ Immune response                                |      |    |
| – Innate                                         | +    | +  |
| – Adaptive (↑IFN- $\gamma$ , IL-6, IL-17, IL-21) | -    | +  |
| ○ Toll-like receptors permeability               | ↓    | ↑  |



➤ Clinical

- CNS/PNS
  - Gluten ataxia, 75% had antibodies to TG6, a glutaminase isoenzyme mostly in the brain
    - Changes in cerebrum (cortex), cerebellum; gluten encephalopathy
  - Peripheral neuropathy
  - Schizophrenia/psychosis
- Musculoskeletal system (MSK)
  - Fibromyalgia
- Skin
  - Psoriasis

➤ Complications

- Nutritional deficiencies / ↓ body mass index (BMI)
- Autoimmune disorders
- Metabolic bone disease
- Connective tissue disorders

➤ Histology

- Normal/mild ↑ IELs
  - Unusual distribution
    - Superficial epithelium
      - Clusters of lymphocytes
    - Lower lamina propria



## Refractory Celiac Disease (RCD)

van Gils T, et al. Nat Rev Gastroenterol Hepatol 2015; 12: 572-9.

### ➤ Definition

- A proven celiac disease (with other causes of villous atrophy excluded) with symptoms which are persistent for > 12 mon while the patient is on a gluten-free diet reflected by normal auto-antibody titres.
- May be
  - Primary resistance
    - After initial introduction of CD and on a GFD
  - Secondary resistance
    - Years after introduction of GFD plus initial response

### ➤ Demography

- Patients with CD ≥ 50 yr of age
- < 2% of CD patients

### ➤ Characteristics

|                                                                                                                                | RCD I            | RCD II       |
|--------------------------------------------------------------------------------------------------------------------------------|------------------|--------------|
| ○ Abnormal / “abnormal” IEL                                                                                                    | -                | +            |
| - Clonality                                                                                                                    | ↓ polyclonal     | ↓ monoclonal |
| ○ HLA-DQ2 homozygosity                                                                                                         |                  | +            |
| - DQ 2.5 homozygosity, or                                                                                                      | +                | -            |
| - DQ 2.5 – DQ8 compound heterozygous                                                                                           | +                | -            |
| ○ Aggressive / ↓ prognosis                                                                                                     | -                | +            |
| ○ T cell ↑ gamma delta TCR                                                                                                     | ↑                | ↓            |
| ○ Surface markers                                                                                                              |                  |              |
| - CD3-, CD14-, CD19-, CD56-                                                                                                    | CD3+, CD8+ < 50% | > 50%        |
| ○ T cell receptors (TCR) α, β                                                                                                  |                  |              |
| - iCD3+                                                                                                                        | -                | + (> 20%)    |
| ○ Anti-apoptotic effect of IL-5 (cytotoxic proteins; ↑ IFN-γ / NKG2-D type (integral) membrane protein-dependent cytotoxicity) | -                | +            |
| ○ Ulcerative jejunoileitis                                                                                                     | -                | +            |
| ○ Severe malnutrition                                                                                                          | -                | +            |

### ➤ Types

- RCD type I
  - ↑ IELs
  - CD8+ cells





- RCD type II
  - CD3+ T cells
  - Immunophenotype no CD8 cells
  - Oligoclonal T cells expression
- Diagnostic imaging
  - CT scan
    - Mesenteric lymphadenopathy
    - Splenic atrophy
  - PET-CT
    - Exclude EATL in all persons with RCD II
- Other enteropathies
  - Autoimmune enteropathy (AIE)
    - Seen in children
    - Treated with
      - Nutritional support
      - Corticosteroids, azathioprine
      - Rituximab
  - Olmesartan-associated enteropathy
    - Likely a class effect of all “sartans”
      - Olmesartan intake to treat systemic hypertension → sprue-like mucosal abnormalities reversed by stopping the medication (non gluten sensitive)
  - Enteropathy-associated T-cell lymphoma (EATL)
    - A complication of refractory celiac disease, type II (RCD II), a complication of chronic untreated CD, which often presents with stenosis or perforation of small bowel
    - Treatment
      - Surgery for complications
      - Nutrition support
      - Medications
        - Chemotherapy
      - Autologous stem cell transplantation (auSCT)
    - Poor prognosis
- Differential diagnosis
  - Slowly responding (to GFD) CD
    - CD+, tTG-, GFD+ ≥ 50 yr of age may supply be slow responders to GFD
  - Giardia lamblia infection
    - Active CD IEL, > 30/100 epithelial cells
    - Giardiasis, < 30/100 epithelial cells
  - Common variable immunodeficiency (CVD)
    - Suspect from history of
      - Infection
      - Pulmonary complications
      - Cancer
    - Responds to immunomodulators plus anti-TNF

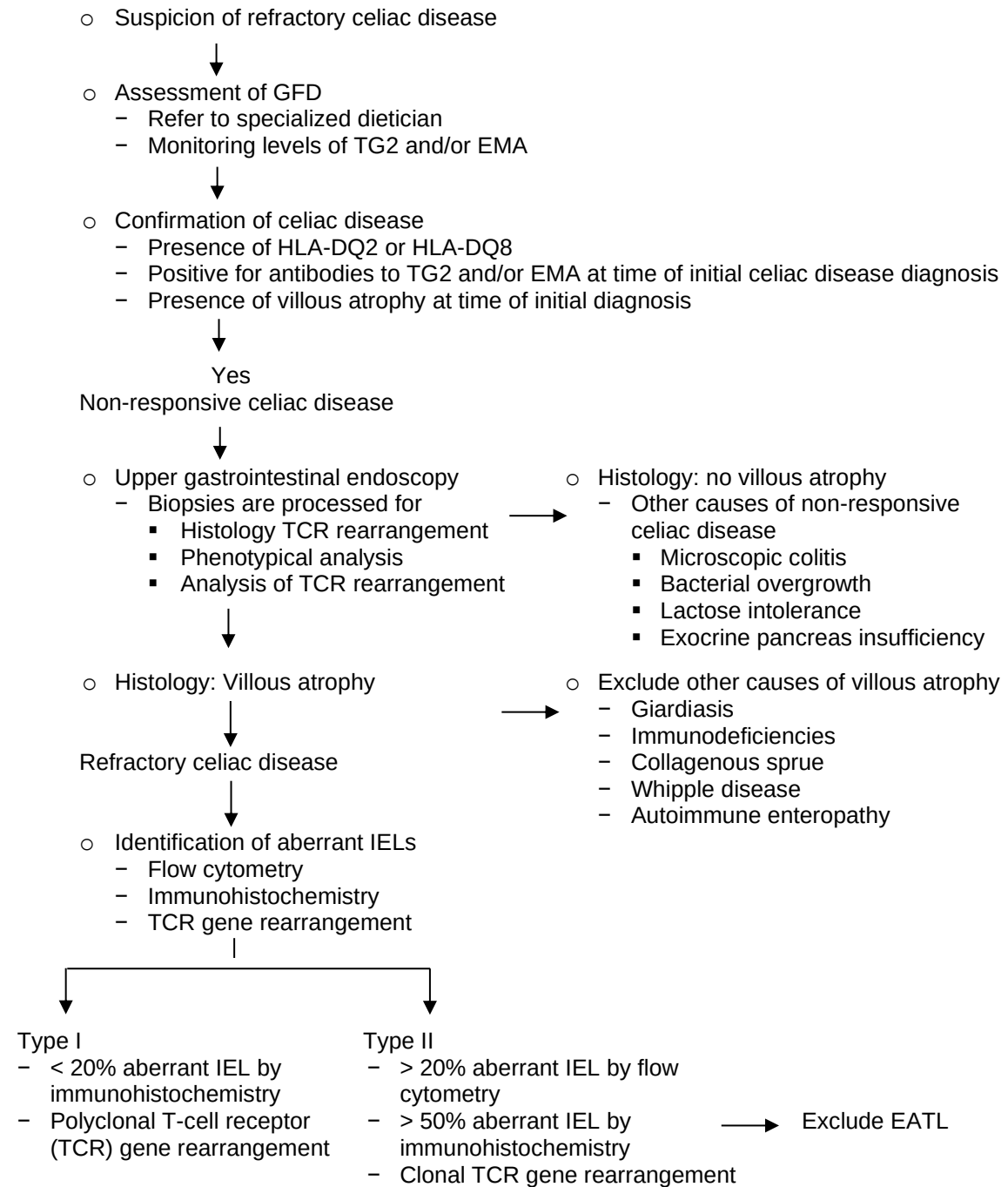


- Collagenous
  - Histology
    - ↑ thickness of subepithelial band of collagen
    - ↑ infiltration
      - Lymphocytes, plasma cells
      - Neutrophils, eosinophil
  - May respond to thiopurines
- Treatment
- RCD I
  - Nutritional support +/- immunosuppression
    - Topical / non-topical corticosteroids
    - Thiopurines
    - Infliximab
  - ↓
  - 5 yr survival rate, no treatment ~80%
    - Improvement in biopsy, but normalization in ~50%
- RCD II
  - Nutritional support
  - Cladribine
    - ↓ aberrant cells in 40%
  - auSCT
    - 5 yr survival
      - Responders ~85%
      - Non-responders ~20%
  - Regular testing for EATL
    - Flow cytometry
    - EGD plus biopsies
    - PET-CT
  - EATL
    - Develops in 50% of RCD II is 5 yr
      - Chemotherapy (CHOP, CHOEP, mAbs)
      - AuSCT
      - Surgery
    - Survival rate, ~5 yr ~10%

Abbreviations: auSCT, autolysis stem cell transplantation; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, plus prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; EATL, enteropathy-associated T-cell lymphoma; EGD, esophagogastroduodenoscopy; GFD, gluten-free diet; iCD3, intracellular CD3; IEL, intraepithelial lymphocytes; mAb, monoclonal antibody; SCD3, surface CD3; TG2, transglutaminase 2; tTG, tissue transglutaminase; yr, years



- Diagnostic approach for patients with suspected refractory celiac disease



Printed with permission: van Gils T, et al. Nat Rev Gastroenterol Hepatol 2015; 12: 572-9.  
 (Figure 2)



## SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

### Small Intestinal Bacterial Overgrowth (SIBO): ACG Guidelines (2020)

Pimentel M, et al. Am J Gastroenterol 2020; 115; 165-78

#### ➤ Definition

- Small intestinal overgrowth (SIBO)
  - "... a clinical syndrome [most commonly associated with bloating] cause by the presence of excessive [ $\geq 10^3$  CFU/mL] number of bacteria [coliforms, gram-negative aerobic and anaerobic species that ferment carbohydrates producing  $H_2$  gas] in the small bowel causing gastrointestinal (GI) symptoms.
  - Positive hydrogen breath test after 75 g of glucose, or 10 g of lactulose (fermentable carbohydrates) → exhaled breath hydrogen  $\geq 20$  ppm above baseline within 90 min (only one peak of hydrogen is acceptable)
- Intestinal methanogen overgrowth (IMO)
  - Constipation associated with the presence of excessive methanogens (methanogenic Archaea, especially *Methanobrevibacter smithii*) producing methane ( $CH_4$ )
    - A positive methane breath test is associated with constipation (OR = 3.51; 95% CI 2.0 – 6.16)
  - Positive methane breath test after 75 g of glucose, or 10 g lactulose → exhaled breath  $CH_4 \geq 10$  ppm at any point during the test (alternate cut-off:  $\uparrow 10$  ppm of  $CH_4$  over baseline)

#### ➤ Pathophysiology

- Mechanisms for Maintaining Small Bowel Ecological Homeostasis

| Mechanism              | Rationale                                                                                                      |
|------------------------|----------------------------------------------------------------------------------------------------------------|
| ○ Gastric acid         | - Most ingested bacteria in food cannot survive the acidic stomach                                             |
| ○ Pancreatic enzymes   | - Digestive enzymes in the proximal small bowel may also digest bacterial products → ↓ substrates for bacteria |
| ○ Bile acids           | - Bile acids can have detergent effect on bacterial membranes                                                  |
| ○ Small bowel motility | - Migrating motor complexes (MMCs) and other events clean the small intestine of debris during fasting         |
| ○ Ileocecal valves     | - The ↓ retrograde movement of colonic flora into the small bowel                                              |
| ○ Immune system        | - Important in the maintenance of stable microbiota of the intestinal lumen                                    |



- Give components of the small intestinal mucosal barrier against enteric infection.

| Components                                                 | Function                                                                                                                                                                        |
|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Lumen                                                    |                                                                                                                                                                                 |
| – Mucus/mucins                                             | ▪ Block penetration of ingested antigens                                                                                                                                        |
| – Proteases: pepsins, pancreatic tryptic enzymes           | ▪ Breakdown of ingested antigens                                                                                                                                                |
| – Gastric acid (pH)                                        | ▪ Breakdown of ingested antigens                                                                                                                                                |
| – Bile acids                                               | ▪ Breakdown of ingested antigens                                                                                                                                                |
| – Indigenous microbionics                                  | ▪ Competitive inhibition                                                                                                                                                        |
|                                                            | ▪ <i>Direct</i> : competition for essential nutrients and bacterial receptor sites; creation of restrictive physiological environments; secretion of antibiotic-like substances |
|                                                            | ▪ <i>Indirect</i> : chemical modification of bile salts and dietary fats, induction of protective Ig responses, stimulation of peristalsis                                      |
| ○ Epithelium                                               |                                                                                                                                                                                 |
| – Epithelium: glycocalyx (on villi)                        | ▪ Innate immune response                                                                                                                                                        |
|                                                            | ▪ Antigen presentation                                                                                                                                                          |
|                                                            | ▪ Block penetration of ingested antigens (tight junctions)                                                                                                                      |
| – Defensins                                                | ▪ Antimicrobial peptides                                                                                                                                                        |
| – Trefoil factors                                          | ▪ Protection from a variety of deleterious agents (bacterial toxins, chemicals and drugs); provide restitution after mucosal injury                                             |
| – Secretory-IgA (s-IgA)                                    |                                                                                                                                                                                 |
| – Paneth cells                                             | ▪ Enteric microbial peptides                                                                                                                                                    |
| ○ Immune system                                            |                                                                                                                                                                                 |
| – GALT-associated IgA, IgG, IgM (serum)                    | ▪ Clear antigens penetrating gastrointestinal barrier/systemic immunity                                                                                                         |
|                                                            | ▪ Assist in opsonization and phagocytosis of antigens                                                                                                                           |
| – Lymphoid follicles in lamina propria (aka Peyer patches) | ▪ Clear antigens penetrating gastrointestinal barrier                                                                                                                           |
| – Intraepithelial lymphocytes (IEL)                        | ▪ Innate and acquired immune responses                                                                                                                                          |
| – Mesenteric lymph nodes                                   | ▪ Phagocytosis and antigen presentation                                                                                                                                         |
| – M cells                                                  | ▪ Overlie lymphoid follicles                                                                                                                                                    |
|                                                            | ▪ Bind, process and deliver pathogens to lymphocytes, macrophages and mucosal lymphoid system                                                                                   |
|                                                            | ▪ Peyer patches                                                                                                                                                                 |
| – Dendritic cells                                          |                                                                                                                                                                                 |
| ○ Muscle                                                   |                                                                                                                                                                                 |
| – Intestinal peristalsis                                   | ▪ Block penetration of ingested antigens                                                                                                                                        |

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- Conditions Associated with Small Intestinal Bacterial Overgrowth

| Category                   | Condition                                                                                                                                                                                       |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Mechanical causes        | <ul style="list-style-type: none"> <li>- SI tumour</li> <li>- Volvulus</li> <li>- Intussusception</li> <li>- Postsurgical causes</li> <li>- SI diverticulitis (inherited)</li> </ul>            |
| ○ Motility                 | <ul style="list-style-type: none"> <li>- IBS</li> <li>- Mitochondrial diseases</li> <li>- Myotomy</li> <li>- Neuropathy</li> <li>- Pseudo-obstruction</li> <li>- Visceral myopathies</li> </ul> |
| ○ Medications              | <ul style="list-style-type: none"> <li>- Anticholinergics</li> <li>- Opiates</li> <li>- Potent antisecretory agents</li> </ul>                                                                  |
| ○ Malabsorptive conditions | <ul style="list-style-type: none"> <li>- Celiac disease</li> <li>- Cirrhosis</li> <li>- Pancreatic insufficiency</li> </ul>                                                                     |
| ○ Immune-related           | <ul style="list-style-type: none"> <li>- Human immunodeficiency virus (HIV) infection</li> <li>- Combined variable immunodeficiency IgA deficiency IgA deficiency</li> </ul>                    |
| ○ Systemic disease         | <ul style="list-style-type: none"> <li>- Amyloidosis</li> <li>- Diabetes</li> <li>- Scleroderma</li> </ul>                                                                                      |
| ○ Patient-related          | <ul style="list-style-type: none"> <li>- ↑ age</li> <li>- Female gender</li> </ul>                                                                                                              |



➤ Clinical

• Recommendation

- Small intestinal bacterial overgrowth (SIBO)
  - Bloating (common)
  - Distention “gas”; flatulence
  - Abdominal pain
  - Diarrhea
  - Deficiency
    - Especially vitamins B12; iron
- No single symptom can be specifically attributed to SIBO

➤ Laboratory

- May be
  - ↓Fe / iron deficiency anemia
  - ↓B12 / macrocytosis, subacute combined degeneration of posterior columns of spinal cord

MCQ Trick

Because excess microbes produce increased folate, serum levels of this vitamin are usually normal or increased in persons with SIBO.

- Give the two vitamins which are not utilized by the microbiome, and which are produced in ↑amounts in SIBO.
  - Folate
  - Vitamin K

Another Mind-Bender

- Give the significance of ↑ methane in the breath after oral administration of glucose or lactulose.
  - ↑ methane in the breath is
    - associated with constipation
    - **not** associated with SIBO
  - Explanation
    - The organisms in the small intestine which produced methane are not bacteria, but are “archaea”
    - The ↑methane in the breath after glucose/lactulose does not represent SIBO



## SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the commonest methanogen in the small intestine which metabolizes glucose/lactulose to produce ↑breath methane in persons with constipation who are having a glucose/lactulose breath test.
  - The commonest methanogen in the small intestine is “methanobrevibacter smithii”

### ➤ Diagnosis

#### • Recommendations

#### ❖ Breath Testing (surrogate marker for intraluminal small intestinal microbes)

- Indications
  - In IBS plus suspected SIBO (conditional recommendation, very low level of evidence)
  - In persons with suspected motility disorders ((conditional recommendation, very low level of evidence)
  - In persons with previous abdominal surgery followed by abdominal pain, gas/bloating +/- diarrhea (conditional recommendation, very low level of evidence)
  - In persons with constipation, test for methane production from methane-producing organisms using glucose/lactulose testing (conditional recommendation, very low level of evidence)
  - Do **not** do breath testing for SIBO in asymptomatic persons on PPIs (conditional recommendation, very low level of evidence)
- Standardized methods
  - Before testing, stop
    - Antibiotics, for 4 wk
    - Prokinetics, for 1 wk
    - Laxatives, for 1 wk
    - Complex carbohydrates, for 1 day (fermentable foods)
    - Fast for 8-12 h
  - During test
    - 250 mL of water with test dose of glucose / 75 g / lactulose, 10 g
    - Body rest
    - No smoking
  - After antibiotic treatment for a person with SIBO suspected from an abnormal breath test
    - Retesting may correlate with symptom improvement, with normalization of breath hydrogen





- Give the performance characteristics of using glucose, fructose, or lactulose as test substances for H<sub>2</sub> or CH<sub>4</sub> breath tests.

|             | Performance Characteristics* |             |      | Disadvantages                                                                                                                                                                        |
|-------------|------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             | Sensitivity                  | Specificity | Dose |                                                                                                                                                                                      |
| ○ Glucose   | 20% - 93%                    | 30% - 86%   | 75 g | <ul style="list-style-type: none"> <li>- ↓ sensitivity to detect distal SIBO (proximal) absorption → false neg result</li> <li>- Hyperglycemia</li> <li>- Gut dysmotility</li> </ul> |
| ○ Lactulose | 31% - 68%                    | 44% - 100%  | 10 g | <ul style="list-style-type: none"> <li>- ↑ rate of transit to colon</li> <li>- ↑ colonic fermentation</li> </ul>                                                                     |
| ○ Fructose  | 48%                          | 71%         | 75 g | <ul style="list-style-type: none"> <li>- Fructose malabsorption is common → ↑ effect test dose in mid-/distal small intestine</li> </ul>                                             |

\*as compared with properly collected small bowel aspirates

#### ➤ Treatment

- ↓symptoms / nutrient deficiencies occurring with clearance of SIBO
- Correct underlying causes/deficiencies (including malnutrition)
- Antibiotics (please see table)
  - For recurrence of SBO symptoms
    - Repeat course of antibiotics
    - Low dose antibiotic maintenance
    - Possible benefit of probiotics
- Small Intestinal Luminal Aspiration and Culture
  - Small bowel aspiration is the “gold standard” against which surrogate tests are compared for the diagnosis of SIBO/IMO
- Procedure
  - Sterile gloves
    - Use deep (D3/D4) duodenal intubation, minimal initial suctioning during resection of EDG, aspiration of luminal contents with catheter with multiple side holes, aspirate ~5 mL of luminal contents, rapid processing
    - ↓ microbial diversity (16s ribosomal RNA assessment [~RBA])
    - ↑ Escherichia
    - ↑ Shigella
    - ↑ Aeromonas
    - ↑ Pseudomonas
    - ↓ Acinetobacter
    - ↓ Citrobacter
    - ↓ Microvirgula



- Cut-off point
  - Aspirate  $\geq 10^3$  CFU/mL
- Concordance between aspirate and breath tests
  - Only 65%
- Clinical associations
  - Irritable bowel syndrome (IBS)
    - SIBO “microbiome dysbiosis”
    - Wide range of antibiotics used
      - Rifaximin gives a 76% correction of initially positive breath test
  - Small intestinal dysmotility
- Give the role of the migrating myoelectric complexes (MMCs) in the pathogenesis of SIBO.
  - MMC III
    - “An intense phasic and tonic contractile event that begins in the stomach on proximal bowel and sweeps through towards the colon, propelling chyme, secretions, and bacteria, and offering a natural protection against SIBO”
      - ↓ MMCs
      - Neuropathy
      - Myopathy
      - Vagotomy
      - Drugs (↓ propulsion)
- Treatment
  - Underlying disorders
  - Symptoms (Conditional recommendation, low level of evidence) [a potentially to correct initially abnormal H<sub>2</sub>/CH<sub>4</sub> breath test]
    - To ↓ symptoms
    - Possible to correct an abnormal CH<sub>4</sub>/H<sub>2</sub> breath test
  - Complications
    - E.g., nutrient deficiency
  - Antibiotics
    - A wide range small studies of low quality
      - Acute
        - Rifaximin
        - Ciprofloxacin, norfloxacin
        - Doxycycline
        - Neomycin
        - Amoxicillin-clavulanic acid
    - Recurrent
      - Repeat successful previous antibiotic
      - Maintenance therapy with whatever was the successful antibiotic
      - Alternate from 1 antibiotic to another

- Variable outcomes of symptoms
- Correction of abnormal breath test



- Diet
  - Poor quality data; patient may choose to try
    - ↓ fibre diet
    - ↓ probiotics (inulin)
    - FODMAP diet
  - Probiotics cause
    - ↓ H<sub>2</sub> production in repeated testing (OR = 1.61; 95% CI 1.19-2.17)
    - ↑ risk of SIBO
    - D-lactic acidosis
- Fecal microbial transplantation (FMT)
  - Only anecdotal data for indication of SIBO
  - In recipient, may cause
    - Constipation, and
    - Methane-positive breath test (e.g., FMT for *C. difficile* infection)

#### Therapeutic Alert

- “...the FDA has issued warnings about multidrug resistance organisms passed on to recipients during FMT”

- Suggested Antibiotics for Treatment of Small Intestinal Bacterial Overgrowth

| Antibiotic                      | Recommended Dose       | Efficacy   |
|---------------------------------|------------------------|------------|
| ○ Rifaximin*                    | 550 mg t.i.d.          | 61% - 78%  |
| ○ Amoxicillin-clavulanic acid   | 875 mg t.i.d.          | 50%        |
| ○ Ciprofloxacin                 | 500 mg b.i.d.          | 43% - 100% |
| ○ Doxycycline                   | 100 mg qd to b.i.d.    |            |
| ○ Metronidazole                 | 250 mg t.i.d.          | 43% - 87%  |
| ○ Neomycin                      | 500 mg b.i.d.          | 33% - 55%  |
| ○ Norfloxacin                   | 400 mg qd              | 30% - 100% |
| ○ Tetracycline                  | 250 mg q.i.d.          | 88%        |
| ○ Trimethoprim-sulfamethoxazole | 160 mg / 800 mg b.i.d. | 95%        |

\* very high cost, questionably little better than some more economical choices

Printed with permission: Pimentel M, et al. Am J Gastroenterol 2020; 115: 165-178 (Table 5)



## CROHN DISEASE

### Characterizing the Gut Metabolome, and Its Targeting in the Management of IBD

Lavelle A and Sokol H. Nat Rev Gastroenterol & Hepatol 2020; 17; 223-36

- Definition
  - “Metabolomics is the study of small molecules (< 1500 Da) in a biological sample or tissue, and a range of high-throughput analytical techniques and platforms are available”, e.g.,
    - Gas/liquid chromatography
    - Mass spectroscopy
    - Nuclear magnetic resonance
  - These data sets are analysed with bioinformatic and statistical analysis, e.g.,
    - Machine learning
    - Not work analysis
- The microbiome produces multiple metabolites
  - The alterations in the microbiome in IBD produce metabolites which may contribute to the pathogenesis of IBD:
    - Acylcarnitine
    - Bile acid derivatives
    - Hippurate
    - Polyamines
    - Short-/medium-chain fatty acids (SCFAs, MCFAs)
    - Sphingolipids
    - Tricarboxylic acid cycle intermediates
    - Tryptophan metabolites (indole)
- Short chain fatty acids (acetate, butyrate, propionate)
  - Actions
    - ↑ B / Treg responses
    - Regulate
      - Intestinal macrophages
      - Appetite control
    - ↑ secretion
      - Peptide YY (PYY)
      - Glucagon-like peptide 1 (GLP-1)
    - Energy source
    - ↑ inflammasome (↑ IL-18)
    - ↑ browning of white adipose tissue (WAT)
    - ↓ proliferation (via histone deacetylase [HDAC] inhibitor)



- SCFAs and their effects on the host
  - Brain and white adipose tissue (WAT)
    - Acetate
      - ↑ Satiety
      - ↑ Browning of WAT
  - Gut
    - Short chain fatty acid (SCFA) mediates diverse effects on
      - Host metabolism, including
        - ↑ satiety and
        - ↑ browning of white adipose tissue (WAT) (acetate)
    - Propionate/ Butyrate
      - ↑ intestinal glucogenesis
      - ↑ GLP1
      - ↑ PYY
  - Propionate is a precursor of intestinal glucogenesis
    - Propionate and butyrate increase peptide YY (PYY) and glucagon-like peptide 1 (GLP1) secretion.
    - Mucosal immunity
      - Supporting B cell development, differentiation, and expansion of regulatory T (T<sub>reg</sub>) cells
      - Antiproliferative effects via histone deacetylase (HDAC) inhibition
      - Maintenance of mucosal integrity by means of inflammasome activations and IL-18 production, and
      - Effects on colonic dendritic cells and macrophages that promote the differentiation of T<sub>reg</sub> cells
- Bile acids (BA)

#### Normal Metabolism

- Bile acids form micelles to aid in lipid digestion and absorption
- Bile salt hydrolase (BSH) activity deconjugates bile acids
- Unconjugated bile acids are passively reabsorbed where
  - Conjugated bile acids are actively reabsorbed in the distal ileum → production of fibroblast growth factor 19 (FGF19) → ↓ bile acid synthesis in the liver
- Bile acids that reach the colon are transformed into the secondary bile acids by bacteria.



- Immune/metabolic effects achieved by way of
  - Farnesoid X receptor (FXR) binding to BA
    - Controlled by fibroblast growth factor 19 (FGF19) →
      - ↓ lipogenesis
      - ↓ glucogenesis
      - ↑ hepatic regeneration
      - ↑ antimicrobial peptides
      - ↑ resistance to colonization to CDI (Clostridioides infection)
  - Transmembrane G protein coupled receptor 5 (TGR5)
    - ↑ sensitivity to insulin
    - ↑ energy expenditure
    - ↑ relaxation of gallbladder
    - ↓ Kupffer cells response to LPS (lipopolysaccharide) by ↓ NF-kB / ↑ IL-1, -6, ↑TNF
  - Pregnane X receptor
  - Vitamin D receptor
  - Constitutive androstane receptor

#### Dysmetabolism

- Bile acid decomposition can be altered in primary sclerosing cholangitis (PSC)
- Dysbiosis → ↓ BSH activity
- Intestinal resection or ileal inflammation → ↓absorption of bile acids, ↑ colonic primary bile acids
- Loss of transformation to secondary bile acids and desulfation → imbalance of primary and secondary bile acids in the colon

Abbreviations: ASBT, apical sodium-bile acid transporter; FXR, farnesoid X receptor; PXR, pregnane X receptor; TGR5, transmembrane G protein-coupled receptor 5; VDR, vitamin D receptor



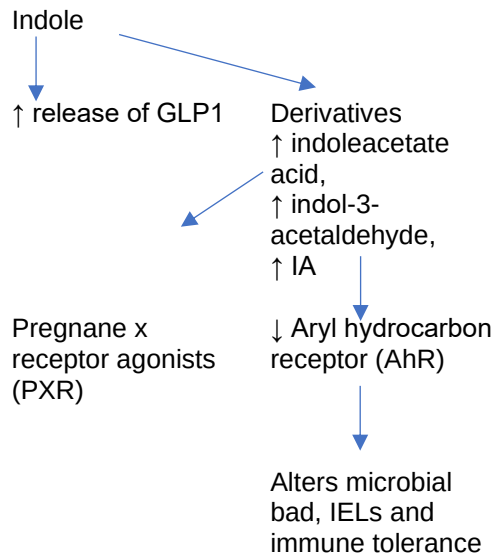
- Tryptophan

- Essential, aromatic amino acid
  - GI tract is major metabolic site
- Metabolism
  - Dietary tryptophan metabolism

- Host pathways
  - Kynurenine
  - Serotonin

- Rate-limiting enzymes
  - Intestine
    - Indoleamine 2,3-dioxygenase 1 (mucosa)
    - Tryptophan hydroxylase 1 (ECC)
  - Liver
    - Tryptophan 2,3 dioxygenase

- Microbial pathway

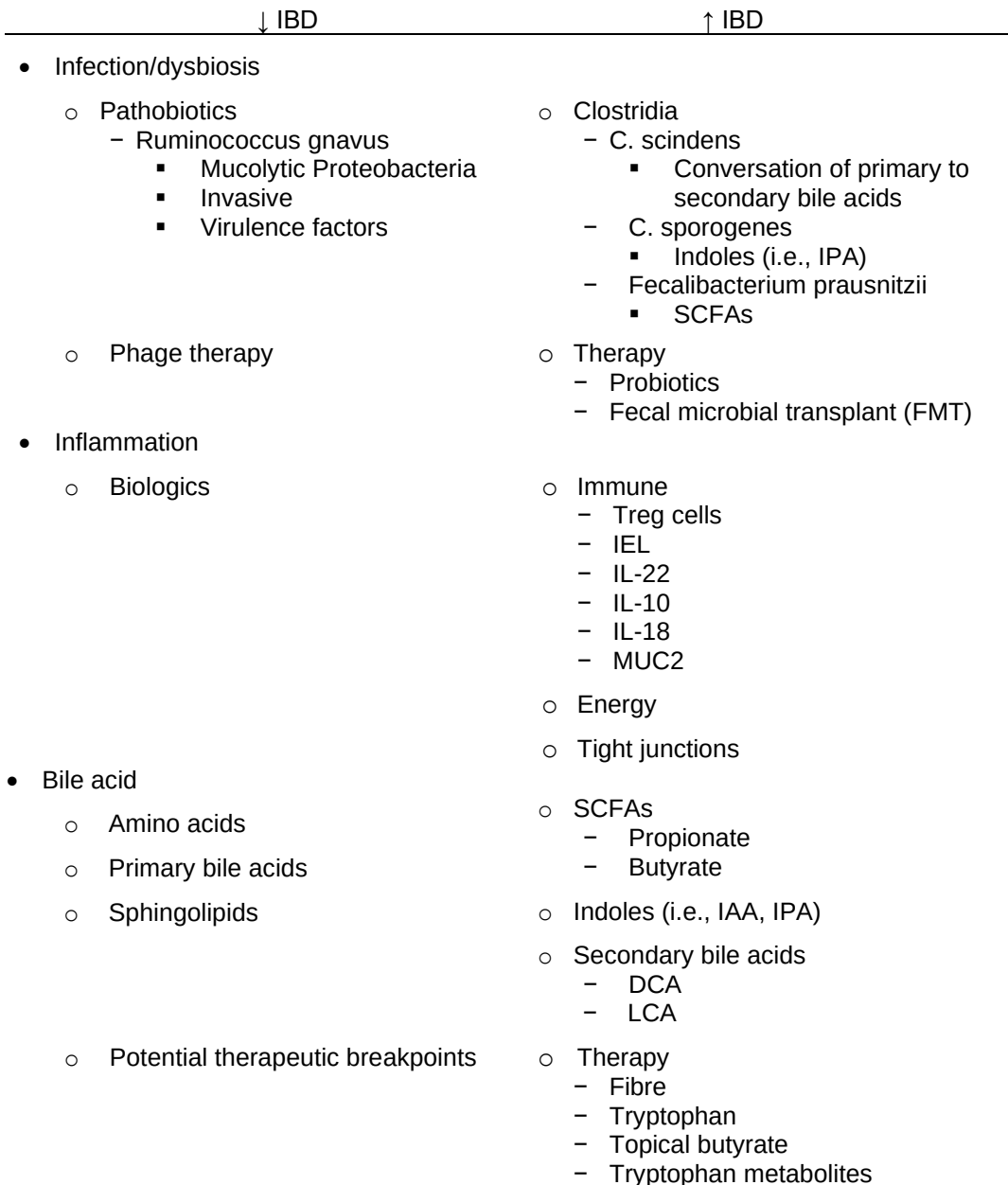


- In health, the major pathway for dietary tryptophan is the kynurenine (Kyn) pathway → serotonin and associated metabolites
- Tryptophan metabolized by commensal microbiota to → indoles, aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR) agonists (with diverse effects on mucosal immunity and homeostasis)
- In IBD, dysbiosis leads to
  - Loss of microbial activation of tryptophan →
  - ↑ metabolism down the kynurenine pathways

Abbreviations: BA, bile acid; ECCs, enterochromaffin cells; GI, gastrointestinal; GLP1, glucagon-like peptide 1; HDAC, histone deoxylase; IBD, inflammatory bowel disease; IELs, intraepithelial cells; MCFA, medium-chain fatty acid; PYY, peptide YY; SCFA, short-chain fatty acid; TNF, tumour necrosis factor; WAT, white adipose tissue



## ❖ The Cycle of Circular Causality in IBD



These include both traditional (immunomodulatory), microbiome-targeted (probiotic, fecal microbiota transplant (FMT) and phage), diet and direct metabolite manipulation.

Abbreviations: DCA, deoxycholic acid; IAA, indole acetic acid; IEL, intraepithelial lymphocyte; IPA, indole-3-propionic acid; LCA, lithocholic acid; MUC2, mucin 2; SCFA, short-chain fatty acid; Treg cell, regulatory T cells





## Pathogenesis of Idiopathic Inflammatory Bowel Disease (IBD)

Kudelka MR, et al. Nat Review Gastroenterol Hepatol 2020; 17: 597-616

### ❖ Genetics

- Family history
  - First-degree relatives
    - ↑ risk if IBD x10
  - Ashkenazi Eastern European Jews
    - ↑ risk x4
  - Monozygotic twins
    - Concordance
      - CD, 65%; UC, 15%
  - Family members may also show concordance for disease risk, location, disease behaviour
  - Genetic factors which have been found in IBD patients account for < 25% of the inheritability
- Susceptibility genes
  - Numerous genes, with different genes for disease risk, location, behavior
    - Total number if with genes 200
      - Associated with other autoimmune conditions, 113
    - Specific
      - For UC, 23`
      - For CD, 30
    - Account for disease variance
      - UC, 8%
      - CD, 14%
  - Susceptibility genes for IBD plus
    - Mycobacterial infections (tuberculosis)
    - Host interaction with microbes
      - Nucleotide-binding Oligomerization Domain containing 2 (NOD2) gene (aka Caspase-recruitment domain 15 (CARD15))
      - Truncation and missense mutations

### ❖ Environmental factors

- Hygiene and interactions with microbiome may be important, especially early life experience and onset of IBD (intestinal microbiota/dysbiosis)
- Smoking → ↑ risk of CD, ↓ risk of UC (mechanism unknown)
- Oral contraceptive agents (OCA), especially in smokers
- Use of NSAIDs
- Born/living in Northern latitudes



- Appendicitis/appendectomy ↓ risk of developing UC
- “Western diet” of ↓ dietary fibers / ↑ red meat, saturated fats, refined sugars
- Anxiety/depression more common in persons with IBD, but controversial whether this is causative
  - Interestingly, treating depressed persons ↓ risk of developing IBD
- ❖ Intestinal Microbiome
  - Uncertain effects of antimicrobials / prokinetics / microbes in stool of IBD patients
    - ↑ aggressive effects
      - Fusobacterium
      - Proteobacteria
      - Ruminococcus gnavus
    - ↓ protective effects
      - Bifidobacterium
    - ↓ diversity
  - But,
    - Fecal diversion from inflamed segments of bowel will ↓ inflammation, and
    - Delivering stool to ileal pouch will cause pouchitis (ileum to pouch)
    - In CD, there is ↑ responsiveness of mucosal T cells to the enteric flora, again suggesting a possible negative effect of the microbiome
- ❖ Intestinal Epithelial Barrier
  - Colonocytes develop features which may produce colitis
    - ↓ metabolism of butyrate
    - ↓ thickness of positive glycoprotein mucus
    - ↑ colonocyte apical membrane
      - Leakiness → ↑ passage of bacteria / bacterial antigens into mucosa
      - Disruption
  - Barrier function
    - ↓ mucus (UC)
    - Tight junctions (TJs) abnormal proteins → ↑ leakiness (CD) → ↑ immune activation
- ❖ Gut Microbiota and Intestinal Epithelial Cell Glycosylation in IBD
  - Glycans in the epithelial cells of the intestine
 

|                                                                                                                                                                                                |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>○ Functions</li> <li>– Provide ligands to microbiota</li> <li>– Cell adhesion / growth / death / migration</li> <li>– Homeostasis / immunity</li> </ul> | } | <ul style="list-style-type: none"> <li>○ Changes related to IBD</li> <li>– ↓ MUC2 barrier</li> <li>– Disruption of epithelial barrier</li> <li>– Altered mucosal immunity / glycan-binding adhesins</li> <li>– Altered glycosylation due to genetic mutation in genes which regulate glycosylation / fucosylation</li> <li>– ↓ COSMC (a molecular chaperone) → disruption of colonic mucus layer → ↑ contact of bacteria with colonic epithelium</li> </ul> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



- Glycogens encode
  - Glycan-binding proteins
  - Glycosyl transferases
  - Sugar transporters
- Glycans attached to macromolecules to form glycoconjugates glycoproteins / lipids
- Types
  - N-linked / O-linked glycans
    - Glycocalyx
    - Secreted glycoproteome
  - Synthesis
    - N-glycans
      - Endoplasmic reticulum (ER)
      - Golgi apparatus (GA)
    - O-glycans
      - Mucin attached to proteins of surface of cells (accounts for 80% of human MUC2)
  - Includes
    - ABO blood group antigens
    - Lewis antigens
- Epithelial Glycosylation in IBD
  - Implicated in IBD
    - FUT1 and COSMC
      - Alteration of mucin type O-glycans
    - Examples
 

|                                                                                                 |                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>▪ Crohn disease</li> <li>▪ Ulcerative colitis</li> </ul> | <ul style="list-style-type: none"> <li>– Cytokines ILCST</li> <li>– Glycosyltransferase/glucosidase, FUT2</li> <li>– Lectin LGAL59</li> <li>– Transcription, HNF4A</li> <li>– Ion channel SLC9D3</li> <li>– Glycosylation/glucosidase MANBP, MAN2A1</li> </ul> |
|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
  - Effects of altered glycosylation
    - Altered immunity
      - Altered uptake of antigens
      - Mucin 1 (MUC2) dependent tolerogenic imprinting
      - Recruitment of leukocytes to crypts
    - Glycan-lectin interactions
      - Host and foreign lectins
    - MUC2 synthesis/stability
      - ↑ gut permeability / ↑ MUC2 degeneration
    - Host-microorganism interaction
      - Intraepithelial cell (IEC) binding / glycan induction
      - Dysbiosis
      - Dysregulation of nutrients by microorganisms



❖ Dendritic cells

- Antigen-presenting cells (APCs) in lamina propria
  - Sample contents in lumen (microphagia)
  - Presentation of antigen to T cells (MHC class II plus co-stimulatory signal)
  - Microbial antigens binding to APCs → activate APCs take up ↑antigens which are degraded in proteosomes
  - APCs / MHC class II and CD3 T-cells receptor → antigen-specific interaction between CD4+ T cells and macrophages
    - plus co-stimulatory signals → activation of T cells
    - Without the co-stimulatory signals, CD3 T cells bind to MHC class II → apoptosis

| Signals | Binding        |
|---------|----------------|
| - TNF   | ▪ TNF receptor |
| - CD40  | ▪ CD40 ligand  |
| - B7    | ▪ CD28         |

❖ Paneth cells

- Secrete defensin (endogenous antimicrobial peptides)
- ↓ defensin produced in persons with CD

❖ T cells produce

- Growth factor IL-2
- Proinflammatory tumour necrosis factor (TNF)
- Mononuclear cells → NFκB → regulates transcription of IL-6, -8 and TNF
- TNF →
  - ↑ activation of neutrophils
  - ↑ expression of MHC class II on lateral epithelial cells
  - ↑ inflammation

• Profiles of Microbial and Immune Cells Vary Along the Human Colon

- Microbial and immune cells displayed a range of spatial patterns.
  - Rich, uneven IgA\* microorganisms
  - IgA
  - Bacteroides
  - Th 1 cells
 }     ▪ High in sigmoid colon
- Th 17 cells
  - Treg cells
 }     ▪ High in cecum
- IgA abundances ↑ along the colon, ↑ IgA+ B cell and ↑ IgA binding in regions containing ↑number of species (richness) and uneven microbial members. Bacteroides species abundance ↑ along the colon and correlated with ↑ T helper 1 (Th1) cells and a ↓ T helper 17 (Th17) cells.
- Regulatory T (Treg) cells do **not** vary in abundance, but do display a variety of gene expression signatures



❖ NOD2/CARD15

○ NOD2 abnormal

Abnormal sensing of intracellular bacteria MDP



Activation of NFκB



↓ innate immunity

○ ↑ risk of CD disease-associated variants

- Homozygous, OR 17
- Heterozygous, OR 2.5

○ Associated with

- Young age of CD onset
- Ileal involvement
- Strictures

○ Note that although ~25% of CD patients have abnormal NOD2/CARD15, disease penetrance is low

- Homozygotes, < 5%
- Heterozygotes, < 1%

• Ulcerative colitis

○ The NOD2 genes found on chromosome 16 in patients with CD are not seen in sufferers

- NOD2/CARD15 gene has 2 CARD domains
  - Nucleotide-binding domain
  - Leucine-rich repeats (LRRs)
    - Variants of LRR region → ↓ binding to MDP
- Cytosolic protein sensor of bacterial muramyl dipeptide, a component of bacterial peptidoglycan)
- Found in Paneth cells / other intestinal epithelial cells, fibroblasts, lymphocytes, macrophages
- NOD2 in mononuclear cells → ↓ activation of nuclear factor κβ (NFκβ)

Abbreviations: ATC16L1, autophagia-related 16-like 1; CARD15, Caspase recruitment domain; CD, Crohn disease; IBD, inflammatory bowel disease; IL, interleukin; IRGM, immunity-related GTPase [guanosine triphosphate]; LP, lamina propria; LRR, leucine-rich region; MDR, muramyl factor κβ; NLR, NOD-like receptors; NOD2, nucleotide-binding oligomerization domain; NSAIDs, non-steroidal anti-inflammatory drug; OCA, oral contraceptive agent; OR, odd ratio; SNP, single nucleotide polymorphism; Th, helper T cell; TLR, toll-like receptors; Treg, regulatory T cell; UC, ulcerative colitis



❖ IL-23 and associated gene products

- Microbial signals
  - Dendritic cells
  - Macrophages
- $$\begin{array}{c}
 \left. \begin{array}{l} \text{Dendritic cells} \\ \text{Macrophages} \end{array} \right\} \text{IL-23} \rightarrow \uparrow \text{Th17 activity} \\
 \uparrow \\
 \text{IL-23 by CD4+ cells} \\
 \uparrow \\
 \text{IL-6, TGF}\beta
 \end{array}$$
- IL-23 gene variants → ↑ susceptibility to CD but to UC, but
  - Persons with UC who carry NOD2 polymorphism have ↑ risk of pouchitis after total colectomy and formation of ileoanal pouch
- UC genes shared with CD
  - IL-12, -23; IRCM, MST, NKX, STAT

➤ Autophagia-related genes

- Autophagy: portions of cytoplasm become enclosed by a membrane, which delivers the cytoplasmic isolate to lysosomes (“inflammasomes”)
  - Contained in the isolate are proteins which are
    - Aggregated
    - Old
    - Misfolded
  - ATG16L1 } ↓ autophagous
  - IRGM }
  - Abnormal interface between intracellular pathogens and then presentation to T cells
- Adaptive trafficking
 

Abnormal IL-12 / IL-23 pathway

↓

↑ Th17 (Th1/TH2 > Treg activity)
- Functions
  - Activates
    - Toll-like receptors
    - NOD-like receptor
  - } IFN
  - Delivers HLA class II molecules in antigen presenting cell (APCs) for antigen-specific binding
  - ↑ autoimmune
  - ↓ inflammation / kills (↓) pathogens
- Autophagia related genes
  - ATG16L1 (autophagia-related 16 like 1) gene
    - Expressed by intestinal epithelial cells, antigen presenting cells (APCs), and T-cells
    - Has a single nucleotide polymorphism (SNP) that
      - Encodes an amino acid substitution in exon 8 (alanine → threonine) → protective versus development of CD



- Immunity-related GTPase [guanosine triphosphatase] family member M (IRGM) gene → resistance to intercellular pathogens and toxics
  - Seen in both CD and in UC
- Apoptosis
  - Th9 cells → ↑ apoptosis of enterocytes → ↓ mucosal healing
  - NK T cells → IL-13 → ↑ injury
- ❖ Adhesion molecules trafficking of leucocytes into intestinal mucosa
  - Selectins → rolling of leucocytes along endothelium
    - On surface of leucocytes
      - Adhesion molecules (integrins) activated by IL-8 / other chemokines
  - Ligands/integrins plus on surface of endothelium of vessels in intestinal wall
  - Intestinal specific adhesion molecules (CAM) → spreading of endothelial cells → diapedesis of WBCs
    - Mucosal adhesin CAM
    - E-cadherin ( $\alpha$ EB7)
    - Integrins localized  $\alpha$ 4 $\beta$ 7 intraepithelial lymphocytes (IELs)
    - Constitutively expressed on endothelial vessels in lamina propria
  - Dendritic cells (APCs) in
    - Peyer's patches
    - Small bowel draining lymph nodes

$\left. \begin{array}{l} \text{Peyer's patches} \\ \text{Small bowel draining lymph nodes} \end{array} \right\}$

Metabolize vitamin A → retinoic acid → ↑ expression of
 
    - $\alpha$ 4 $\beta$ 7 integrin
    - CCR9 on T/B cells
  - Leukocytic trafficking
    - Integrins, ICAM1 - ↑ leukocytes in tissue
    - ↑ mucosal immune response
    - Expression of  $\alpha$ 4 $\beta$ 7/CCR9 homing integrins
      - ↓
      - Lymphocytes expressing  $\alpha$ 4 $\beta$ 7/CCR9 interact with MadCAM
        - ↓
        - Lymphocytes return to intestinal lamina propria (LP)
          - ↓
          - LP lymphocytes contain Th1, Th2, Th17 (↑ Th17) T reg cells
            - ↓
            - Prevent unchecked inflammation



## Crohn Disease (CD): Natures Review

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

### ➤ Demography

- Incidence highest in Ashkenazi Jews, and persons living in Northern latitudes
  - Peak 20 to 40 yr
- Increasing incidence
  - Persons < 5 yr, > 65 yr, new Canadians and their children when moving from low- to high-prevalence countries, such as Canada
- Prevalence of IBD (CD plus UC)  $\sim 500/10^5$  in Western Countries
  - In Canada CD prevalence  $\sim 325/10^5$  (UC,  $\sim 250/10^5$ )

### ➤ Natural History

- Bowel damage at time of diagnosis  $\geq 50\%$  → ↑ poor prognosis
- Intestinal complications within 10 yr of diagnosis  $\sim 50\%$  (strictures, fistulae)
  - Physical resections within 10 yr of diagnosis,  $\sim 50\%$
  - Surgery required within 20 yr of diagnosis  $\geq 50\%$
  - Perianal disease within 1 yr of CD diagnosis, 30%
- Extraintestinal manifestations (EIM) in  $\sim 30\%$
- Giving immune modulators / anti-TNF therapy within 2 yr of diagnosis of CD →
  - ↓ formation of strictures
  - ↓ surgery (duodenal/perianal)
- Disease phenotypes
  - Inflammatory, strictures (fibrosis), penetrating (fistulae)
  - Phenotypes may change over time
    - $\sim$  equal phenotypes
- Disease location
  - Usually stable over time
  - About equal proportions of ileal, ileocolonic, and colonic +/- additional upper GI tract involvement

### ➤ Risk Factors (Causes/Associations)

#### ❖ Environment

- Smoking
  - ↑ risk of CD 2x
- “Western diet” ↑ likelihood of
  - Early onset
  - ↑ need for
    - Immunosuppression
    - Surgery
  - ↑ post-operative recurrence





- Diet may influence gut microbiome and gut dysbiosis may → ↑ risk of CD
  - Specific aspects of diet
    - ↓ fibre
- Vitamin D, low intake
  - Early onset of CD
  - Poor clinical course
    - Frequent changes in diet → ↓ diversity microbiota
- Dietary components may result in epigenetic modifications → CD phenotypes
- ↑ risk
  - Drugs
    - Antibiotic use in childhood
    - Oral contraceptive agents (OCAs)
- ↓ risk
  - Breastfeeding
  - Use of statins
- Appendectomy
  - Early onset, poor prognosis
- Genetics
  - Early suspicion of genetic component
    - Family history of CD ~15%
    - Concordance rates for CD monozygotic twins, ~50% (in UC, ~15%)
  - Genome-wide association studies
    - Loci associated with CD > 200 (odd ratios low, 1.1 to 1.2; genetic factors likely contribute only about 13% causation of CD)
    - There is likely an aggregate risk of these altered loci
- Major loci of interest
  - NOD2 (aka CARD15); intracellular pattern recognition receptors → innate immune proteins → activate
    - NFκB-dependent and mitogen activated protein kinase dependent gene → anti-inflammatory cytokines → ↓ ability to destroy bacterial → altered microbiome
    - Associated with ileal CD phenotype, but not structuring
    - Non-synonymous coding risks in NOD2, ATG and IL23R in white populations, with different risk locus in Asian (transethnic differences)
  - NOD2-like receptors
  - IL-23 receptors gene (IL23R)
  - IL-10 receptor genes
    - Early onset CD
    - Highly penetrant
    - Mendelian-like inheritance
  - Susceptibility polymorphism encoding components of intestinal barrier (please see below)



➤ Intestinal barrier

- Components
  - Mucus, epithelial membrane including junctions, intraepithelial cells (IELs)
  - These components interact with luminal content e.g., microbiome, diet, digestive enzymes, bile acids
- Junctional proteins
  - Claudin 5/8
  - E1-cadherin
  - Guanine nucleotide binding protein (GNBP) subunit  $\alpha 12$
  - Zonula occludens (ZO)

➤ Immunity

• Intraepithelial lymphocytes (IELs)

- Antigen-experienced T cells which maintain gut homeostasis
- Communicate with
  - Innate/adaptive immune cells through NKG2D ligands
    - $\uparrow$  activity of natural killer cells (NK cells)
    - $\uparrow$  ILC1 (group 1 innate lymphoid cells)
  - Receive signals from
    - Th17 cells (T helper cells that produce IL-17)  $\rightarrow$  IL-17, IL-22, ILC3,  $\delta$  T cells
- Environmental factors in CD  $\rightarrow$  stress to endoplasmic reticulum  $\rightarrow$  abnormal unfolded protein response (uPR)  $\rightarrow$  inflammation of gut
  - uPR activation is influenced by
    - p. THr300 Ala (ATG 16 L1 polymorphisms)
    - IRE1 $\alpha$  (uPR sensor, an inositol requiring enzyme)
    - NF- $\kappa$ B (nuclear factor  $\kappa$ B)
    - STAT3 signalling
- CD8  $\alpha$ -expressing CD4+ IELs
  - “modulate the activity of other immune cells”
  - Produce anti-inflammatory TGFB (transforming growth factor-B), and IL-10 (from dendritic cells), as well as IL-17A and IFN- $\gamma$  (interferon gamma)
- In CD, IEL dysfunction  $\rightarrow$ 
  - $\uparrow$  activity of cytotoxic T lymphocytes
  - $\downarrow$  anti-inflammatory activity
- Paneth cells
  - Specialized IECs in base of small intestinal crypts of Lieberkühn
    - CD polymorphism of ALG16L1, IRGM, LRRK2, NOD2

• Innate Immunity

- Cell
  - Neutrophils/monocytes
    - Initially phagocytoses pathogenic microorganisms
    - Later accumulated material  $\rightarrow$   $\downarrow$  barrier function  $\rightarrow$   $\uparrow$  inflammation
    - $\downarrow$  NADPH oxidase in CD  $\rightarrow$   $\uparrow$  autophagy ( $\downarrow$  inflammatory response to killed E. coli)



- Macrophages
    - Clear apoptotic/senescent cells → control tissue remodelling
  - Lymphocytes: ILC1 (group 1 innate lymphoid cells; including Paneth cells)
    - Types T<sub>NK</sub>, ILC1/2/3 lymphoid tissue inducer cells (ILC1)
    - ↑ in CD, ↑ ILC1, ↓ ILC3 (↑ ILC3 to ILC1 plasticity)
    - Damaged gut epithelium → ↑ ILCs → restores epithelial barrier to normal
  - Dendritic cells
    - Express TLR2/4 (toll-like receptors 2/4)
    - Cross-talk between innate/adaptive immunity
- Adaptive Immunity in CD, ↑ Th1/17 response to
    - Dendritic/macrophages → proinflammatory cytokines IL-12/-18-23 → ↑↑ Th1/Th17 response → ↑ IL-17, IFN- $\gamma$ , TNF → further ↑ IL-1/-6/-8/-12/-18, TNF by monocytes, macrophages, endothelial cells
    - IL-12/-23
      - IL-12, p40, p35
      - IL-23, p40, p19

}

- Originate in innate immune cells
      - Drivers/mediators of inflammation

}

- Act through receptors (IL-12, R $\beta$ I, IL-23R) → act on T cells  $\alpha\beta$ , and ILC3 → ↑ JAK2 - STAT3 signals
    - IL-23 → activates GMCS (granulocyte macrophage colony stimulating factor / ↑ IFN- $\gamma$  → ↓ Treg cells in CD, ↓ response to Treg cells
    - Th17 cells
      - Proinflammatory cytokines (IL-12, -23, -27, -35) stimulate conversion of immature to mature Th17 cells which play a major role in the development of chronic inflammatory
      - IL-17A → ↓ inflammation and also ↑ target function barrier function
      - Pregnancy is safe and beneficial for patients with IBD
        - Microbiome stable during T2/T3 (not T1)
        - ↑ Th2 (tolerance phenotype)
        - ↑ anti-inflammatory human chorionic gonadotropin), estrogen, progesterone
        - ↓ IL-17, ↑ IL-10
- Dysbiosis of Microbiome
- There is no microbiota composition or marker microorganisms that are specific to CD.

- Bacteria
  - Generally speaking, in CD4
    - ↑ enterobacteria
    - ↓ bacteroides, Firmicutes

}

- ↓ diversity of organisms
  - Microbiome different between active versus inactive CD
    - ↑ Caudovirales bacteriophage sequences
    - ↑ Retroviridae
    - ↑ Synechococcus phage S CB57 viruses

}

- ↓ diversity



- Causes of Crohn Disease
  - Intestinal homeostasis is maintained by the equilibrium between the luminal content and the mucosal immune system in the lamina propria.
  - The intestinal epithelium orchestrates this equilibrium because of its mechanical function (as a physical barrier and its role in immune responses).
  - Specialized intestinal epithelial lymphocytes (IELs) have important roles in intestinal immunity.
    - For example
      - Paneth cells are intestinal epithelial cells (IECs) present at the base of crypts of Lieberkühn and constitutively produce antimicrobial peptides, whereas
      - Microfold (M) cells are IECs present in the gut-associated lymphoid tissue (not shown) that sample luminal antigens and present in the gut-associated lymphoid tissue (not shown) that sample luminal antigens and present them to cells of the adaptive immune system.
  - After contact with an antigen, antigen-presenting cells (APCs) such as dendritic cells present antigen to T-cells and B cells → initiate a controlled inflammatory response.
  - Epithelial barrier dysfunction (owing to, for example, polymorphisms in NOD2 and nuclear factor kB (NF-kB) signalling pathway genes) → luminal contents entering the lamina propria → dendritic cells activating inflammatory T cell types (such as naïve T helper (Th0) cells, T helper 1 (Th1) cells, Th17 and Th2 cells → produce proinflammatory cytokines (such as IFN and tumor necrosis factor (TNF)) in response to luminal contents, macrophage → proinflammatory cytokines IL-12 and IL-23 → activate natural killer (NK) cells → perpetuation of the intestinal inflammation (production of proinflammatory cytokines)
  - Luminal contents include dietary components and gut microbiota IL-4, IL-6, IL-21 and IL-22 are also produced by Th0 cells in response to activation of dendritic cells.
- Clinical
  - There are several systems used for disease activity of Crohn disease (such as Crohn Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI), but
    - Clinical symptoms do **not** correlate well with the severity of endoscopic or histopathological damage
      - Stool frequency and abdominal pain may best reflect active disease
    - Better to target “complete remission” by endoscopy or cross-sectional imaging
    - Surrogate markers include C-reactive protein (CRP), and fecal calprotectin (FC)
    - Patient-related outcomes (PROs) may reflect alterations in treatment-associated disease activity
      - PRO2 score of < 8 approximately similar to a CDAI of 150 (clinical remission)
  - Laboratory based
    - No biomarkers
    - Poor correlation to endoscopic healing
      - Now used less and less for clinical trials, and is not in routine clinical practice



- Quality of life (QoL) scoring system
  - Health-related quality of life (HRQoL)
    - Definition, "...a multidimensional concept that includes physical, emotional and social features of health functioning"
  - In addition to the GI-related symptoms EIM, and complications, patients with IBD have ↓ QoL because of
    - ↑ stress perceived
    - ↓ social support (especially loss/lack of spousal support)
    - Concerns related to reproductive failure
    - Use of tobacco/corticosteroids
  - Examples of QoL scoring systems used in IBD
    - 32-item Inflammatory Bowel Disease Questionnaire IBDQ-32
    - Shorter questionnaires
      - 10 items, SIBOQ
      - 9 items, IBDQ-9
- HRQoL should be built into regular assessment of the IBD patient's well being and therapeutic response.
- Factors that affect QoL domains in CD
  - The QoL of patients is assessed in physical, psychological, social and economic domains.
    - Quality of life in patients with Crohn disease is affected by
      - Disease symptoms (including lack of predictability of flexus)
      - Complications
      - Extraintestinal manifestations, and
      - Therapies that are used to treat the disease, and which may have considerable adverse effects, and high cost not always covered on medical insurance, inconvenience of administration
  - Physical status and functional abilities
    - Pain (e.g., abdominal, and joint pain)
    - Defecation (e.g., diarrhea, bloody stool, and fecal urgency / incontinence)
    - Sleep disorders
    - Energy levels (e.g., fatigue)
  - Psychological status and well-being
    - Body image
    - Emotional status (e.g., depression, anxiety and anger)
  - Social and interpersonal interactions
    - Relationships (e.g., ability to attend social events)
    - Sexual functions (e.g., frequency of intercourse; receptivity and initiative; pleasure and orgasm)
  - Economic and/or vocational status
    - Education (e.g., ability to attend school and participate in sports and recreation)
    - Work (e.g., ability to work)



- Extraintestinal Manifestations (EIMs) do **not** reflect the severity of the underlying IBD.
  - Joints
    - Ankylosing spondylitis (AS)
    - Peripheral arthropathy, type 2 polyarticular
  - Skin
    - Pyoderma gangrenosa (PG)
  - Biliary tree
    - Primary sclerosing cholangitis (PSC)
- Give the most commonly identified deviation from best medical practice found in audits of patients admitted to hospital for their IBD.
  - Prophylactic anticoagulation for patients admitted to hospital for active IBD is still not a reflex consideration to guideline-based therapy.
- Diagnostic imaging
  - Choices of cross-sectional imaging
 

|                                                                                       |                                                                                                                          |                                      |                                                                                                                                                         |
|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>- BUS</li> <li>- CTE</li> <li>- MRI</li> </ul> | <ul style="list-style-type: none"> <li>▪ Bowel ultrasound</li> <li>▪ CT enteropathy</li> <li>▪ MR enteropathy</li> </ul> | <div style="font-size: 3em;">}</div> | <ul style="list-style-type: none"> <li>- Comparable performance characteristics for diagnosis of CD, and its complications (Sn, Sp &gt; 90%)</li> </ul> |
|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
  - Pelvic MRE for diagnosis of fistulas, abscesses
- Endoscopy
  - Distribution
    - Patchy, with “skip lesions”
  - Ulceration
    - Diameter
      - < 5 mm      - Aphthous ulcers
      - > 5 mm      - Ulcers (deep ulcers invade into muscularis propria)
  - Appearance
    - Cobblestone
  - Small bowel capsule endoscopy (SBCE)
    - Indication
      - High suspicion of CD, but negative standard diagnostic imaging/endoscopy
      - A normal SBCE has high negative predictive value (NPV)
      - Risk of capsule retention when patient has obstructive symptoms/stenosis, 13%
  - Endoscopic remission is defined as the absence of ulcerations few localized erosions would not represent “ulceration”, but multiple small erosions throughout the intestine would represent ulceration)
    - Endoscopic scores include
    - Mucosal healing is a prediction of long term clinical outcome
      - Likelihood of
        - Clinical remission maintained ↑ 3x
        - Clinical relapse after treatment stopped ↓ 2x
        - ↑ steroid-free remissions
        - ↓ hospitalization / ↓ surgery



## ❖ Radiographic

- Remission
    - No diagnostic imaging changes
  - Response
    - Fewer diagnostic imaging changes
    - Grading of radiological severity but done with MRE (MR enterography) or SBUS (small bowel ultrasound) than CTE (CT enterography)
    - Grading of radiological severity but done with MRE (MR enterography) or SBUS (small bowel ultrasound) than CTE (CT enterography)
    - Scoring systems
      - CTE 0 – CTE3 (for CT)
      - MaRIA and London systems (for MRI)
- } – Suggestive of active inflammation
- {
  - ↓ hospitalization / surgery
  - ↓ use of corticosteroids

## ➤ Histopathology

- Key features
  - Inflammation
    - Focal/discontinuous, chronic
  - Crypts
    - Focal irregularity (discontinuous crypt distortion)
  - Granuloma
    - Not related to crypt injury
  - Villi
    - Distorted architecture of ileal villi

## ➤ Laboratory

- Anemia, ↑ WBC, ↓ albumin
  - Changes reflect disease activity, dietary alterations, and intestinal losses
- ESR, CRP
  - C-reactive protein synthesized in hepatocytes in response to ↑ proinflammatory cytokines, but false-positive in 1/3 and false-negative in 1/3
- Fecal calprotectin (fCal)
  - Composition
    - Calcium-containing anti-microbial protein, which constitutes 60% of the cytosolic neutrophils lost into the gut lumen in IBD
    - Good surrogate marker for disease activity: ↑ sensitivity to follow treatment response, and good negative predictive value
  - Useful to guide “treatment-to-target”, but some controversy as to optimal cut-off value for normality
- Serological markers



- Commercially available, but not recommended for routine practise to differentiate CD, UC and other forms of colitis.

| Serology                                                     | CD        | UC        | Non-IBD Colitis |
|--------------------------------------------------------------|-----------|-----------|-----------------|
| - ASCA+ (Saccharomyces cerevisiae antibodies)                | 60% - 70% | 10% - 15% | < 5%            |
| - pANCA+ (perinuclear antineutrophil cytoplasmic antibodies) | 10% - 15% | 60% - 70% | < 5%            |

- Of clinical interest
  - Patients with proven CD but who are pANCA+, “.... usually have a clinical phenotype resembling that of UC”
- Of research interest antibodies to
  - Organisms
    - CBIR7
    - Fluorescence-associated sequences 12
    - Outer membrane porin C
    - Pseudomonas
  - Bacterial cell wall
    - Mannobiose
    - Laminaribioside carbohydrate
    - Chitobioside
    - Lamarin

➤ Surveillance of colonic dysplasia in patients with IBD

- Stool DNA (genetic analysis)
  - Performance characteristics
 

| Condition         | Sensitivity | Specificity |
|-------------------|-------------|-------------|
| ▪ CRC             | 100%        | 89%         |
| ▪ Dysplasia grade |             |             |
| - High            | 100%        |             |
| - Low             | 67%         |             |
- The authors of this “primer” go beyond the recommendations of other guidelines for surveillance for CRC in patients with IBD (CD, UC) by adding consideration of
  - Extent of colon affected < > 50%
  - Presence of
    - Pseudopolyps
    - Strictures
    - Primary sclerosing cholangitis (PSC)
  - Family history of CRC in first degree relatives > < 50 yr
- Surveillance should begin 8-10 yr after a confirmed diagnosis of Crohn disease (CD), at intervals that are determined by risk factors, such as
  - Primary sclerosing cholangitis (PSC)
  - Pan-ulcerative colitis (pancolitis)
  - Active inflammation
  - Pseudopolyps
  - Family history of colorectal carcinoma





- Patients at low risk (without active inflammation or with restricted colitis should be endoscopically assessed (with histopathological analysis of biopsy samples) every 5 yr.
- Those at intermediate risk (with 3 yr of mild inflammation and/or pseudopolyps and/or family history of CRC in first-degree relatives (FDRs) older than 50 yr) should be assessed every 3 yr.
- High-risk patients (those with 1 yr of moderate inflammation, stricture, PSC or family history of CRC in FDRs younger than 50 yr) should be assessed annually.

#### ➤ Treatment

- The gold standard for treatment target is “endoscopic mucosal healing (EMH)”
  - EMH is defined as “....resolution of the intestinal lining and regression or disappearance of endoscopic lesions”
    - At some point, transmural healing on cross-sectional imaging and normalization of histopathology may be added as desirable therapeutic targets.
  - Benefits of EMH
    - ↓ relapse
    - ↓ hospitalization
    - ↓ fistulae
    - ↑ steroid-free interval remissions
    - ↑ resection-free intervals
- Complete remission
  - Remission of symptoms
  - EMH
- Early onset CD
  - CD diagnosed within 18 mon of development of symptoms
  - Because EMH leads to better outcomes, and EMH is more likely with biological drugs, at least in high-risk CD patients, biological therapy targeted to achieve mucosal healing should be introduced
    - Within the first two yr of diagnosis
    - Before use of immunosuppressants
    - Before development of CD-associated complications
  - Treatment of early CD with biologics represent a “therapeutic window of opportunity” to heal inflammation before the development of strictures, fistulae, perianal disease.
- Drug withdrawal after achieving remission
  - Stopping IM plus biologic (combination therapy) ~50% (signifying that ~50% remain in remission)
- Starting doses of corticosteroids for mild-to-moderate CD
  - Budesonide 9 mg po per day, or higher (1 mg/kg per day)
  - Severe CD / colonic CD
- Azathioprine (AZA) maintenance
  - Use in low-risk CD patients who had induction therapy with corticosteroids
  - Use to ↓ immunogenicity in patients recovering, anti-TNF therapy
    - Immunogenicity is less with vedolizumab and ustekinumab



- Anti-TNF agents
  - “first-line therapy in high-risk patients
- Therapeutic drug monitoring (TDM) in patients with IBD is
  - “.... more efficacious to optimize care.... than empirical dose escalation” (more cost-effective)

Abbreviations: ASCA, anti-saccharomyces cerevisiae; AZA azathioprine; BUS, bowel ultrasound; CD, Crohn disease; CRC, colorectal cancer; CTE, computed tomography enterography; EIM, extraintestinal manifestations; EMH, endoscopic mucosal healing; GMCS, granulocyte macrophage colony stimulation factor; GNBp, guanine nucleotide binding protein; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; IBDQ-32/-9, 32/-9- item Inflammatory Bowel Disease Questionnaire; IELs, intraepithelial lymphocytes; IFN, interferon; IL, interleukin ILC, innate lymphoid cells IV, intravenous; MRE, magnetic resonance enterography; NPV, negative predictive value; NSAIDs, non-steroidal anti-inflammatory drugs; OCAs, oral contraceptive agents; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; po, per OS / by mouth; PSC, primary sclerosing cholangitis; QoL, quality of life; SBCE, small bowel capsule endoscopy; Sn, sensitivity; Sp, specificity; T1,2,3, first, second or third term of pregnancy; TDM, therapeutic drug monitoring; TGF, transforming growth factor; Th, helper T cell; TLR, toll-like receptor; TNF, tumour necrosis factor; T<sub>NK</sub>, natural killer T cell UC, ulcerative colitis; uPR, unfolded response protein; yr, year; ZO, zona occludins

#### ❖ Induction of Remission

##### • Adalimumab

Adalimumab for induction of remission in Crohn's disease (Abbass M, et al. Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD012878. DOI: 10.1002/14651858.CD012878.pub2)

- Three placebo-controlled RCTs with 114 adults with severely active CD (CDAI 220 to 450) treated with adalimumab versus placebo improved with the anti-TNF therapy at 4 wks.

| Outcome                                                                                       | Placebo | Adalimumab (RR; 95%CI)                                       |
|-----------------------------------------------------------------------------------------------|---------|--------------------------------------------------------------|
| – Failure to achieve clinical remission                                                       | 91%     | 76% (RR, 0.85; 95%CI, 0.79 to 0.9; high certainty evidence)  |
| – Failed to achieve a                                                                         |         |                                                              |
| ▪ 70-point clinical response                                                                  | 66%     | 44% (RR, 0.68; 95%CI, 0.59 to 0.79; high certainty evidence) |
| ▪ 100-point clinical                                                                          | 76%     | 57% (RR, 0.77; 95%CI, 0.69 to 0.86; high certainty evidence) |
| – No difference in adverse events (AEs), including severe AEs                                 |         |                                                              |
| ▪ Superior quality of life (IBD questionnaire, or short-form 36 (moderate-certainty evidence) |         |                                                              |



## ❖ Maintenance of Remission

Adalimumab for maintenance of remission of Crohn disease (Townsend CM, et al. Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD012877. DOI: 10.1002/14651858.CD012877.pub2)

- On an intention to treat basis, the results of six RCTs was assessed in patients with moderate-to-severe CD in remission, and treated with adalimumab vs placebo, azathioprine, 6-mercaptopurine or mesalamine, and followed for one of two yrs.

| Outcome | Placebo | Adalimumab (RR; 95%CI) |
|---------|---------|------------------------|
|---------|---------|------------------------|

### • Versus placebo

- Failure to maintain clinical remission at 52 wk to 56 wks 86% 59% (RR, 0.70; 95%CI, 0.64 to 0.77; high certainty evidence)
- Failure to maintain clinical or endoscopic response at 52 to 56 wks
  - CD patients who received previous anti-TNF therapy 93% 69% (RR, 0.76; 95%CI, 0.68 to 0.85; moderate certainty evidence)
- Failure to maintain clinical remission at 24 to 26 wks 79% 51% (RR, 0.66; 95%CI, 0.52 to 0.83; moderate certainty evidence)
  - No difference in adverse events (AEs), including severe AEs

| Azathioprine/<br>Mesalamine | 6-MP | Adalimumab |
|-----------------------------|------|------------|
|-----------------------------|------|------------|

### • Versus active comparators

- 104 wks in ileocolic resection CD patients 54% 13% (RR, 0.23; 95%CI, 0.06 to 0.07; high certainty evidence)
  - Failure to maintain endoscopic remission 57% 6% (RR, 0.11; 95%CI, 0.02 to 0.75; very-low certainty evidence)
- 50% 9% (RR, 0.18; 95%CI, 0.02 to 1.33)

Vedolizumab for induction and maintenance of remission in Crohn's disease (Hui S, et al. Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD013611. DOI: 10.1002/14651858.CD013611. Accessed 04 June 2022)

- Crohn disease (CD) is thought to have a pathophysiology which "... involve(s) interplay between genetic susceptibility, immune and environmental factors".
- Despite several new therapeutic agents to treat patients with active CD, about half of patients fail to achieve remission at one year after diagnosis.
  - The failed response may be primary non-response, or secondary loss of response



- Vedolizumab is a humanized monoclonal antibody which inhibits the  $\alpha 4\beta 7$  integrin from binding to the MAdCAM-1 molecule on the endothelium of vessels in the GI tract.
  - Thus, vedolizumab is unlikely to have serious adverse effects of rarely causing progressive multifocal leukoencephalopathy (PML), as was the cause with an older integrin, natalizumab non-specific.
  - Vedolizumab induces and maintains remission in patients with moderate to severe UC.
- Abdominal pain in CD
  - Pain in patients with CD is common, and is usually due to active disease, strictures or adhesions, abscess/peritonitis.
    - Between 20% and 50% of CD patients in remission may have unexplained pain, which may be due to an associated functional abdominal pain disorder (FAPD).
      - A wide range of pharmacological agents may be used, as well as alternate therapies such as acupuncture, TENS, as well as range of psychological approaches such as cognitive behavioural therapy (CBT).

#### ❖ IL-12/23 p40 inhibitors

- Ustekinumab (UST)
  - Monoclonal antibody which targets the standard p40 subunit of interleukin (IL)-12 and IL-23 (IL-12/23 p40)

|                                                                             | Placebo | Ustekinumab                                                      |
|-----------------------------------------------------------------------------|---------|------------------------------------------------------------------|
| ○ Failure to maintain clinical remission at 22 wk (UST 90 mg SC at wk 8/16) | 58%     | 73% (RR, 0.80; 95%CI, 0.63 to 1.02; moderate certainty evidence) |
| ○ Failure to maintain clinical remission at 44 wk (UST 90 mg SC q8/12 wk)   | 64%     | 49% (RR, 0.76; 95%CI, 0.64 to 0.91; moderate certainty evidence) |
| ○ Failure to maintain clinical response at 22 wk                            | 31%     | 58% (RR, 0.53; 95%CI, 0.36 to 0.79; moderate certainty evidence) |
| ○ Failure to maintain clinical response at 44 wk (UST 90 mg SC q8/12 wk)    | 56%     | 41% (RR, 0.74; 95%CI, 0.60 to 0.91; moderate certainty evidence) |
| – No differences in rate of adverse events                                  |         |                                                                  |



- Briakinumab

Anti-IL-12/23p40 antibodies for maintenance of remission in Crohn disease. (Davies SC, et al. Cochrane Database of Systematic Reviews 2019, Issue 12. Art. No.: CD012804. DOI: 10.1002/14651858.CD012804.pub2)

|                                                                                                                                                                                                                                                                                                                                           | Placebo | Ustekinumab                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------|
| ○ Failure to maintain clinical remission at 22 wk (UST 90 mg SC at wk 8/16)                                                                                                                                                                                                                                                               | 58%     | 51% (RR, 0.84; 95%CI, 0.58 to 1.20; low certainty evidence) |
| ○ Failure to maintain clinical response at 24 wk                                                                                                                                                                                                                                                                                          | 53%     | 33% (RR, 0.64; 95%CI, 0.40 to 1.02; low certainty evidence) |
| ○ Moderate-certainty evidence suggests that ustekinumab is probably effective for the maintenance of clinical remission and response in people with moderate to severe CD in remission without an increased risk of adverse events (high-certainty evidence) or serious adverse events (moderate-certainty evidence) relative to placebo. |         |                                                             |
| ○ The effect of briakinumab on maintenance of clinical remission and response in people with moderate to severe Crohn's disease in remission was uncertain as the certainty of the evidence was low.                                                                                                                                      |         |                                                             |

**Fatigue in IBD**

Interventions for fatigue in inflammatory bowel disease (Farrell D, et al. Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD012005. DOI: 10.1002/14651858.CD012005.pub2. Accessed 05 June 2022)

- There is at best low certainty for successful management of fatigue in patients with IBD.
  - Pharmacotherapy
    - Adalimumab induction therapy (40 mg SC every other week), or ferric maltol
  - Psychotherapy
    - Cognitive behaviour therapy (CBT), or solution-focused therapy
  - Electroacupuncture
- The effects of interventions of the management of fatigue in IBD are uncertain.
  - "...electroacupuncture may result in a large reduction in fatigue compared to control and sham electroacupuncture, the overall certainty of the evidence is low due to sparse data."



## Management of Luminal Crohn Disease (CD): Clinical Practice Guidelines (CAG, AGA, 2019)

Panaccione R, et al. J Can Assoc Gastroenterol 2019; 20: e1-e34

- Targets
  - The outcomes for this guidelines “....treat-to-target strategy”
- Outcomes
  - Symptoms  $\pm$  quality of life  $\pm$  CRP, fecal calprotectin (fCal)  $\pm$  diagnostic imaging  $\pm$  colonoscopy appearance + histopathology of mucosal biopsies
    - Clinical trials vary in the chosen therapeutic targets and clinical outcomes
      - Scoring systems are available for severity / prognostic assessment, but are generally used only in research trials
  - The objective is to identify patients with Crohn disease who are at  $\uparrow$  risk (“high risk) of complications of the disease, including
    - Relapse
    - Complications (e.g., strictures, perianal disease)
    - Need for surgery/corticosteroids
  - Some of these high risk factors include
    - Patient
      - Young, smoker
      - Early use of corticosteroids / need for surgery
      - Long disease history
    - Disease
      - Upper GI, jejunum, rectal / perianal fistulizing disease (every site, except ileocolonic CD)
    - Laboratory
      - $\downarrow$  albumin,  $\downarrow$  hemoglobin
      - $\uparrow$  C reactive protein (CRP),  $\uparrow$  fecal calprotectin (fCal)
    - Colonoscopy
      - Deep ulceration
    - Diagnostic imaging (not in guidelines)
      - Mesenteric “creeping fat” on MRI
      - Abnormalities of blood flow over ileum (RLQ) on Doppler ultrasound
      - Cross-sectional imaging to document resolution of inflammation, CT enterography (CTE), MR enterography (MRE), small bowel ultrasound (SBUS)
    - Note: do **not** consider patient to be high risk based on symptoms alone, because of the potential subjective variability of these endpoints.



- Scoring clinical systems
  - Symptomatic response
    - “meaningful improvement in symptoms as judged by both patient and physician”
  - Corticosteroid treatment
    - “corticosteroid resistance” is “a lack of symptomatic response despite a course of oral prednisone of 40-60 mg/day (or equivalent) for a minimum of 14 days
    - “Corticosteroid dependence: is the “...inability to withdraw oral corticosteroid therapy without recurrence of symptoms, or
    - “....asymptomatic relapse within 3 mon of discontinuing corticosteroid therapy”, or
    - “...the need for more than 1 course of corticosteroid therapy within a year”
  - High risk patient
    - The patient with clinical disease, laboratory or endoscopy factors which are associated with
      - ↑ risk of relapse
      - Disease which is more aggressive/complex

#### Recommendations

- Determine disease based upon a combination of factors related to the patient, the disease, laboratory findings, endoscopy, [cross-sectional imaging, histopathology, and not just on the basis of symptoms] (GRADE: Strong recommendation. Good practice statement, quality of evidence not assessed).
  - Define disease activity based upon clinical symptoms, objective (laboratory) measuring of inflammation and factors which predict ↑ risk of complications
    - Do **not** base disease activity upon just symptoms / symptom scoring systems
- Treatment
  - Antibiotics

#### Recommendation

- Do **not** use antibiotics to induce or to maintain complete remission (GRADE: Conditional recommendation, very low-quality evidence for induction of remission, low-quality evidence for maintenance of remission)
- Note the combination of all trials using antibiotics supports the above recommendation, but when the 2 trials with rifaximin are removed, the efficacy of antibiotics is **not** different from placebo.



- Sulfasalazine, 5-aminosalicylic acid (5-ASAs)

#### Recommendations

- Mild CD only in the colon
  - Use sulfasalazine (4 to 6 g/day po) [in 5-ASA, 4 to 4.6 g/d] to induce complete remission (GRADE: Conditional recommendation, very low-quality evidence Evaluate symptom response in 2 to 4 mon of treatment) (not all guidelines agree with the recommendation regarding the use of 5-ASA in patients with Crohn disease)
- Sulfasalazine vs. placebo
  - Modest effect mild on colonic disease.
  - Does not prevent relapse
    - Do **not** use for maintenance therapy.
- 5-aminosalicylic acid (5-ASA)
  - **No** role in patients with CD (GRADE: Conditional recommendation, low-quality evidence for induction of remission, moderate-quality evidence for maintenance of remission)
- Budesonide
  - A dose of 9 mg po per day in patients with mild to moderate ileal / R. colon CD has 2x to 3x greater odds to induce remission for these sites, than placebo, but is inferior to prednisone to induce remission (RR, 0.85; 95% CI, 0.75 – 0.97)
    - Budesonide is comparable to mesalamine for induction of remission
    - However, the lower efficacy of budesonide to induce remission than cortisone is balanced by fewer adverse effects (RR, 0.64; 95% CI, 0.57 to 0.76)
  - The median time to symptomatic remission using budesonide is almost 3-4 wk, and the response ratio reaches a plateau at 8 wks.
    - Assessment of efficacy of budesonide should be made after 4 to 8 wk therapy
  - Do **not** use budesonide to maintain remission
    - In the first few months of use if budesonide, the locally acting corticosteroid delays the time if recurrence of active CD, but by one yr after the initial episode of active CD for which the budesonide was used to achieve remission, the maintenance of remission is no different than placebo.

#### Recommendations

- First line therapy for patients with mild-moderate relapse of ileocolonic CD, 9 mg/day po for 4 to 8 wks (GRADE: Conditional recommendation, low-quality evidence) then
  - Evaluate for symptomatic response to determine the possible need to change therapy (GRADE: Conditional recommendation, very low-quality evidence)





- Do **not** use budesonide for maintenance therapy (GRADE: Conditional recommendation, low-quality evidence)
  - At one year budesonide is no better than placebo, although it takes longer for a relapse to develop
    - Budesonide has ↑ risk of adverse effects compared to placebo in maintenance trials (RR, 2.19; 95% CI, 1.08 to 4.46)
- Note that budesonide less effective than corticosteroids to induce remission at 8 wk (RR, 0.85, 95% CI 0.75 to 0.97) but there were fewer adverse effects
- Corticosteroids (CS)
  - Mild relapse
    - Equivocal support for using prednisolone 40 to 60 mg/day po, or budesonide 9 mg/day po
  - Moderate relapse
    - Use prednisone 40 to 60 mg/day po, or budesonide 9 mg/day po
    - Assess response in 2 to 4 wk to
      - Determine response
      - Change therapy
    - For patients with moderate colonic disease beyond the right side [of the colon], it is likely that prednisone would be used first line rather than budesonide.
    - Comparison of efficacy for symptomatic remission of prednisone is budesonide (RR, 0.85; 95% CI, 0.75-0.97)
    - Cautionary use of corticosteroids (adverse effects)
      - CNS                      psychosis, depression
      - Bone                      vascular necrosis
      - Endocrine              diabetes mellitus
      - Reduce the risk of osteoporosis in CD by also placing the patient on calcium and vitamin D supplements
  - Severe CD relapse (hospitalization)
    - Methylprednisolone 40 to 60 mg/d IV
    - Evaluate response in 1 wk
      - Response
        - Day 3, ~40%
        - Day 5, 76% to 78%
        - Day 10, 93%
        - Do not use corticosteroid [or budesonide] for maintenance of remission
  - Some authorities recommend **not** to use corticosteroid for longer than 3 mon



## Recommendations

- Moderate to severe CD (GRADE: Strong recommendation, low-quality evidence)
  - Induction of symptomatic remission, CS superior to placebo (PL) (RR, 1.99; 95% CI, 1.51 to 2.64)
    - Adverse effects, CS vs. placebo; RR, 4.89; 95% CI, 1.98 to 12.07
  - Evaluate symptomatic response at 2-4 wk (GRADE: Strong recommendation, very low-quality evidence)
- Moderate CD, not responding to budesonide 9 mg/d po → prednisone 40 to 60 mg po to induce complete remission within 2 to 4 wk (GRADE: Conditional recommendation, low-quality evidence)
- Patients with severe CD requiring hospitalization
  - Use methylprednisolone 40-60 mg/day IV to induce complete remission (GRADE: Conditional recommendation, low-quality evidence)
    - Symptomatic remission day 3, 39%
      - 5, ~77%
      - 11, 93%
    - This high beneficial effect is not altered by the previous use of steroids (for example, a patient treated for active CD with prednisone who fails to respond adequately, is admitted to hospital and treated with IV solumedrol)
    - ↑ risk of infection with maintenance therapy with corticosteroid (HR, 1.57, 95% CI, 1.17 to 2.10, P = 0.02)

## Recommendation

- Access symptomatic response within 7 day to determine need to change therapy (GRADE: Strong recommendation, very low-quality evidence)
- Do **not** use corticosteroid (or budesonide) to maintain remission (GRADE: Strong recommendation, low-quality evidence)
  - “...**no** significant reduction in the odds ratio of relapse with ongoing corticosteroid therapy compared with placebo at 6, 12, or 24 mon
- ❖ Immunosuppressants
  - Azathioprine (thiopurine)
    - Following corticosteroid-induced remission, azathioprine may be used for maintenance of remission
      - “...among patients who achieve symptomatic remission while on a thiopurine, ongoing maintenance therapy may be beneficial”
      - Continuing azathioprine ↓ risk of relapse: RR, .39; 95% CI, 0.21 to 0.74
      - This maintenance benefit lasts at least 6-18 mon: RR, 1.19; 95% CI, 1.04 to 1.34
      - Maintenance therapy with azathioprine ↓ risk of first surgical resection by 40%
        - Note that the time to onset of action of thiopurines is 3-4 mon



#### Complication Alert

- Azathioprine is associated with adverse effects (AEs) such as leukopenia / ↑ risk of infection, pancreatitis, hepatic dysfunction, non-melanoma skin cancer, and allergic reactions.
  - Some of the AEs are serious (RR, 2.45, 95% CI, 1.22 to 4.9)
- Of special note is the rare complication of young boys on azathioprine, the development of fetal HSTCL, hepatosplenic T-cell lymphoma.

#### Recommendation

- Do **not** use azathioprine or 6-MP monotherapy to induce complete remission of CD, regardless of severity (GRADE: Conditional recommendation, low-quality evidence)
  - These thiopurines are effective for their steroid-sparing effect (compared with placebo, RR, 1.34; 95% CI, 1.02 to 1.77), but
    - No significant differences in symptom response
  - Also, thiopurines are slow to act (3-4 mon), and this is much too long for an agent to be used to induce remission
  - Note: "...some members of the consensus group stated that they would use thiopurines in selected patients in conjunction with corticosteroids during the induction period"
  - Editor's note: there is **no** clear definition given for the term "selected patients", and this practice does not appear to be supported by evidence. The guidelines have been permissive to include this as a practice possibility.

#### • Thiopurines

##### Recommendations

- Thiopurines may be used in selected patients (low risk of disease progression) for maintenance of a prednisone induced remission (GRADE: Conditional recommendation, very low-quality evidence).
- Modest effect of thiopurines to maintain remission of steroid-induced CD relapse (RR, 1.19; 95% CI, 1.05 to 1.34)
  - This benefit of thiopurine for maintenance persists for 1 yr, but not for 2 .
    - Persons on long term azathioprine have ↑ adverse effects, including some which cause withdrawal of this immunosuppressant (RR, 2.45; 95% CI, 1.22-4.90)

#### Therapeutic Alert

- Persons on long term azathioprine have ↑ risk of developing
  - Cervical dysplasia
  - Skin warts
  - Small intestinal lymphoma
- Pediatricians are hesitant to use azathioprine for their young patients with IBD, because of their ↑ risk of serious hepatosplenic T-cell lymphoma (HSTCL) and non-melanoma skin cancers.



- Methotrexate (MTX)
  - MTX po, SC, IM max bioavailability ↑ 15% to 25% when given SC vs. po
  - MTX 25 mg/wk is effective to induce symptomatic remission in corticosteroids-dependent patients with CD (RR, 1.95; 95% CI, 1.09 to 3.48, P = 0.025)
  - MTX can also be given subcutaneously.
  - MTX 15 mg/wk IM but not superior to placebo to maintain remission in patients who achieve remission with corticosteroids plus MTX (RR, 1.67; 95% CI, 1.05 to 2.67; P = 0.04)
  - For MTX as well as AZA/thiopurines, if the patient fails to respond or has worsening of CD activity within 12-16 wks, treatment should be changed (“modification of therapy”)

#### Recommendations

- Methotrexate may be used for patients with moderate-severe CD who are corticosteroid
  - Dependent
  - Resistant
 (GRADE: Conditional recommendation, very low-quality evidence)
  - MTX may be continued for 12 to 16 wk when they should be reassessed for the possible need to change therapy
    - MTX should **not** be used to induce remission because of its slow onset of action (GRADE: Conditional recommendation, very low-quality evidence)
- MTX 25 mg/wk in corticosteroid-dependent CD patients with
  - Symptom remission with MTX, 39%; with placebo, 19% (RR, 1.95; 95% CI, 1.09-3.48; P = 0.025)
  - MTX added to CS-dependent patient has a steroid sparing effect (P = 0.026)
    - MTX is similarly effective as are azathioprine / 6-mercaptopurine
- SC MTX has ~20% ↑ bioavailability as compared with po MTX
- If failure of thiopurine or methotrexate to produce steroid-free remission in 12-16 wk → modify therapy (GRADE: Conditional recommendation, very low-quality evidence)
- Thiopurine methyltransferase (TPMT)
  - Some guidelines recommend that all persons being placed on thiopurines must first be tested for genotype, or the 6-TG levels monitored during therapy.
  - The assessment of TPMT genotype / phenotype is not a stated recommendation in the “boxed” guideline statements, but
  - In the test the author acknowledge that “...a TPMT assay should be performed before introduction of treatment [with thiopurine]...”
- Editor’s note
  - If the TPMT is low, then the patient’s initial dosing of thiopurines should be very low, or not used at all
  - Regardless of the TPMT measurements, all patients on azathioprine must be frequently monitored with a CBC count, and the AZA / 6-MP immediately stopped with ↓ WBC.



- Anti-tumor necrosis factor (ATNF) biologics
  - Moderate-to-severe CD recurrence
    - Use infliximab or adalimumab plus azathioprine to induce and to maintain symptomatic remission as well as to complete remission (RR, 0.82; 95% CI, 0.73 to 0.91) as well as mucosal healing
      - This recommendation includes moderate-to-severe recurrences in which patient has failed corticosteroids.
    - “Currently there is insufficient evidence to support routine switching to biosimilar anti-TNF agents in patients with stable CD”.
    - Combination therapy
      - ↓ development of anti-TNF antibodies (0.9% vs. 14.6%)
      - ↑ median serum infliximab trough levels (3.5 µg/mL vs. 1.6 µg/mL)
      - ↑ endoscopic improvement at 6 mon (84% vs. 64%; P= 0.019) but not at 12 mon (80% vs. 7%; P= 0.36)
      - MTX added to anti-TNF therapy ↓ risk of formation of antibodies, but there was no improvement in clinical response.
    - The guideline committee was not able to recommend for or against using the combination of anti-TNF therapy plus MTX
    - Assess symptom response to anti-TNF for induction therapy at 8 to 12 wks
      - If patients do **not** respond to a 8 to 12 wk induction period with anti-TNF, they are not likely to respond with longer therapy.
      - If therapy results in symptomatic remission in 8 to 12 wk → perform colonoscopy to determine if there is mucosal healing / complete remission.
  - If patient is doing well on one anti-TNF, do **not** switch to another
  - Some patients who experience only a partial induction response to infliximab or adalimumab may benefit from
    - Dose intensification optimization

Loss of clinical response

- Use therapeutic drug monitoring (TDM)
  - Higher trough drug concentrations
  - Presence of antibodies to anti-TNF

2x greater  
3x greater

- Elective switching
  - Do **not** switch from one anti-TNF to another if the patient is doing well.

Loss of efficacy/tolerance within 1 yr

- Taking infliximab
  - Switch to adalimumab
  - Continue on infliximab

47%  
16%

} Required dose optimization  
or stopping the anti-TNF  
(dose interruption)



## Recommendations

- Use infliximab (IFX) or adalimumab (ADA) in persons with moderate-severe luminal CD
- Combine with thiopurine when starting anti-TNF (GRADE: Conditional recommendation, low-quality evidence) or methotrexate (GRADE: Conditional recommendation, very low-quality evidence for infliximab, very low-quality evidence for adalimumab)
  - If they have risk factors for poor prognosis (GRADE: Strong recommendation, moderate-quality evidence)
  - If they have failed induction of remission on corticosteroids, thiopurines, or methotrexate (GRADE: Strong recommendation, high-quality evidence)
- To induce complete remission
- Evaluate benefit at 8 to 12 wk of therapy
- Evaluate anti-TNF induction treatment at 8-12 wk (GRADE: Strong recommendation, very low-quality evidence)
- When starting anti-TNF therapy, adding low dose azathioprine or methotrexate to improve pharmacokinetics, but not to induce clinical remission
  - Induction of remission occurred with infliximab (IFX) and with adalimumab (ADA), but not with certolizumab (CZP)
- Editor's note: The guideline committee recommended statement supporting the use of IFX/ADA in patients with medium-severe CD who have failed conventional therapy.
  - However, the full test stated that “..the consensus group agreed that these agents [IFX, ADA] should likely be reserved for patients with risk factors [e.g., clinical, disease, laboratory, and endoscopic factors associated with high risk of relapse, complicated OP, or surgery
  - IFX OR, 2.8; 95% CI, 1.4 to 7.2
  - ADA OR, 2.9; 95% CI, 1.6 to 5.5
  - CZP OR, 1.4, 95% CI, 0.95 to 2.0
- Etanercept is **not** effective to induce symptomatic remission in CD
- Symptomatic response with anti-TNF induction treatment
  - Good response → anti-TNF for maintenance (GRADE: Strong recommendation, high-quality evidence)
    - Do **not** switch to another anti-TNF (GRADE: Conditional recommendation, low-quality evidence)
  - Suboptimal response → ↑ dose if same anti-TNF (GRADE: Conditional recommendation, very low-quality evidence)
  - Loss of response → dose optimization (GRADE: Conditional recommendation, very low-quality evidence)
- Anti-TNF therapy also provides mucosal healing (IFX plus azathioprine, 30% vs. 17% for monotherapy with therapeutic drug monitoring (GRADE: Conditional recommendation, very low-quality evidence)
- Use anti-TNF therapy early in the patient's relapse of CD may provide
  - Superior mucosal healing at wk 30 (45% vs. 10%,  $P = 0.011$ )
  - High rates of symptomatic remission at 1 yr



- In some studies, the incidence of adverse effects has been similar in anti-TNF vs. placebo groups (RR, 0.99; 95% CI, 0.90 to 1.08)
- If there is initially a suboptimal response for induction of remission with IFX/AZA, use dose intensification function to achieve complete remission (primary non-response)
  - Mucosal healing can also be achieved with adalimumab vs. placebo, 27% vs. 12% (P = 0.56), given for 12 wk (↑ dose or ↓ dosing interval of anti-TNF)
- If anti-TNF therapy results in clinical response, continue anti-TNF to achieve and maintain complete remission.
  - If less of a response to anti-TNF maintenance, use dose optimization to recapture complete remission (secondary loss of response)
- IFX and ADA are recommended for induction of remission of active CD.
  - IFX, ADA, and certolizumab pegol (CZP) are recommended for maintenance of remission
    - Use continuous, not episodic therapy to maintain 54 wk benefit (50% vs. 7%, P = 0.007) in order to ↑ maintenance response, ↑ duration of maintenance and to ↓ risk of recurrence.
- Adverse effects of IFX, ADA, or CZP on 54 wk maintenance: compared to placebo, “no statistically significant difference in the incidence of any adverse effect” (RR, 0.93; 95% CI, 0.84 to 1.03).
- Primary/secondary loss of response of ADA therapy is ~20% per yr and for IFX, 13% per yr
  - With dose intensification of ADA, there is symptomatic
    - Response, ~70%
    - Remission, 40%
  - With dose intensification of IFX, there is symptomatic
    - Response, 84 to 90%
    - Remission, ~30%
- Dose optimization: perform therapeutic drug monitoring (TDM)
- When patient doing well on anti-TNF maintenance
  - Do **not** switch to another anti-TNF [including to a baseline]
  - Elective switching from one anti-TNF to another → ↓ response within 1 yr IFX
    - continued IFX, 16% ↓ response
    - switch to ADA, 47%, ↓ response

▪ Required dose optimization, or stopping new anti-TNF

#### ❖ Non-anti-TNF biologics

- If patient with active CD fails to respond to “conventional therapy”
  - Thiopurines/methotrexate
  - Anti-TNF

▪ Use vedolizumab or ustekinumab to induce complete remission



- Vedolizumab (VEDO)
  - Anti-TNF naïve
    - Symptomatic remission (OR, 1.76; 95% CI, 1.11 to 2.78)
    - Failure to achieve remission (OR, 0.86; 95% CI, 0.79 to 0.94; P= 0.001)
    - At 1 yr
      - Mucosal healing, 63% (deep remission)
      - Symptomatic remission plus mucosal healing, 26% (complete remission)
      - ↑ rate if corticosteroids
    - No recommendation (no evidence) for or against adding immunosuppressant to vedolizumab
  - Non-anti-TNF naïve
    - If patient on anti-TNF and requiring corticosteroids because they
      - Fail to achieve/maintain corticoid-free symptomatic remission → vedolizumab
    - Patients who have been on anti-TNF therapy have ↓ likelihood of achieving mucosal healing
  - Evaluate for symptomatic response to vedolizumab at 10 to 14 wk to determine if there is a need to modify therapy.
  - Once symptomatic response achieved with vedolizumab
    - Continue therapy to achieve and to maintain complete remission
    - For maintenance of remission with vedolizumab
      - Naïve to anti-TNF (RR, 1.49; 95% CI, 1.19 to 1.86)
      - Not naïve to anti-TNF “there was a statistically significant risk difference of ~15 for vedolizumab once every 4 wk and once very 8 wk versus placebo
    - Benefit of maintenance of vedolizumab

| Remission       | 52 wk | 152 wk all patients | Anti-TNF<br>Naïve | Anti-TNF<br>Not naïve |
|-----------------|-------|---------------------|-------------------|-----------------------|
| Symptomatic     | 35%   | 74%                 | 82%               | 66%                   |
| Mucosal healing | 63%   |                     |                   |                       |

- No recommendation was made for or against treating vedolizumab failure with ustekinumab
- Use with moderate severe CD/UC
  - Not responding to conventional therapy (including anti-TNF) (1.11 to 2.78) → VEDO to induce complete remission, and then reactivate symptomatic response in 10 to 14 wks
  - No recommendation for or against combination therapy with azathioprine or methotrexate
  - If successful symptomatic response with vedolizumab, continue vedolizumab to achieve and to maintain complete remission
    - 52 wk symptomatic remission, ~35% (RR, 2.20; 95% CI, 1.4 to 3.44); anti-TNF naïve, RR of maintaining remission, 1.49; 95% CI, 1.19 to 1.86





- Anti-TNF naïve, VEDO superior to placebo for
  - Symptom remission (OR, 1.76; 95% CI
  - Failure to achieve symptomatic remission
- No recommendation for or against combination therapy of VEDO plus azathioprine / methotrexate 3 yr (RR, 0.86; 95% CI, 0.79 to 0.94, P = 0.001)
- 1 yr maintenance
  - Symptomatic remission, 35% - 74% (82% anti-TNF naïve, 66% with prior anti-TNF failure)
  - Mucosal healing, 63%
  - Deep remission, 26% (mucosal healing plus symptomatic remission)
  - ↑ corticosteroid-free remission

## Recommendations

- Moderate/severe CD, failure to achieve complete remission on any of corticosteroids, thiopurines, methotrexate, a anti-TNF therapy → use vedolizumab to induce complete remission (GRADE: Strong recommendation, moderate-quality evidence)
- Also use vedolizumab if anti-TNF therapy does not provide corticosteroid-free remission/maintenance (GRADE: Conditional recommendation, low-quality evidence)
- Evaluate for symptomatic response to vedolizumab at 10-14 wk (GRADE: Conditional recommendation, very low-quality evidence)
- If vedolizumab induction produces complete symptomatic response → vedolizumab maintenance (GRADE: Strong recommendation, moderate-quality evidence)
- Ustekinumab (UST)
  - Failure of conventional therapy, use ustekinumab, both in those patients who were anti-TNF naïve (~55%) and non-naïve (34%) (greater benefit in secondary non-responders to anti-TNF) to achieve
    - Symptomatic remission at 6 wk (RR, 0.8; 95% CI 0.85 to 0.92)
    - Mucosal healing
    - Corticosteroid-free remission at week 52
  - Evaluate for response of 6 to 10 wk to determine if therapy should be altered
    - There's an early response group, 6 wk, and a later subresponse group.
  - No recommendation for or against starting ustekinumab with or without thiopurine or methotrexate.
  - Patients who have not demonstrated a response before the second subcutaneous dose modification of therapy.
    - If a response occurs, subsequent assessment may include endoscopy to confirm complete remission.
      - The optimal timing for this colonoscopic evaluation for mucosal healing is "...currently uncertain"



- If ustekinumab induction therapy results in symptomatic response, continue ustekinumab to achieve and to maintain complete remission.
  - Symptomatic remission at
    - 22 wk, versus placebo 42% vs. 27%
      - Absolute difference, 14%; 95% CI, 2 to 27.1; P = 0.03
    - 52 wk vs. placebo, 51% vs. 36%
      - Absolute difference, 15%; 95% CI, 4.86 to 25.3; P = 0.005
  - Symptomatic remission at wk 49
    - Anti-TNF naïve 57%
    - Not naïve ~40%
  - Corticosteroid-free remission, ustekinumab vs. placebo, 48% vs. 30%; P = 0.004
- No recommendation made for or against treating ustekinumab failure with vedolizumab

#### Recommendations

- Use with moderate-severe CD not responding to conventional therapy (including anti-TNF) →ustekinumab (UST) to induce complete remission (GRADE: Strong recommendation, moderate-quality evidence), then reevaluate symptomatic response in 6 to 10 wk (GRADE: Conditional recommendation, very low-quality evidence).
  - If successful symptomatic response to UST, continue maintenance therapy with UST to achieve and to maintain complete remission (GRADE: Strong recommendation, moderate-quality evidence)
  - No recommendation for or against combination therapy of UST plus azathioprine or methotrexate

#### ❖ Miscellaneous others

- Do **not** use probiotics, omega-3 fatty acids, enteral nutrition, diet modification, marijuana or naltrexone to induce or to maintain symptomatic remission of CD.

#### Recommendations against

- Do **not** use for induction or maintenance of suboptimal remission
  - Diet
    - Probiotics (GRADE: Strong recommendation, very low-quality evidence)
    - Omega-3 fatty acids (GRADE: Strong recommendation, moderate-quality evidence)
    - Enteral nutrition (GRADE: Conditional recommendation, very low-quality evidence)
    - Dietary modification
  - Pharmacological agents
    - Naltrexone (GRADE: Conditional recommendation, low-quality evidence for induction of remission, very low-quality evidence for maintenance of remission)
    - Marijuana (GRADE: Conditional recommendation, very low-quality evidence)



## Medical and Surgical Management of Patients with Crohn Disease: Guideline (BSG, CSSG, and BSG, 2019)

Lamb CT, et al. Gut 2019; S1-S106.

### ➤ Definition

- There is no single underlying definition of Crohn disease and a combination of investigative modalities is needed to confirm the diagnosis.

### ➤ Differential between Crohn disease (CD) and Ulcerative Colitis (UC)

|                                                   | CD                                                                                                                                                                     | UC                                                                           | Exceptions                                                                                                                     |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| ○ Distribution                                    | <ul style="list-style-type: none"> <li>- Focal/patchy</li> <li>- Skin lesions</li> <li>- All parts of luminal</li> <li>- GI tract</li> <li>- Rectal sparing</li> </ul> | <ul style="list-style-type: none"> <li>▪ Diffuse</li> <li>▪ Colon</li> </ul> | <p>Partially-treated UC may be patchy</p> <p>Backwash ileitis</p> <p>Use of the therapeutic enema may cause rectal sparing</p> |
| ○ Histopathology                                  | <ul style="list-style-type: none"> <li>- Granulomas</li> <li>- Focal inflammation</li> </ul>                                                                           | <ul style="list-style-type: none"> <li>-</li> <li>+</li> </ul>               | <p>Cryptolytic granulomas may rarely occur in UC</p>                                                                           |
| ○ IBD unclassified occurs in ~10% of IBD patients |                                                                                                                                                                        |                                                                              |                                                                                                                                |
| - Reclassification                                |                                                                                                                                                                        |                                                                              |                                                                                                                                |
| ▪ UC → CD (colitis)                               | 3%                                                                                                                                                                     |                                                                              |                                                                                                                                |
| ▪ CD → UC                                         | < 3%                                                                                                                                                                   |                                                                              |                                                                                                                                |

### ➤ Classification

#### • Montreal classification

- Note that the Montreal classification does not include the findings of endoscopic mucosal biopsies or of advanced imaging.
  - The extent/severity of disease is often more extensive on histological than on endoscopic (macroscopic features) examination, which may change the “L” (location) component of the Montreal classification



- Montreal and Paris classifications of Crohn disease

|                         | Montreal |                                         | Paris          |                                                                                 |
|-------------------------|----------|-----------------------------------------|----------------|---------------------------------------------------------------------------------|
| ○ Age at diagnosis (yr) | A1       | <17                                     | A1a            | <10                                                                             |
|                         |          |                                         | A1b            | 10–17                                                                           |
|                         | A2       | 17–40                                   | A2             | 17–40                                                                           |
|                         | A3       | >40                                     | A3             | >40                                                                             |
| ○ Location*             | L1       | Terminal ileal ± limited caecal disease | L1             | Distal 1/3 ileum ± limited caecal disease                                       |
|                         | L2       | Colonic                                 | L2             | Colonic                                                                         |
|                         | L3       | Ileocolonic                             | L3             | Ileocolonic                                                                     |
|                         | L4       | Isolated upper disease†                 | L4a            | Upper disease proximal to ligament of Treitz†                                   |
|                         |          |                                         | L4b            | Upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum†    |
| ○ Behaviour             | B1       | Non-stricturing, non-penetrating        | B1             | Non-stricturing, non-penetrating                                                |
|                         | B2       | Stricturing                             | B2             | Stricturing                                                                     |
|                         | B3       | Penetrating                             | B3             | Penetrating                                                                     |
|                         |          |                                         | B2B3           | Both penetrating and stricturing disease, either at the same or different times |
|                         | P        | Perianal disease modifier‡              | P              | Perianal disease modifier‡                                                      |
| ○ Growth                |          |                                         | G <sub>0</sub> | No evidence of growth delay                                                     |
|                         |          |                                         | G <sub>1</sub> | Growth delay                                                                    |

B2: Stricturing defined as the occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic, or surgical examination combined with pre-stenotic dilatation and/or obstructive signs or symptoms but without evidence of penetrating disease.

B3: Penetrating disease: defined as the occurrence of bowel perforation, intra-abdominal fistulae, inflammatory masses and/or abscesses at any time in the course of the disease, and not secondary to postoperative intra-abdominal complications (excludes isolated perianal or rectovaginal fistulae).

\*Defined as endoscopic or macroscopic extent.

†Upper disease in Montreal classification describes disease proximal to the terminal ileum. In both Montreal and Paris: L4 and L4a/b may coexist with L1, L2, L3.

‡Perianal abscesses, ulcers or fistulae (but not skin tags or fissures).

Printed with permission: Lamb CT, et al. Gut 2019; S1-S106 (Table 7)



- Early Crohn disease
    - CD duration of  $\leq 18$  mon for diagnosis without previous exposure to immunomodulators and/or biological
      - Early treatment with biologics may be more effective, as is the early use of azathioprine in children
  - Clinical
    - Crohn Disease Activity Index (CDAI)
      - “Cumbersome”
        - Not used except in non-research studies
    - Harvey Bradshaw Index
      - $ABI \leq 4$  clinical remission
    - Patient Reported Outcome Measures (PROMs)
    - IBD Control PROM
      - “...reliable 8 item measures which correlate well with other quality of life measures and should be used to monitor patient’s perspective of their disease”
- Do **not** correlate well with objective markers of inflammation
- Diagnostic imaging
  - MRI activity score

#### Recommendations

- Use cross-sectional imaging (MRE, SBUS), rather than conventional barium fluoroscopy or nuclear medicine, because of their better performance characteristics for the determination of luminal plus extraluminal disease, and their safety in terms of radiation exposure.
- Luminal barium fluoroscopy techniques
  - Low diagnostic accuracy
  - Replaced by cross-sectional imaging techniques
- Cross-sectional imaging techniques
  - Small bowel ultrasound (SBUS)

- Use MRE to detect small bowel CD, and SBUS for colonic CD

#### ➤ Laboratory

- Surrogate markers for inflammation/endoscopy are under evaluation, e.g., C-reactive protein (CRP), fecal calprotectin (fCal)



➤ Endoscopy

- Crohn Disease Endoscopic Index of Severity (CDEIS)
  - Simplified Endoscopic Activity Score for Crohn disease (SES-CD)
- Use to assess mucosal healing in research studies

• Simple Endoscopic Score for Crohn's disease (SES-CD)

|                             |                                |   |
|-----------------------------|--------------------------------|---|
| ○ Size of ulcers (diameter) | - Absent                       | 0 |
|                             | - Aphthous ulcers, 0.1–0.5 cm  | 1 |
|                             | - Large ulcers, 0.5–2 cm       | 2 |
|                             | - Very large ulcers, >2 cm     | 3 |
| ○ Ulcerated surface         | - None                         | 0 |
|                             | - <10% of the segment          | 1 |
|                             | - 10–30% of the segment        | 2 |
|                             | - >30% of the segment          | 3 |
| ○ Affected surface          | - None                         | 0 |
|                             | - <50% of the segment          | 1 |
|                             | - 50–75% of the segment        | 2 |
|                             | - >75% of the segment          | 3 |
| ○ Presence of narrowing     | - None                         | 0 |
|                             | - Single, passable by scope    | 1 |
|                             | - Multiple, passable by scope  | 2 |
|                             | - Not passable, frank stenosis | 3 |

\* Record these findings for ileum, right colon, left colon, and rectum, and total the numbers to create the score

Printed with permission: Lamb CT, et al. Gut 2019; S1-S106 (Table 8)

• Rutgeerts Score

- Endoscopic remission or recurrence in neoterminal ileum assessed from ileocolonoscopy after patients have undergone ileal resection surgical

• Ileocolonoscopy (ICS)

- “Gold-standard” first-line investigation
- Provides access to
  - Score CD (UC) activity



- Esophagogastroduodenoscopy (EGD)
  - Details CD in proximal/upper GI tract in ~ 20%
    - Usually associated with ileal/colonic CD

#### Recommendations

- Persons suspected of having CD should have
  - Ileocolonoscopy with multiple ileal/colonic mucosal biopsies, and
  - Perform diagnostic imaging to determine presence, location and activity of small bowel (Agreement 98%)
- In patients with CD plus upper GI tract symptoms, perform EGD (GRADE: weak recommendation, very low-quality evidence. Agreement: 91%).
- Balloon-associated enteroscopy
  - Indications
    - Therapy (e.g., dilation of strictures)
  - Diagnostic yield 64% (95% CI, 42% to 83%)
  - Major complications
    - Bleeding, perforation, 0.72% (95% CI, 0.56% to 0.90%)
- Video capsule endoscopy (VCE)
  - Use bowel preparation with polyethylene glycol (PEG), plus antifoam agent (European expert technical review / meta-analysis)
  - Approximation of comparative diagnostic yield for CD
    - CTE, MRE, small bowel ultrasound (SBUS), 85% to 95%
    - VCE, 52% to 71% (because of possible retention of VC by stricture)
    - ICS, 25%
    - Barium fluoroscopy, 16% to 36%
    - Push enteroscopy, 9%

| Performance Characteristics | Sensitivity |      | Specificity |      |
|-----------------------------|-------------|------|-------------|------|
|                             | MRE         | SBUS | MRE         | SBUS |
| – CD presence / extent      | 80%         | 70%  | 95%         | ~80% |
| – Colonic disease           | 47%         | 67%  |             |      |

- Capsule endoscopy has greater sensitivity for mucosal small bowel Crohn disease than do radiological imaging techniques
  - Can generally be performed when inflammatory small bowel disease is still suspected despite normal or equivocal cross-sectional imaging.
  - Minor changes found at capsule endoscopy may be insufficient in isolation to diagnose Crohn disease, particularly if there has been recent non-steroidal anti-inflammatory drug (NSAID) use (GRADE: weak recommendation, moderate-quality evidence. Agreement 91%).



- Use VCE when CD suspected
  - Clinical features
    - No NSAID intake for > 1 mon
  - MRE/CTE normal/equivocal
- Use of prior test capsule when
  - Obstructive symptoms, or
  - Known stricture (GRADE: weak recommendation, low-quality evidence. Agreement: 94%).
- Use VCE when cross-sectional imaging is negative or equivocal, but CD is still suspected.
  - VCE may be diagnostic in this situation because of its likely greater sensitivity to diagnose CD
- Stop use of NSAIDs  $\geq$  1 mon before performing VCE (VCE may not be sufficiently specific by itself to diagnose CD)

➤ Treatment:

❖ Induction of remission

Recommendations

- Mild/moderate CD
  - Treat mild/moderate active ileocecal CD with ileal-release budesonide 9 mg po per day to induce remission (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).
  - Treat active Crohn colitis with an 8 wk course of systemic corticosteroids to induce remission (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).
  - Budesonide, prednisolone, ileal-releasing
    - Equivalent efficacy (~50%) of budesonide 9 mg po od for 8 wk to induce remission of mild/moderate (CDAI < 150) active ileocolonic CD, as prednisolone 4 mg po od, tapering to 5 mg at 8 wk
      - Budesonide has fewer steroid-associated adverse effects, but is much more expensive
        - For severe CD (CDAI > 300), budesonide is inferior to prednisolone (RR, 0.52; 95% CI: 0.28 to 0.95)
    - Ileal-releasing budesonide helps to heal proximal / right-sided CD
- Moderate/severe CD
  - Use systemic corticosteroids for patients with uncomplicated moderate/severe CD (GRADE: strong recommendation, high-quality evidence).
    - Use prednisone po/IV, for all locations of CD





- Use early biological therapy in patients with moderate/severe extensive/complicated CD (GRADE: weak recommendation, moderate-quality evidence. Agreement: 87%).
- Anti-TNF therapy
  - Failed prednisone / immunosuppressants (for induction or maintenance “step up” therapy)
  - Severe acute CD
  - Perianal disease
  - There is growing evidence that “high-risk” patients with CD should have early use of biological therapy
  - High-risk factors include
    - Age of diagnosis < 40 yr
    - Severe CD (complex)
      - Strictures
      - Penetration
      - Perianal fistulae
    - Requirement to use corticosteroids to control the index flare
  - Surrogate markers for high-risk disease possibly benefiting from early biologic therapy
    - Fecal calprotectin (fCal)
    - Gene expression signature from peripheral blood CD8 T cells
    - MRI/ small bowel ultrasound (SBUS) findings (e.g., thickened bowel wall / mesentery, ↑ blood flow)
- Antibiotics
  - Pooled trials of numerous antibiotics have suggested a class benefit efficacy for active CD.
    - RR for continued CD activity, 0.85; 95% CI: 0.73 to 0.99
  - High-dose rifaximin (800 mg b.i.d.) in an extended-release formation is beneficial for active CD but is expensive and not yet licensed for the purpose.
  - Antibiotics such as metronidazole, clarithromycin, azithromycin play an important role in the treatment of
    - Infection e.g., abscess, C. difficile, small intestinal bacterial overgrowth [SIBO]
    - Perianal fistulizing CD
- Nutritional therapy
  - Correction of malnutrition is essential in the care of all patients with IBD.
    - Avoidance of corticosteroids is desired and
    - Patients are motivated to adhere strictly to exclusive enteral retention (EEN) for 8 wk (GRADE: weak recommendation, very low-quality evidence. Agreement: 87%).
  - Polymeric feeds are as beneficial as element or semi-elemental feeds in patients with CD and are more palatable and therefore better tolerated.
  - Give EEN po/ nasogastric tube (NG), using polymeric (whole protein) and semi-elemental (peptide) based solutions
  - Symptom relief may occur within 10 d, and mucosal healing in 8 wk



- Consider laparoscopic localized ileorectal surgical resection for patients with CD who
  - Fail medical therapy
  - Relapse after initial medical therapy
  - Prefer surgery rather than continued drug therapy
 (GRADE: weak recommendation, moderate-quality evidence. Agreement: 93.5%).
- In persons with ileocecal CD
  - Resection (RES) is equivalent to infliximab therapy (IFX) (LIR!C study)
  - Median follow-up period of 4 yr

| Original treatment | Switching to other treatment |
|--------------------|------------------------------|
| IFX → RES          | 39%                          |
| RES → IFX          | 26%                          |

- Note that the surgical resection group had exclusions
  - Previous resection
  - SB CD > 40 cm
  - Abscesses
  - Pre-stenotic dilation

#### ❖ Maintenance of remission

- 5-aminosalicylic (5-ASA)

#### Recommendations

- Do **not** use for induction or maintenance treatment of CD (GRADE: strong recommendation, moderate-quality evidence. Agreement: 98%).
- Do **not** use systemically or locally acting corticosteroids for maintenance therapy [no longer than 3 mon from start to finish of tapering doses for induction of moderate/severe CD (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).

- Thiopurine (TP)

#### Recommendations

- Do **not** use thiopurine (TP) for induction of remission of active CD.
- Use TP or methotrexate (MTX) for maintenance therapy early after moderate/severe CD has gone into remission with prednisolone
  - Thiopurines (GRADE: strong recommendation, low-quality evidence)
  - Methotrexate (GRADE: strong recommendation, moderate-quality evidence) should be considered to minimise risk of flare as prednisolone is withdrawn (Agreement: 93%).



- Azathioprine/mercaptopurine can be used as monotherapy in the maintenance of remission in Crohn disease (GRADE: strong recommendation, low-quality evidence. Agreement: 100%).
  - Azathioprine/mercaptopurine are superior to placebo to maintain remission of CD (OR, 1.7; 95% CI: 1.3 to 2.6 systemic review and network analysis]; number needed to treat (NNT) = 9 [Cochrane review])
- Methotrexate (MTX)

#### Recommendation

- Use MTX 15 mg q1wk SC plus folic acid 5 mg q1wk or 1 mg po od for maintenance therapy of CD (GRADE: weak recommendation, moderate-quality evidence. Agreement: 88%).

- Infliximab (IFX)

#### Recommendation

- Use biological therapy for CD patients who are refractory to immunomodulators.
  - Currently, the choice is between infliximab, adalimumab, vedolizumab, or ustekinumab; other biologics are soon to be approved. (GRADE: strong recommendation, very low-quality evidence. Agreement: 95.7%).
- Use infliximab with a thiopurine for induction or maintenance therapy ((GRADE: strong recommendation, high-quality evidence. Agreement: 97.7%).
  - IFX 5/10 mg/kg, one infusion produced 58% response at wk 2 and 39% to 45% at wk 30/54 (Accent 1)
    - In routine clinical practise, the initial clinical response to IFX was higher (89%) as also was the sustained response (63%)
  - Using a combination of IFX plus azathioprine for induction therapy was
    - Superior to IFX alone to achieve clinical remission
    - ↓ need for increasing the dose of IFX
    - ↓ need to switch drug
  - Use IFX plus methotrexate to ↓ immunogenicity (stronger evidence for azathioprine than for MTX (GRADE: weak recommendation, moderate-quality evidence. Agreement: 91%).
  - Immunogenicity increases with the duration of use of IFX, and with interruption of IFX therapy.
  - The mechanism of this benefit of dual therapy is thought to be ↓ production of antibodies to IFX (the ↓ immunogenicity [by ~25%] and ↓ ATI [antibodies to IFX] would allow the full therapeutic potential of IFX



- Adalimumab
  - The optimal dose of anti-TNF naïve patients with moderate/severe CD is adalimumab 160 mg SC at time 0, 80 mg SC at wk 2 and, with remission rates (CDAI < 150) in 36% vs. placebo 24%, P=0.001
  - ADA is effective for induction therapy in persons with secondary IFX failures, and for maintenance therapy (CHARM; GAIN studies)
  - ADA is effective to
    - Induce and to maintain long term endoscopic mucosal healing
    - Improve outcome in patients who achieved deep healing (EXTEND trial)
  - Loss of efficacy of ADA to immunotherapy and production of antibodies to ADA, and improvement in induction/maintenance ratio achieved by using modulation therapy is less than the benefit of combination therapy with infliximab (DIAMOND study).

#### Recommendation

- There is little to choose between adalimumab and infliximab in efficacy in luminal Crohn disease, and considerations of a practical, cost, and convenience nature as important in the choice of anti-TNF therapy.

- Vedolizumab

#### Recommendation

- "...a monoclonal antibody to the  $\alpha 4\beta 7$  integrin and blocks trafficking to the gut by blocking of  $\alpha 4\beta 7$  to the mucosal addressin cell adhesion molecule 1 (MAdCAM-1).
- Use vedolizumab in both anti-TNF naïve patients with CD, as well as in those who had failed previous anti-TNF therapy, both for induction (GRADE: strong recommendation, moderate-quality evidence), as well as for maintenance therapy (GRADE: strong recommendation, high-quality evidence. Agreement: 96%).
- Rates of induction and maintenance of remission are modestly better in persons who are naïve to treatment with anti-TNF therapy, than in those who have been treated with anti-TNF and have failed (GEMINI-1/-2 studies).

| Treatment History                                                             | Response    | Remission |                     |
|-------------------------------------------------------------------------------|-------------|-----------|---------------------|
| – Anti-TNF naïve                                                              | 48% / 30%   | 27% / 15% |                     |
| – Previously failed anti-TNF                                                  | 40% / 23%   | 22% / 11% |                     |
| – Persons who responded to vedolizumab continued to be in remission over time |             |           |                     |
| ▪ 2 yr                                                                        | 83%         |           |                     |
| ▪ 3 yr                                                                        | 89%         |           |                     |
| – Comparing                                                                   |             |           |                     |
|                                                                               | Vedolizumab | anti-TNF  | HR, 95% CI          |
| ▪ Remission at 1 yr                                                           | 38%         | 34%       | 1.27 (0.91 to 1.27) |
| ▪ Steroid free remission                                                      | 26%         | 18%       | 1.75 (0.90 to 3.43) |
| ▪ Endoscopic healing                                                          | 50%         | 41%       | 1.67 (2.23 to 2.47) |



- Ustekinumab

#### Recommendation

- "...an anti-IL-12/23 p40 antibody
- Use ustekinumab in both anti-TNF naïve patients with CD, as well as in those who had failed anti-TNF therapy, both for induction and for maintenance therapy (GRADE: strong recommendation, high-quality evidence. Agreement: 98%).
 

|                                                                                                                                                                                                     | <u>Clinical response at wk 8; 6 mg/kg, 130 mg/ (placebo)</u> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| - Mostly anti-TNF naïve                                                                                                                                                                             | 58%, 47% / 32% (P < 0.001, both doses)                       |
| - Previously failed anti-TNF                                                                                                                                                                        | 38%, 34% / 20% (P = 0.001, both doses)                       |
| <ul style="list-style-type: none"> <li>▪ Clinical maintenance anti-TNF refractory, wk 44, ustekinumab 41% vs. placebo 26% (P=0.01; IM-UNITI study)</li> </ul>                                       |                                                              |
| - Refractory to anti-TNF <ul style="list-style-type: none"> <li>▪ Treated with ustekinumab</li> <li>▪ Clinical benefit with 3 mon, 68%</li> <li>▪ Benefit maintained, 68% (GETAID study)</li> </ul> |                                                              |
- ↑ risk of infection (serious, opportunistic) from treatment with corticosteroids, immunosuppressants, and
  - This ↑ risk of infection is greatest with use of corticosteroids

- Switching from anti-TNF therapy

#### Recommendations

- When a CD patient requires a change in treatment from anti-TNF (e.g., failed therapy, adverse effects), consider
  - Vedolizumab or ustekinumab, or
  - Surgical resection
 (GRADE: weak recommendation, very low-quality evidence. Agreement: 98%).
- When a CD patient is corticosteroids-dependent, +/- on immunomodulatory +/- biological therapy, consider
  - "alternate medical treatment, or
  - Surgical resection
 (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.8%).
- Autologous hematopoietic stem cell transplantation / leukocytosis – do **not** use until benefit proven (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).



➤ Proximal jejunal or extensive small bowel Crohn disease

Recommendation

- About 15% of persons with CD
  - Have disease proximal to the terminal ileum
  - Of these, half will have jejunum involvement
- Use early biological therapy and nutritional assessment / support for patients with jejunal or extensive small bowel CD (GRADE: weak recommendation, very low-quality evidence. Agreement: 100%).
- Give features which are more common with jejunal CD.
  - ↑ risk of
    - Strictures
    - Relapse within 2 yr
    - Relapse after bowel surgery

Proximal jejunal CD may be an indication for ↑ risk of complicated disease, and thus these are patients who might benefit from early use of biological therapy

➤ Gastroduodenal CD

Recommendations

- For gastroduodenal CD which is mild, use PPIs at standard dose/dosing; po, od, 30-60 min before first med of the day
    - Moderate/severe disease, treat as per usual protocol for other sites of CD, using
      - With corticosteroids, immunosuppressants and/or biologicals (GRADE: weak recommendation, very low-quality evidence. Agreement: 92.7%)
      - Consider early use of biologicals.
  - Use nutritional support, as appropriate
  - Use dilation for esophageal strictures, using guideline-based protocol
  - Refractory disease
    - Use surgery as a last resort (GRADE: weak recommendation, very low-quality evidence. Agreement: 97.6%)
- |                                     |                                                             | Do <b>not</b> use       |
|-------------------------------------|-------------------------------------------------------------|-------------------------|
| ○ No stenosis: therapeutic sequence | – PPI, corticosteroid (CS), immunomodulator (IM) / anti-TNF | ▪ Adalimumab or surgery |
| ○ Stenosis                          | – Balloon dilation, PPI, CS/IM surgery                      | ▪ Infliximab            |
- Nutritional therapy
    - Gastrostomy tube delivery for CD which is
      - Severe
      - Stricturing



- Orofacial granulomatous (OFG)

- Definition

- Chronic granulomatous condition of the face and oral cavity, which may be associated with Crohn disease (CD).

Recommendation

- Investigate the GI tract for possible Crohn disease in persons with oropharyngeal dysphagia plus GI symptoms, positive markers of inflammation and positive fecal calprotectin (GRADE: weak recommendation, very low-quality evidence. Agreement: 100%).

- Treatment

- OFG
  - Topical steroids (triamcinolone) injected into lesions
  - Tacrolimus
  - Infliximab
  - Diet
    - Cinnamon
    - Benzoate-free
    - Exclusive enteral nutrition (EEN)
- OFG plus CD
  - Treat CD in usual manner
  - Consider intralesional injection and diet therapy

- Stricturing CD

Recommendation

- Use a multidisciplinary team (MDT) to optimize care of patients with small bowel structuring CD (agreement 100%)
- Inflammation plus fibrosis occur together in most strictures
  - Multidisciplinary team (MDT) is recommended (CREOLE study)
  - A prognostic score for studies has been developed based on
    - Severity / duration of obstructive symptoms
    - Use of immunosuppressive therapy at baseline
    - MRE demonstration of length of stricture
    - Intermediate small bowel dilation
    - Enhancement on delayed T1-weight sequence and
    - Absence of fistula



- Medical therapy
  - Symptomatic strictures
    - Adalimumab success at wk 24 64%
    - Response to anti-TNF is best with
      - Symptoms that are severe but of short duration
      - Moderate dilation on MRE, and
      - A high CREOLE score
  - Investigate for and treat associated small intestinal bacterial overgrowth (SIBO)
- Surgical resection

#### Recommendation

- Multidisciplinary team use anti-TNF if ↑ CREOLE score
  - Consider possible role of strictureplasty
  - Multiple strictures in a patient without short gut may be preferable to treat with a single resection rather than multiple strictureplasty (agreement 100%)

#### • Strictureplasty

#### Recommendations

- For short strictures (< 10 cm), consider strictureplasty rather than resection for small bowel Crohn strictures
  - Need to preserve bowel
  - Multiple strictures
- For long strictures (> 10 cm), use non-standard strictureplasty, e.g., Michelassi procedure, enterostomy (GRADE: strong recommendation, very low-quality evidence. Agreement: 97.3%).
- Indications
  - Strictures-single or multiple
  - With or without active inflammation
  - Previous small bowel resection, even if extensive
  - “impending “short gut” syndrome
- Contraindication
  - Fistulae/abscesses
  - Carcinoma / possible carcinoma
- Benefit
  - Treatment of outcomes without
    - Loss of bowel
    - ↑ risk of recurrence / re-operation
- Techniques
 

|                                 |                          |
|---------------------------------|--------------------------|
| – Length of stricture (< 10 cm) | ▪ Heineke-Mikulicz       |
| – Intermediate (10 to 15 cm)    | ▪ Finney                 |
| – Long ≥ 15 cm                  | ▪ Michelassi enterostomy |





- Endoscopic balloon dilation (EBD)

#### Recommendation

- Use endoscopic balloon dilation (EBD) of ileocolonic anastomotic strictures
  - < 4 cm
  - No sharp angulation
  - Non-penetrating
- Repeat EBD may be necessary
- There are high rates of
  - Recurrence
    - Complications

(GRADE: weak recommendation, low-quality evidence. Agreement: 94.4%).

- Use for all types of CD strictures, including anastomotic stricture
  - EBD may delay later surgical resection or strictureplasty
    - Systematic review has suggested that 5 yr after EBD, the cumulative rate of surgery is 75%

#### Recommendation

- Treat intra-abdominal abscesses in CD with IV antibiotics plus percutaneous radiological drainage.
- If surgical drainage necessary, avoid doing a surgical, resection at that time.

(GRADE: weak recommendation, very low-quality evidence. Agreement: 91.9%).

- Non-perianal fistulising CD and abscesses

#### Recommendation

- Use anti-TNF therapy to induce / maintain remission in patients with non-perianal fistulizing CD.
- Intra-abdominal abscess
  - Treat sepsis
    - IV antibiotics
    - Nutritional deficiencies, including
      - Exclusive enteral nutrition (EEN)
    - Percutaneous radiological drainage
  - Continue standard medical care
  - Surgery if
    - Above fails, or
    - Presence of free peritonitis

- ↓ risk for need of later surgical drainage / resection
- ↓ stoma rate
- ↓ morbidity



- Fistulae (Enteroenteric, Enterovaginal and enterovesical fistulae)

#### Recommendations

- Fistula closure
  - Medical therapy
    - Rectovaginal 38%
    - Enterovesical 66%
  - Surgical therapy
    - Risk factors (enterovesical fistulae) (for need of surgery)
  - GI
    - Sigmoid colon origin of fistula
    - Small bowel obstruction/fistulization
    - Abscess
  - GU
    - Ureter obstruction
    - Urinary tract infection
  - Indications for surgery
    - Risk factors above
    - Failed medical therapy
      - Non-response
      - Recurrence
- Genital fistulae

| Treatment     | Response |                                                |
|---------------|----------|------------------------------------------------|
|               | Partial  | Complete                                       |
| – Antibiotics | Poor     | Poor                                           |
| – Thiopurines | 24%      | 13%                                            |
| – Anti-TNF    | 30%      | 17%                                            |
| – Surgery     |          | 22% (complete response after > 1 surgery, 39%) |

- Enterocutaneous fistulae (ECF)

#### ➤ Causes/associations

- Acute Crohn disease
- Strictures
- Surgical anastomoses
- Abscess, intra-abdominal
- Limited data to support recommendation
  - Medical therapy for non-operative ECF
  - Post-operative ECF (GETAID), treated with anti-TNF therapy
    - Healing ~1/3, but 1/2 of these recurred over a median of 3 yr
  - Formation of intra-abdominal abscess in 1/3



## Recommendation

- Low volume enterocutaneous fistulae (ECF)
  - Use immunomodulator and biologic
- High volume ECF
  - Surgery

(GRADE: weak recommendation, very low-quality evidence. Agreement: 100%).

## • Perianal Crohn disease

### Recommendation (diagnostic imaging)

- Evaluate fistulising perianal CD with MRI plus EUA (examination under anesthesia) by experienced surgeon, and where available, use endoanal ultrasound (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).
- At EUA, assess rectal mucosa for possible proctitis (proctitis is associated with ↑ risk of patient needing proctectomy (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).
- Pelvic MRI vs. examination under anaesthesia (EUA)
  - Comparative sensitivity of 85%
  - MRI also detected non-fistulizing perianal disease e.g., small abscesses
- EUS may detect anal ulceration / setons
  - Permits drainage of abscess and insertion of setons
- Endoanal ultrasound (EUS)
  - Overall comparative sensitivity, but
  - More sensitive than MRI
- Optimal assessment
  - Perform 2 tests (EUA, EUS, MRI)

## ➤ Treatment

### Recommendation

- Place setons to ↓ risk of reaccumulation of perianal sepsis in fistulising CD (GRADE: strong recommendation, high-quality evidence. Agreement: 100%) (unknown when the optimal time to remove setons (Agreement: 97.1%).
- Seton placement plus anti-TNF
- Do **not** routinely place a seton in patient with rectovaginal fistulae
  - Unless there is an abscess.
  - Remove setons after 5 infusions of infliximab (allows healing of fistula where seton was placed)



- Anti-TNF therapy

#### Recommendations

- Use infliximab for first-line biological therapy for complex perianal fistulae.
  - Start infliximab immediately after achieving “adequate drainage of sepsis” (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).
- Infliximab induction therapy, 5 mg/kg (or 10 mg/kg)
  - Complete fistula closure in 55% (38%) vs. placebo, 13% (Accent I)
  - Fistula closure at
    - 14 wk, 69% (Accent II)
    - 54 wk, 36% vs. 19% (P=0.009, Accent II)
- Adalimumab (secondary endpoint, closing perianal / abdominal fistulae)
  - Complete fistula closure wk 56, 33% vs. placebo 13% (P=0.016)
  - Combining adalimumab plus ciprofloxacin resulted in a 53% wk 24 (↑ speed but not the longer term rate of healing)

- Miscellaneous

- The role of vedolizumab and ustekinumab in perianal CD remains to be established.
- Adipocyte-derived stem cell therapy (darvadstrocel) injected into the CD tissue had a modest benefit vs. placebo for perianal disease, and further studies are awaited.

#### Recommendation

- Surgical fecal stream with formation of a defunctioning stoma improves symptoms of perianal CD in 2/3 of patients, but
  - Early after the diversion of stool, CD inflammation may remain in the pelvis plus in the defunctional bowel (initially was improved)
  - When the bowel continuity is restored, perianal disease recurs in 83%
    - The rate of successful reversal is reduced if there is rectal involvement

- Surgery

#### Recommendation

- Surgical options for perianal Crohn fistulae (advancement flap, LIFT [ligation of intersphincter tract], infill procedures) should be offered in selected patients after counselling as long-term results are poor, particularly for those with complex disease and ongoing disease activity (Agreement 97%)
- Proctectomy more likely required if there is rectal disease (29%) than if there is no rectal disease (4%)



- Post-surgical management of CD

- Post-surgical recurrence

|              | 1 yr | 3 yr |
|--------------|------|------|
| - Endoscopic | 73%  |      |
| - Clinical   | 20%  | ~50% |

Clinical Gem

- Endoscopic evidence of ICD after ileocolonic resection for CD predicts CD recurrence and future symptoms/complications.

Recommendation

- The patient with symptoms suggestive of a recurrence after ileocolonic resection for CD must first be assessed for recurrent mucosal inflammation, using ileocolonoscopy (ICS).
    - If not this is possible, use
      - Cross-sectional imaging MRE +/-
      - Fecal calprotectin

(GRADE: weak recommendation, low-quality evidence. Agreement: 97%).

➤ Diagnosis

- Imaging
    - MRE, SBUS, endoscopy (biopsy, and calculate Rutgeerts score)
  - Laboratory
    - fCal (fecal calprotectin > 100 µg/g stool) predictive value to differentiate endoscopic relapse vs. remission (TOPPIC study)
    - Performance characteristics
      - Sensitivity, 95%
      - Specificity, 54%
      - Overall accuracy, 77%
      - Negative predictive value (NPV), 69%
      - Positive predictive value 93%

- Other causes of post-surgical symptoms

Recommendation

- Recurrent symptoms often ileocolonic resection, which are not due to CD recurrence of inflammation.
    - Consider other diagnose such as bile salt malabsorption, small intestinal bacterial overgrowth syndrome, or other conditions



- Related to CD
  - Bile salt malabsorption
  - Small intestinal bacterial overgrowth (SIBO)
  - Lymphoma / adenocarcinoma
  - Short gut syndrome
  - Anastomotic strictures
- Small bowel
  - Unmasked celiac disease
- Colon
  - Irritable bowel syndrome
- The patient with symptoms after ileocolonic resection for CD where inflammation has been excluded, give a therapeutic trial of a bile acid sequestrant (cholestyramine or colesevelam (GRADE: strong recommendation, moderate-quality evidence)
  - If the empirical trial of bile acid sequestrants is not effective or if the diagnosis is unclear, consider a Se-HCAT scan (Agreement 97%)

➤ Differential diagnosis

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- Give the laparoscopic surgical complication other than anastomotic strictures following post ileocolonic resection in patients with Crohn disease.
  - Laparoscopic surgical resection may result in hernia developing in the surgical site, not usually causing symptoms from intermittent intestinal obstruction.

- Bile salt induced diarrhea can be investigated with
  - SeHCAT
  - Stool bile acid measurements
  - Blood measurement of
    - ↓ fibroblast growth factor -19 (FGF-19)
    - ↑ C4 (7-alpha hydroxycholestenone)
    - 14-C-glycine breath test.
  - Consider using empiric trial of bile acid sequestrant



- Smoking cessation
  - Smoking doubles the CD patient having a clinical/endoscopic recurrence of CD after an ileocolonic resection.

#### Recommendation

- All CD patients who are smokers to completely avoid all tobacco products (GRADE: strong recommendation, moderate-quality evidence. Agreement: 100%).
- Post-surgical follow-up and assessment for recurrence of CD and possible benefit of prophylactic maintenance therapy.
  - Assessment of symptoms of active CD is not adequate to predict the rescue of active disease.
    - Remember that the CD can be active and endoscopically present long before the patient becomes symptomatic.
  - Endoscopic recurrence of CD is present in 73% of CD patients having had ileocolonic resection of all inflammatory disease.
    - Only 1/3 these patients with endoscopic recurrence have symptoms

#### ➤ Risk factors for CD recurrence after surgery

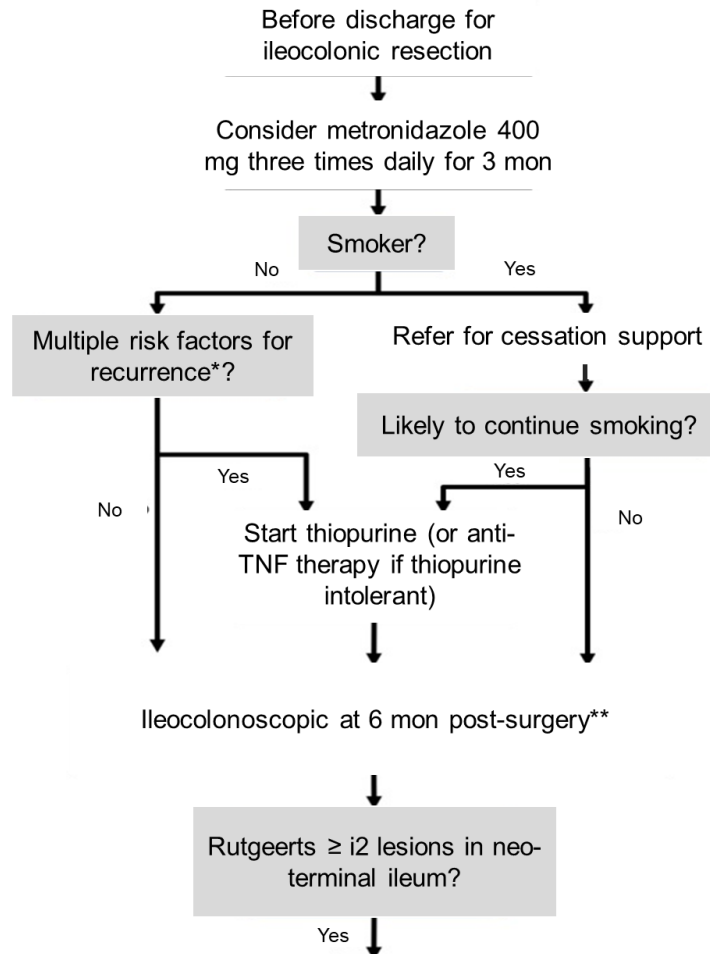
- Pre-surgery
  - Patient
    - Smoker
    - Active disease
      - The main predictive factor for recurrent CD in the neo-terminal ileum after ileocelectomy is preoperative disease activity.
  - Bowel
    - Abscess/fistulae/perianal disease
    - Length > 50 cm
- Post-surgery
  - Histopathology
    - Proximal section margin containing active CD
    - Resection specimen showing granulomas
    - Myenteric plexitis
  - ↑ Rutgeerts score

#### Recommendations

- At 6 mon following ileocolonic resection for CD, perform ileocolonoscopy
  - To access the neoterminal ileum for endoscopic evidence of CD (Rutgeerts scale), and
  - To consider treatment / preventive measures before development of symptoms
  - MRE is used if ileocolonoscopy not possible (Agreement: 89%)



- Medical prophylaxis after ileocolonic resection for Crohn disease



Escalate immuno-suppressive therapy by one step:  
Nil → thiopurine → anti-TNF therapy → high-dose anti-TNF therapy

\*Risk factors for recurrence (two or more of):

- Smoking
- Penetrating disease
- Multiple resections
- Perianal fistulae
- Extensive small bowel disease
- Residual active disease
- Granulomas or myenteric plexitis

\*\* If not possible consider cross-sectional imaging or fecal calprotectin as alternative

Printed with permission: Lamb CT, et al. Gut 2019; S1-S106 (Figure 3)





## Recommendation

- Use thiopurines to ↓ CD recurrence after ileocolonic resection, starting immediately post-surgery if “significant risk factors for recurrent CD, or
    - At 6 mon post-surgery ileocolonoscopy (or MRE/fCal if ICS not possible), and
      - If endoscopic recurrence (Rutgeerts ≥ 2 lesions in neoterminal ileum) (GRADE: weak recommendation, low-quality evidence).
    - If the anastomosis is not within reach of endoscopic examination, then cross-sectional imaging with MR enterogram may be performed (Agreement: 89.2%).
    - Do **not** use 5-ASA for prevention of CD recurrence after IC surgery (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.2%).
- Start  
thiopurine  
or anti-TNF  
therapy
- Immunosuppression
    - Use azathioprine to ↓ risk of clinical/endoscopic relapse of CD after ileocolonic resection, both in smokers and in non-smokers (TOPPIC trial; Cochrane review)
  - Anti-TNF therapy
    - Both infliximab and adalimumab ↓ risk of endoscopic +/- clinical relapse
    - Infliximab vs. placebo remission at 3 yr 93% vs. 56%
      - Persons in clinical/endoscopic remission who are maintained on IFX for 2 yr post-surgery, if relapse occurs when IFX is stopped, then retreatment on low dose IFX (3 mg/kg q8wk) will result in return to remission in 100%
    - Relapse post-operatively is higher in CD patients who have been on multiple anti-TNF drugs in the past.
    - The 2-yr clinical and endoscopic recurrence is much lower in CD patients who are maintained on adalimumab or azathioprine, as compared to those maintained on 5-ASA.
  - 5-ASA; antibiotics
    - 5-ASA produce a very modest reduction in clinical/endoscopic recurrence, as compared with immunosuppressants/biologics.
    - Metronidazole (400 mg po t.i.d.) maintains remission for 3 mon but not longer, and 23% of CD patients had to stop the antibiotic because of side effects.



- The role of colonoscopy (or MRE if not tolerate) 6 mon after ileocelectomy for CD.
  - In the POCER trial of CD patients with ileocolonic resection, a management plan was developed based upon the patient's smoking habits and their other risk factors ( $\geq 2$ ) for recurrence.
    - Patient
      - Smoker
    - Disease
      - Extensive
      - Residual active
      - Penetrating
      - Fistulizing, perianal
    - Surgery
      - Multiple resections
      - Extensive small bowel disease
    - Histopathology
      - Granulomas
      - Myenteric plexitis
  - Metronidazole, 3 mon post-op  
 High risk group → thiopurines adalimumab (if intolerant to thiopurines) → 6 mon ICS/MRE  
 → thiopurine  
 → adalimumab  
 → adalimumab plus thiopurine

| Treatment        | Clinical       | Endoscopic     |
|------------------|----------------|----------------|
| - Active therapy | 27%            | 49%            |
| - Standard care  | 40% (P = 0.08) | 67% (P = 0.03) |



## Recommendations for Patients with Surgically Induced Remission of Crohn Disease (CD)

Nguyen GC, et al. Gastroenterology 2017; 152: 271-5

Nguyen GC, et al. Gastroenterology 2014; 146: 835-848

### ❖ Early Post-operative Therapy

#### Recommendations

- Use early post-operative anti-TNF $\alpha$  therapy +/- thiopurines (Conditional recommendation, moderate quality of evidence)
  - May use nitroimidazole for 3-12 mon
  - Do **not** use mesalamine, budesonide, or probiotics (Conditional recommendation, low quality of evidence and very low quality of evidence)
- Perform post-operative endoscopic monitoring (patient even in asymptomatic patients) at 6-12 mon after surgical resection, regardless of whether patient is taking pharmacotherapy (Conditional recommendation, moderate quality of evidence)
  - If post-surgical endoscopic monitoring in an asymptomatic patient shows endoscopic recurrence → initiated/optimize anti-TNF $\alpha$  +/- thiopurine (Conditional recommendation, moderate quality of evidence)

### ❖ Prophylaxis of Venothrombosis of Patients with IBD (Crohn disease, ulcerative colitis)

#### Recommendations

- Risk of venous thrombosis
  - Overall 3x ↑ risk in patients with IBD (GRADE: low-quality evidence. Vote: agree strongly, 92%; agree with minor reservations 8%)
    - Risk in hospital ↑6x (GRADE: low-quality evidence)
    - ↑ risk with active IBD > in remission (GRADE: low-quality evidence. Vote: agree strongly 92%; agree with minor reservations, 8%)
- Prophylaxis of VTE
  - Outpatients
    - No previous VTE → no anti-coagulation (AC) required
      - IBD flare (GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly, 92%; agree with minor reservations, 8%)
    - Previous VTE → AC (unless previous VTE related to major surgery)
  - Inpatients
    - Admission not related to IBD → AC (even if IBD remission) (GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly, 62%; agree with minor reservations 38%)
    - Admission related to IBD (IBD flare moderate-severe) → unfractionated heparin (uFH) / low molecular weight heparin (LMWH) / fondaparinux
  - GI bleeding related to IBD
    - Non-severe → AC (GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly, 92%; agree with minor reservations, 8%)
    - Severe mechanical thromboprophylaxis (GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly, 62%; agree with minor reservations, 38%)
    - Severe, becomes non-severe IPC → AC (GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly, 100%)



- Major surgery (general abdomen-pelvic → AC (GRADE: Strong recommendation, moderate-quality evidence. Vote: agree strongly, 100%)
  - Cesarean section (GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly, 84%; agree with minor reservations, 8%)

## ❖ Treatment

### Recommendations

- IBD in remission
  - First VTE
    - No provoking factor → AC maintenance with periodic review (GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly, 77%; agree with minor reservations, 23%)
    - First VTE, IBD in remission, with provoking factor → AC for either 3 mon, or 1 mon after risk factor (active IBD) has resolved
      - No need to test for another hypercoagulable state (inherited, acquired) (GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 77%; agree with minor reservations, 23%)
    - Active IBD → AC for 3 mon after risk factor (active IBD) has resolved
- First venothrombotic event (VTE)
  - Inactive IBD
    - Unrelated provoking factor
      - AC for 3 mon, and until risk factor resolved for at least 1 mon (GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly, 62%; agree with minor reservations, 38%)
      - AC until IBD in remission for 3 mon (GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly, 62%; agree with minor reservations, 38%)
  - Active IBD
- Symptomatic acute thrombosis of portal vein (PV), splenic vein (SV), mesenteric vein (MV)
  - Inactive IBD
    - Unrelated provoking factor AC for 3 mon and until risk factor resolved for 1 mon (GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly, 92%; agree with minor reservations, 8%)
  - Inactive
    - No other provoking factor – AC for life, periodic review (GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly, 85%; agree with minor reservations, 15%)
  - Active IBD
    - AC until IBD in remission for 3 mon (GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly, 85%; agree with minor reservations, 15%)
- Asymptomatic
  - IBD inactive
    - No AC (GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly, 62%; agree with minor reservations, 38%)



## Perianal Fistulizing Crohn Disease: Toronto Consensus (2018)

Steinhart AH, et al. J Can Assoc Gastroenterol 2018; 1(4):141-154

### ➤ Classifications

- Complicated fistulizing CD
  - Active rectal CD/ anal stenosis plus fistula
    - Multiple/branching fistula
    - Rectovaginal fistula
- Parks
  - Inter-
  - Trans-
  - Supra-
  - Extra-

}

  - Sphincteric
- Van Assche score of fistular activity

### ➤ Demography

- ~25% of persons with CD develop fistulas
  - Of these, ~70% require surgical treatment

### ❖ High-risk factors (for aggressive/complex CD)

- The low-risk patient with CD lacks these factors.

- Patient
  - Young
  - Smoker
  - Long duration of CD
  - Early use of corticosteroids
- Disease
  - Fistulizing perianal CD
  - Extensive involvement of luminal disease
  - Deep ulcers
- Laboratory
  - ↓ albumin, ↓ hemoglobin, ↑ C-reactive protein (CRP)
  - ↑ fecal calprotectin (fCal)

### ❖ Anatomy

- MRI, EUS, DRE/EUA but **not** CT are recommended in patients with CD suspected as having perianal disease (CT has false negative rate of 50%)
- Closure of a fistula should be established by MRI/EUA
  - If these diagnostic imaging methods are not available, then use EUS/DRE unless there are
    - Complications
    - Need for fecal diversion/proctectomy



- Accuracy for classification of fistulas
  - EUS, MRI, EUA comparable, > 85%
  - Use any combination of the two of these, and accuracy is ~100%

#### Recommendation

- When there is suspicion of perianal disease in a patient with CD
  - Do MRI/EUS (depending upon availability/expertise)
 GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 62%; agree, 38%

#### ➤ Investigation

- Signs/symptoms of active fistulizing (CD)
  - Perform EUS or MRI (depending upon local expertise/availability)
 (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 62%; agree, 38%)

#### ➤ Diagnostic Imaging

- Complications: perianal abscess, anal stenosis
  - MRI
  - EUS
- To document closure of fistula
- Perform EUS/MRI to define the anatomy in all patients with CD who are suspected to have active fistulizing disease.
  - CT has poor performance characteristics in this setting (50% false negative)

#### ➤ Surgical referral

- Refer patients with fistulizing CD for a surgical consultation (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 67%; agree, 29%; uncertain, 5%)
  - In the 25% of CD patients who develop perianal fistula
    - ~70% require surgery
      - Abscess drainage
      - Fistulotomy/fistulectomy
      - Seton placement

#### • Importance of Surgical Consultation

- On average, medical therapy (antibodies, ATNF, immunosuppressants) will close fistula in ~50% in 6 mon



- For those failing medical therapy, surgery may be very helpful

| Procedure                                  | Success Rate |
|--------------------------------------------|--------------|
| – Anal plug                                | ~60%         |
| – Fecal diversion                          | ~64%         |
| – Proctectomy after failed fecal diversion | ~40%         |

#### Recommendation

- Refer patient with fistulizing CD to surgery early after inadequate medical therapy (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 57%; agree, 43%)
- On the horizon
  - Allergenic-derived mesenchymal stem cells (ASC)
  - Tacrolimus
  - Hyperbaric oxygen therapy (HBOT)

#### ❖ Complicated/complex

- Management of complex, complicated fistulizing disease in a patient with CD is best achieved using both medical and surgical approaches.
  - The combined approach is superior to any one drug
  - Consult a colorectal surgeon, if available

#### Recommendation

- Involve an expert experienced surgeon in the care of the patient with complicated fistulizing CD (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 67%; agree, 29%; uncertain, 5%)

#### ➤ Treatment

#### ❖ Pharmacotherapy for symptom response

- Antibiotics, initial therapy
  - Ciprofloxacin or metronidazole (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 48%; agree, 48%; uncertain, 5%)
    - ↓ fistula drainage RR, 0.80; 95% CI, .66 – .98)
    - Ciprofloxacin monotherapy > 50% ↓ number of fistulae
      - Cipro plus adalimumab vs. only adalimumab
        - Closure of all draining fistula at wk 12, 65% vs. 33%; P = 0.009
      - Treatment benefit of ADA plus antibiotic lost at 18-24 wk



- Antibiotics
  - In patients with perianal CD
    - Use either ciprofloxacin or metronidazole for 4 to 12 wk
      - ↓ outcome failure to reduce fistula drainage (RR, 0.80; 95% CI, 0.66-0.98)
    - After the course of antibiotics has been stopped
      - Most fistula with drainage recur

#### Recommendation

- Use antibodies for short-term ↓ symptoms from perianal CD (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 48%; agree, 48%; uncertain, 5%)
- Anti-TNF therapy
  - Indication (healing; IFX)
    - ≤ 4 wk (RR, 0.62; 95% CI, 0.48 – 0.81)
    - ≥ 4 wk (RR, 0.80; 95% CI, 0.65 – 0.98)
 (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 67%)
- ATNF alone, indication
  - Infliximab for closure of perianal fistula is effective (RR, 0.62; 95% CI: 0.48-0.81)
    - However, a mixture of trial results, and "...a systematic review of 6 trials reported no significant effect of anti-TNF therapy [IFX, ADA] for the outcome of failure to heal fistulizing disease (RR, 0.88; CI 0.66-1.11)

#### Recommendations

- Despite the heterogenous and variable results, the authors of the guideline recommend that ATNF be used to achieve symptom response in patients with perianal CD (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 67%).
- When starting ATNF therapy, use combination therapy of ATNF plus thiopurine or methotrexate (GRADE: Conditional recommendation, low-quality evidence for infliximab; very low-quality evidence for adalimumab. Vote: strongly agree, 5%; agree, 81%; uncertain, 5%; disagree, 10%)
- Maintenance of remission (IFX or ADA)
  - Loss of response at wk 54
    - IFX, 42%, placebo, 62% ( $P < 0.001$ )
  - Complete absence of drainage, 36%; vs. PL, 19% ( $P \geq 0.009$ )
  - Fistula closure at wk 56
    - ADA, 33%; PL 13% ( $P = 0.040$ )
 (GRADE: Conditional recommendation, low-quality evidence. Vote: strongly agree, 52%; agree, 38%; uncertain, 5%; disagree, 5%)





- ATNF maintenance
  - Infliximab, ACCENT, 54 wk
    - Responders to IFX
      - Lose response (vs placebo) 42% vs. 62% ( $P < 0.001$ )
      - Complete absence of drainage 36% vs. 19% ( $P = .009$ )
  - Adalimumab (ADA), CHARM, wk 56 responders to ADA
    - Closure, ADA vs. placebo 33% vs. 13%
  - In persons who have perianal CD in whom it is planned to stop ATNF therapy, first perform MRI/EUS to determine if there has been healing of the fistulas.
  - In those persons with perianal CD who respond to ATNF therapy, first perform MRI/EUS to determine if there has been healing of the fistulae.

## Recommendations

- Dual anti-TNF
  - Combine maintenance therapy of IFX/ADA with thiopurine/methotrexate (GRADE: Conditional recommendation, very low-quality evidence for adalimumab. Vote: strongly agree, 5%; agree, 81%; uncertain, 5%; disagree, 10%)
  - Note that there is a paucity of trial data to support this statement
    - The possible benefit is extrapolated from data on the benefit of combination therapy in luminal CD
- Inadequate response to pharmacotherapy (medically refractory)
  - Refer for surgical management (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 57%; agree, 43%)
  - Surgical therapy provides a good rate of success: successful closure (all procedures) ~53% at 6 mon
  - Anal plug, 32%
  - Seton removal, 25% ( $P = 0.19$ )
- In patients with fistulizing CD who are initiated on ATNF, use combination therapy with methotrexate (GRADE: Conditional recommendation, low-quality evidence for infliximab; very low-quality evidence for adalimumab. Vote: strongly agree, 5%; agree, 81%; uncertain, 5%; disagree, 10%)

Abbreviations: ADA, adalimumab; ATNF, anti- tumour necrosis factor; CD, Crohn disease; CI, confidence interval; ERAF, endorectal advancement flap; EUA, examination under anaesthesia; EUS, endoscopic ultrasound; IFX, infliximab; MAF, mucosal advancement flap; MRI, magnetic resonance imaging; MTX, methotrexate; TNF, tumour necrosis factor; wk, week

- Complicated fistulization
  - Obtain surgical consultation (colorectal surgeon)
  - Medicosurgical term is optimal
    - Rate of fistula healing
      - Medical 43%
      - Medical plus surgical, 53%



- Antibiotics
  - Ciprofloxacin
  - Metronidazole
- > 50% ↓ number of fistulae (RR, 1.64; 95%CI, 1.16 to 2.32; P = 0.005)
  - 4 to 8 wk to ↓ drainage
- Conditional consensus suggestion "...antibiotics may be useful as an initial management strategy to
  - ↓ drainage
  - Prevent abscess formation
  - Bridge to a more definitive [surgical] treatment strategy
- Use anti-TNF therapy to improve symptomatic response
  - If symptomatic response to anti-TNF, continue anti-TNF to achieve and to maintain remission
    - Combine anti-TNF with azathioprine and methotrexate
- Anti-TNF
  - Ciprofloxacin plus adalimumab is superior to adalimumab monotherapy to close all drainage fistula (symptomatic remission) at wk 12 (65% vs. 33%; P = 0.009)
    - **No** long term benefits
- Modest benefit: the data are mixed, with 6 trials showing benefit, and 2 showing no benefit
  - Healing of fistulas with infliximab: RR, 0.62; 95% CI, 0.48 to 0.81
  - Treatment for > 4 wk: RR, 0.80; 95%CI, 0.65 to 0.98
  - Certolizumab **not** recommended because of lack of response
- While continued maintenance therapy is recommended after an initial response to anti-TNF, if stopping therapy is being considered.
  - Perform MRI imaging before stopping anti-TNF therapy
- Combination therapy
 

|                                                                                      |   |                                            |   |            |   |                                                                          |
|--------------------------------------------------------------------------------------|---|--------------------------------------------|---|------------|---|--------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>- Infliximab</li> <li>- Adalimumab</li> </ul> | } | Plus azathioprine, 3 yr<br>response rates: | } | 66%<br>43% | } | ▪ Recommendation based upon good long-term response rates in IBD overall |
|--------------------------------------------------------------------------------------|---|--------------------------------------------|---|------------|---|--------------------------------------------------------------------------|
- Surgical consultation recommended early as part of the treatment plan
  - Continue the team approach so that if medical therapy fails to provide adequate symptomatic response, surgical management may be considered/reconsidered.
- If patient with CD → perianal fistulas requiring
  - Surgery 70%
  - Bowel resection ~30%



## Therapeutic Drug Monitoring (TDM) in Patients with Crohn Disease Treated with Anti-TNF therapy or with Thiopurines

Vande Casteele N, et al. Gastroenterology 2017; 153: 835-857.

### ➤ Definition

- TDM "...measuring serum drug concentration (typically at trough) and anti-drug antibodies (ADABs)" with a view to help to "...evaluate potential reasons for failure of therapy and define next steps in management" to optimize therapy.

### ❖ Biologics (anti-tumour necrosis factor [ATNF])

### ➤ Pharmacology

- Biologics are monoclonal antibodies, "...protein-based drugs that can bind to an antigen with great specificity and possesses powerful effector functions"
  - Metabolism
    - Receptor mediated endocytosis into cells of the reticuloendothelial system → proteolytic metabolism
- The body recognizes the therapeutic proteins as "non-self", and produce a humoral or cell-mediated immune response → ADAB
  - blocking the binding site of the biologic, or
  - forming complexes (Drug-ADABs) → ↑ clearance
- The response to the biologic is determined by its concentration at the site of its receptor, so that the therapeutic response is influenced by concentration of the biologic and to ADAB.

### ❖ Active IBD

- In patients with active CD treated with anti-TNF therapy, reactive therapeutic drug monitoring TDM may be clinically useful in response to new / or maintenance treatment changes.
  - Maintenance therapy with anti-TNF then, development of CD symptoms (secondary loss of response) TDM vs. non-TDM clinical remission in ~40% vs. 30% (RR, 0.78; 95% CI: 0.40-151)
- Types of failure
  - Mechanistic failure of switching from anti-TNF (ATNF) to non-TNF pathways (failure of ATNF)
    - ATNF, ADAB+/-
  - Pharmacokinetic (↓ ATNF)
    - Non-immune mediated ADAB-
    - Immune mediated ADAB+



- “Switching” options
  - Within class, same mechanism of action (MOA), or
  - Outside of class different MOA
- ATNF, ADAb+/-
- Dose escalation
  - ↓ ATNF, ADAb-, or
  - ↓ ATNF, low level ADAb+

Abbreviations: PK, pharmacokinetic, ATNF, anti-tumour necrosis factor dose escalation

- Challenges
  - Ideal concentration of ATNF not well-defined and varies
    - Induction vs. maintenance
    - Remission symptoms or endoscopy
    - Severe vs. mild disease activity
    - Lumen vs. perianal disease
    - UC or CD
  - Lack of response might not be related to drug, but to non-inflammatory complications
    - Strictures
    - Associated
      - Irritable bowel syndrome (IBS)
      - Small intestinal bacterial overgrowth (SIBO)
      - Bile acid diarrhea (BAD) / Bile acid malabsorption (BAM)
- Maintenance therapy

| Trough ATNF    | Trough<br>Concentration<br>Threshold |                                              |
|----------------|--------------------------------------|----------------------------------------------|
| – Infliximab   | ≥ 5                                  | } ▪ Values may be different for<br>UC vs. CD |
| – Adalimumab   | ≥ 7                                  |                                              |
| – Certolizumab | ≥ 20                                 |                                              |

- These trough concentration thresholds apply to most IBD patients for ATNF maintenance therapy, but
  - As noted above, dose escalation may be useful for some, e.g.,
    - ↓ ATNF, ADAb-, or
    - ↓ ATNF, ADAb+, but low level
  - Note that in CD patients with positive antibodies [ADAb] to infliximab (ATI), the antibodies were transient in 25%



- Thioguanines
  - Genetic polymorphisms > 25
    - 4 alleles account for ~90% of this variability
  - Thiopurine methyltransferase (TPMT)

| Activity       | TPMT Phenotype | % of population |                             |
|----------------|----------------|-----------------|-----------------------------|
| – Intermediate | ▪ Heterozygous | 4% to 11%       | OR, 4.3; 95% CI: 2.7-6.9    |
| – Low/absent   | ▪ Homozygous   | 0.3% (~1/300)   | OR, 20.8; 95% CI: 3.4-126.9 |

- Some guidelines recommend that all patients with IBD who will be placed on azathioprine / 6-MP must first have TPMT testing, if available.

#### Clinical Gem

- “Blood transfusion in a 3-mon interval before TPMT phenotyping might yield unreliable results.”

#### Recommendation

- Homozygous for TPMT (↓↓ activity)
  - Do **not** use thioguanines
- Heterozygous for TPMT (↓ activity)
  - Start azathioprine (AZA), 1 mg/kg per day, or 6-mercaptopurine (6-MP) 0.5 mg/kg per day
- Wild type (normal TPMT activity), start AZA 2.0-2.5 mg/kg per day, or 6-MP, 1-1.5 mg/kg per day
- Regardless of patient's TPMT status
  - Scheduled intensive testing of peripheral blood white blood cell count (WBC) must be performed, and where falling WBC, undertake immediate ↓ dose / discontinuation of AZA/ 6-MP.



❖ A Word or Two from the Experts

- "...the quality of evidence supporting routine TPMT testing to guide thiopurine dosing was deemed low based on RCTs."
- "Given the low prevalence of heterozygous and homozygous TPMT genotypes, the [low] benefit of routine TPMT testing is likely to be very small"
- Even if TPMT is normal, intensive surveillance of WBC is necessary
- "However, there is minimal risk to perform the test and it neither increases nor alleviates the potential burden of routine laboratory monitoring needed for patients treated with thiopurines."

- Author's suggestion
  - If the TPMT test is available, use it because some guidelines suggest you do so
  - Doing so may make life easier for you if there is a medicological issue.

• TDM with measurement of RBC 6-TGN concentration

- When patients with CD are treated with thiopurines, it is possible to measure the concentration of 6-thioguanine (6-TGN) in their red blood cells.
- The target level has been suggested to be  $> 230 \text{ pmol} / 5 \times 10^8 \text{ RBCs}$ , but this cut-off value is disputed
  - This uncertainty applies as well to the use of thiopurines in either CD or UC

Suggestion

- While there is only very low-quality evidence, in some patients with IBD who are treated with weight-based doses of thiopurines, there may be a role for TDM using RBC concentration of 6-TGN.



## DIAGNOSTIC PROCEDURE

### Quality Indicators for Small Bowel Capsule Endoscopy (CE) and Deep Enteroscopy (DE)

Leighton JA, et al. Am J Gastroenterol 2022; 117: 1780-1796.

- Guidelines have been published, providing “specific criteria for training, required stents, and granting of clinical privileges to perform CE and DE” (Spada C, et al. Endoscopy 2019; S1: 574-598; Faulx AL, et al. Gastrointest Endoscopy 2017; 85: 273-281; and Faigel DO, et al. Gastrointest Endosc 2005; 61: 503-505) (ASGE Guideline)
- Recommendation for quality indicators include
- These recommendations have been updated and include
  - Structural measures                      ■ Healthcare environment
  - Process measures                        ■ Care at the time of delivery
  - Outcome measures                      ■ Results of care
- These recommendations have been updated and include new data and new considerations.

#### ➤ Capsule endoscopy (CE)

❖ Preprocedure (performance target are represented as a recommended percentage [%])

\*Type of measure

- Process
  - Demonstrating competence in CE, 100%
  - CE for an indication that is documented in a published, standard test of appropriate indicators, 90%
    - Indications (ASGE and ESGE Indications for CE)
      - Obscure GI bleeding / suspected small bowel bleeding
      - Iron-deficiency anemia
      - Crohn disease, suspected/known
      - Celiac disease, complicated/refractory
      - Polyposis syndromes, inherited\*
      - Small bowel imaging, abnormal

\*Familial adenomatous polyposis, Peutz-Jeghers syndrome

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; ESGE, European Society for Gastrointestinal Endoscopy



➤ Contraindications

- Absolute

- Suspected/known
  - Obstruction
  - Stenosis, unless surgery is planned
  - Known perforation
- Swallowing difficulty (dysphagia)
  - Including
    - Eosinophilic esophagitis
    - Achalasia
    - Scleroderma esophagus
    - Altered mental status
    - Neuromuscular disease of pharynx, esophagus, stomach
- Gastric motility disorders
- Zenker diverticulum

- Relative

- Pregnancy
  - Cardiac devices, implanted
    - Defibrillators
    - Pacemakers
    - Left-ventricular assist devices
- } Very low risk

- Use a test luminal potency before CE in patients with ↑ risk of CE retention, 90%

➤ Definition of CE retention

- Capsule remaining in intestine for  $\geq 2$  wk
- Frequency
  - Overall, 2%
  - Known Crohn disease, 5%
- Oral ingestion of the capsule may be safely performed
- Options
  - Patency capsule (PC, parylene coating, dissolves within 30 h in GI tract
  - Prediction of safe passage of CE
    - Sensitivity, 97%
    - Specificity, 83%
  - Follow up of PC
    - CT, MRE in < 30 h after ingestion of PC





SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Diaphragmatic strictures are caused by intake of NSAIDs
  - Give the optimal imaging methods for these.
    - Patency capsule, no CE, CT, or MRE
- Performing CE in a timely manner after an episode of overt, suspected small bowel bleeding (90% performance target)
  - For patients with suspected small bowel bleeding, admit to hospital and perform CE within 48 h to
    - Achieve diagnosis within 90%
    - To decrease risk of
      - Repeat hospitalization
      - Morbidity
      - Mortality
- ❖ During procedure
  - Performing endoscopic capsule placement for patients with contraindications to swallow the capsule, or for patients at risk of gastric retention, 80%
- ❖ Post-procedure
  - Perform photo documentation and document\* small bowel transit time (SBTT), 80%
    - Take a systemic approach to identify anatomic landmarks
      - Duodenum
      - Cecum/stoma

} ▪ Determine SBTT
    - Perform SBTT, determine approach for deep enterostomy (DE) of lesion on a time-based index
      - First 60% of SBTT antigrade (po\_ → maximal insertion length of 240-360 cm
      - ≥ 75% retrograde (PR; PPV, 95%; NPV, 97%) → maximum insertion length of 102-180 cm
      - Total enterostomy (600 cm of small bowel) in ~45 to 86%
    - Recommend an appropriate management plan, based upon the findings of CE, 80%
- \*method for video interpretation of CE, 80%
  - Global assessment
  - Video reading time < 20 frames/sec (use shover speed in jejunum to ↓ risk of missing lesions)
  - Do **not** use automated software algorithms (not yet technically reliable)



- Document completeness and adequacy of visualization of the mucosa (ideally, 95%)
  - SBTT  $\geq 2$  h
  - Adequacy of bowel preparation
- Document CE complications and adequacy of visualization of the mucosa, 95%
  - Record timing of complications and action taken
- Record when patient requires abdominal radiography after CE determine if CE is retained (not completed), 90%
  - Indications to assess passage of CE
    - Asymptomatic, but capsule not seen in cecum or in feces
    - Symptomatic, suspected
      - Obstruction
      - Perforation
  - When to do diagnostic imaging
    - At time of onset of symptoms → urgently remove capsule by endoscopy/surgery
    - If capsule still retained at 2 wk (capsule not seen in cecum at time of procedure, or in stool within 2 wk)
  - Complete a report in the electronic health report, 98%
- Deep Enterostomy (DE)
- ❖ Preprocedure
- Demonstrate competency in DE, 100%
  - Learning procedures required
    - At least 30, probably
    - For spiral enteroscopy
      - At least 5 procedures
- Indication
  - The basic indication for DE is to confirm risk and abnormal CE, CT, MRE diagnose (biopsy) highly suspected lesion when CE is unexpectedly normal



- Give examples of CE findings which may be interpreted differently on BE.

| CE                                                                                                                                                                                                                                                                                                                                                                   | BE                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>○ Vascular lesions</li> <li>○ Thick folds</li> <li>○ Mass/polyp</li> </ul>                                                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>- Redness of mucosa</li> <li>- Prominent veins</li> <li>- Poor distention of bowel with contrast</li> <li>- Normal anatomy <ul style="list-style-type: none"> <li>▪ Pylorus</li> <li>▪ Ampulla of Vater</li> <li>▪ Ileocecal valve</li> <li>▪ Intestinal folds</li> </ul> </li> </ul> |
| <ul style="list-style-type: none"> <li>○ Other indications <ul style="list-style-type: none"> <li>- Celiac disease</li> <li>- Crohn disease</li> <li>- ERCP when anatomy altered</li> <li>- Foreign bodies</li> <li>- Masses/polyps</li> <li>- Percutaneous endoscopic jejunostomy (PEJ)</li> <li>- Small bowel bleeding</li> <li>- Stricture</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>▪ Removal</li> <li>▪ Biopsy/removal</li> <li>▪ Endoscopic hemostatic therapy</li> <li>▪ Dilation</li> </ul>                                                                                                                                                                           |

- Review CE/CTE/MRE before DE (ideally 80%)
- Discuss the management of anticoagulation with the patient, and document which approach taken (ideally 90%)
  - Therapeutic DE considered high risk
    - Risk of bleeding after DE
      - Overall, 0.2%
      - After polypectomy, 3%
  - No published guidelines for stopping anticoagulants before therapeutic DE, but it is suggested that for
    - ASA/NSAIDs
      - Continue
    - Anticoagulants / other antiplatelets
      - Stop before therapeutic DE
- Document the choice of the method of intubation of DE, based on SBTT or as cross-sectional imaging (ideally 95%)
- ❖ During procedure
- Perform DE in a timely manner (ideally 90%)
  - Perform DE within 72 h after ongoing / suspected small bowel bleeding (perform CE within 24 h) in order to maximize diagnostic yield



- Is intestinal insufflation with CO<sub>2</sub> when performing DE, 90%
  - CO<sub>2</sub> insufflation → ↑ depth of penetration
  - ↓ patient discomfort
- Estimate the depth of insertion / advancement of DE, 90%
  - Use the push-and-pull cycle of the procedure to make an estimate of depth of insertion (accurate within ~10%)
- Mark the spot of maximal distal insertion of DE (if appropriate), 90%
  - If lesion not reached by DE
    - Tattoo the spot of maximal insertion of the DE
- Describe and give treatment of “clinically significant” lesions, 98%
  - Ulcers/tumours – Biopsy/mark for resection
  - Bleeding – Endoscopic hemostatic therapy (EHT) e.g., vascular lesion
  - Polyps – Polypectomy
  - Strictures – Dilation, safe if stricture is
    - Single
    - Short, < 5 cm
    - Straight
    - Smooth, i.e., not ulcerated
- Describe and Treat Vascular Lesions
  - Nomenclature of lesions
    - Flat/punctate
    - Raised/pulsating
    - Raised plus surrounding venous dilation
  - Angiectasia
  - Dieulafoy lesion
  - Arteriovenous malformation (AVM)
  - The risk of rebleeding is increased by the
    - Number if comorbidities
    - The patient having a left ventricular assist device
- ❖ Post-procedure
- Prepare a complete report, including
  - Specific technique / accessories used
  - DE findings
  - Complications / adverse events similar for deep enterotomy (double balloon) and for single balloon enterostomy (SBE)
    - Document and give management, 95%
    - Bleeding, EHT
    - Obstruction, dilation of strictures / NSAID diaphragm
    - Perforation
    - Pancreatitis (< 1% of patients having DE [not with SBE], especially antigrade DE)

98%



## COLON

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Afzaal, Tamoor

Hudson, David

Iablokov, Vadim

Howarth, Nisha



## IRRITABLE BOWEL SYNDROME (IBS)

### Irritable Bowel Syndrome (IBS): ACG Clinical Guideline (2021)

Lacy BE, et al. Am J Gastroenterol 2021; 116: 17-44

(Please also see Moayyedi P, et al J Can Assoc Gastroenterol 2019;2(1):6-29)

#### ➤ Definition

- A simple, understandable definition (NICE; national Institution of Health and Care of Excellence)
  - Recurrent abdominal pain and abnormal defecation for  $\geq 6$  mon, in the absence of alarm symptoms/signs
- A scholarly definition – Rome IV criteria

Abbreviation: NICE, National Institute of Health and Care of Excellence

- Rome IV diagnostic criteria for irritable bowel syndrome (IBS)
  - Recurrent abdominal pain on average at least one day per week in the last three mons associated with two or more of the following criteria
    - related to defecation
    - associated with a change in the frequency of stool
    - associated with a change in the form (appearance) of stool
  - These criteria should be fulfilled for the last 3 mon which symptom onset at least 6 mon before diagnosis
    - Bloating is common but is not mandatory for the diagnosis
    - Some authorities suggest that IBS is a disorder of positive diagnostic strategy, while in clinical practice IBS is usually a diagnosis of exclusion
    - However, the Rome criteria have a relatively poor predictive value

#### ➤ Demography

- Prevalence (Canada, USA, EU) ~5% of the adult population
  - Prevalence of post-infection IBS ~11% (95% CI, 8.2 to 15.8)

#### ➤ Clinical

- Give the reason why
  - Visceral pain is usually initially generalized (poorly localized).
    - Sensory inputs from the abdominal viscera travel through  $\geq 1$  (1-3) main thoracic splanchnic nerves, ending in the dorsal horn of the spinal cord, before proceeding to the brainstem and cortex.
    - The pain characteristics and location may be helpful clinically to shorten an otherwise long differential diagnosis of the cause of abdominal pain
    - Lateralization of abdominal pain suggests that the pain is non-visceral in origin



- Recommendations

- Diagnosis

- Use a positive diagnostic strategy to
  - ↓ time to initiate appropriate therapy
  - ↓ cost-effectiveness
- Negative predictive value (NPV) of fCal > c-reactive protein (CRP) or erythrocytic sedimentation rate (ESR)
- Performance characteristics of
  - fCal vs endoscopy for IBD
    - Sensitivity (Sn: 93% (CI 85% to 97%))
    - Specificity (Sp: 96% (CI 79% to 99%))
  - fCal, active IBD vs IBS
    - Sn: 67% to 87%
    - Sp: 96% to 100%
    - PPV, 92% to 100%
    - NPV, 80% to 87%
    - Pooled increase, 88%

Abbreviations: CI, confidence interval; fCal, fecal calprotectin; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

- ❖ tTG/EMA/IgA (Strong recommendation; moderate quality of evidence)

- ACG Guidelines (the differences between the ACG and the CAG guidelines is note)
  - Perform laboratory testing for celiac disease (CD) (tissue transglutaminase [tTG / endomysial antibodies [EMA] plus qualitative IgA measurement in persons with IBS-diarrhea predominant (IBS-D)

- Normal population

- Seroprevalence of CD in North America, ~1.4% (95% CI 0.7% to 2.2%)
- Biopsy proven CD, ~0.5% (take at least 6 duodenal mucosal biopsies)

|  | Prevalence | 95% CI | Pooled odds ratio | 95% CI |
|--|------------|--------|-------------------|--------|
|--|------------|--------|-------------------|--------|

- IBS population

- Seropositive 2.6% 1.6% to 3.8% 2.75 1.35-5.61
- Biopsy positive 3.3% 23% to 45% 4.48 2.33-4.60

- CAG Guidelines (the differences between these recent ACG Guidelines and those of the CAG are noted)

Reference: [http://journals.lww.com/ajg/Fulltext/2013/05000/ACG\\_Clinical\\_Guidelines\\_Diagnosis\\_and\\_Management.7.aspx](http://journals.lww.com/ajg/Fulltext/2013/05000/ACG_Clinical_Guidelines_Diagnosis_and_Management.7.aspx)

- Recommend anti-tTG (IgA) plus quantitative IgA
- If EGD performed, take ≥ 6 biopsies from duodenum



CAG Guidelines\* – IBS Statement 1:

- Do serological testing to exclude celiac disease in patients with suspected IBS.
  - GRADE: Conditional recommendation, low-quality evidence
  - Vote: Strongly agree, 50%; agree, 50%

\*The ACG guidelines are compared to those of the Canadian Gastroenterology (CAG)

Moayyedi P, et al. J Can Assoc Gastroenterol 2019; 2(1): 6-29

- The presentation of CD is highly variable – asymptomatic to frank malabsorption to malignancy
- A recent meta-analysis including 36 studies, showed the prevalence of CD in different IBS subgroups
  - Highest prevalence of CD was reported in IBS with diarrhea (IBS-D)
    - Positive anti-EMA or tTG, 5.8% (95% CI, 3.0% - 9.1%)
  - IBS with mixed or alternating bowel habits (IBS-M)
    - Positive anti-EMA or tTG, 3.4% (95% CI, 1.4% - 6.2%)
  - Lowest prevalence was reported in IBS with constipation (IBS-C)
    - Positive anti-EMA or tTG, 2.1%, (95% CI, 0.9% - 3.8%)
- ❖ CRP, fecal calprotectin (fCal)
- ACG Guideline: measure CRP/fCal
  - CRP: Strong recommendation; moderate quality of evidence)
  - Lactoferrin (LF) (Strong recommendation; very-low quality of evidence)
  - Probability of IBD in IBS
    - Overall, 0.5% to 1.2%)
    - Symptoms > 5 yr, 2.6 to 5x ↑ risk

The longer the duration of IBS symptoms have been present, the more likely the patient may have IBD
- CAG Guidelines – Statement 3:
  - Do **not** test for fecal calprotectin in persons with suspected IBS.
    - GRADE: Strong recommendation, very low-quality evidence
    - Vote: Strongly agree, 67%; agree, 33%





- ❖ Stool test for enteric pathogens
- ACG Guidelines: **Not** recommended
  - IBS may develop within months of an enteric bacterial (*Campylobacter jejuni*, *Salmonella*), viral (Norwalk) or parasitic infection (*Cryptosporidium*, *Giardia lamblia/duodenalis*) (OR 3.51; 95% CI, 2.05-6.00) [known as post-infectious IBS].
  - IBS-PI (IBS post-infection)
    - Risk factors
      - Antibiotic exposure
      - Parasitic (~40%) vs bacterial (~15%)
      - Relative risk of IBS-PI with
        - Giardiasis, 3.4 (95% CI, 2.9 to 3.9)
        - Any parasitic infection
      - History of depression/anxiety
  - Of note
    - Treating an enteric infection does **not** ↓ risk of IBSD
    - Antibiotic use may in fact be a risk factor for IBS-PI
  - Although it is recommended that stool cultures are **not** performed in persons with chronic symptoms from IBS,
    - It is appropriate to screen patients with acute diarrhea lasting days for *Giardia* infection
    - If *Giardia* infection is suspected, such as from the patient being in a high risk group (please see table below from the Centres for Disease Control and Prevention), and stool cultures are negative, duodenal biopsies may be necessary to ↑ diagnostic yield.
- CAG Guidelines
  - Do **not** do routine stool testing for enteric pathogens in all patients with IBS.
    - Conditional recommendation; low quality of evidence
- Centres for Disease Control and Prevention listing of risk factors of development of *Giardia* infection
  - Risk factors for Giardiasis
    - Children in childcare setting, in particular, diaper-age children
    - Close contacts of people with Giardiasis, for example: people living in the same household, or people who care for those who are sick with Giardiasis
    - People who drink water or use ice made from places where *Giardia* may live (for example, untreated or improperly treated water from lakes, streams, or wells)
    - Backpackers, hikers and campers, who
      - Drink unsafe water, or
      - Do **not** practice good hygiene (for example proper handwashing)
    - People who swallow water while swimming and playing in recreational water
    - People who are exposed to human feces through sexual contact
    - International travellers where *Giardia* may live, especially in lakes, river, springs, ponds, and streams



❖ Colonoscopy

• ACG Guidelines:

- Do **not** perform colonoscopy in persons with IBS-like symptoms unless
  - > 45 yr,
  - Alarm symptoms
  - A family history of colorectal cancer (CRC) or inflammatory disease (IBD)  
(Conditional recommendation; low quality of evidence)
- While the presence of anemia, bleeding, and unintentional weight loss may justifiably be used to perform colonoscopy

“....alarm features in patients with IBS (even including older age of onset of IBS symptoms, or positive family history) have a low predictive value” “...the colonoscopy should be based on considerations independent of IBS symptoms”
- Curiously, colonic polyps have been shown to be less common in IBS (8%) versus non-IBS
  - Recall that celiac disease and Crohn disease are more prevalent in IBS patients (~3% and 7%, respectively)

❖ Per CAG Guidelines

- Do colonoscopy in patients  $\geq 50$  yr who are suspected as having IBS
  - GRADE: Strong recommendation, low-quality evidence
  - Vote: strongly agree, 50%; agree, 50% These guidelines do **not** mention to ↓ colonoscopy age cut-off to
    - $\leq 45$  yr
    - Females, especially in those with risk factors
    - African ancestry
    - Risk factors for microscopic colitis (including intake of PPIs, NSAIDs)

❖ Breath test

❖ No recommendation or Comment by ACG Guidelines

❖ CAG Guidelines:

- Do **not** do routine testing of lactose hydrogen breath tests in evaluating IBS patients.
  - GRADE: Strong recommendation, very low-quality evidence
  - Vote: Strongly agree, 67%; agree, 25%; neutral, 8%
- Do **not** do routine testing of glucose hydrogen breath tests in evaluating IBS patient
  - GRADE: Strong recommendation, very low-quality evidence
  - Vote: Strongly agree, 50%; agree, 50%



❖ Positive diagnostic strategy

• ACG Recommendation

- To improve
  - Time to initiate appropriate therapy [for IBD] (Consensus recommendation; unable to assess using GRADE methodology)
  - Cost-effectiveness (Strong recommendation; high quality of evidence)
- Low-diagnostic yield of additional workup in suspected IBS without alarm features
- Performance characteristics of Rome Criteria for IBS
  - Sensitivity, 70%
  - Specificity, 82%
  - Positive predictive value (PPV), 3.35
    - ↑ specificity by using Rome criteria plus
      - No nocturnal bowel movements (BMs)
      - Normal hemoglobin and CRP
      - ↑ hospital score for depression / anxiety (> 8)
- Cost of care of IBS patient
  - 80% related to exclusion of disease

• Categories of IBS

- Trials are usually targeted at IBS patients within a subgroup based upon their bowel habit (e.g., IBS-D, diarrhea-predominant; IBS-C, constipation predominant; IBS-M, both diarrhea and constipation and IBS-U, undetermined)
  - > 50% of patients with IBS will change from one category to another over one year.
  - The usual pattern of abdominal pain may differ between subgroups

Recommendation

- To accurately categorize a patient with IBS by subtype, the following is recommended:
- Use the Bristol Stool Form Scale (BSFS) to determine the predominant stool consistency.
  - Determine patient's primary stool consistency only on the days s/he reports abnormal bowel movements.
    - Make this determination should be made only when patient is off therapy(ies) that could affect bowel pattern.
    - Daily diaries should be performed for 2 wk for the most accurate assessment.
  - Use once the pattern of the patient's stool consistency to determine subtype decisions according to the Rome IV criteria:
    - IBS-C
      - 25% of bowel movements associated with BSFS 1 or 2, with BSFS 6 or 7 occurring less than 25%.
    - IBS-D
      - 25% of bowel movements associated with BSFS 6 or 7, with less than 25% of bowel movements with BSFS 1 or



- IBS-M
    - 25% of bowel movements associated with BSFS 1 or 2, and
    - 25% of bowel movements associated with BSFS 6 or 7
  - IBS-U
    - Cannot be determined (undetermined)
  - Categorizing patients based on accurate IBS subtype improves patient therapy (Consensus recommendation; unable to assess using grade methodology)
    - The patients' therapy may be modified over time in response to the changes in symptoms of pain and bowel dysfunction
    - The readers who are interested in the seven descriptive types of stool (Bristol Stool Form Scale) are referred to the full publication paper of these guidelines noted in Lacy BE, et al. Am J Gastroenterol 2021; 116: 17-44 (Table 1)
- ❖ Testing for food allergies / adverse reactions to food (ARFs)
- Food allergies
    - 2% of general population
    - Very low specificity of tests for food allergy
- ACG Recommendation
- Do **not** do testing for food allergy sensitivities in IBS patients unless there are “...reproducible symptoms concerning food allergy” (Consensus recommendation; unable to assess using GRADE methodology)
  - Prevalence of ARFs
    - General ARFs in 20%
      - Only 2% of these develop recurrent symptoms when rechallenged
      - Person with IBS, 50%
- ❖ CAG Guidelines:
- Do **not** do food allergy testing to identify possible triggers for IBS symptoms
    - GRADE: Strong recommendation, very low-quality evidence
    - Vote: Strongly agree, 100%
- ❖ Physiological testing for anorectal dysfunction (pelvic floor disorder; dyssynergic dysfunction [DD]), refractory constipation
- ACG Recommendation
- Anorectal dysfunction should be performed in IBS patients with symptoms suggestive of pelvic floor dysfunction / refractory constipation, and when the symptoms have failed to response to standard medical care (Consensus recommendation; unable to assess using GRADE methodology)
  - IBS is an independent risk factor for obstructive defecation (OR, 1.78; 95% CI, 1.21-2.60)



❖ CAG Guidelines:

- Perform anorectal physiology testing in patients
  - With IBS and symptoms suggestive of a pelvic floor disorder and/or
  - Refractory constipation not responsive to standard medical therapy.  
(Consensus recommendation; unable to assess using GRADE methodology)

❖ No Recommendation or Comment by CAG Guideline

- In patients with abnormal rectal examinations suggesting dyssynergic defecation (DD), dyssynergia for
  - Those refractory to conventional treatments
  - Those with pelvic floor symptoms
    - Anorectal manometry (ARM) and balloon exposure test (BET) to identify patients who could be treated with biofeedback therapy.
- The accurate diagnosis of DD requires physiologic testing with abnormalities of a defecation disorder identified in 2 of 3 tests (e.g., anorectal manometry [ARM], Balloon expulsion test [BET], and/or impaired evacuation by imaging)

➤ Demography

- Anorectal dysfunction occurs in up to 40% of patients with IBS-D, -C, or -M

➤ Clinical

- Symptoms alone cannot accurately distinguish IBS from DD
- Signs
  - Inspection abnormality (digital rectal examination, DRE) → ↑ likelihood of pelvic floor disorder
    - Sensitivity, 75%
    - Specificity, 87%
    - Negative predictive value (NPV), 91%
  - DRE findings which suggest a disorder of the pelvic floor
    - Perianal
      - Skin
        - Dermatitis
        - Fissure/fistula
        - ↓ sensitivity
        - ↓ perineal descent on Valsalva maneuver (↑ risk of overflow diarrhea)
    - Anus
      - Prolapse
      - Hemorrhoids
      - Strength of intentional squeeze
      - No relaxation on Valsalva maneuver
    - Rectal lumen
      - Mass stool impaction
      - Distention (↑ size of rectal vault)



- Clinical symptoms, rectal examination findings, and anorectal physiologic testing suggestive of a pelvic floor disorder\*.

| Testing                                                                 | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Rectal examination findings on inspection                             | <ul style="list-style-type: none"> <li>– Dermatitis/perianal erythema</li> <li>– Rectal prolapse</li> <li>– Gaping anus</li> <li>– Hemorrhoids</li> <li>– Fistula or fissure</li> <li>– Rectal scar</li> <li>– Anorectal mass</li> </ul>                                                                                                                                                                                                                            |
| ○ Digital rectal examination findings suggesting dyssynergic defecation | <ul style="list-style-type: none"> <li>– Impaired sensory perception of stool (perineal sensation testing)</li> <li>– Rectal distension and stool impaction</li> <li>– Contraction of the diaphragm, abdomen, and rectum during push maneuvers (abdominal pressure and rectal examination must be performed simultaneously)</li> <li>– Abnormal relaxation of external anal sphincter and puborectalis muscles (or no relaxation with Valsalva maneuver)</li> </ul> |
| ○ Anorectal physiology findings suggesting pelvic floor disorders       | <ul style="list-style-type: none"> <li>– Uncoordinated abdominal, rectoanal, and pelvic floor muscles</li> <li>– Rectal hyposensitivity</li> <li>– Paradoxical increase in sphincter pressure/puborectalis muscle pressure during relaxation or simulated evacuation</li> <li>– Prolonged balloon expulsion time</li> <li>– Inadequate anal relaxation during push maneuvers</li> <li>– Inadequate abdominorectal propulsive forces</li> </ul>                      |

\*Many of these symptoms and examination findings are seen in all subtypes of irritable bowel syndrome and are not specific to pelvic floor dyssynergia.

Printed with permission: Lacy BE, et al. Am J Gastroenterol 2021; 116: 17-44

- Tests
    - Anorectal manometry (ARM)
    - Balloon expulsion test (BET)
    - ↓ evacuation on diagnostic imaging
- Positive results on ≥ 2 of these tests needed to diagnose DD

#### Clinical Timbits

- The patient with ↓ perineal descent on straining
  - ↑ risk of
    - Overflow diarrhea
    - Depression/anxiety



- Give the manometric findings on ARM which predict DD.
  - Pain
    - ↓ pain threshold
  - Contraction of anus
    - Paradoxical
  - ↓ relaxation
- Biofeedback effective in all subtypes of IBS with DD
  - Poor outcome in IBS with DD
    - ↑ rectal sensory threshold
    - ↑ constipation severity scores
    - ↓ colonic transit
    - ↑ assessment of constipation system (ACS)
  - When biofeedback improves BET/defecation index
    - There is associated ↓ pain / ↓ bloating

#### ➤ Treatment

- Treat associated conditions
  - Celiac disease
  - Small intestinal bacterial overgrowth (SIBO)
  - Bile acid wastage (BAW)
  - Microscopic colitis
  - Diabetes
  - Colorectal dysfunction

#### ❖ Diet

- ACG Recommendations
  - Fermentable oligo-, di-, monosaccharide, and polyols (FODMAP)
    - Use on short empirical trial (2-6 wk) of a low FODMAP (dietary fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet to improve the patient's IBS symptoms (Conditional recommendation; very low quality of evidence)
    - Only some studies have shown benefit of low FODMAP diet in patients with IBS (risk ratio 0.69; 95% CI 0.54 to 0.88) (particularly for abdominal pain and bloating)
  - When initiating a trial of low FODMAP foods
    - Provide proper counseling on the proper sequential stages
      - Substitute foods with low FODMAP choices, then
      - Gradually reintroduce FODMAP-containing foods into the diet, and assess symptoms
      - Personalize the patient's diet to exclude foods that specifically triggered their symptoms (e.g., oat bran, barley, beans, psyllium)



- ❖ Herbal Remedies
- CAG Guidelines
  - Do **not** offer herbal remedies to IBS patients to improve IBS symptoms.
    - GRADE: Conditional recommendation, very low-quality evidence
    - Vote: Strongly agree, 73%; agree, 18%; neutral, 9%
- ❖ Soluble fibre
- ACG Recommendations
  - Use an empirical trial of soluble fibres to improve the patient's IBS symptoms (Strong recommendation; moderate quality of evidence)
- ❖ CAG recent systemic review and meta-analysis on fiber in IBS
  - Fiber had a statistically significant benefit for IBS symptoms compared with placebo (RR of IBS not improving – 0.87; 95% CI, 0.80 – 0.94).
  - In summary, soluble, viscous, poorly fermentable fibre may provide benefit patients with IBS,
    - The apparent lack of significant side effects make fibre a reasonable first-line therapy for IBS patients with symptoms.
    - The ability to improve stool viscosity and frequency logically argues for the use of fiber in patients with IBS-C, although the evidence base to support this contention is weak.
- ❖ Anti-spasmodics
- ACG Recommendation
  - Do **not** use anti-spasmodics which are currently available to treat IBS symptoms (Conditional recommendation; low quality of evidence)
    - “the data are decades old and of poor quality”
- CAG Recommendations
  - The most recent trial, completed 30 yr ago, randomized 712 individuals to hyoscine, hyoscine plus paracetamol, paracetamol alone, or placebo for 4 wk.
    - A “response” was achieved by 76% and 64% of individuals receiving hyoscine and placebo, respectively ( $P < 0.05$ ).
    - The most common AEs were dry mouth and blurred vision.





- Argument for anti-spasmodic agents per CAG Guidelines
  - Wide variety of medications available, and not all are effective
  - Of the anti-spasmodics available in Canada:
    - Effective: hyoscine (i.e., buscopan, scopolamine), pinaverium (i.e., dicetel), and dicyclomine (dicycloverine, bentytol)
  - Ineffective: trimebutine
  - Mechanism
    - Hyoscine or dicyclomine
    - Anti-muscarinic (M3)
      - Prevents Ach from binding and contracting smooth muscle
    - Pinaverium
      - Blocks specific voltage-dependent calcium channels located on intestinal smooth muscle
- In the light of the fact that the evidence was very weak, the potential for anti-cholinergic side effects, and the higher quality evidence for other alternative treatment,
  - The consensus group suggested that these agents generally be reserved for use in patients
    - Who Fail other treatments or
    - Whose symptoms are best served by an agent taken as needed for abdominal pain
- Antispasmodics relax intestinal smooth muscle,
  - Thereby ↓ GI motility
  - Alternative antispasmodics available internationally
- Three antispasmodics are commercially accessible in the US.
  - Dicyclomine, hyoscyamine, and hyoscine (with paucity of data supporting their efficacy)
- Dicyclomine has been assessed in 2 small, older trials
  - One-double-blinded study randomized patients (n=97) to 40 mg of dicyclomine (2-4 times standard dosing) or placebo 2-4 times daily for 2 weeks.
    - Neither a standard definition of IBS nor a single primary endpoint was established.
    - Overall, 84% of individuals receiving dicyclomine reported symptom improvement compared with 54% if those taking placebo ( $P = 0.006$ ).
    - 69% and 16% of dicyclomine and placebo-treated patients, respectively, reported adverse effects.
  - A second study enrolled 96 patients; a standardized definition of IBS was not included.
    - Individuals received 20 mg of dicyclomine or placebo 3 times daily for 10 days, with subsequent crossover without a washout period (which increases the likelihood of a carryover effect).
    - Dicyclomine was associated with subjective improvements compared with placebo.
    - No statistical analyses were undertaken.
    - 33% of dicyclomine and 4% of placebo-treated patients developed side effects during the 10-day treatment period.



- Hyoscyamine
    - Available in multiple formulations (short or long acting, oral or sublingual), was assessed in a single clinical study from Sweden performed more than three decades ago.
      - In this trial, 25 individuals were randomized to 0.2 mg of hyoscyamine or placebo for 2 wk. The definition of IBS was not standardized.
      - Hyoscyamine responses were compared with placebo.
      - Adverse event (AE) rates were significantly higher (87% vs 7%, respectively,  $P < 0.001$ )
      - This drug is not available for use in Canada.
  - Hyoscine (scopolamine), primarily used for motion sickness, has been evaluated in three IBS trials, all performed outside the United States.
    - The first trial studied older patients, and
    - One study combined hyoscine, lorazepam, soluble fiber (ispaghula husk), a placebo in 8 permutable blocks with 12 subjects per block.
      - Hyoscine fared no better than placebo over a 12 wk period
    - The second combined hyoscine, amitriptyline with chlordiazepoxide, ispaghula, and placebo in 8 randomized blocks of 21 patients
  - Please see a recent meta-analysis published in the Lancet (2020) for further information:
    - Black, CJ, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol 2020; 5(2): 117-131.
      - Heterogenous studies however, efficacy for spasmodic for abdominal pain symptoms in meta-analysis.
- ❖ Peppermint oil
- ACG Recommendation
    - Use peppermint oil to treat IBS global symptoms (Conditional recommendation; low quality of evidence)
      - “...only a small number of commercially available peppermint oil supplements have undergone rigorous testing of efficacy and safety”
      - All studies tested continuous rather than an as-needed-basis
      - Most studies were small and brief (2 to 12 wk)
        - However, there was evidence for overall reduction in IBS symptoms (RR, 2.39; 95% CI, 1.93-2.97; NNT, 3), and
          - Abdominal pain (RR, 1.78; 95% CI 1.43-2.22; NNT, 4)
  - CAG Guidelines
    - Offer IBS patients peppermint oil to improve IBS symptoms.
      - GRADE: Conditional recommendation, low-quality evidence
      - Vote: Strongly agree, 17%; agree, 83%



❖ Probiotics

• ACG Recommendation

- Do **not** use probiotics to treat IBS global symptoms (Conditional recommendation; very low quality of evidence)
- Interpreting the current literature is problematic because of
  - Small studies
  - Multiple types and strains of probiotics
  - Inconsistent benefits on individual symptoms
  - Lack of rigorous trials based on US FDA endpoints

• CAG Guidelines

Recommendation

- Offer IBS patients probiotics to improve IBS symptoms.
  - GRADE: Conditional recommendation, low-quality evidence
  - Vote: Strongly agree, 25%; agree, 67%; neutral, 8%
- A recent meta-analysis summarized the effect of probiotics in the treatment of IBS
  - 37 trials were eligible for analysis (21 involved probiotic combinations) totalling 4,403 subjects (16-391 subjects per study),
  - Combination probiotics demonstrated a significant pooled effect (RR, 0.79; CI 0.68-0.91) for symptom improvement, but there was evidence of significant heterogeneity ( $I^2 = 72\%$ ) and publication bias by the Egger test.
    - The combination group also benefited from a larger number of studies to pool.
- The meta-analysis further examined the pooled effect on individual symptoms of IBS,
  - A similar pattern was seen whereby combination probiotics seemed to have a modest effect on abdominal pain.
    - NO category of probiotic demonstrated benefits in pooled analysis.
    - Also a recent large blinded probiotic study (although not an IBS trial) demonstrated that a probiotic containing *Lactobacillus acidophilus* and *Bifidobacterium bifidis* produced bloating in the treatment group.
- The Argument for a trial of probiotics per CAG Guidelines
  - The consensus group concluded that while studies suggest benefits with probiotic therapies overall, and with specifically a benefit to combination probiotics, there is insufficient evidence for any particular species.
  - If probiotics are to be used, the consensus group suggested a limited therapeutic trial (e.g., one mon)
  - Probiotics are expensive, but are often viewed by patients as a more natural, low-risk approach to improving IBS symptoms.
    - At 12 weeks, individuals receiving only active hyoscine fared significantly better than those receiving placebo ( $P < 0.02$ )
    - However, these findings must be interpreted with caution because none of the patients in the placebo group experienced improvement at this time point.



- Most common probiotic usage: Align (Bifidobacterium 356624™ bacteria)
    - Recent studies and meta-analysis have a mixed effect, please see below for further details:
      - Ringel-Kulka T, et al. Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Benefit of the Probiotic Bifidobacterium infantis 35624 in Non-Patients With Symptoms of Abdominal Discomfort and Bloating. Am J Gastroenterol 2017;112(1):145-151.
      - Yuan F, et al. Efficacy of Bifidobacterium infantis 35624 in patients with irritable bowel syndrome: a meta-analysis. Curr Med Res Opin 2017;33(7):1191-1197.
  - The meta-analysis consistently referenced for information in regards to probiotic usage <http://eprints.whiterose.ac.uk/165996/APT-1106-2018R2.pdf>
  - Further information on available probiotics in Canada [http://www.probioticchart.ca/PBCAdultHealth.html?utm\\_source=adult\\_ind&utm\\_medium=civ&utm\\_campaign=CDN\\_CHART](http://www.probioticchart.ca/PBCAdultHealth.html?utm_source=adult_ind&utm_medium=civ&utm_campaign=CDN_CHART)
- ❖ Polyethylene glycol (PEG)
  - ACG Recommendations
    - Do **not** use PEG products to treat IBS global symptoms (Conditional recommendation; low quality of evidence)
    - PEG is of benefit to ↓ symptoms in patients with chronic idiopathic constipation (CIC)
      - NNT of 3 for impaired stool frequency/consistency
      - No benefit in IBS-C to improve overall symptoms of pain
        - ↑2x risk of adverse effects (pain, diarrhea)
  - CAG Guidelines
    - Do **not** offer osmotic laxatives to constipation-predominant IBS patients in order to improve overall IBS symptoms.
      - GRADE: Conditional recommendation, very low-quality evidence,
      - Vote: Agree, 92%; neutral, 8%
    - 4 trials in chronic idiopathic constipation (N=573) have yielded a number needed to treat (NNT) of 3 for the beneficial use of PEG (95% CI 2-4) for improvement in stool frequency and stool consistency.



- Randomized controlled trials (RCTs) have failed to show that PEG improves either overall symptoms or pain in patients with IBS-C.
  - The largest (n=139) multicentre, RCT of PEG in IBS-C failed to include abdominal pain as a component of their primary endpoint using instead mean number of spontaneous bowel movements (SBMs) in the last 7 days of the trial.
    - Varying doses of PEG (13.8 - 41.1 g) were allowed; bisacodyl (5-10 mg) could be used as a rescue medication.
- Treatment-related AEs were more frequent in patients treated with PEG compared with placebo (16% vs. 9%, respectively)
  - Reported common side effects were abdominal pain (5%), diarrhea (5%), nausea, and flatulence
    - These occurred in a dose-dependent manner
- While there is this variability, evidence that osmotic laxatives (e.g., PEG) will improve overall IBS symptoms, some evidence suggests it has beneficial effects on constipation.
  - Therefore, the consensus group suggested against the use of osmotic laxatives for overall symptoms, but
  - The consensus group acknowledged that these agents may be useful in some IBS-C patients, particularly as adjunctive therapy in patient who have improved on other treatments but continue to have constipation.

❖ Chloride channel activators (Lubiprostone)

- Use chloride channel activators to treat global symptoms of IBS-C (Strong recommendation; moderate quality of evidence)

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- Give the pharmacological basis for the benefit of lubiprostone in patients with IBS-C.
  - Chemistry                      – Locally acting prostaglandin E1 analog
  - Target                            – High affinity for type 2 chloride channel receptors in the brush border membrane of enterocytes
  - Beneficial effect                – ↑ intestinal secretion of water
    - ↑ intestinal peristalsis
    - ↑ tightness (↓ permeability) of intestinal barrier

- Performance
  - NNT, 12.5
  - Therapeutic gain vs placebo ~8% (18% vs 10%), and only after 3 mon use of lubiprostone 8 µg b.i.d. with meals



## ❖ CAG Guidelines

### Recommendations

- Offer constipation-predominant IBS patients lubiprostone to improve IBS symptoms
  - GRADE: Conditional recommendation, moderate-quality evidence.
  - Vote: Agree, 83%, Neutral 17%
  - Lubiprostone has been evaluated in 3 RCTs and a high-quality systemic review.  
Meta-analysis
    - Meta-analysis: Lubiprostone was found to be more effective than placebo for overall IBS-C symptoms with a relative risk of symptoms persistence of 0.91 (95% CI 0.87-0.95) and an NNT of 12.5.
  - Safety and tolerability
    - Diarrhea (6% - 14%) and nausea (8% - 19%) were the most frequent reported event (11% for both AEs)
    - In a recent analysis of nausea across all IBS-C studies, the overall incidence rate of treatment of nausea in RCTs was significantly greater in patients receiving lubiprostone than placebo (11% vs. 6%, respectively;  $P < 0.01$ ).
    - Nausea rated as moderately severe was more likely to occur in lubiprostone-treated individuals ( $P < 0.05$ ).
    - Overall discontinuation rates were low (1.2%), and comparable with placebo (0.7%)

## ❖ Guanylate cyclase agonists activators (GCA, linaclotide, plecanatide)

### • ACG Recommendation

- Use guanylate cyclase agonists/activators to treat global symptoms of IBS-C (Strong recommendation; high quality of evidence)
- Chemistry
  - Activators/agonists of guanylate cyclase-C
- Target
  - GC-C receptors on brush border membranes of enterocytes
- Beneficial effect
  - Secretagogues → ↑ secretion of  $\text{Cl}^-$  /  $\text{H}_2\text{O}$  (chloride and water)
  - Benefit begins after 1 wk, and continued for 12 wk
    - Improvement of pain, stool frequency, or global IBS symptoms
  - Relative risk of symptom persistence vs placebo
    - Linaclotide (RR, 0.80; 95% CI, 0.76-0.85) (small therapeutic gain); NNT, 6
    - Plecanatide (RR, 0.88; 95% CI, 0.82-0.94), NNT, 10

### • CAG Guidelines

- Offer constipation predominant IBS patients linaclotide to improve IBS symptoms.
  - GRADE Strong recommendation, high-quality evidence
  - Vote: Strongly agree, 83%; Agree, 17%



- Guanylate cyclase – C (GC-C) agonists target GC-C receptors residing in the apical membrane of intestinal epithelial cells – generally classified as secretagogues.
  - There are currently two US FDA – approved agents for the treatment of IBS-C – linaclotide 290 µg and plecanatide 3 mg.
    - Both activate GC-C receptor, increasing intestinal fluid secretion and peristalsis, with preclinical trials identifying reduced activation of visceral nociceptive neurons.
  - Linaclotide has been studied in three North American phase IIb/III trials and evaluated in several systematic review/meta-analyses
    - Individually, each trial has demonstrated that linaclotide is more effective than placebo for improving overall IBS symptoms.
      - Relative risk of symptom persistence in individuals consuming 290 µg of linaclotide once daily compared with placebo of 0.8 ((5% CI 0.76-0.85; NNT = 6) and an OR of response of 2.43 (95% CI 1.48-3.98; NNT = 6)
    - The most common treatment emergent AE, diarrhea, was experienced by approximately 20% of individuals receiving linaclotide, compared with 3% receiving placebo (P < 0.0001).
      - Severe diarrhea was recorded in 2% this population, and 5% of individuals in this cohort withdrew from the trials because of this AE.
  - CAG Guideline on the use of Prucalopride
    - A systematic review including either RCTs, provided high-quality evidence that prucalopride, a 5-HT<sub>4</sub> agonist, was effective in patients with chronic idiopathic constipation (CIC).
      - 71% of patients failed to respond to prucalopride vs 87% with placebo; NNT 5; 95% CI, 4-8
    - A less selective 5-HT<sub>4</sub> agonist, tegaserod demonstrated efficacy in IBS-C in a meta-analysis of 11 RCTs.
    - The consensus group did **not** recommended
      - Using the medication for global symptoms but
      - Endorsed its role in treating CIC
- ❖ 5-HT<sub>4</sub> agonists (Tegaserod)
- ACG Recommendation
    - Use for IBS-C in women < 65 yr with ≤ 1 cardiovascular risk factor, if chloride channel / guanylate cyclase-C activators failed to improve their IBS-C symptoms (Conditional recommendation; low quality of evidence)
    - Chemistry
      - Neurotransmitter, which stimulates the serotonin (hydroxytryptamine) type 4 receptor (5-HT<sub>4</sub>).



- Beneficial effects
  - Stimulation of colonic smooth muscle
    - ↓ GI transit time / ↑ speed of GI transit
  - ↓ visceral hypersensitivity (present in persons with IBS)
  - Subjective global assessment of relief (SGA), 48% for tegaserod vs. 37% for placebo
    - Note the small therapeutic gain (TG), ~10%
  - A second similarly designed study showed a TG of ~5%
  - Persistence of symptoms with tegaserod vs. placebo (RR, 0.85; 95% CI, 0.80-0.90)
  - The number of adjudicated cardiovascular (CV) events in the tegaserod group vs placebo was numerically but not significantly higher
    - Those who developed a CV event had ≥ 1 risk factor, explaining why tegaserod should **not** be used in persons with more than 1 risk factors
- CAG Guidelines
  - Do **not** offer constipation-predominant IBS prucalopride to improve overall IBS symptoms.
    - GRADE: Conditional recommendation, very low evidence
    - Vote: Strongly agree, 33%; Agree, 58%; Neutral, 8%
  - Eleven randomized, placebo-controlled trials have evaluated the efficacy of tegaserod for IBS-C
    - The first study was multinational, double-blind, placebo-controlled 12-week trial, during which 881 patients were treated with either tegaserod (2 or 6 mg b.i.d.), or placebo.
      - The primary endpoint, a subject global assessment of relief (SGA), was met by 46% and 50% of patients receiving 2 and 6 mg b.i.d. of tegaserod, respectively, compared with 37% of those receiving placebo ( $P < 0.05$ ).
      - At 12 weeks, patients randomized to the 6 mg, but not the 2 mg dose were more likely to report an improvement in individual symptoms of pain or discomfort. Stool consistency and stool frequency also improved.
    - A second large (all female) multinational trial compared tegaserod (6 mg b.i.d.) with placebo over 12 wk.
      - The SGA primary endpoint was met by 44% of tegaserod, compared with 39% of placebo-treated patients ( $P < 0.033$ ).
      - Improvements in secondary endpoint, including abdominal pain ( $P < 0.003$ ), stool consistency ( $P < 0.0001$ ), stool frequency ( $P < 0.005$ ), and bloating ( $P < 0.05$ ), were also more likely to be achieved by patients randomized to tegaserod.
  - A systematic review and meta-analysis of these 11 trials was performed
    - In brief, 9242 patients with IBS were evaluated
      - Overall, patients treated with tegaserod were less likely to have persistent IBS-C symptoms compared with those treated with placebo (RR, 0.85; 95% CI 0.80-0.90)





- The most common AE was diarrhea, occurring in 6% of patients treated with tegaserod compared with 2% of those treated with placebo.
  - In terms of serious AEs, it was approved for the treatment of IBS-C in women in 2002, but voluntarily withdrawn from the market 5 yr later because of concerns over a small excess of cardiovascular (CV) event.
- Two separate external adjudications of a large clinical trial database of patients with IBS, chronic constipation, and dyspepsia were recently performed to identify and evaluate potential CV events.
  - In the first adjudication, 0.1% of patients in the tegaserod group had confirmed CV ischemic events.
    - All 14 patients had at least 1 CV risk factor, and 11 had a minimum of 2 risk factors.
    - There were 7 (0.06%) major CV events (MACEs); 4 in women younger than 65 yr, and 1 in a man older than 65 yr.
  - In the second adjudication, there were 7 (0.06%) confirmed CV ischemic events ( $P = 0.3$ ) and 4 (0.03%) MACE ( $P = 0.03$ ) in the tegaserod group vs. none in the placebo group.
  - In women younger than 65 yr without a history of CV ischemic disease and  $\leq 1$  CV risk factor, only 1 (0.01%) CV ischemic event and no MACE were reported in the tegaserod group vs. none in the placebo group. Additional analyses found no evidence of increased proarrhythmic risk or platelet aggregation within these studies.
- In 2019, based on this evaluation, tegaserod was approved again for treatment of IBS-C by the FDA (USA).
  - However, tegaserod is not available for practice in Canada
- Plecanatide has been evaluated in three individual phase IIb/III studies and 1 subsequent systemic review / meta-analysis.
  - The 3 mg plecanatide daily dose achieved a relative risk of symptom persistence of 0.88 (95% CI 0.83-0.94; NNT = 10) and an OR of response to treatment of 1.87 (95% CI, 1.47-2.38; NNT = 9) compared with placebo.
  - Diarrhea, severe diarrhea, and withdrawal due to diarrhea were reported by 4%, 0%, and 1% of individuals, respectively, in the plecanatide studies, with no significant differences identified between in placebo and plecanatide cohorts.
- ❖ Bile acid sequestrants (BAS)
  - Demography
    - Bile acid malabsorption (BAM) and bile salt-induced diarrhea are present in about 25% of patients with IBS-D
  - Laboratory Test (for BAM)
    - SeHCAT nuclear medicine scan
    - Blood
      - $\uparrow$  fibroblast growth factor 19 (FGF-19)
      - $\uparrow$  C4 concentration



- Stool ↑ 24 h stool content of bile acids
- Breath test      – C14 glycocholic acid breath test
- Duodenal aspirate      – ↑ secondary / ↓ primary bile acids  
                                    – ↑ deconjugated / ↓ conjugated bile acids
- Evidence
  - ~ half of IBS-D patients given a bile acid sequestrant had improvement in their IBS score
  - The most common test for BAM is the SeHCAT test (not readily available).
    - A recent meta-analysis has examined the prevalence of BAM in subject with IBS-D.
      - Based on pooled data from 6 studies using SeHCAT testing 28% (CI 23% - 34%) of patients with IBS-D met the predefined threshold for BAM on SeHCAT in the random effects model.
      - However, there was significant heterogeneity (72%)
  - Newer stool studies measuring bile acids stool were predictive of higher stool wet weight in a study comparing healthy subjects with those with IBS-D and IBS-C.
    - Two serum markers help to identify subjects
      - Serum testing supports that a ↓ fibroblast growth factor (FGF-19) and ↑ C4 may be suggestive of BAM.
      - Serum C4 is higher in IBS-D compared with IBS-C, or with healthy subjects with correlation of C4 to stool bile acids as well.
- CAG Guideline
  - Do **not** offer diarrhea-predominant IBS patients' cholestyramine to improve their IBS symptoms.
    - GRADE: Conditional recommendation, very low-quality evidence
    - Vote: Strong agree, 8%; Agree, 83%; Neutral, 8%
- Background
  - Bile acid malabsorption (BAM) is a condition characterized by an inability to reabsorb sufficient bile acids in the terminal ileum.
    - Excessive bile acids in the colon are expose to colonic flora
    - Leading to ↑ production of secondary bile acids which can increase colonic secretion of fluid, thereby resulting in diarrhea.
  - There are three potential mechanisms for ↑ bile acids to reach the colon.
    1. Iatrogenic surgical resection leading to ↑ loss of the distal small bowel → ↓ absorbing capacity of bile excreted by the biliary system during digestion → ↑ spilling of BA into colon → ↑ cGMP → ↑ secretion of Cl<sup>-</sup>/H<sub>2</sub>O (diarrhea)
      - ↑ small intestinal bacterial overgrowth (SIBO)
    2. Cholecystectomy leading to a change in timing of bile delivery to the small intestine.
    3. An idiopathic form possibly related to the differential reabsorption of bile acids in given individuals has been identified



➤ Evidence

- Bile acid sequestrants have previously been suggested as a treatment for IBS-D.
  - One open-label study examined the presence of BAM (through SeHCAT, FGF-19, and C4), and response to treatment with colestipol in a cohort of individuals with IBS-D.
    - In the open-label study, 27 subjects with IBS-D noted a significant improvement in IBS severity scores, and 15/27 (56%) were considered responders based on study definitions.
    - In a recent single-centre trial, open-label colesevelam, at a dose of 1,875 mg daily, there was ↑ bile acid retrieval from the stool with a modest ↓ Bristol Score ( $P = 0.0043$ ) among the 12 subjects treated.
  - In the absence of widely accessible, reliable testing, and given the lack of controlled trials of bile acid sequestrants in patients with IBS-D; the use of these therapies should be at the discretion of the clinician.
- ACG Recommendation
  - Do **not** use bile acid sequestrants to treat global IBS-D symptoms (Conditional recommendation; very low quality of evidence)
    - Editor's comment: In persons with IBS-D, in whom there are patients with bile acid malabsorption (BAM), short empiric trials of cholestyramine may be beneficial when other agents have failed.
      - When tests for BAM become more available, the targeted rather than empirical testing for BAM will be more rational

❖ Rifaximin

- ACG Recommendation
  - Use rifaximin to treat global IBS-D symptoms (Strong recommendation; moderate level of evidence), with additional experimental data to support its use for two additional treatment for symptom recurrence
  - Rifaximin vs. placebo for 2 wk improved abdominal pain and stool consistency in 41% vs. 32% of patient with IBS-D (NNT, 9), presumably by modifying a speculated abnormal microbiome.
    - Retreatment of IBS-D after one successful course of therapy will improve symptoms again.
    - The 2 wk use of rifaximin is safe
      - Number needed to harm (NNH) is 8971
      - “No significant disruption in the microbiome” found
- CAG Guidelines
  - Consensus group does **not** make a recommendation for or against offering diarrhea-predominant IBS patients one course of rifaximin therapy to improve their IBS symptoms.



➤ Evidence

- Two identically designed, large scale double-blind studies, rifaximin resulted in a significant benefit over placebo using an interim US FDA endpoint.
  - In the month after a 2-week course of rifaximin, 41% of subjects had an improvement of abdominal pain and stool consistency, compared with 32% with placebo ( $P < 0.001$ ) when both trial results were pooled in the follow-up month.
- In a third trial, the efficacy of rifaximin retreatment was assessed.
  - All subjects initially received open label rifaximin.
  - After this initial treatment, 44% of subjects responded to rifaximin.
    - The remaining 64% eventually relapsed, and were then randomized to receive rifaximin or placebo for 2 weeks.
    - After treatment, rifaximin was superior to placebo at improving IBS-D symptoms.
      - This study supported approval for rifaximin for treatment with up to 2 additional treatments for symptom recurrence.
- A recent meta-analysis summarized 5 controlled trials using rifaximin in patients with IBS-D. These demonstrate a significant benefit of rifaximin over placebo with an NNT of 9.
  - In another summary of IBS treatment, rifaximin had the most favorable safety profile with the number needed to harm (NNH 8,971), contrasts with treatment with tricyclic antidepressants (TCAs)

❖ 5-HT<sub>3</sub> antagonist (Alosetron)

• ACG Recommendation

- Use alosetron for women who have had IBS-D for > 6 mon, and who previously failed conventional therapy (Conditional recommendation; low quality of evidence)
- Alosetron is a 5-HT<sub>3</sub> receptor antagonist, which
  - ↓ pain
  - Slowing intestinal transit, ↑ dwell time to ↑ absorption of Na<sup>+</sup>/H<sub>2</sub>O and to ↓ diarrhea
- Benefit in IBS-D
  - Relative risk (RR) of symptom persistence vs. placebo (RR, 0.79, 95% CI, 0.69-0.90; NNT = 8)
  - Overall symptom improvement (RR, 1.58; 95% CI 1.42-1.72)
- Pooled adverse effects (AEs)
  - Any complication (including ischemic colitis, and constipation with obstruction/perforation)
  - RR of any AE, 1.16 (95% CI, 1.08-1.25)
  - Current adjudicated incidence rate (with low doses of 0.5 to 1 mg po b.i.d.):

| AE                         | Per 1000 patient-yr of exposure |
|----------------------------|---------------------------------|
| ▪ Colonic ischemia         | 1.03                            |
| ▪ Complicated constipation | 0.25                            |



- Other 5-HT<sub>3</sub> agonists for IBS-D
  - Ondansetron
    - ↓ stool frequency, improved consistency
    - No benefit for abdominal pain / discomfort
- CAG Guidelines
  - Conditional recommendation, low quality of evidence
    - Alosetron is **not** currently available in Canada.
  - Two meta-analyses have confirmed its efficacy for IBS-D.
    - The first yielded a relative risk of symptom persistence of 0.79 (95% CI 0.69-0.90; NNT = 7.5)
    - The second showed an overall symptom improvement; RR, 1.58 (95% CI 1.42-1.75) based on 3 RCTs.
    - An in-depth analysis of three trials assessing global symptom improvement – each to enrolling women with severe IBS-D.
      - Two studies (both double-blinded, randomized, controlled trials) assessed the efficacy of varying dosage of alosetron ranging from 0.5 to 1.0 mg b.i.d.
      - Overall global improvement ranged from 12% to 32%, compared with placebo ( $P \leq 0.02$  for all comparisons)
      - A double titration (0.5-1.0 mg b.i.d.), real world, open label, prospective observational analysis, used the US FDA's current IBS-D clinical trial composite endpoint and identified an overall response rate at 45%.
  - Safety profile of alosetron has been of concern since it was voluntarily withdrawn in 2000, because of post-marketing reports of ↑ rates of ischemic colitis, complicated constipation (obstruction or perforation), and death.
    - Subsequent safety analyses yielded pooled RRs of any AE of 1.16 (95% CI 1.08-1.25)
      - Constipation was the AE most likely to occur within all of 4.55 (95% CI 3.30-6.28)
    - A follow-up meta-analysis of 8 trials (4,987 patients) yielded an overall NNH of 10.
  - Alosetron was reintroduced under a risk evaluation and mitigation strategy (REMS) in 2002, limiting its use to women experiencing chronic (> 6 mon), severe IBS-D symptoms, who previously lacking response to traditional therapies.
  - Initial safety concerns have been tempered by follow-up data revealing less stable adjudicated incidence rates of ischemic colitis and ↓ rates of complicated constipation (1.03 cases and 0.25 cases / 1000 patient-yr of exposure, respectively), likely attributable to restricted prescribing dosages of 0.5 to 1.0 mg b.i.d.
  - Ondansetron and another 5HT-3 agonist, are US FDA approved for the treatment of chemotherapy, radiation, or postoperative nausea or vomiting.
    - Two small crossover studies have assessed the merits of ondansetron for IBS-D
    - Both reporting improvements in bowel symptoms (i.e., frequency and consistency), but not in abdominal pain or discomfort.
      - AEs were recorded in one trial, and only constipation occurred at a higher rate in the ondansetron cohort compared with placebo (9% vs. 2%).
      - No cases of severe constipation or ischemic colitis were identified.



❖ Opioid receptor agonists/antagonists

• ACG Recommendation

- Use opioid agonists/antagonists to treat women/man with global symptoms of IBS-D (Conditional recommendation; moderate quality of evidence)
  - Target opioid receptors
  - Peripheral acting
    - Agonist
      - Mu and kappa receptors, plus
    - Antagonist
      - Delta opioid receptors
  - Beneficial use
    - $\geq 30\%$  from baseline in the daily average score
    - $\downarrow$  worst abdominal pain on  $\geq 50\%$  of the days evaluated
    - A daily stool consistence score  $< 5$  on the Bristol Stool Form Scale
    - Benefit at weeks 12 and 24, as compared with placebo (approximate average values for two studies)

|               | 12 wk | 24 wk |
|---------------|-------|-------|
| – Eluxadoline | 26%   | 29%   |
| – Placebo     | 17%   | 20%   |

- Contraindications
  - Alcohol
    - Alcohol use disorder (ALD); alcoholism, abuse, addiction;  $\geq 4$  alcohol drinks/day
  - Pancreas
    - History of pancreatitis
  - Gallbladder
    - Previous cholecystectomy

• CAG Guidelines

Recommendations

- Use eluxadoline in diarrhea-predominant IBS patients to improve IBS symptoms.
  - GRADE: Conditional recommendation, moderate-quality evidence.
  - Vote: Strongly agree, 8%; Agree, 67%; Neutral, 25%
- Two large, phase 3, randomized, double-blind, placebo-controlled studies have been evaluated for the efficacy and safety of eluxadoline, in adults meeting Rome III criteria for IBS-D.
  - The primary end point of these studies, defined “a priori” to meet US FDA guidelines, was a decrease from baseline of  $\geq 30\%$  in the daily average score for worst abdominal pain on  $\geq 50\%$  days evaluated, and on the same days, daily stool consistency score of  $< 5$  using the Bristol Stool Form Scale.
    - Efficacy results were pooled from a 26 week study and the 1st 26 weeks of a separate 52 week study.



- The primary efficacy endpoint was met by patients treated with eluxadoline 75 mg or 100 mg twice daily compared to those treated with placebo.
  - During the first 12 week (26% and 17%, vs. 17%, respectively) ( $P < 0.001$  vs placebo).
  - During the first 26 weeks of the 2 trials (27 % and 31% vs. 20%;  $P < 0.001$  vs. placebo)
  - The NNT for symptom improvement was 10 and 14 for the 75 mg dose (weeks 1-12 and weeks 1-26, respectively), while the NNT for the 10 mg dose was 10 and 9 (for weeks 1-12 and weeks 1-26, respectively).
- The most common reported AE with eluxadoline use was constipation (8% vs. 3% for placebo).
  - This tended to occur within the first 3 mons of treatment.
- Nausea was reported by 8% of patients (vs. 5% for placebo); cardiac events were few and were not different between drug and placebo.
- A pooled safety analysis identified Sphincter of Oddi spasm in 0.5% of patients.
  - All occurred in those without a gallbladder (post-cholecystectomy)
- Pancreatitis occurred in 0.4% of patients.
  - Lipase normalization generally occurred within days after stopping eluxadoline.
- Contraindications
  - Do **not** use eluxadoline in patients with a history of pancreatitis, or in those without a gallbladder.
  - Patients with a history of alcoholism / alcohol abuse / addiction / those who consume more than 3 alcohol-containing beverages per day.

#### ❖ Loperamide

#### • CAG guidelines

- Do **not** offer diarrhea-predominant IBS patients continuous loperamide use to improve IBS symptoms (may ↓ diarrhea, but not global symptoms)
  - GRADE: Conditional recommendation, very-low quality evidence.
  - Vote: Strong agree, 17%; Agree, 83%

#### ❖ Neuromodulatory drugs

#### ➤ Subtypes

- Tricyclic antidepressants (TCAs; amitriptyline, desipramine, imipramine, nortriptyline)
- Selective serotonin reuptake inhibitors (SSRIs)
  - Less effective than TCAs
- Actions
  - ↓ visceral / central pain
  - Anti-cholinergic effects (↓ rate if intestinal transit / ↓ diarrhea / bloating in IBS-D, when given in higher dose)

▪ ↓ abdominal pain in IBS



- Recommended daily doses
  - Secondary amines
    - Desipramine, 25-100 mg/d
    - Nortriptyline, 25-75 mg/d
  - Tertiary amine
    - Amitriptyline, 50-100 mg/d
    - Imipramine, 50-100 mg/d
  - Adverse effects (AEs) less for secondary amines
    - ↓ anti-cholinergic/-histaminic AEs
    - ↓ sedation
    - ↓ constipation
- ACG Recommendation
  - Use TCAs to treat global symptoms of IBS (Strong recommendation; moderate quality of evidence)
  - Benefits
    - ↓ abdominal pain
      - Failure to improve (TCA, 43%; placebo, 64%)
      - RR of failure to improve on TCA 0.65 (95% CI, .55-0.77)
      - NNT = 5 (95% CI, 3.5-7)
    - ↓ global IBS symptoms (RR, 1.36; 95% CI, 1.07-1.71)
  - Adverse events
    - Drowsiness, dry mouth (RR, 1.59; 95% CI, 1.23-2.06)
- CAG Guidelines
  - Offer IBS patients low dose tricyclic antidepressants (TCAs) to improve IBS symptoms
    - GRADE: Strong recommendation, high quality evidence
    - Vote: Strongly agree, 25%; Agree, 75%
  - TCA are a class of agents, now commonly referred to as neuromodulators, which include amitriptyline, nortriptyline, imipramine, desipramine.
    - TCAs are believed to improve visceral pain and central pain by acting on
      - Norepinephrine and dopaminergic receptors (thus making them attractive candidates for the treatment of IBS-related abdominal pain)
      - Their anticholinergic effect slowing GI transit (thereby improving symptoms of diarrhea in some patients)
      - Psychological distress may also improve (because of the effect of dopaminergic and norepinephrine receptors)
  - 12 RCTs evaluated the efficacy and safety of TCAs for the treatment of patients with IBS.
    - Patients with IBS randomized to a TCA were more likely to not improve in global IBS symptoms compared with those randomized to placebo.
      - 23% did not improve, compared with 64% of those randomized to placebo
      - The RR of IBS symptoms do not improve with TCA therapy was calculated at 0.65 (95% CI 0.55-0.77)
      - The NNT with TCAs was 5 (95% CI 3.5-7)





- Tricyclic antidepressants should not be used in patients with known bundle branch block or QT prolongation.
  - Mechanism of action of tricyclic antidepressants primarily involves inhibition of serotonin and noradrenergic receptors. Blockade of muscarinic and adrenergic receptors also occurs, but to a lesser degree.
  - Secondary amines generally have less antihistaminic and anticholinergic effects and are thus less likely to cause sedation or constipation.
    - Tertiary amines (amitriptyline and imipramine) are more likely to have antihistaminic and anticholinergic side effects.
  - A systematic review and meta-analysis evaluated 7 RCTs that evaluated the effect of antidepressant therapy on abdominal pain.
    - Antidepressants were more likely to improve symptoms of abdominal pain than PL
      - However, the beneficial effects were due to TCA therapy, not to SSRIs.
  - A separate systemic review and meta-analysis showed that TCAs improved global symptoms in patients with IBS relative to placebo (related risk 1.36 [95% CI 1.07-1.71]).
  - The safety profile of TCAs for the treatment of IBS has been reviewed in several publications.
    - Meta-analysis of 6 clinical studies found that AEs occurred at a significantly greater rate with TCAs than with placebo (RR, 1.59; 95% CI 1.23-2.06).
      - Drowsiness and dry mouth occur most commonly
    - In a of 5 studies, IBS-D pooled analysis showed
      - Incidence of dry mouth (36% vs. 15%), insomnia (24% vs. 13%), constipation (23% vs. 6%), flushing (23% vs. 5%), palpitations (9% vs. 2%), and decreased appetite (8% vs. 1%) was significantly greater with TCAs relative to placebo.
      - NNH of 9 for experiencing an AE
      - NNH of 18 for prompting discontinuation
  - Patients should start on a low dose (e.g., 10 mg of amitriptyline or 10 mg of desipramine), with gradual dose titration upward to achieve therapeutic relief of symptoms while minimizing side effects.
    - Anecdotally, patients with IBS-D may respond better because of the anti-cholinergic properties of TCAs, which may improve symptoms of urgency and diarrhea.
    - Caution should be directed toward potential side effects, including dry mouth, dry eyes, urinary retention, constipation, and cardiac arrhythmias.
- ❖ Gut-directed psychotherapies (GDPs)
- ACG Recommendation
    - Use gut-directed psychotherapies (as adjunctive to standard medical therapies) to treat global IBS symptoms (Conditional recommendation; very low quality of evidence)
  - CAG Guidelines
    - Offer IBS patients cognitive behavioural therapy (CBT) to improve IBS symptoms.
      - GRADE: conditional recommendation, very low-quality evidence
      - Vote, Agree 83%; Neutral 17%



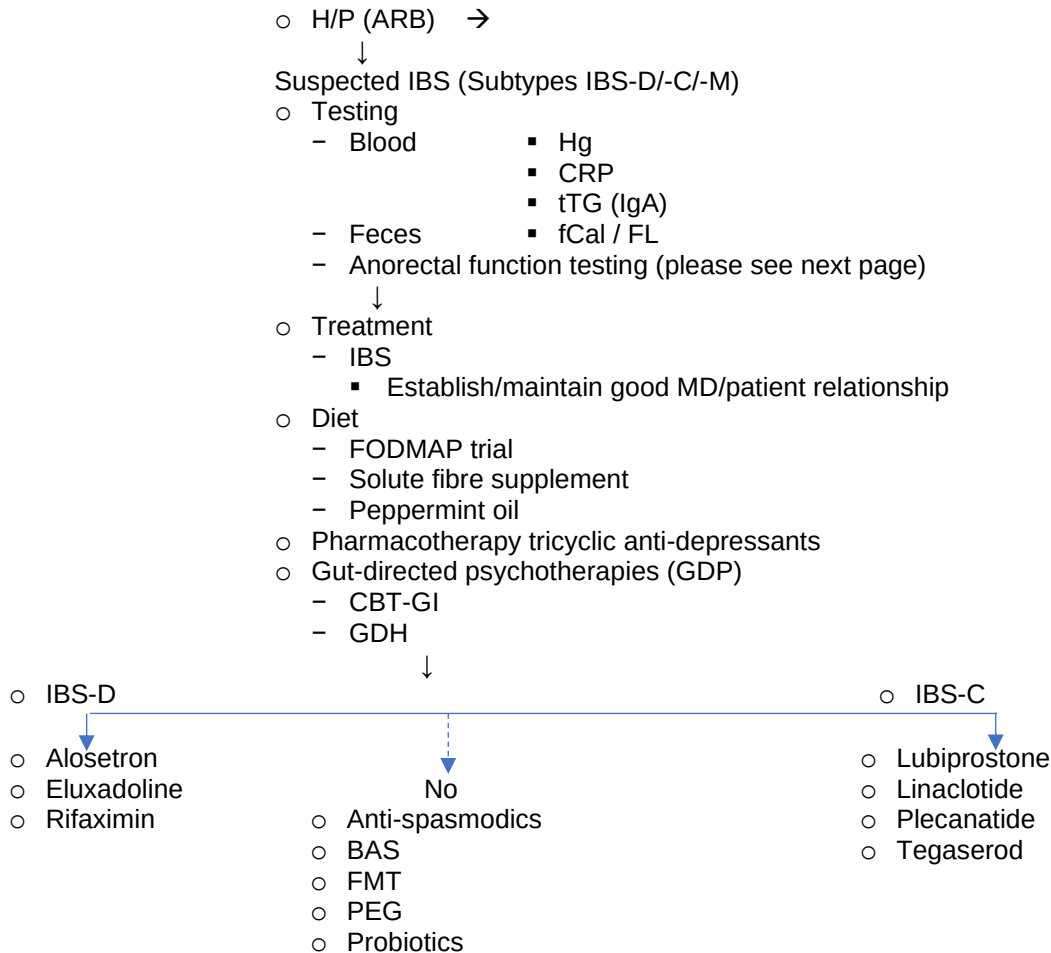
- The consensus group did **not** make a recommendation (neither for nor against) offering IBS patients
  - Relaxation techniques
  - Short term psychodynamic psychotherapy
- Subtypes
  - Cognitive-behaviour therapy (CBT-GI)
    - Mindfulness +/- stress reduction
  - Gut-derived hypnotherapy (GDH)
- Mechanism of action
  - GDPs (CBT-GI and GDH) act on emotional centres of the brain → modify cognitive and affective features which are in the appreciation of the gut input (perceive, interpret, regulate)
- Indications
  - Adjunctive to standard therapies in persons with moderate/severe IBS, especially in persons without comorbid mental health conditions
- ❖ Fecal microbiota transplantation (FMT)
  - ACG Recommendation
    - Do **not** use FMT for the treatment of global IBS symptoms (Strong recommendation; very low quality of evidence)
      - “...evidence to support FMT for the treatment of IBS is limited and of very low quality and cannot be recommended at present”
- ❖ No comment or recommendation per CAG Guidelines
  - A comprehensive literature review by Xu, et al. identified 4 studies which used Rome III criteria for the diagnosis of IBS; only 2 had been released in full manuscript form at the time of publication of the review
    - In the intention-to-treat analysis of 4 studies, a total of 254 patients were included (152 received FMT, and 102 received placebo).
      - At 12 week follow-up, patients who received donor FMT reported a 49% response rate compared with a 51% response rate in those who received placebo FMT.
    - No significant difference was noted in global symptoms in patients treated with FMT, as compared with placebo (RR, 0.93; 95% CI 0.48-1.79, P = 0.83)
- ❖ Biofeedback
  - IBS is a common disorder that includes both abdominal pain and changes in stool or consistency.
  - “... therapy in which participants use technology to track a process that is not normally under conscious control (e.g., heart rate, tension of the anal sphincter) in order to see how relaxed states of mind affect these measures.



- Research have proposed that achieving more relaxed states through the tool of biofeedback may help to improve the symptoms of IBS.
- “...proposed biofeedback (BF) plus standard therapy (ST) vs ST alone

| Treatment                 | RR, 95%CI                     | Certainty of evidence |
|---------------------------|-------------------------------|-----------------------|
| - BF + ST vs ST           | RR, 4.20; 95%CI: 1.4 to 12.58 | Very low              |
| - BF + ST vs sham BF + ST | RR, 2.33; 95%CI: 1.13 to 4.80 | Very low              |

- Algorithm for Suggested Management of Patient with IBS



Abbreviations: BAS, bile acid sequestrants; CBT-GI, cognitive behaviour therapy directed to GI tract; DRE, digital rectal examinations; fCal, fecal calprotectin; FL, fecal lactokin; FMT, fecal microbiome transplantation; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GDH, gut-directed hypnotherapy; GDP, gut directed psychotherapy; IBS, irritable bowel syndrome; IBS-C, IBS constipation predominant; IBS-D, IBS diarrhea predominant; P, physical examination; PDS, positive diagnostic strategy; PEG, polyethylene glycol; TCAs, tricyclic antidepressants

Source: Vasant DH, et al. Gut 2021; 70: 1241-40.



## Irritable Bowel Syndrome (IBS): Guideline (CAG; 2019)

Moayyedi P, et al J Can Assoc Gastroenterol 2019;2(1):6-29.

### ❖ Diagnosis

#### Recommended

- Serological testing for celiac disease (IBS-D)
  - Prevalence of positive celiac antibody tests in patients with IBS, ~1.6%
  - Odds ratio (OR) of positive celiac serology with IBS in persons
    - RR, 2.94, 95% CI, 1.36 – 6.35
- Colonoscopy at  $\geq 50$  yr
  - In persons with new-onset IBS symptoms (note that this is the age-specific time for average risk colonoscopy / FIT testing in non-IBS persons)
    - Author's note: Canadian guidelines do **not** yet reflect the US guideline recommending the time for average risk persons to have colonoscopy at 45 yr, but the data supporting age of 5 yr is strong, and likely future guidelines will reflect this literature.
- Not recommended
  - C-reactive protein (CRP)
    - Good negative predictive value:  $\text{CRP} \leq 0.5$  mg/dL predicts that the probability of the patient having IBD is  $\leq 1\%$
    - But, "because the underlying risk of having IBD among the general population with symptoms is  $< 1\%$ , it is unclear what additional value CRP testing would have in IBS patients"
  - Fecal calprotectin (FC)
    - The predictive value of FC increases with the cut-off for a normal concentration

| FC $\mu\text{g/g}$ Stool | Risk of IBD |
|--------------------------|-------------|
| $< 40$                   | $\leq 1\%$  |
| 1000                     | ~80%        |

    - Measure FC if there is a high suspicion of IBD
    - Routine testing is not supported, because neither a low nor high level of FC is predictive of IBS

### ❖ Per CAG Guidelines

- On Meta-analysis: A low FC level could exclude IBD ( $< 40$   $\mu\text{g/g}$  predicted a  $\leq 1\%$  chance of IBD), and the likelihood of IBD is increased with increasing FC levels 1000  $\mu\text{g/g}$  predicted a 79% of IBD).
  - The evidence statement was graded as very low quality due to the use of case control study designs which overestimate the diagnostic accuracy of use of the test.
    - Note: Levels between 50 to 150  $\mu\text{g/g}$  are equivocal for the diagnosis of IBD



- Although FC levels may be predictive of IBD, the consensus group agreed that because IBS is associated with only a mild risk of IBD, FC testing should be performed only in patients in whom there is high suspicion of IBD.
  - Perform colonoscopy at age < 50 yr if no alarm symptoms or no family history of IBD/CRC

- |                                                                                           |                                           |
|-------------------------------------------------------------------------------------------|-------------------------------------------|
| – Regardless of age of patient with IBS, there is ↑ risk within 10 yr of their developing |                                           |
| ▪ Any organic (GI) disease                                                                | HR, 1.77; 95% CI, 1.63 to 1.92; P < 0.001 |
| ▪ Colorectal cancer (CRC)                                                                 | HR, 1.72; 95% CI, 2.54 to 3.17; P < 0.001 |
| ▪ IBD                                                                                     | HR, 1.95; 95% CI, 1.49 to 2.48; P < 0.001 |
| ▪ Microscopic colitis (MC)                                                                | HR, 1.72; 95% CI, 1.58 to 1.87; P < 0.001 |

- Alarm symptoms are surprisingly poor to predict the presence of CRC
  - Predictors of CRC
    - Abdominal mass
    - Dark red rectal bleeding
  - Not predictors of CRC: rectal bleeding (other than dark red rectal bleeding), altered bowel habit, anemia, ↓ weight
  - However, “...the likelihood of organic disease increased with increasing number of alarm features”, especially in IBS-D
- Testing for food allergies
  - Food allergies are reported in 1% to 4% of the general population, and of these, ~70% are actually food intolerances (not true allergies)
  - Common food triggers for GI symptoms include carbohydrates, fatty foods, biogenic amines (wine/beer, salami, cheese), and histamine-releasing foods (milk, wine/beer, pork)
  - “If a particular food triggers GI symptoms, remove it from the diet, but allergy testing is unlikely to provide any additional benefit”
- Breath test with lactose
  - About 50% of persons with IBS may report lactose intolerance, and this is similar to a non-IBS population
  - Lactose malabsorption/intolerance may occasionally explain IBS symptoms, but the data” ....do **not** support the routine use of lactose [hydrogen, H<sub>2</sub>] breath testing in IBS patients”
    - The best “test” for lactose intolerance is the brief use of a lactose-free diet, and for the patient to choose on this personal basis



- Breath test with glucose (to diagnosis small intestinal bacterial overgrowth [SIBO])
  - In persons with IBS, 25% have an abnormal glucose H2 breath test, and the odd ratio (OR) if the prevalence of SIBO in patients with IBS compared with controls without GI symptoms (health persons) was 6.29 (95% CI, 4.55 to 8.68) but other control groups have not been widely studied
  - There are studies reporting on the role of antibiotics on GI symptoms in persons with a positive versus a negative glucose breath test
- Beneficial effects on only some symptoms
  - Global symptoms (SMA – 0.21; 95% CI, -0.31 to -0.10, P=0.0001)
  - Pain, abdominal (as above)
  - Bloating (SMD -0.13; 95% CI -0.24 to 0.02; P=0.02)
  - Flatulence (SMD -0.23; 95% CI -0.38 to -0.08; P=0.03)
- Overall, psychological therapy was superior to placebo
  - RR of IBS not improving 0.69 (95% CI 0.62 to 0.77: number needed to treat (NNT) 4: 95% CI, 3-5)

❖ Psychological therapies

- No benefit
  - Relaxation therapies
  - Stress management
  - Self-administered cognitive behaviour therapy (CBT)
  - Short term psychodynamic psychotherapy
  - Mindful meditation training CBT by internet

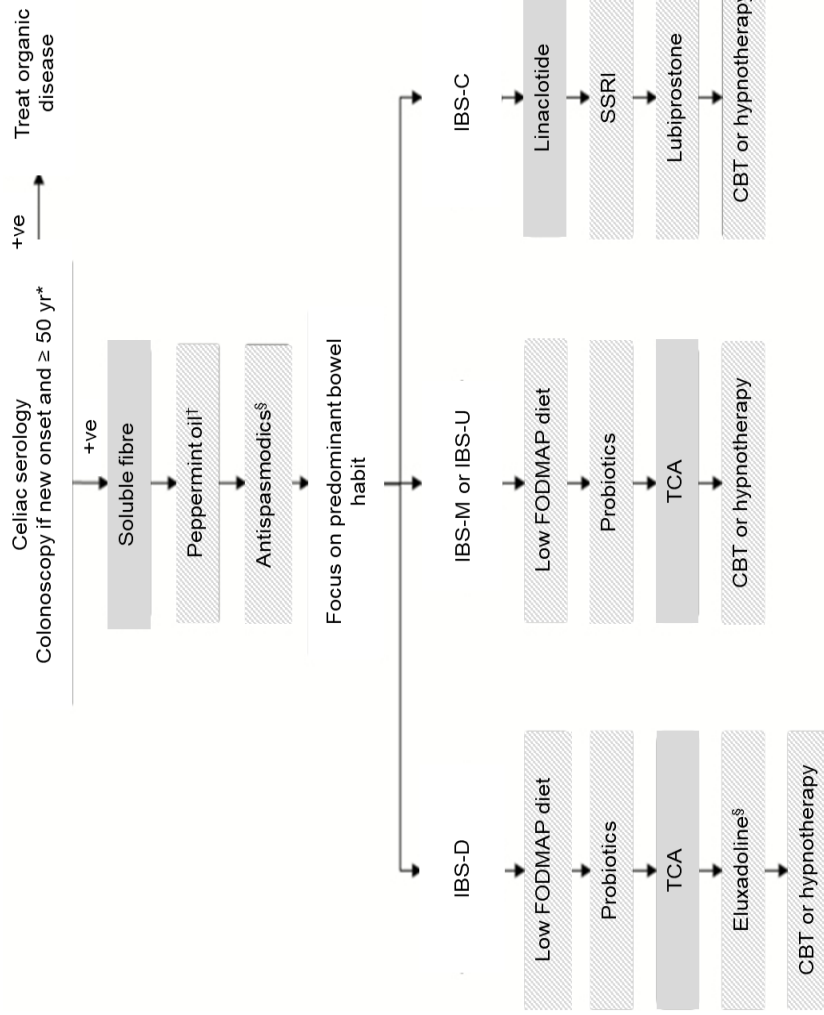
○ Benefit

| Description of Psychotherapy           | RR   | 95% CI       | NNT | 95% CI |
|----------------------------------------|------|--------------|-----|--------|
| – Cognitive behaviour therapy (CBT)    | 0.60 | 0.44 to 0.53 | 3   | 2-6    |
| – Hypnotherapy                         | 0.74 | 0.63 to 0.87 | 4   | 3-8    |
| – Multicomponent psychological therapy | 0.72 | 0.62 to 0.83 | 4   | 3-7    |
| – Dynamic psychotherapy                | 0.63 | 0.39 to 0.93 | 3   | 2-25   |
| – Active psychological therapy         | 0.50 | 0.38 to 0.84 | 3   | 2-9    |



## ❖ Pharmacological therapies

- Consensus guided algorithm for the management of IBS.



\*Reduce age threshold to ≥45 yr if female with IBS-D; †, if bloating/pain main feature; §, if pain main feature.

Abbreviations: CBT, cognitive behaviour therapy; FODMAP, fermentable oligo-, di-, monosaccharide polys; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-M, mixed IBS; IBS-U, unclassified IBS; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; Source: Moayyedi P, et al J Can Assoc Gastroenterol 2019; 2(1):6-29 (Figure 8)



- Anti-spasmodics
  - Overall, anti-spasmodics are superior to placebo to ↓ symptoms of IBS
    - RR of IBS symptoms not improving 0.65 (95% CI, 0.56 to 0.76; P < 0.00001; NNT 5; 95% CI, 4-8)
  - Dicyclomine, hyoscine butyl bromide, and pinaverium are effective (“benefit”), and are available in Canada
  - No benefit
    - Alverine
    - Mebeverine
    - Pirenzepine
    - Prifinium
    - Propinox
    - Rociverine
    - Trimebutine
  - Benefit

| Name                                                    | RR of IBS<br>not improving | 95% CI       | P       | NNT | 95% CI |
|---------------------------------------------------------|----------------------------|--------------|---------|-----|--------|
| – Otilonium                                             | 0.70                       | 0.54 to 0.90 | 0.005   | 5   | 4-11   |
| – Pinaverium bromide                                    | 0.56                       | 0.38 to 0.82 | 0.003   | 4   | 3-6    |
| – Hyoscine bromide                                      | 0.63                       | 0.51 to 0.78 | 0.0001  | 3   | 2-25   |
| – Cimetropium bromine                                   | 0.38                       | 0.20 to 0.71 | 0.002   | 3   | 2-12.5 |
| – Drotaverine                                           | 0.31                       | 0.19 to 0.50 | 0.0001  | 2   | 2-3    |
| – Dicyclomine (dicyclomine)<br>hydrochloride            | 0.65                       | 0.45 to 0.95 | 0.02    | 4   | 2-25   |
| – Tricyclic antidepressants<br>(TCAs), low dose         | 0.65                       | 0.55 to 0.77 | 0.00001 | 4   | 3-6    |
| – Selective serotonin<br>reuptake inhibitors<br>(SSRIs) | 0.68                       | 0.51 to 0.91 | 0.01    | 4   | 2.5-20 |

Adapted from: Moayyedi P, et al J Can Assoc Gastroenterol 2019;2(1):6-29.

#### Treatment Tips and Suggestion of Consensus Group

- TCAs may be better for IBS-D
  - SSRIs may be better for IBS-D
- These benefits of TCAs (SSRIs are not correlated with changes in depression, likely because of the low doses used)





❖ Recommended

- Diarrhea-predominant IBS (IBS-D)
  - Eluxadoline (a synthetic modulator of the opioid receptor)
    - $\mu$ -opioid receptors
    - $\delta$ -opioid receptors in GI tract

| Outcomes                                                                                                                                                                                                                                                                           | RR of IBS<br>not<br>improving | 95% CI                                           | P                            | NNT                | 95%<br>CI            |                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------|------------------------------|--------------------|----------------------|--------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>○ Benefits               <ul style="list-style-type: none"> <li>– All symptoms</li> <li>– Stool consistency</li> </ul> </li> <li>○ No benefits               <ul style="list-style-type: none"> <li>– Abdominal pain</li> </ul> </li> </ul> | 0.91<br>0.88<br><br>0.95      | 0.85 to 0.97<br>0.80 to 0.96<br><br>0.89 to 1.02 | 0.004<br>< 0.01<br><br>0.006 | 12.5<br>10<br><br> | 8-33<br>6-25<br><br> | } ▪ ↓ symptoms<br>begin to<br>occur in wk 1<br>of treatments |

- Eluxadoline is available in Canada
  - Although it may improve some GI symptoms in persons with IBS-D, there are numerous adverse effects .
- Give the common contraindications to the use of eluxadoline in IBS-D.
  - Alcohol use disorder (AUD)
  - Liver
    - ↓ hepatic function
  - Biliary tree
    - Bile duct obstruction
    - Cholecystectomy
  - Pancreas
    - Pancreatitis
    - Sphincter of Oddi
  - Colon
    - Chronic/severe constipation



### MCQ Alert

- % in persons with IBS, the risk of requiring a cholecystectomy is ↑ 2-3x

- Cholestyramine
  - Dose response to cholestyramine based on severity of bile acid malabsorption, based upon 7 day SeHCAT scanning (retention of tauroselcholic [75 selenium acid])
  - Editor's note: the benefit of sequestering bile acids increases with severity of the malabsorption (severe BAM, 96%; mild BAM, 70%)
    - In IBS-D patients who does not respond to other agents, cholestyramine may be beneficial

- Rifaximin

| Trials                                                   | RR of IBS not improving | 95% CI       | P     | NNT | 95% CI |
|----------------------------------------------------------|-------------------------|--------------|-------|-----|--------|
| – All trials / significant heterogeneity between trials  | 0.82                    | 0.72 to 0.95 | 0.006 | 9   | 6-12.5 |
| – Only trials with low risk of bias                      | 0.87                    | 0.82 to 0.93 | -     | 11  | 8-20   |
| – Not approved by Health Canada for the treatment of IBS |                         |              |       |     |        |

- Constipation-predominant IBS (IBS-C)

- Benefit

| Medication                              | RR of IBS not improving | 95% CI       | P       | NNT  | 95% CI |
|-----------------------------------------|-------------------------|--------------|---------|------|--------|
| – Lubiprostone                          | 0.91                    | 0.87 to 0.95 | 0.0001  | 12.5 | 8-25   |
| – Linaclotide                           | 0.81                    | 0.77 to 0.85 | 0.00001 | 6    | 5-8    |
| ▪ Also effective for abdominal pain     |                         |              |         |      |        |
| ▪ Adverse effects: diarrhea, flatulence |                         |              |         |      |        |

Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome; NNT, number needed to treat; P, probability; RR, relative risk



- ❖ Not recommended (controversial: may be effective second-line therapy)
  - Loperamide (blocks  $\mu$ -opioids receptor)
  - Significantly ↓ stool frequency, improves stool consistency and urgency
    - Did not benefit abdominal pain, or global IBS symptoms
      - Editor's comment: although loperamide does not ↓ global IBS symptoms or abdominal pain, many IBS-D sufferers would appreciate the clear benefit in stool-related symptoms.

| Clinical Features            | RR of stool frequency not improving                  | 95% CI      | P    |
|------------------------------|------------------------------------------------------|-------------|------|
| ▪ ↓ stool frequency          | 0.2                                                  | 0.05 to 0.9 | 0.01 |
| ▪ Improve stool consistency: | 100% improved, versus 20% to 45% on placebo; p=0.006 |             |      |
| ▪ Urgency                    |                                                      |             |      |

- Osmotic laxatives
- 5-HT<sub>4</sub> agonist, prucalopride
  - Effective for constipation relief in patients with chronic idiopathic constipation (CIC) but not in IBS-C

Abbreviations: BAM, bile acid malabsorption; CI, confidence interval; CRC, colorectal cancer; CRP, C-reactive protein; FIT, fecal immune testing; GFD, gluten-free diet; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome; MC, microscopic colitis; SIBO, small intestinal bacterial overgrowth; SSRIs, selective serotonin receptor inhibitors; TCAs, tricyclic antidepressants



## Management of Irritable Bowel Syndrome (IBS): Guidelines of British Society of Gastroenterology (BSG; 2021)

Vasant DH, et al. Gut 2021; 70: 1241-40.

- This guideline updates that of the British Society of Gastroenterology (BSG) published in 2007, and uses the Rome IV diagnostic criteria for the irritable bowel syndrome (BS)
- Symptom-based criteria are used to make a positive diagnosis of IBS, as per the 2016 Rome IV criteria.

### ➤ Rome IV diagnostic criteria

- Recurrent abdominal pain, on average at least 1 day per week in the last 3 mon, and associated with two or more of the following:
  - Related to defecation
  - Associated with a change in frequency of stool
  - Associated with a change in stool form
 plus
- Criteria fulfilled for the last 3 mon with symptoms present for at least 6 mon prior to diagnosis

| IBS-C                                                                                                 | IBS-D                                                                                                 | IBS-M                                                                                                 | IBS-U                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| ≥ 25% of bowel movements of Bristol stool form types 1 or 2, < 25% of Bristol stool form type 6 or 7. | ≥ 25% of bowel movements of Bristol stool form types 6 or 7, < 25% of Bristol stool form type 1 or 2. | ≥ 25% of bowel movements of Bristol stool form types 1 or 2, ≥ 25% of Bristol stool form type 6 or 7. | Patients who meet criteria for IBS, but who do <b>not</b> fall into one of the other three subgroups according to Bristol stool form type. |

- The subgroups include
  - IBS-C, IBS with constipation
  - IBS-D, IBS with diarrhea
  - IBS-M, IBS with mixed bowel habits
  - IBS-U, IBS which is unclassified

Abbreviations: IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed bowel habits; IBS-U, IBS unclassified



### The Rome IV

- Patients excluded by Rome IV criteria as having IBS may have another functional bowel disorder, and it is possible that therapeutic data from studies using Rome III may not be applicable to Rome IV criteria.

### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Differences between the Rome IV and the Rome III criteria for IBS, which help to explain why among persons who believe they have IBS, 80% fulfill the criteria for Rome III, whereas 60% fulfill Rome IV criteria. (These "...highly restrictive criteria [of Rome IV]" may not include the same kind of patients and their therapeutic response, as patients with IBS entered into the therapeutic studies using the more inclusive Rome III and thereby possibly reflect a severity of IBS seen in primary/secondary care versus tertiary care)

| Symptoms (Chronic/Fluctuating)                            | Criteria |          |
|-----------------------------------------------------------|----------|----------|
|                                                           | Rome IV  | Rome III |
| ○ Abdominal                                               |          |          |
| - Pain                                                    | +        | +        |
| - Discomfort                                              | -        | +        |
| ○ Pain associated with defecation                         | -        | +        |
| ○ Minimum frequency of pain                               | ≥ 1/wk   | ≥ 3/mon  |
| ○ Pain relieved with defecation                           | +        |          |
| ○ Definition includes a disorder of gut-brain interaction | +        | -        |

- Because of the relative restrictive nature of Rome IV criteria, a definition of IBS formulated in the National Institute of Health and Care of Excellence (NICE) guideline may be more suitable for clinical diagnosis of IBS.
- In patients seen in a primary care setting
  - Abdominal pain/discomfort
  - Associated with altered
    - Stool frequency, or
    - Stool form

For ≥ 6 mon, and in the absence of alarm symptoms/signs

Note: "...bloating is not required to fulfill the Rome IV criteria but, if present, is highly supportive of IBS, and is often accompanied by visible abdominal distention"

- ↑ likelihood of diagnosis being IBS vs. not being IBS in persons meeting Rome IV criteria
  - IBS-C, 22x
  - IBS-M, 11x



- The National Institute for Health and Care Excellence (NICE) guideline definition of IBS (abdominal pain or discomfort, in association with altered bowel habit, for at least 6 mon, in the absence of alarm symptoms or signs)
  - Pragmatic
  - May be more applicable to patients with IBS in primary care than diagnostic criteria derived from patients in secondary care, such as the Rome IV criteria (recommendation: weak, quality of evidence: low).
- Demography
  - Prevalence depending upon diagnostic criteria
    - Country source of data
      - Calculated pooled global prevalence of IBS, 11%
      - Rome Foundation global survey of IBS
        - Rome IV criteria, 4%
        - Rome III, 10%
  - Peak age, 18-39 yr
  - F > M, OR 1.8, 95% CI: 1.7 – 2.0
- Pathophysiology
  - “... a disorder of altered bidirectional communication between the gut and brain (via the [disordered] gut-brain axis”  
“a biopsychosocial aetiology ... a disorder of gut-brain interaction”
  - Components
    - Brain
      - Central nervous system (CNS) / Autonomic nervous system (ANS)
      - Altered visceral perception
    - Gut
      - Motility
      - Infection
      - Inflammation
      - Inherited
- Central Nervous System (CNS) / Autonomous Nervous System (ANS)
  - Interoceptive signals from gut, plus memories of these signals → activation of brain regions
    - hypersensitive/hypervigilance (↑ visceral perception)
    - Anxiety from symptoms
    - ↓ inhibition of visceral/somatic stimuli
    - ↓ parasympathetic / ↑ sympathetic nervous system activity
    - Altered visceral perception
  - ↓  
 Modulation  
 anxiety/depression  
 Cognition  
 Emotion

↓ visceral perception to mechanical/electrical stimuli in 20% of IBS patients  
 ↓ visceral perception in 20% of IBS patients
 
    - Correlates with abdominal distention



- Motility/Transit

- Abnormal colonic transit time (CTT)
    - IBS-D, 25% to 45%
    - IBS-D → IBS-M, 10% to 20%
- }     ■ Also, abnormal orocecal transit time

| Function                                                                                                                          | IBS-D | IBS-C |
|-----------------------------------------------------------------------------------------------------------------------------------|-------|-------|
| - Transit rate (time; CTT)                                                                                                        | ↑     | ↓     |
| - High amplitude contractions of the colon                                                                                        | ↑     | ↑     |
| - Motility                                                                                                                        | ↑     | ↓     |
| - Inverse correlation with CTT consistency of <ul style="list-style-type: none"> <li>▪ Stool</li> <li>▪ Pain, bloating</li> </ul> |       |       |
| - Serotonin concentration                                                                                                         | ↑     | ↓     |

- Pain, bloating, and flatulence correlate with both
  - Oro-cecal and colonic transit times
  - Inversely with stool consistency
- In IBS-D, abdominal pain also correlates with high amplitude contractions

- Epithelial Permeability ./ Immune Function

- ↑ epithelial permeability
  - Dysbiosis of microbiome
  - Post-infectious irritable bowel syndrome (PI-IBS)
  - “Stress”
  - Food antigens
- }     - ↑ permeability to antigens (e.g., LPS)
- }     - ↓ barrier function
- }     ■ ↑ mast cells (SB; DC, RS)
- }     ■ ↑ IL-10
- }     ■ ↑ histamine release

Abbreviations: DC, descending colon; LPS, lipopolysaccharide; PI-IBS, post-infectious irritable bowel syndrome; RS, rectosigmoid; SB, small bowel

- Microbiome

- Infections (bacterial, parasitic, viral) → trigger IBS (post-infectious IBS [PI-IBS])
  - Curiously, IBS symptoms may be triggered by use of antibiotics
- No specific microbiome profile associated with IBS, but
  - In IBS-D / IBS-C, there are “... subtype-specific and symptom-related variations in microbial composition and function”



- Genetics / epigenetics
  - Suggestive findings
    - Familial clustering of IBS
    - Single nucleotide polymorphisms (SNPs)
    - DNA methylation
    - Various miRNAs associated with
      - ↑ intestinal permeability
      - ↑ visceral sensitivity
- Approach
  - History/physical, including family history for celiac disease, IBD/IBS, colorectal cancer (CRC)
    - Include questions re
      - Other functional disorders of GI tract, as well as functional somatic disorders
      - Anxiety, depression, abuse, alarm symptoms (common [in 80%] patients with IBS)
  - CBC, C-reactive protein (CRP) / fecal calprotectin (FC) > 100 µg/g is abnormal
  - Abdominal film to exclude fecal loading in IBS-C
  - Tissue transglutaminase (tTG) controversial for first-line testing in patients with IBS-D
  - Age, appropriate fecal food immune testing (FIT) or CRC screening (colonoscopy) (note that this suggestion is not supported by all experts)
- Recommendations
  - Establish an effective doctor-patient relationship and a shared understanding of target outcomes.
    - Such a relationship leads to
      - ↑ quality of life and symptoms
      - ↓ healthcare visits
      - ↑ adherence to treatment (recommendation: strong, quality of evidence: low).
  - Patients with IBS would like to have ↑ empathy / support as well as information from clinicians about the nature of the condition, diagnosis and symptom management options (recommendation: strong, quality of evidence: low).
  - Patients presenting with symptoms of IBS for the first time in primary care should have
    - A complete blood count (CBC)
    - C reactive protein (CRP) / erythrocyte sedimentation rate (ESR)
    - Celiac serology and, in patients <45 yr with diarrhea, a fecal calprotectin (to exclude inflammatory bowel disease).
    - Local and national guidelines for colorectal and ovarian cancer screening should be followed, where indicated (recommendation: strong, quality of evidence: moderate).
  - Clinicians should make a positive diagnosis of IBS based on symptoms, in the absence of alarm symptoms or signs, or abnormalities on simple blood and stool tests (recommendation: strong, quality of evidence: moderate).





- Referral to gastroenterology in secondary care is warranted when there is
    - Diagnostic doubt
    - Patients with symptoms that are severe
    - Refractory to first-line treatments
    - Where the individual patient requests a specialist opinion (recommendation: weak, quality of evidence: low).
      - Author's suggestion refer to specialist / second opinion if patient is doubtfully of their diagnosis/management, and if you believe they require reassurance and support to avoid further unnecessary investigations.
  - Colonoscopy
    - Indications
      - Age-appropriate screening for CRC
      - Possible microscopic colitis
      - Female  $\geq 50$  yr
      - Associated autoimmune disease
      - Drugs
        - Severe watery nocturnal diarrhea, < 12 mon
        - Drugs
          - NSAIDs
          - PPIs
          - SSRIs/SNRIs
          - Statins
  - Where appropriate, consider investigations for
    - Celiac disease
    - Bile acid wastage (BAW; aka bile acid malabsorption [BAM])
    - Small intestinal bacterial overgrowth (SIBO)
    - Microscopic colitis
    - "Unmasked" lactose intolerance
    - Pancreatic exocrine insufficiency (PEI)
    - Defecatory disorder / overflow diarrhea
- Recommendations
- There is no role for colonoscopy in patients with IBS except in those with alarm symptoms or signs  
Symptoms suggestive of IBS with diarrhea who have atypical features and/or
    - Relevant risk factors that  $\uparrow$  the likelihood of them having microscopic colitis (female sex, age  $\geq 50$  yr, coexistent autoimmune disease, nocturnal or severe, watery, diarrhea, duration of diarrhea <12 mon unexplained, weight loss or use of potential precipitating drugs including non-steroidal anti-inflammatory drugs, proton pump inhibitors, etc.) (recommendation: strong, quality of evidence: moderate).
  - In patients with symptoms suggestive of IBS plus diarrhea, plus
    - Atypical features such as nocturnal diarrhea, or a prior cholecystectomy
      - Perform 23-seleno-25-homotaurocholic acid (nuclear medicine) scanning or
      - Serum 7 $\alpha$ -hydroxy-4-cholesten-3-one to exclude bile acid diarrhea (recommendation: strong, quality of evidence: low).



- In patients with IBS and coexisting symptoms suggestive of a defecatory disorder or fecal incontinence, perform
    - Anorectal physiology tests to select those who might benefit from biofeedback (recommendation: weak, quality of evidence: low).
  - Do **not** test for exocrine pancreatic insufficiency, or with hydrogen breath testing to rule out small intestinal bacterial overgrowth (SIBO) or carbohydrate intolerance, in patients with typical IBS symptoms (recommendation: strong, quality of evidence: weak).
  - Explain to the patient the diagnosis of IBS
    - Its underlying pathophysiology and the natural history of the condition, including common symptom triggers.
    - Introduce the concept of IBS as a disorder of gut brain interaction, gut brain axis and
      - How this is impacted by diet, stress, cognitive, behavioural and emotional responses to symptoms, and post-infective changes (recommendation: strong, quality of evidence: weak).
  - All patients with IBS should take regular exercise (recommendation: strong, quality of evidence: weak)
- Treatment
- Again, stress the importance of establishing an effective doctor-patient relationship and a shared understanding
- ❖ Dietary therapies
- Identify if patient has food-related symptoms (e.g., milk, soda pop, fatty foods)
  - ↓ intake of alcohol, caffeine fatty or spicy foods
  - Place on fermentable, oligo-, di-, monosaccharides and polyols (FODMAP) diet
  - ↑ soluble fibre (e.g., ispaghula, not wheat bran) maximum 30g/d
  - Probiotics
  - “Food elimination diets based on IgG antibodies are not recommended”
- FODMAP Diet
- FODMAPs → ↓ risk of removing symptomatic control diet (RR, 0.71; 95% CI : 0.61 – 0.83)
    - First part of FODMAP diet, wk 4 to 6, is the “elimination” phase, to be followed by a long-term personalized slow reintroduction phase
    - Success of long-term open-label studies ~50%
  - It is recommended that a registered dietician be involved with the patient for the elimination and personalization component of the use of FODMAP diet (possibly because of FODMAP → ↓ fecal bacteria (total / Bifidobacter)



- Gluten-free-diet (GFD)
  - There is no evidence for the benefit of a GFD in IBS except for patients with proven celiac disease
    - Some persons with IBS report ↓ symptoms on a GFD, perhaps because a
      - GFD approximated a FODMAP, or
      - Associated non-celiac gluten sensitivity (NCGS)
- Recommendations
  - Offer first-line dietary advice to all patients with IBS (recommendation: strong, quality of evidence: weak).
  - Do **not** advice food elimination diets based on IgG antibodies in patients with IBS (recommendation: strong, quality of evidence: moderate).
  - Take soluble fibre (such as ispaghula) for global symptoms and abdominal pain in IBS.
    - Avoid insoluble fibre (e.g., wheat bran), as it may exacerbate symptoms.
  - Start soluble fibre at a low dose (3–4 g/day), and built up gradually to avoid bloating (recommendation: strong; quality of evidence: moderate).
  - Use a diet low in fermentable oligosaccharides, disaccharides and monosaccharides and polyols (FODMAP) as a second-line dietary therapy for global symptoms and abdominal pain in IBS.
    - Its implementation should be supervised by a registered dietitian
  - Reintroduce fermentable oligosaccharides, disaccharides and monosaccharides and polyols according to tolerance (recommendation: weak, quality of evidence very low).
  - Do **not** use a gluten-free diet in IBS unless the patient has proven celiac disease (recommendation: weak, quality of evidence very low)
- Probiotics
  - Meta-analysis of 37 RCTs demonstrated ↓ symptoms in IBS patients

| Probiotic         | RR   | 95% CI       |                                                             |
|-------------------|------|--------------|-------------------------------------------------------------|
| – Bifidobacterium | 0.79 | 0.70 to 0.91 | } Use probiotic for ~12 wk before deciding upon its benefit |
| – Escherichia     | 0.56 | 0.79 to 0.93 |                                                             |
| – Lactobacillus   | 0.75 | 0.60 to 0.94 |                                                             |
| – Combinations    | 0.79 | 0.70 to 0.81 |                                                             |



➤ Recommendation

- Use probiotics, for global symptoms and abdominal pain in IBS.
  - It is not possible to recommend a specific species or strain of probiotic
  - Patients wishing to try probiotics, advise the patient to use the selected products up to 12 weeks, and then discontinue them if there is no improvement in symptoms (recommendation: weak, quality of evidence: very low).

❖ Pharmacological

➤ First-line

- Anti-diarrheal
  - Loperamide
  - $\mu$ -opioid agonist  $\rightarrow$   $\downarrow$  activity of myenteric plexus
    - $\rightarrow$   $\uparrow$  intestinal transit time
    - $\rightarrow$   $\uparrow$  absorption of water ( $\uparrow$  dwell time" because of  $\uparrow$  intestinal transit time)
- Anti-spasmodics
  - Anti-muscarinic ( $\downarrow$  motility)
  - Smooth muscle relaxants (direct acting relaxants of intestinal smooth muscle)
    - Benefit
      - $\downarrow$  global symptoms
      - $\downarrow$  abdominal pain
    - Neither mebeverine or alverine are of benefit
    - Peppermint oil of benefit
      - $\downarrow$  global symptoms
      - $\downarrow$  abdominal pain
    - Ranking of “traditional” therapies (meta-analysis)

| Treatment         | Global Symptoms | Abdominal Pain |
|-------------------|-----------------|----------------|
| – Peppermint oil  | #4              | #3             |
| – Anti-spasmodics | #3              | #2             |
| – TCAs            | #2              | #1             |

- Laxatives for IBS-C
  - Mixed effects for benefit of constipation / abdominal pain, and only short-term (~4 wk) studies
  - Polyethylene glycols (PEG)
    - May be effective for IBS-C associated constipation, but  $\uparrow$  abdominal pain



## Recommendations

- Use loperamide for diarrhea in IBS-D.
  - However, abdominal pain, bloating, nausea and constipation are common, and may limit tolerability.
  - Titrating the dose carefully may ↓ these adverse effects (recommendation: strong; quality of evidence: very low).
- Use certain antispasmodics for global symptoms and for abdominal pain in IBS.
  - Common side effects are: dry mouth, visual disturbance and dizziness are common side effects (recommendation: weak, quality of evidence: very low).
- Use peppermint oil to ↓ global symptoms, and to ↓ abdominal pain in IBS.
  - Gastroesophageal reflux is a common side effect (recommendation: weak, quality of evidence: very low).
- Use polyethylene glycol (PEG) for constipation in IBS.
  - Abdominal pain is a common side effect (recommendation: weak; quality of evidence: very low)

## ➤ Second-line, IBS-D

### • Gut-brain neuromodulators

#### ○ Benefits

| Treatment                                                  | Global Symptoms<br>RR (95% CI) | Abdominal Pain<br>RR (95% CI) |
|------------------------------------------------------------|--------------------------------|-------------------------------|
| – Tricyclic antidepressants (TCAs)                         | 0.65 (0.55 to 0.77)            | 0.59 (0.43 to 0.83)           |
| – Selective serotonin reuptake inhibitors (SSRIs)          | 0.68 (0.51 to 0.91)            | Not effective                 |
| – Serotonin and norepinephrine reuptake inhibitors (SNRIs) | No RCTs in IBS                 |                               |
| – Preglobulin                                              | More data needed               |                               |

## Recommendations

- Tricyclic antidepressants (TCAs; gut-brain neuromodulators) as second-line drugs for global symptoms and abdominal pain in IBS.
    - TCAs can be initiated in primary or secondary care, but
      - Give a careful explanation as to the rationale for their use is required
      - Patients should be counselled about their side-effect profile.
      - They should be commenced at a low dose (e.g., 10 mg amitriptyline once a day), and titrated slowly to a maximum of 30–50 mg once a day
- (Recommendation: strong, quality of evidence: moderate)



- Selective serotonin reuptake inhibitors (SSRIs) (gut-brain neuromodulators) are used as second-line drug for global symptoms in IBS.
  - Can be initiated in primary or secondary care
  - Give careful explanation as to the rationale for their use
  - Patients should be counselled about their side-effect profile (recommendation: weak, quality of evidence: low)
- Eluxadoline
  - $\mu$ - $\kappa$ - $\delta$ -opioid receptor antagonist for IBS-D
  - $\downarrow$  transit /  $\downarrow$  visceral hypersensitivity
  - Superior to placebo to
    - $\downarrow$  pain (RR, 0.89; 95% CI: 0.84-0.94)
    - $\downarrow$  diarrhea (improve stool consistency) (RR, 0.87; 95% CI: 0.83-0.91)
  - Serious adverse effects
    - Pancreatitis
    - Sphincter of Oddi spasm
  - Contraindications
    - Hepatobiliary tree
      - Liver disease, severe
      - Pancreatitis
      - Sphincter of Oddi spasm
      - Cholecystectomy
    - Alcohol use disorder / alcohol dependence
- Alosetron, Ramosetron, Ondansetron
  - 5-HT<sub>3</sub> receptor antagonists, used for women with IBS-D
  - $\downarrow$  transit /  $\downarrow$  visceral sensitivity
    - Alter rectal compliance
  - Superior to placebo approved by FDA
    - Composite end point for IBS-D
      - Alosetron, RR, 0.69; 95% CI 0.60-0.8
      - Ramosetron, RR, 0.78; 95% CI: 0.67-0.91
    - Abdominal pain, stool consistency
  - Alosetron and ramosetron are unavailable in many countries.
  - Ondansetron titrated from a dose of 4 mg once a day to a maximum of 8 mg three times a day is a reasonable alternative.
  - Constipation is the most common side effect.
  - This drug class is likely the most efficacious for IBS with diarrhea (recommendation: weak, quality of evidence: moderate to high)
  - 5-HT<sub>3</sub> receptor antagonists have risk for potential development of ischemic colitis
  - Ondansetron superior to placebo to
    - $\downarrow$  urgency
    - $\downarrow$  bloating
    - Improve stool consistency



#### Treatment Comment

- “This drug (5-HT<sub>3</sub> receptor antagonist) class is likely the most efficacious for IBS with diarrhea” (5-HT<sub>3</sub> receptor antagonists)

#### – Ranking of therapy

| Treatment    | FDA composite endpoint<br>plus global symptoms | Abdominal<br>pain | Stool<br>frequency |
|--------------|------------------------------------------------|-------------------|--------------------|
| – Alosetron  | #1                                             |                   | #1                 |
| – Ramosetron |                                                | #1                |                    |

- Rifaximin
  - Use rifaximin (non-absorbable antibiotic)
    - Its effect on abdominal pain is limited
    - Not available for this indication in many countries (recommendation: weak, quality of evidence: moderate)
  - A non-absorbable antibiotic
  - Superior to placebo for
    - The FDA composite end point for IBS-D (RR, 0.92; 95% CI: 0.86-0.98)
    - For stool consistency
  - Adverse effects
    - Headache

#### Recommendations

- Eluxadoline (a mixed opioid receptor drug) is contraindicated in patients with
  - Prior sphincter of Oddi problems
  - Cholecystectomy
  - Alcohol dependence
  - Pancreatitis
  - Severe liver impairment
 (recommendation: weak, quality of evidence: moderate)

#### ➤ Second-line Treatment for IBS-C

- Secretagogues
  - Linaclotide
    - Guanylate cyclase (GC) c agonist
      - Action in jejunum and ileum to stimulate ↑ cGMP
    - Benefits in
      - ↑ completely spontaneous bowel movements (CSBMs) ≥ 1 / wk (RR: 0.82; 95%CI, 0.78-0.87)
      - ↓ bloating



- Plecanatide
  - GC-agonist, binding in a pH-dependent manner
    - Action mainly in jejunum
  - Benefit
    - Improves FDA composite end point (RR, 0.88; 95% CI: 0.82-0.94)
    - ↓ abdominal pain
- Lubiprostone
  - Prostaglandin E derivative → activates type 2 chloride channels (Cl C type 2)
  - Benefits
    - Improves FDA composite and point for IBS-C (RR, 0.87; 95% CI: 0.78-0.96)
    - ↓ abdominal pain
    - ↑ CSBMs ≥ 1
    - ↓ bloating
- Tenapanor
  - Inhibitor of sodium (Na<sup>+</sup>) – hydrogen (H<sup>+</sup>) exchanger (NHE-3)
  - Benefits
    - Improves FDA composite score (RR, 0.85; 95% CI: 0.79-0.92)
    - ↓ abdominal pain
    - ↑ CSBMs ≥ 1
    - ↓ bloating
- 5-HT<sub>4</sub> agonists
  - Tegaserod prokinetic, ↑ rate of transit
  - Indications
    - Women < 65 yr, IBS-C, no cardiovascular disease (because of small drug-related risk of ischemia)
  - Benefit
    - Vs placebo (RR, 9.95; 95% CI: 0.80-0.91)
    - ↓ bloating

| Treatment                 | Linacotide | Plecanatide | Lubiprostone | Tenapanor | Tegaserod |
|---------------------------|------------|-------------|--------------|-----------|-----------|
| ▪ CSBMs ≥ 1 wk            | +          |             |              | +         |           |
| ▪ Abdominal pain          |            | +           | +            | +         |           |
| ▪ Bloating                | +          |             | +            | +         | +         |
| ▪ FDA composite and point |            | +           | +            |           |           |

- Ranking of therapy
  - Network meta-analysis
    - Linacotide 290 mg po od ranked first across all endpoints, including bloating
  - Indirect comparisons
    - No significant differences between drugs





- Recommendations for second line drugs for IBS-C
  - Linaclotide (guanylate cyclase-C agonist)
    - Likely to be the most efficacious secretagogue available for IBS with constipation
    - Diarrhea is a common side effect  
(recommendation: strong, quality of evidence: high)
  - Lubiprostone (chloride channel activator)
    - Less likely to cause diarrhea than others
    - Patients should be warned that nausea is a frequent side effect  
(recommendation: strong, quality of evidence: moderate)
  - Plecanatide (guanylate cyclase-C agonist)
    - Diarrhea is a common side effect, and is no less likely than with linaclotide or tenapanor  
(recommendation: strong, quality of evidence: high).
  - Tenapanor (sodium-hydrogen exchange inhibitor)
    - Diarrhea is a frequent side effect.  
(recommendation: strong, quality of evidence: high)
  - Tegaserod (5-Hydroxytryptamine 4 receptor agonist)
    - Diarrhea is a common side effect  
(recommendation: strong, quality of evidence: moderate).
  - Use IBS-specific cognitive behavioural therapy (CBT)
    - For global symptoms in IBS  
(recommendation: strong, quality of evidence: low).
  - Use gut-directed hypnotherapy
    - For global symptoms in IBS  
(recommendation: strong, quality of evidence: low).
  - Psychological therapies when symptoms have not improved after 12 mon of drug treatment.
    - Referral can be made at an earlier stage, if accessible locally, and based on patient preference  
(recommendation: strong, quality of evidence: low).
- Psychological therapies
  - If patient have not improved after 12 mon of diet / pharmacological treatment, consider psychological therapy.
    - The best long-term psychological therapies are
      - Cognitive behaviour therapy (CBT) (emotions, thoughts, actions, beliefs, education, stress management, GI-specific anxiety)
        - CBT face-to-face (RR, 0.62; 95% CI: 0.48-0.80)
        - CBT can be therapist-given or therapist-guided (therapists must have IBS training)
        - Endorsed by BSG and NICE guidelines



- Gut-directed hypnotherapy
  - IBS protocols
  - Tailored to patient's symptoms
  - 6-12 face-to-face weekly sessions
  - Benefit: RR of remaining symptomatic (0.73, 95% CI: 0.55-0.97) vs education/support (RR, 0.76; 95% CI, 0.49-0.91)
  - > 75% of IBS patients have a  $\geq 50$  point  $\downarrow$  IBS severity score, plus  $\downarrow$  anxiety /  $\downarrow$  depression

➤ Recommendations

- Severe or refractory IBS symptoms
    - Review the diagnosis, and consider further targeted investigation (recommendation: weak, evidence: very low).
    - Use an integrated multidisciplinary approach (recommendation: weak, evidence: very low).
  - Avoid
    - Opioids
    - Unnecessary surgery
    - Unproven, unregulated diagnostic
    - Therapeutic approaches incentivised by financial or reputational gain should be avoided (recommendation: strong, evidence: very low).
  - Consider use of combination gut-brain neuromodulators (termed “augmentation”) for more severe symptoms, with vigilance for risks of serotonin syndrome (recommendation: weak, evidence: very low).
- Severe or Refractory IBS Symptoms
    - No accepted definitions
      - Suggested meaning of refractory IBS” “...patients whose symptoms have not improved with interventions, some of whom may also have severe symptoms”
      - The patient with severe / refractory IBS may possibly have an organic disorder, such as
        - Abdominal pain syndrome (centrally mediated)
        - Narcotic bowel syndrome
        - Small intestinal dysmotility
      - In IBS-D, consider possible
        - Celiac disease
        - Collagenous/lymphocytic (microscopic colitis)
        - Exocrine pancreatic insufficiency (EPI)
        - Small intestinal bacterial overgrowth (SIBO)
    - Treatment
      - Pharmacological
        - Augmentation (combination of gut-brain neuromodulation)
      - Surgical
        - Temporary loop ileostomy, with later conversion to colectomy if IBS symptoms improved



- Fecal Microbial Transplantation

#### MCQ Temptation

- Give the use of fecal microbial transplantation (FMT) for the treatment of severe refractory IBS.
  - None!
    - Meta-analysis of 5 RCTs demonstrate no significant benefit compared to placebo (RR, 0.98; 95% CI: 0.58 to 1.66), and
      - In fact 2 pooled studies showed that placebo was superior to capsules containing pooled donor stool (RR, 1.96; 95% CI: 1.19-3.20)

#### ➤ Recommendation

- Successful completion of large clinical trials will require pragmatic inclusion criteria, minimization of the participant trial burden, and effective recruitment strategies that reach into community settings.
  - Virtual (remote access) trial approaches will reduce geographical exclusion/variation.
- A priority-setting partnership would best discern valuable research questions.

Abbreviations: ANS, autonomic nervous system; BAW, bile acid wastage; CBC, complete blood count; CBT, cognitive behaviours therapy; CI, confidence interval; CNS, central nervous system; CRP, C-reactive protein; CSBMs, completely spontaneous bowel movements; CTT, colonic transit time; DC, descending colon; EPI, exocrine pancreatic insufficiency; ESR, erythrocyte sedimentation rate; F, female; FC, fecal calprotectin; FDA, Food and Drug Administration (of United States of America [USA]); FMT, fecal microbial transplantation; FODMAP, fermented oligo-/di- monosaccharides and polyols; GC, guanylate cyclase; GFD, gluten-free diet; HT, hydroxytryptamine; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome, constipation predominant; IBS-D, irritable bowel syndrome, diarrhea predominant; IBS-M, irritable bowel syndrome, mixed (D/C); IBS-u, irritable bowel syndrome, undiagnosed; IL, interleukin; LPS, lipopolysaccharide; M, male; mon, month; NCGS, non-celiac gluten sensitivity; NHE-3, sodium (Na<sup>+</sup>) / hydrogen (H<sup>+</sup>) exchanger-3 NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; PEG, polyethylene glycol; PI,-IBS, post-infections irritable bowel syndrome; RCT, randomize controlled trials; RR, relative risk; RS, rectosigmoid; SB, small bowel; SIBO, small intestinal bacterial overgrowth; SNRIs, serotonin norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitor; SWPs, single nucleotide polymorphisms; TCAs, tricyclic antidepressants; tTG, tissue transglutaminase; wk, week; yr, year



## Complementary and Alternative Medicines (CAM) for Treatment of Functional GI Disorders

Deutsch JK, et al. Am J gastroenterol 2020; 115: 350-364

|                                                    | Proven Product Benefits                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Unproven                                                                                                                                                                              |
|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| • Nausea and Vomiting                              | <ul style="list-style-type: none"> <li>○ Pyridoxine (vitamin B6) – Unknown</li> <li>○ Cannabis – for cannabinoid <ul style="list-style-type: none"> <li>– Cholinergic neurons in myenteric/submucosal plexus stimulated to ↓ motility / ↓ secretion</li> </ul> </li> <li>○ Relaxation therapy</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>○ Ginger <ul style="list-style-type: none"> <li>– Hyperemesis syndrome</li> </ul> </li> <li>○ P6 acupuncture</li> <li>○ Rikkunshito</li> </ul> |
| • Functional Dyspepsia (bloating, epigastric pain) | <ul style="list-style-type: none"> <li>○ Acupuncture</li> <li>○ Artichoke leaf <ul style="list-style-type: none"> <li>– ↑ bile flow</li> <li>– Antioxidant</li> <li>– Antispasmodic</li> </ul> </li> <li>○ Capsaicin – ↓ type C pain fibers</li> <li>○ DigeZyme® (mixture of amylase, lipase, protease)</li> <li>○ Iberogast – Allosteric effect on 5-HT3 receptors</li> <li>○ Licorice</li> <li>○ Peppermint – Please see above</li> <li>○ Plantain banana <ul style="list-style-type: none"> <li>– Digestive effect on carbohydrates, lipids, protein</li> <li>– ↑ gastric mucus</li> </ul> </li> <li>○ Turmeric <ul style="list-style-type: none"> <li>– ↑ bile secretion / ↑ gallbladder contraction – Antispasmodic</li> </ul> </li> </ul> |                                                                                                                                                                                       |
| • Irritable bowel syndrome                         | <ul style="list-style-type: none"> <li>○ Aloe vera – Protective, laxative, anti-inflammatory, analgesic</li> <li>○ Acupuncture – Unknown</li> <li>○ Berberine <ul style="list-style-type: none"> <li>– ↓ monoamine oxidase</li> <li>– ↑ Na<sup>+</sup>/H<sup>+</sup> exchanger 3 (NHE3)</li> <li>– ↑ aquaporin 4</li> </ul> </li> <li>○ Glutamine – ↓ permeability of intestine</li> <li>○ Iberogast – Spasmolytic → ↓ antral contraction, ↑ relaxation of fundus</li> <li>○ Peppermint oil – Please see above</li> <li>○ Psyllium</li> <li>○ Turmeric – Please see above</li> <li>○ Cognitive behaviour therapy</li> <li>○ Gut derived hypnotherapy</li> <li>○ Low FODMAP diet</li> </ul>                                                      | <p>Mechanism of action – unknown</p>                                                                                                                                                  |



## ABNORMAL BOWEL MOVEMENT

### Irritable Bowel Syndrome, Constipation Predominant (IBS-C) and Chronic Idiopathic Constipation (CIC)

Ford AC, et al. Am J Gastroenterol 2014; 109: S2-S26

#### ➤ Treatment

##### • IBS-C

- General
  - Psychosocial/cognitive behaviour therapy
  - Supportive caring physician
- Diet
  - Fibre supplements
  - Peppermint oil
  - Probiotics
- Pharmacotherapy
  - Antibiotics (Rifaximin)
    - Relieves total IBS symptoms and bloating (Recommendation: weak; Quality of evidence: moderate)
  - Antidepressants (serotonin reuptake inhibitor)
    - Tricyclic antidepressants, selective
    - Effective in symptom relief
    - Side effects may limit patient tolerance
    - (Recommendation: weak; quality of evidence: high)
  - Antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, dicyclomine)
    - Symptomatic short term relief
    - Adverse events common
    - (Recommendation: weak; quality of evidence, low)
  - 5-HT3 antagonists (alosetron)
    - ↓ symptoms in females
    - (Recommendation: weak; quality of evidence: moderate)
    - Do **not** use 5-HT4 agonists or mixture of 5-HT3 plus 5-HT4 or loperamide
    - (Recommendation: weak; Quality of evidence: very low)

#### Recommendations

- Psyllium, but not bran, provides total symptom relief in IBS (Recommendation: weak; Quality of evidence: moderate)
- Peppermint oil superior to placebo to improve symptoms (Recommendation: weak; Quality of evidence: moderate)
- Probiotics improve total symptoms, bloating and flatulence (Recommendation weak; Quality of evidence: low)



- Prebiotics/symbiotic not recommended in IBS-C predominant (Recommendation: weak; Quality of evidence: very low)
- Lubiprostone and linaclotide are superior than placebo (Recommendation: strong; quality of evidence: high)
- Do **not** use polyethylene glycol (PEG) (Recommendation: weak; quality of evidence: very low)
- Chronic Idiopathic Constipation (CIC)
  - General
    - Biofeedback (for pelvic floor dyssynergia)
  - Diet
    - Fibre (Recommendation strong; quality of evidence: low)
  - Over-the-counter agents
  - Probiotics (Recommendation: weak; quality of evidence: very low)
  - Pharmacotherapy (effective)
 

|                |                |                             |                                                                            |
|----------------|----------------|-----------------------------|----------------------------------------------------------------------------|
| – Laxatives    | Osmotic        | PEG                         | Recommendation: strong;<br>quality of evidence: high                       |
|                |                | Lactulose                   | Recommendation: strong;<br>quality of evidence: low                        |
|                | Stimulants     | Bisacodyl<br>Picosulfate    | Recommendation: strong;<br>quality of evidence: moderate                   |
| – Prokinetics  | 5-HT4 agonist  | Prucalopride                | Recommendation: strong;<br>quality of evidence: moderate                   |
| – Prosecretory |                | Lubiprostone<br>Linaclotide | Recommendation: strong;<br>quality of evidence: high                       |
|                | IBAT inhibitor |                             | Grading not appropriate as no<br>implication for current CIC<br>management |
  - Biofeedback
    - Effective in CIC patients with pelvic floor dyssynergia, when performed by “...a trained and skilled therapist” (Recommendation: weak; quality of evidence: low)

Abbreviations: CIC, chronic idiopathic constipation; IBAT, ileal bile acid transporter; IBS-C, irritable bowel syndrome, constipation predominant; IBS-D, irritable bowel syndrome, diarrhea predominant; PEG, polyethylene glycol; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants



## Laboratory Evaluation with Functional Diarrhea (FD) and Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D) in Adults: AGA Guidelines (2019)

Smalley W, et al. Gastroenterology 2019;157(3):851-854

Also, please see Carrases Labra A, et al. AGA technical Review on the evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology 2019; 157: 859-880.

- Spectrum of considerations in this guideline:
  - These guidelines are intended to reduce practice variation and promote high-quality and high-value care for this patient population,
  - These guidelines apply to the evaluation of the immunocompetent patient with “watery” diarrhea of at least 4 wk duration.
  - This would exclude those patients with
    - Bloody diarrhea
    - Diarrhea with sign of fat malabsorption
    - Presentations with alarm features (such as weight loss, anemia, and hypoalbuminemia)
    - Patients with a family history
      - Inflammatory bowel disease (IBD)
      - Colon cancer
      - Celiac disease
    - Those with a travel history to regions with recognized specific diarrhea-related pathogens
- Laboratory
  - Blood markers for inflammation
    - C-reactive protein (CRP) threshold 5 to 6 mg/L
      - Sensitivity 0.73 (95% CI, 0.64 to 0.84)
      - Specificity 0.78 (95% CI, 0.58 to 0.91)
    - Erythrocyte sedimentation rate (ESR)
      - Lower estimates of diagnostic accuracy in IBD, as compared with CRP measurements
  - In patients with chronic diarrhea use fecal calprotectin (fCal) or fecal lactoferrin (FL) to screen for IBD (Conditional recommendation, low quality evidence)
    - Threshold values to provide high sensitivity to screen for IBD
      - fCal, 50 µg/g: sensitivity for IBD, 0.81 (95%CI: 0.75-0.86); specificity, 0.87 (95%CI: 0.78-0.92)
      - FL, 4.0-7.25 µg/g: sensitivity for IBD, 0.79 (95%CI: 0.73-0.84); specificity, 0.95 (95%CI: 0.63-0.99)
  - Do **not** test stool for ova/parasites unless
    - Recent travel to / immigration from high-risk areas (Conditional recommendation, low quality evidence)
  - Do **not** use erythrocyte sedimentation rate (ESR) or C-reactive protein to screen for IBD in patients presenting with chronic diarrhea (conditional recommendation; low quality evidence).



- Stool tests for infection (culture and sensitivity [C/S] ova and parasites [O&P])
  - Giardia is a common cause of chronic diarrhea
    - C/S, O/P performs inferiorly to
      - Polymerase chain reaction (PCR) for small subunit ribosomal RNA for giardia
      - Giardia antigens
- Sensitivity/specificity both > 95%
- Test for Giardia infection (antigen test or polymerase chain reaction [PCR]) (Strong recommendation, high quality evidence)
- Serology for celiac disease
  - Tissue transglutaminase (tTG IgA) threshold 7 to 15 AU/mL
    - Sensitivity and specificity (each > 90%)
    - Positive tTG-IgA → EGD plus duodenal biopsies
    - Negative tTG
      - Check IgA levels → if ↓ IgA → perform tTG or DGP IgG (deaminated gliadin peptides not affected by patient's deficiency of IgA)
  - Antibodies to
    - Cytolethal toxin B, or
    - Vinculin
- Not recommended
  - Sensitivity 20% to 40%
  - Specificity ~90%

#### Recommendations

- In patients with chronic diarrhea, test for disease with IgA tissue glutaminase and a second test to detect celiac disease in the setting of IgA deficiency (IgG transglutaminase and IgG or IgA deaminated gliadin peptides) (Strong recommendation, moderate quality evidence)
- Test for bile acid induced diarrhea (BAD; aka bile acid wastage [BAW])
  - Blood
    - 7α-hydroxy-4-cholestene 3-one (C4)
    - Fibroblast growth factor 19 (FGF19)
  - Stool
    - 72 h stool collection for total bile acids
  - Breath
    - C14 glycocholate breath test
  - Duodenal fluid
    - Ratio of primary to secondary BA
    - Ratio of conjugated to unconjugated BA
    - Bacterial colony count of fluid (research)
  - Nuclear scan
    - Bacterial 75 Selenium homotaurocholic acid for retention of BA
- Test for bile acid diarrhea (BAD)
  - In patients presenting with chronic diarrhea (conditional recommendation, low quality evidence)
  - If testing not available use empirical trial of bile sequestering agents.

Abbreviations: BA, bile acid; BAD, bile acid (induced) diarrhea; C&S, culture and sensitivity; CRP, C-reactive protein; DGB, deaminated gliadin peptides; ESR, erythrocyte sedimentation rate; fCal, fecal calprotectin; FD, functional diarrhea; FGF19, fibroblast growth factor; FL, fecal lactoferrin; h, hour; IBD, irritable bowel syndrome; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome, diarrhea predominant; O&P, ova and parasites; PCR, polymerase chain reaction; tTG, tissue transglutaminase





## Treatment of Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome with Constipation (IBS-C)

Brenner DM, Am J Gastroenterol 2022; 117: S1.

Harris LA and Chang CH. Am J Gastroenterol 2022; 117: S2-S5;

Sayuk GS, et al. Am J Gastroenterol 2022; 117: S6-S13

### ➤ Adverse effects

- When taken in excess, these anti-cathartic agents may cause
  - Diarrhea
  - Nausea/vomiting
  - Abdominal pain
  - Bloating (especially with metabolized osmotic laxatives)
  - Headache (especially with Tegaserod ®)
  - Pancreatic insufficiency / malabsorption (especially with castor oil)

### ➤ Mechanisms of action

| Class             | Mechanism of Action                   |                                                                                                      |
|-------------------|---------------------------------------|------------------------------------------------------------------------------------------------------|
| ○ Laxatives       | - Osmotic                             | ▪ Creates an osmotic gradient → ↑ water and electrolytes secretions into the intestinal lumen        |
|                   | - Stimulant                           | ▪ ↑ water and electrolyte secretions and ↑ peristalsis                                               |
|                   | - Anionic                             | ▪ ↓ surface tension of the oil-water interface of the stool → enabling ↑ water/fat stool penetration |
| ○ Prokinetics     | - 5-HT4 agonist                       | ▪ ↑ gastrointestinal motility                                                                        |
| ○ Secretagogues   | - GC-C agonist                        | ▪ ↑ intracellular cGMP, ion gradient →<br>- ↑ fluid secretion<br>- ↓ colon nociception               |
|                   | - CIC-2 activator                     | ▪ Creates an ion gradient that → water and sodium secretion into the intestinal lumen                |
| ○ NHE3 inhibitors | - Sodium-hydrogen exchanger isoform 3 | ▪ ↓ sodium absorption in the gastrointestinal tract → ↑ colonic transit                              |

Abbreviations: 5-HT4, selective serotonin type 4; cGMP, cyclic guanosine monophosphate; CIC, chronic idiopathic constipation; CIC-2, chronic channel protein 2; GC-C, guanylyl cyclase C; IBS-C, irritable bowel syndrome with constipation; NHE3, sodium-hydrogen exchanger isoform 3; OTC, over the counter; PEG, polyethylene glycol; QoL, quality of life

Adapted from: Sayuk GS, et al. Am J Gastroenterol 2022; 117: S6-S13 (Table 1)



➤ Efficacies

| Drug                                     | IBS-C Indication                                                        | Efficacy                                                                         | Adverse Events                                                                                            |
|------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| ○ Lactitol (PEG 3350)                    | CIC                                                                     | - Improves stool consistency/frequency                                           | ▪ Abdominal pain and distention, diarrhea, nausea, flatulence, vomiting, bloating, electrolyte imbalances |
| ○ Bisacodyl, Sennosides (anthraquinones) | Short-term constipation                                                 | - Improved stool consistency/frequency<br>- ↓ straining                          | ▪ Diarrhea, abdominal pain, nausea, vomiting, headache                                                    |
| ○ Docusate                               | Occasional constipation                                                 | - Softened stool                                                                 | -                                                                                                         |
| ○ Prucalopride                           | CIC                                                                     | - Improved stool consistency/frequency<br>- ↓ straining                          | ▪ Nausea, abdominal pain, diarrhea, headache                                                              |
| ○ Tegaserod                              | IBS-C in women <65 yr without history of cardiovascular ischemic events | - ↑ stool consistency/frequency<br>- ↓ bloating and discomfort                   | ▪ Nausea, abdominal pain, diarrhea, headache, and cardiovascular events                                   |
| ○ Linaclotide<br>Plecanatide             | CIC, and IBS                                                            | - ↑ stool consistency/frequency / improve QoL<br>- ↓ straining, pain, discomfort | ▪ Diarrhea                                                                                                |
| ○ Lubiprostone                           | CIC, women with IBS-C                                                   | - ↑ stool consistency/frequency<br>- ↓ straining, bloating and pain              | ▪ Nausea, vomiting, abdominal cramping, diarrhea                                                          |
| ○ Tenapanor                              | IBS-C                                                                   | - Improve consistency/frequency                                                  | ▪ Diarrhea                                                                                                |

Adapted from: Sayuk GS, et al. Am J Gastroenterol 2022; 117: S6-S13 (Table 1)



➤ Qualitative Scoring of Constipation

- Bristol Stool Form Scale (BSFS)
  - The BSFS has been used in research studies, one of the best different scale designs used to assess bowel habit, but
    - Minimal validation in this patient population
  - Some patients will present having obtained the BSFS online, and may even provide a photograph of their own stool.
- Types of stools
  - Separate hard lumps
  - Sausage-like
    - Lumpy
    - Cracks on surface
    - Smooth, soft like a snake
  - Soft blobs, "clear-cut edge"
  - Fluffing pieces, ragged edges
  - Watery, no solid pieces

➤ Specific agents

❖ Laxatives

• Osmotic Agents

- Polyethylene glycol (PEG 3350)
  - "... chemically inert, osmotically active polymer..."
    - Not metabolized by intestinal microflora
    - < 1% absorbed and excreted into urine
- Lactulose
  - Breaks down to short chain fatty acids, which are osmotically active so constipation treating benefit may lessen
  - ↑ colonic transit
  - Inferior to PEG 3350
- Lactitol
  - A polyol (synthetic sugar alcohol produced from lactose)
  - ↑ bloating
- Magnesium hydroxide
  - Only use short term
  - Do **not** use in persons with ↓ renal function

• Stimulant laxatives

- Castor oil (ricinoleic acid) - No evidence of long term cathartic colon / cancer in humans
- Anthraquinone
  - Aloe
  - Cascara
  - Senna
- Diphenylmethane agents
  - Bisacodyl
  - Picosulfate sodium



## SO YOU WANT TO BE A GASTROENTEROLOGIST!

Bisacodyl and picosulfate are metabolized to bis- (p-hydroxyphenyl)-pyridyl-2-methane.

- Give the source and name of the enzymes which produce this active metabolite, and give the mechanisms of the secretory and motor effects.
  - Metabolism
    - Mucosal deacetylase
    - Colonic microfloral desulfatase
  - ↑ secretion
    - Prostaglandin E2 (PGE2), and
    - Nitric oxide (NO)
  - ↑ motility
    - Enterochromaffin cell serotonin (5-HT)
- Anion Stool softeners
  - ↓ surface tension of stool → ↑ stool water/fat → softer stools
  - Docusate is inferior to psyllium
    - Limited data for efficacy in CIC, IBS-C
- Secretagogues
  - Guanylyl cyclase C (GC-C) agonists
    - Activation of GC-C acts upon cyclic guanosine triphosphate (cGTP) to produce cyclic guanosine 3', 5' monophosphate (cGMP)
      - Stimulates cystic fibrosis transmembrane conductance regulator (CFTR) → ↑ Cl<sup>-</sup> / H<sub>2</sub>O secretion
      - Intracellular cGMP diffuses to the extracellular area →
        - ↓ visceral nociception
        - ↓ neuronal activation of dorsal horn of spinal cord (occurs in response to "...noxious colorectal distention")
  - Linaclotide
    - Synthetic analog of a heat-stable enterotoxin produced by *Escherichia coli*
    - Contains "...3 intrachain disulfide bridges (thiol bonds)" in the absence of acid-sensing residues in the N-terminus
    - The disulfide/thiol bonds acts to stabilize the ligands in an active conformation
  - Plecanatide
    - Adapted from uroguanylin (an active endogenous ligand of GC-C)
    - Contains 2 intrachain disulfide bridges plus 2 acid sensing amino acids in the N-terminus
    - pH dependent, acting in the small intestine



- Calcium channel activators: chloride channel protein-2 (CIC-2)
  - Lubiprostone
    - Activates atypical type 2 chloride channels (CIC-2) → M3, the active metabolite
      - ↑  $\text{Cl}^-$  /  $\text{H}_2\text{O}$  secretion
      - ↓ pain (analgesia)
    - Metabolized in GI tract (low bioavailability)
    - Give with meals to ↓ nausea
- $\text{Na}^+/\text{H}^+$  exchanger (NHE3) inhibitors
  - Tenapanor
    - ↓  $\text{Na}^+$  /  $\text{H}_2\text{O}$  absorption
      - ↑ transit
      - ↓ visceral hyperalgesia

#### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the mechanism(s) by which the NHE3 inhibitor tenapanor reduces visceral hypersensitivity.
  - Inhibition of  $\text{NH}_3$  normalizes
    - Colonic secretory neuronal excitability, and
    - Transient receptor potential cation channel subfamily V member I (capsaicin receptor)

- Prokinetics
  - Selective serotonin type 4 (5-HT<sub>4</sub>) receptor agonists → ↑ HAPCs (high amplitude propagative colonic contractions) → ↑ contractions of colon, small intestine and stomach
  - Pralopride has "...high affinity and selectivity for the 5-HT<sub>4</sub> receptor, and less for 5-HT, 5-HT<sub>2</sub> receptors and hERG channels" (↓ adverse effects coming from interaction with these other 5-HT receptor and hERG channels such as headache)
- Ileocyte brush border membrane bile acid transporter
  - Elobixibat → ↓ BA (bile acid) absorption into ileocytes → ↑ luminal BA lost into colon → ↑ cGMP activity → ↑  $\text{Cl}^-$  /  $\text{H}_2\text{O}$  secretion

Abbreviations: BA, bile acid; CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine triphosphate; cGTP, cyclic guanosine triphosphate; CIC, chronic idiopathic constipation; CIC-2, chloride channel protein – 2;  $\text{Cl}^-$ , chloride; GC-C, guanyl cyclase C;  $\text{H}^+$ , hydrogen ion;  $\text{H}_2\text{O}$ , water; HAMPs, high amplitude propagative colonic contractions; IBS-C, irritable bowel syndrome with constipation;  $\text{Na}^+$ , sodium ion; NHE  $\text{Na}^+/\text{H}^+$  exchanger; PEG, polyethylene glycol; QoL, quality of life



## Management of Functional Constipation

Vriesman MH, et al Nat Rev Gastroenterol Hepatol 2020; 17: 21-39.

- Definition
  - "...constipation without an organic aetiology [excluded; characterized] hard infrequent bowel movements, often accompanied by symptoms of bloating and abdominal pain [but not fecal incontinence, based on the Rome IV criteria]"
    - Rome IV Criteria (Lacy, BE, et al. Gastroenterol 2016; 150: 1393-1407)
  - Must have  $\geq 2$  of the following criteria for  $\geq 3$  mon
    - $\leq 2$  defecations in the toilet per week
    - Lumpy or hard stools more than 25% of defecations
    - Straining during more than 25% of defecation
    - Sensation of incomplete evacuation more than 25% of defecations
    - Sensation of rectal obstruction / blockage more than 25% of defecations
    - Manual maneuvers to facilitate more than 25% of defecations AND both of the following
      - Insufficient criteria to diagnose for irritable bowel syndrome (no abdominal pain)
      - Loose stools are rarely present without the use of laxatives
- Demography
  - Prevalence ~15%
  - ↑ with age
  - F > M (OR, 2.2)
- Subtypes
  - Normal transit, 65%
  - Slow transit, 5%
  - Rectal evacuation disorder, 30%
- Causes/Associations
  - Patient
    - Inherited
    - Life-style
    - Diet/fluid intake
    - Obesity/physical activity
    - Protein allergy



- Stress
    - Abuse
    - Trauma
  - Psychological
    - Anxiety
    - Eating disorder
    - Depression
  - Behaviour problems
    - Autism
    - Attention deficit / hyperactivity disorder
    - Stool withholding behaviour → frequent fecal impactions → megarectum
    - Megarectum is associated with
      - Overflow fecal incontinence
      - ↓ rectal sensation
      - ↓ sensation / urge to defecation
  - Parental factors
    - Depression
    - Neuroticism
    - Overprotection
  - Colon microbiome
    - Intestinal microbiota have been shown to differ between healthy individuals and small samples of children and adults with functional constipation.
  - Colonic motility factors
    - ↓ HAPCs (high amplitude propagating contractions) in slow-transit FC → ↓ mass movements of contents of colon.
  - Anorectal factors (defecation disorders)
    - Dyssynergic defecation
      - The inability to coordinate the abdominal and pelvic floor muscles to evacuate stools because of paradoxical contraction or inadequate anal relaxation.
    - Anorectal malformations
    - Enterocele or rectocele
    - Descending perineum syndrome
    - Traumatic (e.g., obstetric or surgical)
  - Intestinal conditions
 

|                                                                                                                                              |                                                                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>- Cystic fibrosis</li> <li>- Hirschsprung disease</li> <li>- Neuronal intestinal dysplasia</li> </ul> | <ul style="list-style-type: none"> <li>- Intestinal carcinoma</li> <li>- Stricture</li> </ul> |
|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
  - Metabolic and endocrine conditions
 

|                                                                                                                                                                        |                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>- Celiac disease</li> <li>- Dehydration</li> <li>- Diabetes mellitus</li> <li>- Hypercalcemia</li> <li>- Hypokalemia</li> </ul> | <ul style="list-style-type: none"> <li>- Hypothyroidism</li> <li>- Menopause</li> <li>- Porphyria</li> <li>- Pregnancy</li> <li>- Uremia</li> </ul> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
- Efferent/afferent signals, brain-gut axis



- Neuropathic conditions
  - Autonomic neuropathy    - Myelodysplasia                      - Parkinson disease
  - Botulism                      - Myelomeningocele           - Spinal cord abnormalities
  - Chagas disease              - Myotonic dystrophy          - Spinal cord trauma
  - Multiple sclerosis          - Neurofibromatosis          - Tethered cord
- Myopathy
  - Amyloidosis                      - Systemic sclerosis
- Drugs
  - Anticholinergic agents    - Antipsychotics                      - Chemotherapeutic agents
  - Antidepressants              - Calcium channel blockers    - Opioids
- Clinical
  - Diagnosis of FC is made by history and physical examination satisfying Rome IV criteria
  - Exclude
    - Organic causes of constipation and irritable bowel syndrome (constipation predominant [IBS-C])
    - Consider any alarm symptoms
  - Digital rectal examination (DRE) useful features
    - Inspection                      ■ Perianal disease
    - Palpitation                      ■ Cause of mechanical obstruction
    - Tone (resting and squeeze)
    - Perineal descent on straining
    - Tenderness
    - Paradoxical contraction of the pelvic floor with straining, expelling examining finger from rectal or anal canal
- Diagnostic imaging
  - Abdominal x-ray
    - Fecal loading
    - Air in rectum
    - Air tissue interface
      - Dilation
      - "thumb printing"
      - Rectal gas area > 900 mm<sup>2</sup> (75% accuracy for predicting the presence of a rectal evacuation disorder)
  - Anorectal manometry (to exclude dyssynergic defecation)
    - Muscle (pressure) tone                      ■ Basal/resting
      - Resting anal sphincter pressure (> 90 mmHg), plus negative anorectal pressure differential (more negative than -50 mmHg)
      - Suggestive of rectal evacuation disorder
    - Stimulate/squeezing
      - ↑ squeeze sphincter pressure suggests concurrent anal fissure
    - Sensation                      ■ Rectal hypersensitivity should be confirmed with rectal barostat procedure
    - Reflex                              ■ Rectal-anal





- Parameters measured
  - Resting pressure
    - Resting anal sphincter pressure (> 90 mm Hg), plus negative anorectal pressure differential (more negative than 50 mm Hg)
      - Suggestive of rectal evacuation disorder
  - Squeeze pressure
    - ↑ squeeze sphincter pressure suggests concurrent anal fissure
  - Rectal sensation
    - Rectal sensation in most patients presenting with constipation (rather than fecal incontinence) is useful from megarectum
      - Rectal hypersensitivity should be confirmed with rectal barostat procedure
  - Recto-anal inhibitory reflex
    - Absent recto-anal inhibitory reflex is useful from a megarectum

Adapted from: Vriesman MH, et al. Nat Rev Gastroenterol Hepatol 2020; 17: 21-39 (Table 2)

- Colonic manometry
  - Presence/characteristics of HAPCs after food / stimulant laxative
- Colonoscopy / air contrast barium enema
  - Exclude megarectum/colon
  - Masses
- Balloon expulsion test (BET)
  - Test for pelvic floor dyssynergia
    - Normal expulsion of 40-50 mL size rectal balloon in 1 min
- Colonic transit study (CTS)
  - Ingestion of
    - Radiopaque markers
      - Time-based number of markers in different locations
    - Scintigraphy
    - Radiation-free wireless motility capsule
- Defecography
  - Barium/MRI defecography

Abbreviation: HAPC, high amplitude propagating contraction

## ➤ Treatment

- Diet
  - Take fibre 1.4 g / 1000 kCal per day, to maximum of 30 g/day (> 30 g will ↑ colonic symptoms such as discomfort/distention)
  - Pre-/probiotics (not evidence-based)
  - FODMAP diet (a diet low in fermentable oligo-/ di- / monosaccharides and polyols)
    - Helpful in IBS-C, but not functional constipation (FC)



- Behaviour therapies / biofeedback training
  - Useful for FC / dyssynergic defecation (DD)
  - Biofeedback (superior to placebo)

- Pharmacological Agents

| Drug                                                | Dosage                                                                       |
|-----------------------------------------------------|------------------------------------------------------------------------------|
| ○ Osmotic laxatives                                 |                                                                              |
| – Lactulose                                         | 12-24 g per day                                                              |
| – Polyethylene glycol without electrolytes: PEG4000 | Maintain 10-20 g per day; disimpaction: 80 g per day (for maximum of 3 days) |
| – Polyethylene glycol without electrolytes: PEG3350 | Maintain 10-20 g per day; disimpaction: 80 g per day (for maximum of 3 days) |
| – Milk of magnesia (magnesium hydroxide)            | 2-5 g per day                                                                |
| ○ Lubricants                                        |                                                                              |
| – Mineral oil (liquid paraffin)                     | 15-45 mL per day                                                             |
| ○ Stimulant laxatives                               |                                                                              |
| – Bisacodyl (diphenylmethane)                       | 5-10 mg per day in 1 dose in the evening                                     |
| – Sodium picosulfate (diphenylmethane)              | 4-6 mg per day in 1 dose                                                     |
| – Senna (anthraquinone)                             | 185-370 mg per day                                                           |
| ○ Prosecretory agents                               |                                                                              |
| – Lubiprostone                                      | 24 µg twice daily                                                            |
| – Linaclotide                                       | 145-290 µg per day                                                           |
| – Plecanatide                                       | 3-6 mg per day                                                               |
| ○ Serotonergic agents                               |                                                                              |
| – Prucalopride                                      | 1-2 mg per day                                                               |
| ○ Rectal laxatives                                  |                                                                              |
| – Bisacodyl                                         | 5-10 mg per day in 1 dose in the evening                                     |
| – Sodium phosphate                                  | Fecal impaction (133 mL per dose)                                            |
| – Sodium docusate                                   | Fecal impaction (120 mL)                                                     |
| – Sodium lauryl sulfoacetate                        | Fecal impaction (5 mL/dose)                                                  |

Printed with permission: Vriesman MH, et al Nat Rev Gastroenterol Hepatol 2020; 17: 21-39 (Table 3)

- Fecal disimpaction
  - Polyethylene glycol (PEG)
  - Sodium phosphate/docusate
  - Sulfoacetate
  - Magnesium citrate
  - Suppositories (glycerine, bisacodyl)
- Treat any associated disorder



- Secretory agents
  - ClCh chloride channel / CFTR (cystic fibrosis transmembrane conductance regulator)
  - Activator of guanyl cyclase C receptor (GCCR)
    - Linaclotide
    - Plecanatide
- Encourage adherence to advice re laxatives (usual compliance rate, 37%)
- Serotonergic agonists
  - 5-HT4 agonists → ↑ release of acetylcholine (Ach) → ↑ fluid secretion, ↑ motility
- Bile acids
  - Chenodeoxycholic acid (CDCA) → ↑ fluid secretion
  - Elobixibat
    - Ileal bile acid (BA) transporter inhibitor (↓ BA absorption in ileum, ↑ colonic BA, ↑ colonic secretion of Cl<sup>-</sup>/H<sub>2</sub>O)
- Cholinesterase inhibitors
  - Pyridostigmine (acetylcholinesterase inhibitor) → ↑ Ach → ↑ secretion, ↑ motility
- Transanal irrigation
  - For FC which is not responsive to pharmacologicals
- Surgery
  - Antegrade continence enemas (ACEs)
    - Minimally invasive
      - Percutaneous cecostomy
      - Malone cecostomy
  - ↓
  - ~50% success rate for FCs, but post-treatment stenosis of the stoma is common
  - Ostomies/resections
    - Resection of colon
      - Short distal segment
      - Long colonic section
    - Total abdominal colectomy, with ileorectal anastomosis (success rate > 50%)
    - Subtotal colectomy plus biofeedback
- Neuromodulation
  - Sacral nerve stimulation (SNS)
  - Transcutaneous electrical stimulation (TES)
  - Percutaneous tibial nerve stimulation [bilateral]

▪ Conflicting data, adverse events from abuse

Abbreviations: 5-HT, 5-hydroxytryptamine; ACE, antegrade continence enema; Ach, acetylcholine; CFTR, cystic fibrosis transmembrane conduction regulator; ClCh, chloride channel; CTS, colonic transit study; F, female; FC, functional constipation; FODMAP, fermentable oligo- / di- / monosaccharides and polyols; GCCR, guanyl cyclase C receptor; HAPC, high amplitude propagating contractions; IBS-C, irritable bowel syndrome, constipation dominant; M, male; PTNS, percutaneous tibial nerve stimulation; SNS, sacral nerve stimulation



## ULCERATIVE COLITIS (UC)

### Medical Management of Inflammatory Pouch Complications

Quinn KP and Raffal LE. Am J Gastroenterol 2020; 115: 1439-50

- Ileal pouch anal anastomosis (IPAA) is performed on the 20-30% of patients with UC who require proctectomy for
  - Medically-refractory UC
  - UC-associated colonic dysplasia
    - 2- or 3-stage procedure; modified 2-stage: subtotal colectomy with end ileostomy, then completion proctectomy and formation of IPAA
- Spectrum of Pouch Complications
  - Anal transition zone (ATZ): the tissue interposed between the squamous epithelium of the anoderm and dentate line below and the rectal columnar epithelium above”
    - A “cuff” is left when the pouch-to-anus anastomosis is stapled, rather than hand-sewn
      - With the stapled approach, the head of the stapler has to be passed through the anus and a 1-2 cm segment of rectal mucosa is left in place.
  - Inflammation of the cuff (cuffitis) occurs in ~13% of patients with a stapled IPAA, with bleeding in 1% and pouch failures from cuffitis in < 1%
  - Pouchoscopy shows inflammation, which needs to be confirmed by biopsy
  - Treatment
    - Mesalamine suppositories
    - Corticosteroids topical / topical injection of long-acting CS
- Treatment Alert
  - Do **not** treat refractory pouchitis with continued courses of antibiotics, ASA or corticosteroids
    - Exclude alternate diagnosis , such as Crohn disease
  - If proctitis is refractory to mesalamine/CS
    - Reconfirm diagnosis / exclude other conditions such as Crohn disease
- Pouchitis
  - Occurrence
    - 10 yr, 50%
    - 30 yr, 80%
  - Pathophysiology
    - “...an abnormal immune response to alterations in the pouch microbiota
    - Genetic susceptibility
      - NODs/CARD15
      - IL-1R antagonist
      - Presence of thrombocytosis before IPAA
      - Other autoimmune conditions



➤ Diagnosis

- Pouchitis
  - Diffuse
  - Segmental/patchy
  - Prepouch
    - ↑ risk of PSC
    - Extensive when > 10 cm in length
  - Asymmetric, sharply demarcated inflammation
  - Ischemia
  - Antibiotic
    - Responsive
  - Chronic antibiotic
    - Dependent (CADP)
    - Refractory (CARP)
- Irritable pouch syndrome
- Pouch obstruction / overflow

➤ Histopathology

- Appearance on Pouchoscopy does not correlate with histopathology
- Inflammation
  - May be scored with Pouchitis Disease Activity Index (PDAI)
- May be associated with
  - CMV, C. difficile infection, ischemia
  - Granulomas (in ~10%)

➤ Diagnostic imaging

- CTE/MPE
  - MR pelvis / examination under anesthesia (EUA)
    - Leak/abscess, fistulae
  - Anorectal manometry
    - MR defecography
- } Pouch evacuation disorder

➤ Treatment

• Pouchitis

- Ciprofloxacin superior MET to ↓ PDAI (↓ score  $6.9 \pm 1.2$  vs. 1.7;  $p=0.002$ )
- Metronidazole (MET) improves symptoms (73% vs. placebo, 9%), but not inflammation
- Limited positive evidence for
  - Lactobacillus-containing probiotic
  - De Simone Foundation (previously called VSL#3)
  - 5-ASA po per anus



- Chronic pouchitis
  - Develops in 10-20%
  - Antibiotic-dependent (CADP)
  - Refractory (CARP)
    - Failure to respond to a 4-wk course of antibiotic therapy
      - Requires antibiotic therapy for  $\geq 4$  wk with topical 5-ASA, corticosteroid, immunomodulator, or other biologic agent”
  - CADP
    - De Simone Formulation vs. placebo for maintenance
      - 9 mon, 85% vs. 0% ( $P<0.001$ )
      - 12 mon, 85% vs. 6% ( $P<0.0001$ )
    - PSC-associated pouchitis
      - 5-ASA po / per rectum
    - Budesonide 9 mg/d for 8 wk, 75% remission
    - Biologic agents
      - Anti-TNF (infliximab [IFX], Adalimumab [ADA]): no different than placebo
      - Vedolizumab (gut specific monoclonal antibody against  $\alpha 4\beta 7$  integrin), used in CADP/CARP: 6 mon response
        - Clinical, 52%
        - Endoscopic, 58%
  - Crohn disease of pouch
    - Develops in 13% of patients with IPDA for UC
    - May show pouch-related fistulae, anastomotic strictures, +/- prepouch ileitis, and by called Crohn disease (CD) of pouch
      - Strictures/fistula may develop postoperatively and not related to CD
  - Use
    - IFX/ADA +/- immunomodulators (clinical remission at 8 wk, 64% vs. placebo, 10% ( $P=0.06$ ))
    - Vedolizumab, 6 mon response
      - Clinical, 65%
      - Endoscopic, 54%
    - Ustekinumab, 6 mon response
      - Clinical remission, 11%; not affected by previous treatment with anti-TNF
- Pouch failure
  - Occurs in 5-10% of patients after IPAA
  - Onset
    - $< 12$  mon (after closure of ileostomy) pelvic abscess leak of anastomosis
    - $> 12$  mon chronic pouchitis Crohn disease of pouch



- **Ulcerative Proctitis (UP)**

- Treatment

- ❖ 5-ASA Suppository

- More effective than topical corticosteroid suppositories
- Use od at bedtime
- Response rate to 5-ASA pr is ↑ by also giving 5-ASA po

Recommendation

- "...patients not responding fully to suppositories should have addition of oral 5-ASA therapy" to ↑ efficacy"
- Options for maintenance
  - Continue 5-ASA suppositories
  - Continue 5-ASA po
  - Combined use of both po/pr 5-ASA
  - 5-ASA suppositories only for flare
- It is not clear if the benefit of 5-ASA therapy on the development of UC is related to
  - A direct effect of 5-ASA, or
  - An indirect effect of 5-ASA → ↓ risk of recurrent inflammation / ↑ mucosal healing

- ❖ Corticosteroid suppositories

Recommendation

- For persons who do **not** respond/tolerate 5-ASA pr/po, switch to corticosteroid suppositories. (GRADE: strong recommendation, high-quality evidence. Agreement: 100%).
- Failure to respond to 5-ASA pr for UP
  - Add prednisolone 5 mg suppository (e.g., in AM with PM 5-ASA suppository)
  - Budesonide 4 mg suppository is equivalent to 5-ASA pr 1 g

- ❖ Azathioprine (AZA)

- UC patients in remission for 1-2 yr while on AZA, then should AZA be stopped?

1 yr relapse rate

- Continued 36%
- Discontinued 60%
- UC patients in clinical, biological or endoscopic remission for ≥ 3 yr of AZA
  - Relapse rate after 55 mon, 37%
  - Restarting azathioprine after stopping effective maintenance
    - Remission regained in 92%
- If patient stops maintenance AZA, provide 5-ASA maintenance



- **Acute Severe Ulcerative Colitis (ASUC)**

- **Definition**

- UK, modified Truelove and Witts criteria (MTWC)
  - 6 bloody stools per day
  - Systematic toxicity, with  $\geq 1$  of the following
    - Patient
      - Pulse rate  $> 90$  bpm
      - Body temperature  $> 37.8$  °C
    - Laboratory
      - Hemoglobin  $< 105$  g/L
      - C-reactive protein (CRP)  $> 30$  mg/L

(GRADE: strong recommendation, low-quality evidence. Agreement: 100%)

- Option to MTWC – Toronto Criteria
- Toronto Guidelines
  - $\geq 6$  BM/d with blood
  - $\uparrow$  pulse rate,  $\uparrow$  body temperature
  - $\uparrow$  c-reactive protein

- **Investigation**

- Laboratory
  - Blood
    - Complete blood count (CBC)
    - C-reactive protein (CRP)
    - Electrolytes, including serum magnesium
    - Serum creatinine ( $Cr_s$ )
    - Liver function tests (LFTs; albumin, bilirubin, INR)
    - Liver enzymes (LEs: ALT, AST, AP, GGT)
  - Stool
    - Culture/sensitivity/Ova/parasites
    - C. difficile toxin
    - Stool charting for stool blood, consistency, frequency
  - Diagnostic imaging
    - Abdominal X-ray
    - CT scan of abdomen
    - Chest X-ray [possible TB]
  - Flexible sigmoidoscopy (controversial)
    - No preparation
    - Not performed by learner
    - To determine
      - Extent/severity of UC
      - Possible
        - Left-sided pseudomembranous colitis (PMC) suggestive of C. difficile infection
        - Cytomegalovirus (CMV) infection

(GRADE: strong recommendation, very low-quality evidence. Agreement: 97.9%)





## ❖ Corticosteroid (CS) therapy for ASUC

### Recommendations

- Persons with ASUC should be admitted to hospital and immediately started on IV corticosteroids
  - Methyl prednisolone [40 to 60 mg] bolus IV once a day, or
  - Hydrocortisone 100 mg IV q6h  
(GRADE: strong recommendation, high-quality evidence)
  - Give prophylactics low-molecular weight heparin (LMWH) SC to ↓ risk of thromboembolic disease (GRADE: strong recommendation, moderate-quality evidence. Agreement: 98%)
  - Do **not** delay giving IV CS in ASUC while waiting results of stool culture and C. difficile assay
  - Do **not** ↑ dose or duration of CS longer than day 3 to 5 (represents failure of CS therapy)
- Demography
  - Lifetime risk of UC developing ASUC ~20%
  - Colectomy rate with ASUC
    - First attack ~20%
    - At 2 yr, 23%
    - After several admissions, 38%
- Clinical
  - In the regular care of persons with UC, they should
    - Have vaccinations up to date especially live vaccines
    - Have had serology for HBV and treat where appropriate, including immediately on admission for ASUC, given the possibility of the eventual need for biological therapy
    - Testing for TB (chest X-ray, tuberculin skin test, and manage as appropriate
    - Post-relapse screening/surveillance colonoscopy for colorectal cancer (CRC)
- Laboratory
  - Measure C-reactive protein (CRP) as an indicator of inflammatory response in IBD (UC)
    - The specificity of ESR becomes less with ↑ age
    - Some persons do make CRP, so second choice is ↑ESR / ↑WBC
  - Measure serum magnesium concentration of patient being placed on cyclosporine (CyA)
    - Both CyA and ↓  $Mg^{2+}$  → ↑ risk of seizures
  - Perform tuberculin skin test (TST) / gamma interferon test
  - Perform blood test for carrier state for HBV infection



➤ Treatment

❖ Corticosteroids

- Solumedrol 40-60 mg is the recommended dose of IV corticosteroids in ASUC (less mineralocorticoid effect), and given by bolus infusion.

❖ Prophylactic anti-coagulation

- Because of ↑risk 2-3x for venous thromboembolism (VTE)
  - Give SC low-molecular weight heparin (LMWH) as prophylaxis (please see guidelines on VTE in IBD)
  - LMWH is given, even when patient has rectal bleeding  
In this setting of ASUC, LMWH "...does not precipitate or exacerbate colonic bleeding"

❖ Antibiotics

- Empiric antibiotics **not** recommended
  - For Clostridium difficile infection (CDI)
    - Vancomycin po
  - For amebiasis
    - Metronidazole
- } ■ The Toronto guidelines support the early use of empirical vancomycin po

➤ Prediction of response

- On first encounter in the ER with patient with ASUC
  - Explain to patient, partner, family (as appropriate) that while above 2/3 to 3/4 of patients respond to CS IV, if they have failed to make a marked improvement within 3-5 d of CS IV, then they will require second-line therapy (infliximab [IFX], or cyclosporin IV [CyA])
    - Emphasize that longer duration or higher doses of CS only ↑ risk of infection, and continued time for development of toxic megacolon

❖ Scoring system

- On day 3-5, or determine if CS have been effective based upon 50% ↓ stool frequency, in improvement in admission values of ORD, serum albumin and absence of transverse colon dilation ≥ 5.5 cm on abdominal X ray.
- The declaration of success of the 3-5 day of CS IV is based upon a marked (50%) ↓ in number of bowel measurements per day (preferably confirmed by stool charting), less of abnormal vital signs, marked decline in CRP, and also lack of hypoalbuminemia.
- Addition procedures for need for colectomy



- Sigmoidoscopy
  - British Society of Gastroenterology (BSG) suggests that flexible sigmoidoscopy "...performed with care is safe in ASUS and gives important information...", e.g., disease severity, presence of pseudomembrane, CMV infection
    - Pros
      - Deep ulcers
        - Large erosions
        - Mucosa, extensive loss
    - Cons (Toronto guidelines provide physician the option of not doing flexible sigmoidoscopy) because of ↑ risk of perforation
      - Even if severe endoscopic lesions seen, first-line therapy with CS IV will be used, with no change in the normal dose/duration of CS.
      - Presence of pseudomembranous suggests *C. difficile* infection, but ~50% of pseudomembranes will be beyond the reach of the endoscopy (false-negative test), and in ASUC pseudomembranes may be absent despite presence of CDI.
      - The brief empirical use of vancomycin while awaiting *C. difficile* stool assay is safe and is **not** costly.

#### ❖ Second-line rescue therapy

##### Recommendation

- Failure of first-line CS IV on day 3 to 5 "as judged by suitable scoring system"
  - Give second-line rescue therapy with cyclosporin or with infliximab for patients who have not previously failed thiopurine therapy (GRADE: strong recommendation, high-quality evidence. Agreement: 98%)
    - Note that the Toronto guidelines do **not** include the statement that CyA/IFX for ASUC are not used if the patient has previously failed thiopurines.
- Useful to have multidisciplinary team discussion to select second-line therapy vs. colectomy.
  - Introduce on day 3-5 in patient with ASUC who failed first-line therapy of IV CS (no marked improvement)

#### ❖ Cyclosporin A (CyA)

- CyA 2 mg/kg IV per day, to achieve target trough concentration 150-200 ng/mL
- Response to CyA ~75%
  - With response, switch to oral CyA using dose twice that of the IV dose, with target trough concentration 100-200 ng/mL
- Giving thiopurine maintenance therapy ↑ benefit from 40% to 66%, except in those who have already failed thiopurine, in which case the benefit is less.



- Adverse effects
  - Nephrotoxicity, 6%
  - Serious infections, 8%
  - Seizures, 4%
  - Anaphylaxis, 1%
  - Death, 2%
- Comparing multiple outcomes for patients with ASUC given CyA + AZA (azathioprine) vs. IFX plus AZA are equivalent.
  - Clinical response, ~60%
  - Mucosal healing, ~45%
  - Colectomy rates
    - ~20% - 30% at 3 mon
    - ~40% at 1 yr
- The ease of giving /continuing IFX is easier than CyA, and the infection rate may be lower
- Do **not** switch from CyA → IFX, or switch from IFX → CyA (sequential therapy)
- ❖ Infliximab (IFX)
  - Continue CS, introduce IFX 5 mg/kg on day “0”
  - If inadequate response on day 5 to 7, may repeat 5 to 7 day course of the same dose, or ↑ dose to 10 mg/kg
    - May repeat IFX at 5 mg/kg, or ↑ dose to 40 mg/d
    - If patient responds to IFX, then continue IFX for maintenance therapy
    - When using IFX for maintenance therapy, add AZA in low dose to ↓ risk of forming antibodies to infliximab (ATI) → ↓ response to IFX
    - Dose intensification benefits 50% of patients with ASUC, including ↓ need for colectomy
  - Contraindications
    - Infection
      - Latent TB
      - HBV infection (including healthy carrier)
      - Sepsis
    - Heart failure
    - Demyelination disorders
- ❖ Induction regimen with IFX
  - Multidisciplinary team discussion of accelerated IFX vs. colectomy
  - If after 3-5 d of IFX given on day “0”, the patient with ASUC is “...not responding sufficiently”, either continue 5 mg/kg, or use a higher dose of IFX 10 mg/kg
    - Dose intensification benefits 50% of patients with ASUC, including ↓ need for colectomy



- Surrogate markers for severe UC inflammation, and therefore greater loss of IFX and need for more frequent / high dose infusions
  - CRP > 50 mg/L
  - Albumin < 35 g/L
  - Low blood/tissue concentration of IFX
- ❖ Surgery for UC in ASUC
- Emergency surgery

#### Recommendation

- In patient with ASUC, there must be early / direct interaction between the medical, surgical (specialist colorectal surgeon), stomal, nutritional and mental health persons.
- Failure to respond, deterioration or complications (severe bleeding, megacolon [a devastating complication of severe colitis], perforation) within 7 d, use second-line rescue therapy (IFX, CyA).
  - Subtotal colectomy and ileostomy with preservation of the rectum (long rectal stump) (GRADE: strong recommendation, very low-quality evidence. Agreement: 97%).
- Requires expert / experienced surgeon, e.g., colorectal surgeon
- Perform colectomy, colorectal anastomosis to long rectal stump, for possible second later procedures of removal of rectum and formation of ileoanal pouch anastomosis
  - Formation of pouch never done with initial colectomy
    - Wait 6 mon after first procedure
    - If necessary, at the time of a temporary causing loop ileostomy may be made to ↓ risk of leakage
  - Complications pouch 50%, ↓ female fertility
  - Quality of life similar after surgery for end ileostomy vs. ileal-pouch anal anastomosis (IPAA)



## Care of Patients with Ulcerative Colitis (and Crohn Disease)

Lamb CT, et al. Gut 2019; S1-106.

### ❖ Infections

- Tuberculosis (TB)

### Recommendations

- Suspect TB of the intestine rather than Crohn disease in persons with ileocecal disease plus
  - Birth/living for extended periods in areas where TB infection is endemic
  - Other risk factors for TB  
(GRADE: strong recommendation, very low-quality evidence. Agreement: 98%).
- Patients with IBD who will be placed on anti-TNF therapy must first be screened for TB using clinical stratification, chest X-ray, and interferon-gamma release assays (IGRA)  
(GRADE: strong recommendation, low-quality evidence. Agreement: 98%).
- Clinical features suggestive of TB rather than CD.
  - Patient from a geographic area / population group with ↑ risk of TB
  - Presenting history symptoms of TB
    - Night sweats / fever
    - Abdominal lymphadenopathy
    - Ascites
    - No extraintestinal manifestations
- Laboratory
  - Positive tuberculin skin test / QuantiFERON gold test (QFT-G), compatibly abnormal chest X-ray, TB antibodies
  - Patients with IBD who are on immunosuppressive therapy have ↑ risk of anergy leading to false-negative tuberculin skin test (TST) for TB
    - Preferentially test all patient's TB status using QuantiFERON TB Gold (QFT-G)
- Diagnostic imaging / colonoscopy
  - Patulous ileocecal valve (ICV)
  - Transverse ulcers
  - ≤ 3 colonic segments abnormal
  - Scarring
  - Post-inflammatory polyps



- Enteric Infections

#### Recommendations

- Perform stool cultures for invasive bacterial infections and for *C. difficile* toxins in all patients who present with acute flares of colitis [UC and Crohn Colitis] (GRADE: strong recommendation, low-quality evidence).
  - Treat CDI in IBD with vancomycin po
- Clostridium difficile Infection (CDI)
  - Risk of CDI in IBD patients admitted to hospital for IBD flare, 6%
  - Complications of CDI in IBD
    - ↑ risk in UC (OR 2.96; 95% CI: 1.19 to 7.34)
- Non-*C. difficile* enteric infections
  - Multiplex PCR for human pathogens present in IBD
    - UC 18% (*Campylobacter*, *E. Coli*, *Plesiomonas*)
    - CD 16% (*Campylobacter*, *Novovirus*)
  - Non-*C. difficile* infections associated with IBD relapse, 5%

Abbreviations: aOR, adjusted odds ratio; *E. Coli*, *Escherichia coli*

- Cytomegalovirus

- Difficult to distinguish between CMV infection and CMV disease

#### Recommendations

- Obtain colonic biopsies in patients with moderate/severe refractory UC (especially when refractory to corticosteroids)
  - Examine CMV in tissue with quantitative PCR or immunohistochemistry (GRADE: weak recommendation, low-quality evidence. Agreement: 93%).
- Use ganciclovir 5 mg/kg b.i.d. with corticosteroids in hospitalized patients with moderate/severe UC plus CMV reactivation on colonic tissue testing for CMV (GRADE: strong recommendation, very low-quality evidence)
- Rarely, the patient with severe acute UC on immunosuppressive therapy with CMV infection requires treatment (GRADE: weak recommendation, very low-quality evidence). (Agreement: 88%).

#### ➤ Laboratory

- Blood tests for
  - CMV viremia / blood PCR
    - Poor sensitivity
  - Serology



- Suggested to use more sensitive (Sn) and specific (Sp) immunohistochemistry (IHC) testing on tissue

|                | Sn          | Sp          |
|----------------|-------------|-------------|
| – Quantitative |             |             |
| ▪ PCR          | 65% to 100% | 40% to 100% |
| ▪ IHC          | 93%         | 92% to 100% |

#### ➤ Treatment

- Hospitalized
  - Refractory UC
  - Steroid-refractory
- Treat with ganciclovir if clinical features present or biopsy tissue positive on quantitative PCR, or positive H&E staining with immunohistochemistry for CMV
- May continue corticosteroids, infliximab, cyclosporine unless there is associated systemic CMV disease, e.g.,
  - CNS – Meningoencephalitis
  - Lung – Pneumonitis
  - GI – Esophagitis, hepatitis
- With systemic CMV infections, corticosteroids, immunosuppressants, ant-TNF and cyclosporin must be temporarily **stopped**.

#### ❖ Immunosuppressive therapy

##### Recommendations

- Once diagnosis made for Crohn disease or for moderate/severe ulcerative colitis (UC), perform the following testing
  - TPMT (thiopurine methyltransferase) (some centres perform measurement of the active metabolite, 6-thioguanine [6-TG])
  - HBV HCV, HIV (“...and VZV if no history of chicken pox, shingles, or varicella vaccination”) (GRADE: weak recommendation, very low-quality evidence. Agreement: 89%)
- Before starting treatment with immunomodulatory or biologics
  - Measure TPMT
  - Screen for (retesting is not necessary if these were done at the time of diagnosis),
    - TPMT
    - HBV HCV, HIV (“...and VZV if no history of chicken pox, shingles, or varicella vaccination”) (GRADE: strong recommendation, very low-quality evidence. Agreement: 89%).
- All IBD patients who are initiated on immunosuppressive therapy should receive written information regarding, the benefits, risks, side effects and monitoring of treatment (Agreement 98%)
- Screening at time of diagnosis of IBD
  - Test for
    - HBV, HCV, HIV, HSV, HDV, EBV, VZV
    - Tuberculosis (TB): tuberculin skin test; interferon gamma release assay (IGRA), e.g., QuantiFERON TB gold (QFT-G)
    - Thiopurine methyltransferase (TPMT)





- Assess immunization status and possible need for revaccination
  - Influenza
  - Measles, mumps, rubella (MMR)
  - Meningococcus
  - Pneumococcus
  - Polio
- Risk for HBV/HCV same in patients with IBD as in the non-IBD population
  - HBV, ~2.5%
  - HCV, ~1%
- Epstein Barr Virus (EBV)
  - Rare but serious hematological complications of EBV infection in IBD
  - Hemophagocytic syndrome (not just in young men)
  - Lymphoma type
    - Post-mononucleosis
    - Post-transplantation
- Infection risk and anti-TNF therapy
  - 2x ↑ risk of opportunistic infection in patients with IBD treated with anti-TNF therapy
    - This ↑ risk of opportunistic infection in persons on anti-TNF therapy is associated with
      - Age > 50 yr
      - ↑ disease activity
        - Each ↑ CDAI\* by 100 points is associated with ↑ hazard ratio (HR) for opportunistic infection (HR, 1.31; 95% CI: 1.04 to 1.64)

\*CDAI Crohn Disease Activity Index, older research scoring system to predict disease activity in patients with Crohn disease

- Strongyloides stercoralis

- Common intestinal parasite in tropical / subtropical countries, especially in poor socioeconomic communities “...where environmental conditions favour spread of infection”.

#### Recommendations

- Patients with IBD who will be placed on anti-TNF therapy, and who have “...travelled for long periods or lived in endemic areas” should have laboratory measurements of their eosinophilic count plus serology for Strongyloides (GRADE: weak recommendation, very low-quality evidence. Agreement: 91%).
- Treat with albendazole or ivermectin
- Obtain a vaccination history, and update vaccinations in all patients with CD, and in patients with moderate/severe UC.
  - Do this at the time of diagnosis of IBD, as well as before starting immunomodulators.



- Vaccination

- Do not vaccinate for liver viruses (HAV, HBV) in persons with IBD while they are on immunosuppressants/biologics
    - Safe to vaccinate live viruses 4 wk before starting immunosuppressive therapy, or  $\geq 3$  mon after stopping this therapy
- (GRADE: strong recommendation, very low-quality evidence. Agreement: 93%).

- Influenza

- $\uparrow$  risk in IBD (RR, 1.58; 95% CI: 1.49 to 1.68)
- $\uparrow$  risk of hospitalization
- Vaccination required
  - Be aware that influenza vaccine efficacy is reduced in IBD
- Use injected influenza vaccine, **not** the nasal spray (contains live influenza virus)

#### Recommendations

- Give all patients with IBD who are on immunosuppressants
  - Influenza vaccine every autumn
  - Pneumococcal vaccination PCV13, then give PPSV23 q5yr

(GRADE: strong recommendation, very low-quality evidence. Agreement: 96%)
- Pneumococcus
  - For patients with IBD who are already on immunosuppressants, begin with one vaccination with PCV13 (pneumococcal conjugate vaccine 13, which contains polysaccharide from 13 capsular types of pneumococcus), then  $\geq 2$  mon later give one vaccination with PPSV23.
    - Booster PPSV23 should be given a second time after the first PPSV23 vaccination in persons who have
      - $\downarrow$  splenic function
      - Chronic renal disease
    - The British Society of Gastroenterology (BSG) acknowledges that while there is no evidence for this "...it seems reasonable to give boosters [of PPSV23] to patients on long-term immunomodulatory therapy"
- Hepatitis B virus
  - Perform serological testing for HBV infection in all IBD patients at the time of diagnosis, and again before administration of immunomodulatory or anti-TNF therapy.
    - The efficacy of vaccination for HBV may be reduced in persons with
      - Active IBD, or
      - Immunosuppressive drugs
    - Consider immunization of IBD patients with double-dose Engerix-B



- Herpes zoster virus (HZV)
  - Vaccination for HZV is recommended in patients with IBD, even if they are on low-level immunosuppression.
    - The definition of what is meant by low-level immunosuppression, and the age at which HZV vaccination should be given, varies between countries.

| Variable                                                                                                                                                                                                                                                                                                              | USA CDPC                | UK DHGB Vaccination Guide                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------------------------------------|
| – Age of HZV vaccination, yr                                                                                                                                                                                                                                                                                          | $\geq 60$               | 70 to 79 yr                                           |
| – Prednisolone, mg po od                                                                                                                                                                                                                                                                                              | $< 20$                  | $\leq 20$ , for $> 14$ d, +/- low dose MTX, AZA, 6-MP |
| – Azathioprine (AZA), mg/kg po od                                                                                                                                                                                                                                                                                     | $\leq 3$                | $\leq 3$                                              |
| – Mercaptopurine (6-MP), mg/kg po od                                                                                                                                                                                                                                                                                  | $< 1.5$                 | $\leq 1.5$                                            |
| – Methotrexate (MTX) po sc                                                                                                                                                                                                                                                                                            | $\leq 0.4$ mg/kg per wk | $\leq 25$ mg per wk                                   |
| ○ Shingles vaccination (current UK age recommendation is at age 70 yr, or up to age of 79 yr, if not already given at age 70 yr)                                                                                                                                                                                      |                         |                                                       |
| – May be administered to those on low-level immunosuppression (defined as $\leq 20$ mg prednisolone/day for $> 14$ days, either alone or in combination with low dose non-biological oral immunomodulators (methotrexate $\leq 25$ mg/week, azathioprine $\leq 3$ mg/kg/day, or mercaptopurine $\leq 1.5$ mg/kg/day). |                         |                                                       |

- General considerations regarding vaccination
  - Do **not** give vaccines if IBD patient is on immunosuppression, or has significant protein-calorie malnutrition
    - Live vaccines include
      - BCG
      - Attenuated (oral) influenza vaccine
      - Measles
      - Mumps
      - Rubella
      - Polio
      - Rotavirus
      - Typhoid Ty21a po
      - Varicella zoster
      - Yellow fever.
    - Immunosuppressive therapies of concern include:
      - Glucocorticoids (prednisolone  $\geq 20$  mg/day or equivalent for  $\geq 2$  wk)
      - Thiopurines
      - Methotrexate
      - Biological therapy (including tofacitinib)
  - Immunomodulators should be withheld for 4 wk after administration of live vaccines
  - Live vaccines should be avoided for  $\geq 3$  mons after discontinuing treatment with immunosuppressive therapies.



- Infants exposed to biologics in utero should not receive live vaccines for 6 months after birth.
- IBD patients on immunosuppressant therapy should receive pneumococcal vaccine and annual influenza vaccination (prior to starting treatment if possible) with a single pneumococcal booster at 5 years.

## ❖ Drug Management Strategies

### • Thiopurines (TPs)

#### Recommendations

- All patients with IBD who are being considered for therapy with thiopurines (TPs)
  - Assess for thiopurine methyltransferase (TPMT) deficiency (GRADE: strong recommendation, moderate-quality evidence. Agreement: 100%).
- Responding to results of TPMT assay
  - Low: do **not** use TPs (↑↑ risk of myelosuppression in homozygous / heterozygous TPMT deficiency)
  - Intermediate: ↓ dose to at least 50% of usual dose of TP
  - High: Start AZA 2.0 to 2.5 mg/kg po od (start at full dose, or start at low doses and slowly ↑ to tolerance / to ↓ adverse effects)
- TPMT screening
  - Cost-effective, and ↓ drug toxicity from AZA / 6-MP

#### Treatment Alert

- Patients with IBD who are being considered for therapy with TPs who have associated “significant renal impairment”) must have **reduced dosing** of AZA / 6-MP
  - Creatinine clearance

|               | Usual Dose |
|---------------|------------|
| 10-50 mL/min, | 75%        |
| < 10 mL/min,  | 50%        |

- Cervical dysplasia
  - Women with IBD who are on AZA / 6-MP must have regular screening for cervical dysplasia (GRADE: strong recommendation, very low-quality evidence. Agreement: 96%).
  - High risk group
    - Smokers
    - On prednisone



- Before starting treatment with AZA/6-MP, measure complete blood count (CBC), liver enzymes (LEs), creatinine (Cr), and electrolytes (time 0)
  - Continue monitoring at wk 2, 4, 8, and 12, then q3mon  
Also repeat blood test monitoring 2 wk after any ↑ dose of thiopurine.  
(GRADE: strong recommendation, low-quality evidence. Agreement: 100%)

#### Monitoring Alert

- Aggressively monitor the peripheral white blood cell (WBC) count even in the patient with IBD and normal TPMT activity and who is treated with azathioprine / 6-mercaptopurine (6-MP), since
  - Dangerous immunosuppression may **still occur** in patients on AZA/6-MP and normal TPMT activity.
- The non-TPMT-related immunosuppression of these medications may be related to other unknown factors (such as genotype NUDT15).
- NUDT15 genetic variation is a marker for ↑ risk of excessive myelosuppression in persons taking azathioprine / 6-mercaptopurine, including CD patients who are of East Asian and European ancestry.

#### Recommendations

- Use therapeutic monitoring for thiopurines (TGN and MMP)
  - Optimize dosing of AZA / 6-MP
  - Assess ↑ risk for
    - Myelosuppression
    - Hepatotoxicity
  - **Always** use aggressive monitoring of peripheral blood white blood cell (WBC), regardless of genotype TPMT, NUDIS, TGN MeMP  
(GRADE: weak recommendation, low-quality evidence. Agreement: 93%)
- Consider using low-dose thiopurines (↓ dose to 25% - 33% of usual dose) and add allopurinol 100 mg/d po to ↑ TGN and ↓ MeMP in persons with thiopurine adverse effects due to hypermethylation, e.g.,
  - Nausea/vomiting
  - Flu-like symptoms
  - Hepatotoxicity
 (GRADE: weak recommendation, low-quality evidence. Agreement: 81%)



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- Give the use of determining the HLA haplotypes in a patient with IBD who may be treated with thiopurines.
  - HLA-DQA1\*02:01-HLA-DRB1\*07:01 predicts ↑ risk thiopurine-associated pancreatitis
- Suggested practice before and during therapy with thiopurine
  - Before starting:
    - All patients should receive verbal and written information about their medication
    - Baseline complete blood count (CBC), urinalysis, and liver enzyme measurement, and repeat at least at wk 2, 4, 8, and 12, and then at least q3mon
    - If available, test NUDT15 genotype (especially if CD patients who are of European or East Asian ancestry)
    - Screen for HCV, HBV, HIV
      - Consider HBV vaccination if patient is naïve
    - Check VZV immunity, and vaccinate if low titre
    - Vaccinate for influenza and pneumococcal vaccine
    - Bring check cervical screening up to date
    - Check TPMT, and start at target dose once result available
      - Normal TPMT: 2 mg/kg azathioprine or 1mg/kg mercaptopurine
      - Low: 1 mg/kg azathioprine or 0.5 mg/kg mercaptopurine
      - Very low: **no** thiopurine
    - Age related screening (e.g., breast, colon cancer)
  - Monitoring:
    - CBC, LFTs, LEs analysis (complete blood count, liver function tests, liver enzymes)
- Therapeutic drug monitoring of thiopurines
  - Measuring the guanine metabolites (TGN) and methylmercaptopurine (MeMP) may be useful to detect
    - Over-/under-dosing / variable adherence of the patient
      - ↑ risk of myelosuppression, or inadequate response due to ↓ immunosuppression
    - TP resistance
    - TP hypermethylation
      - ↑ risk of hepatotoxicity
    - Need for alteration of TP doses to
      - ↑ clinical / endoscopic response
      - ↓ risk of hepatotoxicity



- Suggested target concentrations of TGN/MeMP (not yet in widespread clinical practice)

|                              | pmol / 8 x 10 <sup>8</sup> RBC |        |
|------------------------------|--------------------------------|--------|
|                              | TGN                            | MeMP   |
| ▪ Thiopurine                 | 230-400                        | < 5700 |
| ▪ Thiopurine plus infliximab | 105-125                        |        |

- Use and interpretation of thiopurine metabolites

| TGN (pmol/8×10 <sup>8</sup> RBCs) | MeMP (pmol/8×10 <sup>8</sup> RBCs) | Interpretation                                                                  | Treatment change to consider                                                                                                              |
|-----------------------------------|------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Undetectable                    | Undetectable                       | - Poor/variable compliance                                                      | ▪ Patient education<br>▪ Rarely poor absorption                                                                                           |
| ○ Low (< 235)                     | Low/normal (< 5700)                | - Subtherapeutic dosing                                                         | ▪ ↑ dose then repeat metabolite                                                                                                           |
| ○ Low (< 235)                     | High (> 5700 or MEMP: TGN > 11)    | - Thiopurine hypermethylator (occurs in up to 20% of patients with normal TPMT) | ▪ ↓ dose to 25-33% + start allopurinol 100 mg/day, then repeat metabolites                                                                |
| ○ Therapeutic (235–450)           | Normal (5700)                      | - Therapeutic, if responding                                                    | ▪ If responding, continue current dose                                                                                                    |
|                                   |                                    | - Thiopurine resistant (if not responding)                                      | ▪ If not responding, change drug category                                                                                                 |
|                                   |                                    | - Possible supratherapeutic dosing                                              | ▪ ↓ dose and repeat in 4 weeks. If non-responding and TGN low end of normal range, consider ↓ dose azathioprine plus allopurinol as above |
| ○ High (>450)                     | High (>5700)                       | Supratherapeutic dosing                                                         | ▪ ↓ dose then repeat metabolites                                                                                                          |

Abbreviations: MeMP, methylmercaptopurine nucleotides; RBC, red blood cells; TGN, 6-thioguanine nucleotides; TPMT, thiopurine methyltransferase

Printed with permission: Lamb CT, et al. Gut 2019; 68: S1-S106 (Table 10)



- Thiopurine hypermethylation
  - Methylation controls the amount of AZA / 6-MP which is metabolized to TGN or to MeMP
  - ↓ conversion of AZA / 6-MP →
    - ↑ TGN → ↑ therapeutic effect on inflammation, but ↑↑ immunosuppression
    - ↓ MeMP → ↓ risk of hepatotoxicity
  - ↑ conversion of AZA / 6-MP to MeMP (hypermethylation)
    - ↓ TGN ( $< 235 \text{ pmol} / 8 \times 10^8 \text{ RBC}$  → ↓ clinical efficacy
    - ↑↑ MeMP  $> 5700 \text{ pmol} / 8 \times 10^8 \text{ RBC}$  → ↑ hepatotoxicity
  - When the MeMP > TGN by  $\geq 11$  → ↓ dosing of AZA / 6-MP by 25% to 33% (→ ↓ TGN, ↓↓ MeMP) plus add allopurinol 100 mg/d po (to ↓ methylation → ↓ MeMP, ↑ TGN) → ↑ TGN, but still ↓↓ MeMP, 80 MeMP / TGN →  $< 11$ , ↓ clinical efficacy
  - Low-dose AZA plus allopurinol vs. thiopurine monotherapy at usual doses
    - ↓ use of corticosteroids / biologics, 70% vs. 35% (RR, 2.1 [95% CI: 1.07 to 4.11])
    - ↓ adverse effects leading to need to stop azathioprine, 30% vs. 48% (RR, 1.47 [95% CI: 0.76 to 2.85])
    - ↑ clinical response
- Adverse side effects of thiopurines
  - ~1/4 of persons on thiopurines develop adverse effects (AEs)
- Managing side effects of thiopurines
  - Pancreatitis:
    - Do **not** give AZA or MP again, even at low dose (↑ risk of recurrence of pancreatitis)
  - Nausea and vomiting (N/V)
    - Switch from AZA to MP; or
      - Continue same dose but with split dosing
    - If N/V recurs, consider low dose (25–33% of standard dose) AZA or MP + allopurinol 100 mg
  - Flu-like symptoms:
    - Unlikely to resolve on switching from AZA to MP
      - Some evidence for use of AZA/MP + allopurinol 100 mg
    - If convincing that the symptoms represent an early hypersensitivity reaction, there is high risk of recurrence, and so
      - Switch to alternative class of drug
  - Newly abnormal LEs:
    - Stop and check thiopurine metabolites
    - Withhold TP until LE abnormalities resolve
    - If not resolving, investigate as per usual
    - Once resolved, re-challenge with low dose AZA/MP + allopurinol 100 mg
      - This is particularly likely to work if the original metabolites showed hypermethylation (High MeMP levels)





- Myelotoxicity:
  - Check TP metabolites and
    - Alter dosage as appropriate
    - Monitor white cell counts closely
  - If total white cells  $<3.5 \times 10^9/L$  or neutrophils  $<2 \times 10^9/L$ 
    - Withhold TP until counts correct above this level
  - If neutrophils  $<1 \times 10^9/L$ , give febrile patients granulocyte colony stimulating factor (GCSF)
  - If TGN high
    - Restart at lower dose, once abnormality has resolved, and
    - Monitor hematology and TP metabolites carefully
  - If MeMP high
    - Restart low-dose TP with allopurinol 100 mg
  - If TGN low or normal, then likely to reoccur
    - Stop TP

Abbreviations: AZA, azathioprine; MP, mercaptopurine; AZA/MP, azathioprine or mercaptopurine; GCSF, granulocyte colony stimulating factor; MeMP, methylmercaptopurine nucleotides; TGN, 6-thioguanine nucleotides

#### ❖ Methotrexate (MTX)

##### Recommendations

- Supplement taking methotrexate (MTX) with folic acid 1 mg po od, or 5 mg po qwk, taken 1-2 d after taking MTX.
- Altered liver enzymes is usually transitory (occurs in ~25%), but 5% need to stop MTX. Usually liver biopsy is not needed during prolonged use of MTX
  - Risk factors for abnormal FibroScan® (indicating fibrosis/cirrhosis due to MTX)
    - Alcohol  $> 14$  drinks/wk
    - BMI  $> 28 \text{ kg/m}^2$
- Suggestion
  - Pulmonary fibrosis (intestinal pneumonitis)
    - Rare, usually reversible on stopping MTX
    - Perform chest x-ray baseline before starting MTX

##### Treatment Alert:

- MTX is teratogenic **BEWARE!**
  - Caution patient and partner; give each a written warning re toxicity to fetus
  - Couple must use double contraception, or use another drug or device



## Recommendation

- Stop MTX 6 mon before planned conception (GRADE: strong recommendation, low-quality evidence).
  - If conception occurs while mother on MTX, stop MTX and give folic acid 15 mg po od for 6 wk
    - Men using MTX do **not** need to stop MTX before conception (**No** teratogenicity if father of child takes MTX) (GRADE: weak recommendation, low-quality evidence. Agreement: 93%)
- Teratogenicity
  - Plan pregnancy and stop MTX before conception, or “commit to assured contraception” during continued use of MTX
  - Do **not** restart MTX for 6 mon after stopping drug
  - Outcome of low-dose exposure to MTX during first trimester of pregnancy (T1)
    - Termination of pregnancy, 30%
    - Miscarriage, 25%
    - Continuing to term and baby has congenital abnormalities, 12%
- ❖ Anti-TNF drugs
  - Compared with other anti-TNF, infliximab may have
    - “...possible superiority in the induction phase of treatment of UC”
    - “...increased immunogenicity ...potentially increased the need for co-presumption of an immunomodulator, with resulting effects on safety”
    - Using propensity scores in patients with CD, IFX compared to ADA
      - ↓ CD-related
        - Hospitalization/surgery
        - Use of corticosteroid (HR, 0.85; 95% CI: 0.75 to 0.96)
      - CD patients in remission on IFX and switched to ADA (IFX → ADA)
        - ~ half required either dose escalation of ADA, or
        - Switch back from ADA to IFX (IFX → ADA → IFX) for maintenance of remission (SWITCH trial)
- Biosimilar anti-TNF drugs
  - Patients should be fully informed about the biological medicine they are using, particularly if there is a change to a biosimilar from the original molecule”.
    - “Automatic substitution is inappropriate, as all changes should be made with the full agreement and supervision of the prescribing physician” and the patient.
      - “Switching should remain a clinical decision to be made by the physician and patient on an individual basis supported by the scientific evidence and by national recommendation”
  - Note however
    - Switching to biosimilar CT-P13 from IFX in patients with CD was non-inferior to continuing on IFX in terms of disease worsening (26% vs. 30%, respectively) (NOR-SWITCH study)
      - There was no difference between (T-P13 and IFX in anti-drug antibodies (ADA, 7% vs. 8%)



### Treatment Tip

- Before switching from brand IFX to a biosimilar IFX, measure IFX and antibodies to infliximab (ATI) concentrations / titres.
  - If ↓ IFX / ↑ ATI → switch to different class of drug
    - Consider stopping anti-TNF if patient's disease is in “deep remission”

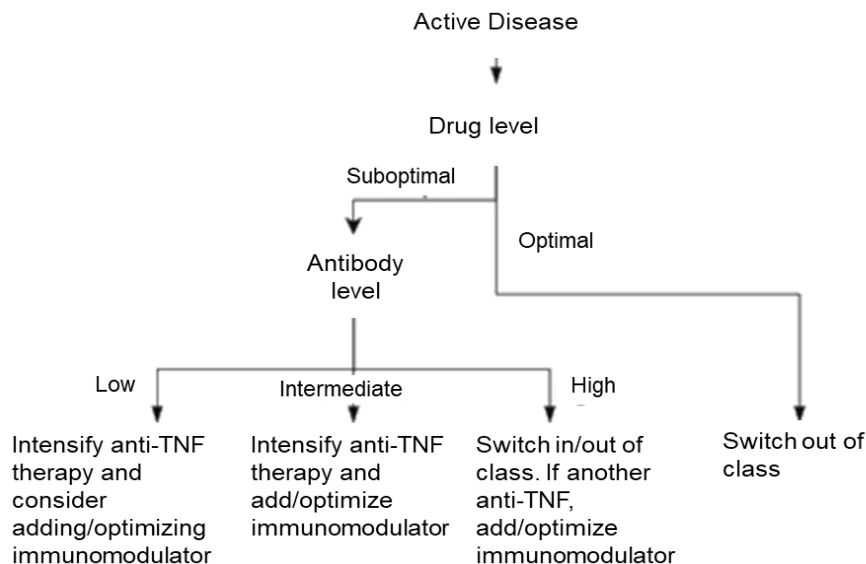
- Anti-TNF induction therapy

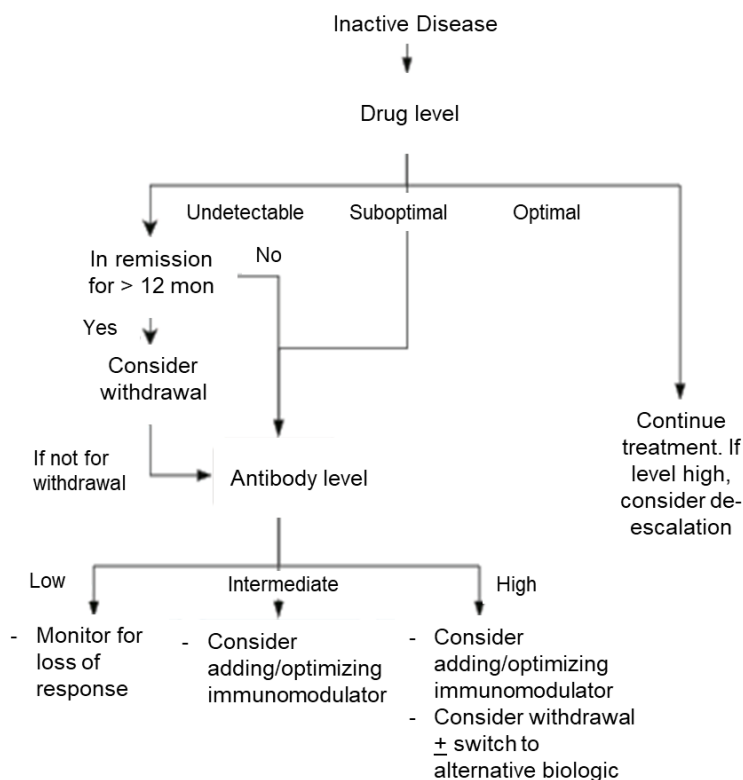
- Non-responders to the usual dose/duration of induction therapy with IFX/ADA do **not** benefit from longer duration of treatment (ACCENT, CHARM studies)
  - Assess clinical response at 4 wk (doses given at T0 and T2 wk)
    - Response → dose optimization
    - Unclear response → CRP, fCal, comparison of clinical scores T0 to T4 / (PROMS study)
    - There may be a role for therapeutic drug monitoring (TDM)
      - Evidence of response → continue
      - No evidence of response → use a different class of biologic

- Therapeutic Monitoring

- Role of measuring trough concentrations of anti-TNF drug
    - Serum levels of IFX at wk 8 correlate with
      - Clinical response
      - Mucosal healing
      - Remission
- ACT 1/2 UC studies, TAXIT CD Study

- Anti-TNF therapeutic drug monitoring





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#### Note

- Optimal drug levels for IFX and ADA are not defined, depend on the assay used, and clinical context
- After dose optimization, the regular use of therapeutic drug monitoring (TDM) in patients in remission is **not** recommended, and further evidence of cost-effectiveness is awaited.
- Non-response
  - Primary
    - Failure to respond to induction therapy
      - TDM may be useful to determine if ↑ dose may be beneficial
      - Measurements of anti-drug antibodies (ADAs) are useful: if positive
        - Switch to another drug in the class, or
        - To another class of drug
  - Secondary loss of response to anti-TNF
    - Antibodies to anti-TNF drug
    - Inadequate drug concentration
      - ↑↑ drug loss into/through inflamed gut



## Recommendation

- When treating initial/secondary anti-TNF failure, measure serum drug concentration and titres of anti-drug antibodies (ADA) to better choose between
  - ↑ dose / ↓ interval of dosing of anti-TNF, switch to an alternate anti-TNF, or
  - Switch to a different class of drug (GRADE: weak recommendation, low-quality evidence. Agreement: 98%).
  - “Starting the patient on immunomodulatory therapy (if not already on this) can abolish the antibody response and restore efficacy, particularly if combined with an antibody response and restore efficacy, particularly if combined with an increase in anti-TNF dose”]

\*Note possible confusion: in the literature, depending upon the context “ADA” may signify “antibodies to adalimumab” or to “anti-drug antibodies”

### ➤ Postulated mechanisms (of loss of response)

- Anti-drug antibodies (ADAs)
  - Immune-mediated naturalizing antibodies to anti-TNF drug
- Non-neutralizing antibodies
- Drug clearing antibodies
- Non-immune mediated (e.g., ↑ drug loss through inflamed gut)

### ➤ Approach

- |                                                                                                                                                                                                                                                                                                                              |   |                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>○ Concentration of anti-TNF drug<ul style="list-style-type: none"><li>– IFX &gt; 3.8 µg/mL</li><li>– ADA &gt; 4.5 µg/mL</li></ul></li><li>○ Positive ADAs<ul style="list-style-type: none"><li>– IFX &gt; 9 µg/mL equivalent</li><li>– ADA &gt; 4 µg/mL equivalent</li></ul></li></ul> | } | <p>Consider</p> <ul style="list-style-type: none"><li>▪ Switch to another anti-TNF, or</li><li>▪ Switch to another class of drug</li><li>▪ Consider concomitant immunomodulator therapy</li></ul> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
- Low concentration of anti-TNF, no ADAs
    - ↑ dose of same anti-TNF
      - Mucosal healing may occur in 50% who have ↑ anti-TNF trough levels
  - Options to ↑ drug levels
    - ↓ infusion interval of IFX 8 wk → 4-6 wk
      - Doubling dose more effective than ↓ interval: sustained response in 50% vs. 39%; OR, 1.5; 95% CI: 0.8 to 2.9
    - ↑ dose from 5 mg/kg → 10 mg/kg
    - If there are low drug concentrations and low-titre ADA, just ↑ dose may activate response (sometimes ADAs are transient) (TAXIT trial)
    - If in the presence of ↓ concentration of IFX plus ATI the response does not increase with the ↑ dose of IFX, start the patient on an immunomodulator (if not already on one)
    - If low IFX levels plus high ATI, and response does not occur with ↑ dose of IFX → add immunomodulator, or switch to adalimumab/ adalimumab plus immunomodulator.



#### Treatment Tip

- Patients who produce antibodies to one anti-TNF have ↑ risk of producing ADAs to a second anti-TNF.
  - If patient was not on an immunomodulatory with the first anti-TNF, consider adding azathioprine / methotrexate when the second anti-TNF is started.

Abbreviations: ADA, anti-antidrug antibodies

#### Recommendations

- Patients with IBD should be reassessed at least once a year for evaluation, possible new developments, such as extraintestinal manifestations, malnutrition, bone health, smoking, psychosocial well-being, response reductions and adverse effects, as well as “...consideration of response and treatment continuation, optimization or cessation” (Agreement: 98%)
- ❖ Vedolizumab (VEDO): adverse effects
  - Risk of an infusion-related reaction (IRR) ~5% (GEMINI studies)
  - Serious infections (Clostridium difficile infection [CDI]), sepsis, and tuberculosis infection occur in about 0.6%)
    - Do **not** use VEDO during active CDI
    - Be aware of this gut specific integrin receptor antagonist and modulator of innate immunity having the rare risk of the adverse effects of progressive multifocal leukoencephalopathy (PML)
    - Risk of malignancy is low
    - ↑ risk of de novo arthropathy (14%), dermatitis (5%), and after extraintestinal manifestations (EIM)
      - At wk 54 of VEDO, there was complete remission of arthropathy (45%), and dermatitis (75%)

#### Vaccination Caution

- Vedolizumab reduces response to orally administered vaccines.
- Do not use if patient has
  - C. difficile infection
  - Risk of progressive multifocal leukoencephalopathy



❖ Cancer Concerns

- Delay use of biologics in IBD patients with past history of cancer.
  - Time
    - 2 yr, low
    - 5 yr, high
  - After successful eradication of tumour, there is still a risk of late metastatic spread from
    - Breast, kidney (renal cell carcinoma)
    - Skin (malignant melanoma)

❖ Stopping rules

- Thiopurines

Recommendation

- Clinical remission plus mucosal healing while on prolonged use of thiopurines
  - “...may stop the drug after discussion of risk and benefits and considering patient preference (GRADE: weak recommendation, low-quality evidence. Agreement: 95%).
  - If relapse recurs when patient taken off thiopurines, the patient usually responds to reintroduction of the drug

|                                                                                                                                                                                                                                         | 1 yr       | 5 yr       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|------------|
| ○ Stopping                                                                                                                                                                                                                              |            |            |
| – Remission for 12 mon on TP, stopping TP, then relapse                                                                                                                                                                                 |            |            |
| ▪ UC                                                                                                                                                                                                                                    | 11% to 77% | 43% to 65% |
| ▪ CD                                                                                                                                                                                                                                    | 16% to 53% | 63% to 85% |
| ○ Restarting                                                                                                                                                                                                                            |            |            |
| – Success of restarting TP after relaps when TP stopped                                                                                                                                                                                 |            |            |
| ▪ UC                                                                                                                                                                                                                                    | 92%        |            |
| ▪ CD                                                                                                                                                                                                                                    | 74% to 96% |            |
| ○ After stopping TP, there is usually ↑ fecal calprotectin (fCal) before symptoms develop, and so measure fCal q3mon where indicated by patient concern of withdrawal of therapy and possibility for early restart of TP (or anti-TNF). |            |            |



- Anti-TNF

#### Recommendation

- Corticosteroid-free (> 1 to 2 yr) TNF-associated induction of clinical remission and mucosal healing → may withdraw anti-TNF therapy.
- “There is insufficient evidence about which clinical factors predict relapse after withdrawal and decisions should be individualized (GRADE: weak recommendation, very low-quality evidence. Agreement: 93%).
- When anti-TNF therapy is withdrawn, monitor fCal to detect possible presymptomatic recurrence (GRADE: weak recommendation, low-quality evidence. Agreement: 98%)

|                                                                            | 1 yr                                                                                                                                                                                                                          | 5 yr |
|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| ○ Remission for 12 mon on anti-TNF, stopping TP, then relapse              |                                                                                                                                                                                                                               |      |
| – UC / IBD-U                                                               | 35%                                                                                                                                                                                                                           | 42%  |
| – CD                                                                       | 39%                                                                                                                                                                                                                           | 54%  |
| ○ Success of reintroducing anti-TNF after relapse when anti-TNF stopped    |                                                                                                                                                                                                                               |      |
| – UC / IBD-U                                                               | 76%                                                                                                                                                                                                                           |      |
| – CD                                                                       | 88%                                                                                                                                                                                                                           |      |
| ○ Risk factors for CD recurrence after stopping anti-TNF induced remission |                                                                                                                                                                                                                               |      |
| – Patient                                                                  | <ul style="list-style-type: none"> <li>▪ Young age</li> <li>▪ Smoker</li> </ul>                                                                                                                                               |      |
| – CD                                                                       | <ul style="list-style-type: none"> <li>▪ Long duration of CD</li> <li>▪ Fistulizing/perianal disease</li> <li>▪ Persisting disease on endoscopy/MRE (lack of mucosal healing)</li> <li>▪ Post-operative recurrence</li> </ul> |      |
| – Laboratory                                                               | <ul style="list-style-type: none"> <li>▪ Anemia</li> <li>▪ ↑ CRP</li> <li>▪ ↑ fCal</li> </ul>                                                                                                                                 |      |
| – Medication                                                               | <ul style="list-style-type: none"> <li>▪ Escalating doses of anti-TNF required</li> </ul>                                                                                                                                     |      |
| ○ Negative predictors (protection against) for relapse                     |                                                                                                                                                                                                                               |      |
| – Mucosal healing                                                          |                                                                                                                                                                                                                               |      |
| – Possibly continued normal fCal on targeted monitoring q3mon              |                                                                                                                                                                                                                               |      |





- Corticosteroids

#### Recommendations

- Prolonged use of corticosteroids is harmful, and unfortunately is common (~50% of IBD patients)
    - Reduce the practise of using corticosteroids: consult a GI/IBD specialist, and ask a multidisciplinary team to explore other treatment options.  
(GRADE: strong recommendation, moderate-quality evidence. Agreement: 98%)
  - Do **not** use corticosteroids (for > 3 mon) to maintain remission.
  - Definitions
    - Steroid dependence
      - "... inability to wean below 10 mg of prednisolone [per day], or 3 mg of budesonide [per day], within 3 mon of starting [prednisone]", or
      - "...disease flare within 3 mon of stopping steroids (about 15% of CD patients)
    - Steroid refractory disease
      - "... active disease despite taking up to 1 mg/kg/d of prednisolone for 7 wk
    - Steroid excess
      - ≥ 2 causes of steroids over 1 yr
  - All IBD patients who receive corticosteroids for active disease should received vitamin D 800 IU/d plus calcium ( $\text{Ca}^{2+}$ ) 800 to 1000 mg/d (GRADE: strong recommendation, very low-quality evidence).
    - Give just vitamin D if the patient's intake of  $\text{Ca}^{2+}$  is adequate
    - If the patient's intake of calcium is not adequate, give vitamin D plus  $\text{Ca}^{2+}$
    - Encourage appropriate life-style changes, e.g., ↓ smoking / alcohol, ↑ physical weight bearing activity (Agreement: 91%)
  - Assess for risk factors for osteoporosis
    - If ↑ risk for osteoporosis, ensure adequate intake of vitamin D and  $\text{Ca}^{2+}$ , and add a bisphosphonate when steroids are started (GRADE: strong recommendation, high-quality evidence), after ensuring adequate calcium intake and supplementing vitamin D (Agreement: 91%).
- ❖ Corticosteroid-related bone disease
- ↑ risk of corticosteroid-related bone disease in patients with UC/CD
    - Osteopenia, ~35%
    - Osteoporosis, 15%

}

Total, 50%
  - Risk factors to be screened for and treated
    - Patient
      - ↓ Body weight
      - ↓ Physical (weight-bearing) exercise
      - Smoking
      - Alcohol excess
    - IBD
      - Inflammation, continued/uncontrolled
      - Use of corticosteroids, high dose / prolonged



- $\text{Ca}^{2+}$  / vitamin D / nutrition
    - ↓ intake of  $\text{Ca}^{2+}$  / vitamin D
    - ↓ absorption of  $\text{Ca}^{2+}$  / vitamin D (CD)
    - Malnutrition
  - Vitamin D
    - Older persons with IBD, give 700-800 IU/d → ↓ hip / non-vertebral fractures
  - CD
    - Supplemental vitamin D 800 IU/d plus calcium ( $\text{Ca}^{2+}$ )
      - 500 to 1000 mg/d → ↑ bone density over 5 yr
      - ↓ bone loss from lumbar spine and forearm (Cochrane review)
- Vitamin D deficiency
    - Monitor/correct vitamin D deficiency (serum concentration < 50 nmol/L in patients with UC/CD) (GRADE: weak recommendation, very low-quality evidence. Agreement: 87%)
    - Vitamin D deficiency is present when blood vitamin D < 50 nmol/L  
Vitamin D deficiency is common in IBD
 

| Prevalence of Vitamin Deficiency |          |            |
|----------------------------------|----------|------------|
| - UC                             | ▪ Mild   | 69%        |
|                                  | ▪ Severe | 36% to 44% |
    - Risk factors
      - IBD-related surgery
      - Race
        - Black and Asian ethnic group
      - Active disease / ↑ fCal
    - Benefits of normal vitamin D levels
      - ↑ remission
      - ↑ length/duration of response to anti-TNF
      - ↓ risk of metabolic bone disease
    - Calcium plus vitamin D
      - If vitamin D is deficient, use high loading dose initially, then lower dose for maintenance.
      - Use vitamin D plus  $\text{Ca}^{2+}$  < 800 mg/d long term
      - If patient taking vitamin D plus  $\text{Ca}^{2+}$ , estimate their intake
      - (<https://webapps.igc.ed.ac.uk/world/research/rheumatological/calcium-calculator>)
      - (<http://www.cgem.ed.ac.uk/research/rheumatology/calcium-calculator>)
    - Steps to ↓ risk of corticosteroid-associated bone disease
      - Avoid using high dose / prolonged dosing of corticosteroids
        - Greatest loss of bone density is in the first 6 mon of use of corticosteroids
      - Daily intake of  $\text{Ca}^{2+}$  before starting corticosteroids, assess
        - Serum  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{2-}$ , vitamin D
        - DEXA Scan for bone mineral density (BMD)
        - Use Fracture Risk Assessment Tool (predicts a yearly risk of a major osteoporotic fracture (<http://www.shef.ac.uk/FRAX/>))



- Patients with IBD should have DEXA Scan before treatment with corticosteroids, then 1 yr later
    - If ↓ DEXA Score, repeat DEXA Scan q1yr
    - If DEXA Score stable
      - Repeat DEXA Scan q2 to 3 yr
  - > 70 yr of age, females/males
    - ≥ 7.5 mg/ equivalent prednisolone-equivalent
    - History of fragility fracture
    - ↑ FRAX score
- } ▪ Consider use of
- Alendronate/risedronate po
  - Zoledronate/teriparatide

#### **Bisphosphonate Alert in Pregnancy**

- Women of childbearing age **must** be taking effective contraception, or be totally sexually inactive, if it is indicated for them to take bone-protective therapy of bisphosphonate po, or teriparatide IV.

#### ❖ Corticosteroid-associated Adrenal Suppression

##### Recommendations

- Patients who have been on corticosteroids (CS) for prolonged periods.
  - IF stopping CS, slowly taper dose
  - Warn patient about symptoms which suggest CS withdrawal, the need to restart CS, and the use even slower taper
- About 50% of IBD patients who have been on moderate-high doses of corticosteroids are at risk of adrenal suppression.
  - The symptoms from corticosteroid adrenal suppression may mimic symptoms of IBD.
  - The blood tests for adrenal suppression (ACTH test, or short Synacthen test) may be abnormal immediately after corticosteroids are stopped and these abnormalities may last as long as ~2 yr

##### Treatment Reality

- There is an urban medical view that the complication of the use of corticosteroid is related to the dose and duration of their use.
  - With regards to corticosteroid-associated adrenal suppression, neither “...dose nor duration are good predictors of ...” this problem
    - Even rectal steroid enemas, and as little as 4 wk of treatment, is sufficient to cause corticosteroid-associated adrenal suppression
- Adrenal insufficiency
  - Is not completely prevented by slow steroid tapering
  - There is no optimal laboratory test to predict optimal tapering of CS
- The reality is
  - The physician must have a high index of clinical suspicion of steroid-associated adrenal suppression.

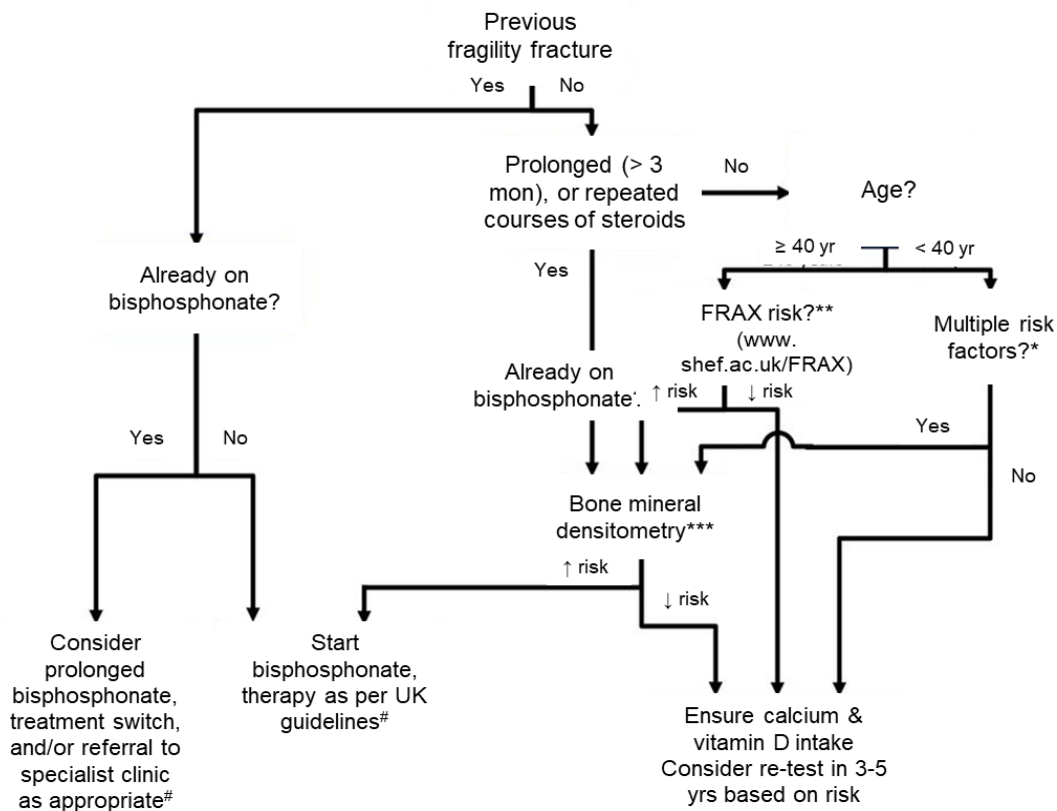


- Suggested precautions

- Assess for
  - Complications, including depression, insomnia
  - Ophthalmology examination yearly
- Measure
  - Body height / weight / waist circumference
  - Serum lipids
  - CBC fasting blood glucose (FBG) / HbA1C (hemoglobin A, C) repeat q3mon
  - Electrolytes (carefully follow K<sub>s</sub>+)
    - Perform if CS therapy planned for ≥ 3 mon, or
    - Repeat CS therapy within 6 mon of a previous course
- Ensure age-based vaccinations are up-to-date and reflect guidelines for patients who are on immunotherapy.

- Osteoporosis prevention and management in IBD

All patients starting corticosteroids should receive an intake of 800-1000 mg calcium (dietary or supplement) and 800 IU vitamin D daily (If vit D deficient treat with 50,000 IU weekly for 6 wk initially) and assess for osteoporosis risk factor\*



\*Assess and modify risk factors wherever possible:

- Prolonged or high dose steroids
- Uncontrolled inflammation
- Weight loss / malabsorption
- Lack of physical activity (esp. weigh-bearing)
- Alcohol excess
- Smoking

\*\*FRAX assumes an average dose of 2.5-7.5 mg/d prednisolone or equivalent, thus may underestimate fracture risk in those taking higher doses.

- Average adjustments over all ages in postmenopausal women and men  $\geq 50$  yr are shown below

|          | Prednisolone equivalent (mg/d) | Average adjustment: hip fracture probability | Average adjustment: major osteoporotic fracture probability |
|----------|--------------------------------|----------------------------------------------|-------------------------------------------------------------|
| ▪ Low    | < 2.5                          | % risk x 0.65                                | % risk x 0.8                                                |
| ▪ Medium | 2.5-7.5                        | None                                         | None                                                        |
| ▪ High   | $\geq 7.5$                     | % risk x 1.2                                 | % risk x 1.15                                               |

\*\*\*Arrange bone mineral densitometry as soon as possible.

- As fracture risk increases within 3 mon of starting corticosteroids, if testing cannot be undertaken within 1 mon, start treatment to prevent osteoporosis should be in high-risk patients.
- Patients on long-term steroids should have a repeat bone densitometry at 1 yr, and if stable, repeated at 2-3 yr intervals, but if declining, repeated annually.
- High-risk threshold for interventions is T score  $-1.5$ , (or a FRAX x 10 yr  $\geq 20\%$  risk for major osteoporotic fracture)

#Intravenous zoledronic acid given annually may be used first line where there is evidence of malabsorption or increased risk of gastrointestinal side effect from oral bisphosphonate use.

- Zoledronic acid should also be considered where patients have developed a fracture despite oral bisphosphonate.
  - For patients intolerant of bisphosphonates or where contraindicated, denosumab or teriparatide are alternative agents.

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#### Clinical Pearl

- Hip pain in a patient with IBD who is on corticosteroids (CS) represents avascular necrosis until proven otherwise by a negative urgent MRI
  - If significant waiting period for MRI, taper/stop CS



## ❖ Pneumocystis jirovecii (PJ) infection

### Recommendation

- In IBD patients on triple therapy, there is
    - Prednisolone  $\geq 20$  mg//d
    - Azathioprine / 6-MP / MTX
    - Biological therapy
  - There is benefit of prophylaxis for PJ pneumonia, such as sulfamethoxazole-trimethoprim, but
    - $\uparrow$  risk of devastating Stevens-Johnson syndrome (SJS)
- (GRADE: weak recommendation, very low-quality evidence. Agreement: 86%).

- PCJ infection is rare in patients with IBD
  - $\uparrow$  risk of PCJ infection
    - Old/frail persons
  - Prophylaxis: clotrimazole

## ❖ Nutritional Care

### Recommendations

- Patients with IBD should have an assessment of their general nutritional states, and “...screening for evidence of recent weight loss and/or assessment of malnutrition risk at each clinic appointment and on hospital admission (Agreement 96%).
  - In patients with IBD who are malnourished / at risk of malnourishment, perform
    - Screening blood work for
      - Iron, folate, vitamin B12
      - Vitamin A, D, E, K (fat soluble)
      - Primary and secondary electrolytes
      - Zn, selenium
- (GRADE: strong recommendation, very low-quality evidence. Agreement: 94%).
- All patients with IBD need regular follow-up and assessment for possible malnutrition
    - Encourage IBD patients to “... eat a varied diet that meets their energy, macro- and micro-nutrient requirements.
  - In those who have malnutrition or who are at risk of malnutrition (~85% of IBD patients have undernutrition), there is benefit from consultation and follow-up with a registered dietician / nutrition support team, including consideration where necessary of enteral or parenteral nutrition (Agreement 100%)
  - Multiple blood tests are used to evaluate the patient for possible nutrient deficiency, but many of these blood tests are not reliable in the presence of inflammation.



- Give the value of the C-reactive protein (CRP) above which blood test measurements for possible nutrient deficiency becomes unreliable.

| CRP, mg/L | Nutrient Deficiency        |
|-----------|----------------------------|
| > 5       | Vitamins B6 and C          |
| > 10      | Vitamin A, D, and selenium |
| > 20      | Plasma zinc                |

- Magnesium ( $Mg^{2+}$ ) deficiency
  - $Mg^{2+}$  deficiency is common in patients with IBD (13% to 88%)
  - Measurements of serum  $Mg^{2+}$  to estimate body deficiency of magnesium are **not** reliable
  - Suspect  $Mg^{2+}$  deficiency from symptoms
    - Fatigue muscle cramps
    - Bone pain
    - ↓ healing
  - $Mg^{2+}$  deficiency may be corrected by slowly giving small amounts of  $Mg^{2+}$  po (po  $Mg^{2+}$  may cause diarrhea, so IV  $Mg^{2+}$  may be necessary)
- Iron
  - Iron deficiency and iron redistribution are common in patients with UC/CD.
  - In iron deficiency
    - Normal transferrin saturation (TS) and
    - Ferritin is an acute phase reactant, and may be falsely normal in IBD that is active; ferritin up to 100  $\mu g/L$  in the presence of inflammation may still reflect iron deficiency).
    - Treat iron deficiency with iron
      - po – Do **not** give po in active IBD
      - IV – Indications
        - Active IBD with Hb < 100 g/L
        - Intolerance to po iron
        - In patient who is required to take erythropoietin po/IV iron is recommended pre-operatively to normalize the hemoglobin concentration without using transfusion of packed red blood cells (please see next section)
- ❖ Patients with IBD plus symptoms of irritable bowel syndrome (IBS)
  - Consider a diet which is low in fermentable oligosaccharide, disaccharide, monosaccharide and polyols (FODMAP)
  - FODMAP diet → ↓ IBS-like symptoms in persons with inactive IBD (FODMAP diet compared with baseline diet, 78% vs. 16%)



## Recommendation

- Use a low FODMAP diet in patients with IBD who are in remission, who have but symptoms of irritable bowel syndrome (IBS) (GRADE: weak recommendation, low-quality evidence. Agreement: 84%)
- Ensure IBD is in remission
- Identify/exclude dietary trigger for symptoms of IBS
- Consider possible lactose intolerance

## ❖ Operative optimization in IBD

### • Nutrition

- Preoperative nutritional assessment
  - BMI < 18.5 kg/m<sup>2</sup>, recent > 10% body weight
    - ↑ risk of
      - Post-operative complications (intraabdominal sepsis; OR, 6.23; 95%CI, 1.75 to 22.52) abscess antibiotics/drainage
      - Mortality
    - Dietary elective surgery to
      - Correct malnutrition
      - Corticosteroid weaning
  - Even if only including malnourished IBD patients before major gastrointestinal surgery, preoperative nutritional support may be needed for 7 to 10 d, with longer periods of support recommended for severe malnutrition ESPEN (European Society of Parenteral and Enteral Nutrition) guidelines.

## Recommendations

- Patients with penetrating or stricturing Crohn disease, or those who are malnourished, may benefit from exclusive or partial enteral nutrition for at least 6 wk preoperatively (GRADE: weak recommendation, very low-quality evidence. Agreement: 97%).
- Before elective surgery, the IBD patient must have
  - Assessment/optimization of their physical and nutritional state condition, including
    - Extent of IBD / complications
    - Abscess drainage (radiological), plus
    - Antibiotic treatment of sepsis
    - Correction of anemia(GRADE: strong recommendation, very low-quality evidence. Agreement: 97%).
- If there is malnutrition detected before surgery, the nutritional support may be oral (including enteral nutrition), or parenteral nutrition, if indicated (GRADE: strong recommendation, very low-quality evidence. Agreement: 97%).





- Anemia
  - Correcting preoperative anemia (hemoglobin concentration < 130 g/L in men, and < 120 g/L in women) → ↓ post-operative risk of
    - GI
      - Hemorrhage
      - Obstruction
      - Perforation
      - Anastomotic leak
    - Non-GI
      - Pneumonia
      - Wound infection
  - Identify and treat anemia well before elective surgery by using iron po/IV
  - If possible do **not** give transfused packed red blood cells (PRBCs) to correct the anemia before surgery
    - Correcting the anemia with transfused PRBCs may ↑ post-operative complications in IBD patients who have an ileocecal perforation (abscess, clots (venothrombosis), dehiscence of wound, anastomosis leak, ileus)
- Corticosteroids

#### Recommendation

- In patient with UC/CD having elective surgery for their IBD, stop/minimize corticosteroids (CS) (to ↓ post-operative complications (GRADE: strong recommendation, low-quality evidence. Agreement: 95%).
  - If the patient has been on CS po for > 4 wk before surgery, in the preoperative interval switch from oral to IV CS (GRADE: strong recommendation, moderate-quality evidence. Agreement: 100%)
  - Beware of possible perioperative adrenal insufficiency

- Pre-operative corticosteroids
  - ↑ risk of infections post-operatively if IBD patient is on CS, especially prednisolone ≥ 40 mg/d
  - In patients with UC, there is ↑ risk of infection within 30 d on even lower doses of CS po
    - Proctocolectomy ≥ 20 mg
  - For IBD patient on CS po, switch to IV hydrocortisone in equivalent dosage (prednisolone 5 mg, hydrocortisone 20 mg methylprednisolone 4 mg)
  - Use supplementary doses (“stress doses”) at surgery, depending upon indication
  - Use post-operative protocols for tapered dosing of CS
    - The patient with UC who undergoes a proctocolectomy, taper CS after surgery, then stop CS completely



- Post-operative prednisolone tapering

| Dose preoperatively                                      | Tapering of prednisolone                                                                                                                                                                                                                                         |
|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ 5-20 mg po od, or > 20 mg po for < 3 wk                | - ↓ one 5 mg tablet q3d, then stop                                                                                                                                                                                                                               |
| ○ > 20 mg po od for > 3 wk at any time in the past 6 mon | - ↓ 10 mg per week until 20 mg, then ↓ 5 mg per wk until 5 mg, then after 2 wk give 2.5 mg for 2 wk, then<br>- Stop the initial dose after surgery is the same dose as before surgery (The initial dose after surgery should be the same dose as before surgery) |

- Pre-operative anti-TNF therapy

- Very small ↑ risk of post-operative infectious complications as a result of use of anti-TNF therapy
  - In patients with CD, the small risk is related to the drug levels of anti-TNF (as well as other disease-related factors, outlined above)
- The development of infectious complications from IBD surgery is related to
  - Use of corticosteroids
  - Fistulae/abscesses
  - ↓ serum albumin
  - ↓ hemoglobin
 } ▪ Concentrations
  - There is no evidence to support the suggestion to stop anti-TNF therapy before IBD surgery.
  - The patient having an IPAA procedure (UC) should have a pre-operative withdrawal of both anti-TNF therapy as well as corticosteroids.
  - In the situation where this non-evidence based suggestion is followed
    - Time the anti-TNF injections to give as long a gap as possible between the time of the surgery and the last dose
  - If the anti-TNF therapy is still indicated after the IBD-related surgery, then restart the medication in the post-operative period

- ❖ Fecal calprotectin (fCal)

- fCal is "...a useful surrogate marker of activity in IBD" i.e., to confirm active inflammation"
  - Use first stool of the day passed in the morning, and store for ≤ 3 d before analysis
- A normal value of fCal has a high negative predictive value for IBD
  - PPV is low at fCal value that has ↑↑ NPV
    - Use fCal > 150 to 250 µg/g to be the cut-off value to prompt performing a colonoscopy (with regards to suggesting active IBD)
- fCal may be falsely increased if
  - Acute diarrhea
  - Associated celiac disease
  - Blood in stool
  - NSAIDs used within post 6 wk



### Laboratory Alert

- Do **not** use fCal for screening/surveillance of colorectal cancer (CRC)

- Performance Characteristics of fCal to Detect Endoscopically Active IBD

- Cut-off values

| fCal, µg/g | Sensitivity | Specificity |
|------------|-------------|-------------|
| 50         | 91%         | 60%         |
| > 100      | 84%         | 66% - 78%   |
| 250        | 80%         | 82%         |

- Interpretation

- fCal < 100 µg/g

- Treat for likely IBS, as long as no alarm symptoms (e.g., rectal bleeding, pain, altered bowel habit, ↓ body weight, unexplained iron deficiency)
        - No family history of CRC / advanced adenomas

- fCal

- 100-200 µg/g
        - > 250 µg/g

→ Routine  
→ Urgent

} Referral for  
consultation/colonoscopy

- Positive fCal associated with

- Remission

- Clinical
      - Endoscopic

- Relapse prediction

- Consider dose escalation of medication for likely underlying relapse / ↑ inflammation
      - Guide timing of withdrawal of maintenance therapy without an early relapse
        - Mucosal healing plus fCal < 300 µg/g predicts IBD relapse rate of 10% to 20% after stopping anti-TNF therapy
        - Mucosal healing plus fCal > 300 µg/kg predicts IBD relapse rate of 30% after stopping anti-TNF therapy (STOR study)

- ❖ Sigmoidoscopy/colonoscopy in active IBD

- Safety

- “Endoscope assessment with a limited unprepared [no preprocedural laxative] sigmoidoscopy and biopsies with minimal air insufflation can be performed by experienced endoscopist”, but “...retroflexion in the rectum is not recommended in the presence of active colitis due to the risk of perforation.”



## Recommendations

- Bowel preparation
  - Poor bowel preparation for colonoscopy
    - Not necessarily related to activity of IBD
  - Within 1 mon of colonoscopy for IBD, some patients may experience unexplained
    - ↑ abdominal symptoms
  - Use split dosing of bowel preparation
    - Avoid use of sodium phosphate, which may cause non-IBD associated aphthous ulcers
- Prescription cessation
  - Non-adherence to intake of prescribed medications in patients with IBD ~30%
    - Many possible causes
      - Try to maintain good patient-physician relationship
      - Educate patients about need to adhere to instructions, and the downside of non-adherence (↑ risk of recurrence / complications / need for corticosteroids / hospitalization / surgery)
- Smoking cessation
  - Ulcerative colitis
    - Stopping smoking in patients with UC in patients with UC has adverse effects which may manifest within the initial 2 to 5 yr of
      - The adverse effects of stopping smoking in UC is the opposite of continuing smoking in CD
      - Smoking in the UC patient with proctocolectomy plus IPAA does not ↑/↓ risk of pouchitis
  - In patients with CD, encourage them to stop smoking to
    - ↓ risk of relapse
    - ↓ need for surgery and
    - ↓ post-operative recurrent CD(GRADE: strong recommendation, low-quality evidence. Agreement: 100%)
  - In patients with UC, encourage then to stop smoking for reasons of their non-GI health, but
    - Inform patient that this may be countered by worsening of their UC, and possible ↑ need to ↑ dose of medications and need for hospitalization.(GRADE: weak recommendation, very low-quality evidence. Agreement: 96%)
  - Crohn disease
    - Advise patients of health dangers of smoking
      - General health / non-GI organs
      - GI organs
        - ↑ CD activity / ↑ recurrence
        - ↑ surgery / ↑ repeat surgery / ↑ surgical complications
        - ↑ hospitalization / ↓ response to corticosteroids / azathioprine



- At any stage of the disease, stopping smoking is beneficial
- Cognitive behaviour therapy and pharmacotherapy may be slightly useful initially but continued abstinence is poor
  - Active measures to stop smoking in patients with CD were initially successful in ~30%, but by 18 mon only 23% remained non-smokers (TABACROHN study)

#### ❖ Mental Health Issues

- Patients with IBD have ↑ risk of
  - Depression/anxiety developing
    - UC (HR, 2.23; 95% CI: 1.92 to 2.60)
    - CD (HR, 2.11; 95% CI: 1.65 to 2.70)
- Depression, anxiety, and stress are associated with
  - ↑ relapse (“stress can promote a flare of IBD”)
  - ↑ hospitalization
  - ↑ abdominal pain
- Treatment
  - Conflicting results, some patients may respond to
    - Psychological therapy e.g., psychotherapy, relaxation, mindfulness, “gut-directed hypnotherapy”
    - Pharmacotherapy
      - CD
        - Tricyclic antidepressants (TCAs)
        - Serotonin selective reuptake inhibitors (SSRIs)
        - Serotonin and norepinephrine reuptake inhibitors (SNRIs)
      - UC
        - TCAs, SSRIs, SNRIs
        - Serotonin modulators
        - Mirtazapine

#### ❖ Abdominal Pain Control

##### Recommendations

- Exclude IBD causes of pain
  - Abscess
    - Inflammation, uncontrolled
    - Strictures/adhesions
- Exclude other non-IBD conditions
  - IBS
    - Visceral hypersensitivity
    - Dysmotility



- Exclude non-GI causes of abdominal pain
  - Depression, anxiety, stress
  - Sleep disturbances
  - Psychosocial factors (Agreement: 96%)
- Pain is particularly difficult to control in
  - Female patients with CD who smoke
  - Associated stress, anxiety / depression, ↓ quality of life
    - IBD
      - Active disease
      - Multiple surgeries
  - Use of anti-depressants and other neuropsychiatric drugs (including use of narcotics) is associated with the use of corticosteroids in patients with IBD)
- Treat the associated IBD active/maintenance therapy, including
  - Extraintestinal manifestations
  - Psychosocial issues
- IBD and opioid use
  - ↓ hearing
  - ↑ risk of
    - Depression (UC)
    - Infection
    - Toxin megacolon / severe acute ulcerative colitis
    - Mortality
- When IBD- / GI- / non-GI conditions have been excluded (“no physical cause can be found”)
  - Propose adjunctive therapy (GRADE: weak recommendation, very low-quality evidence. Agreement: 94%)
  - Discourage use of opioids
  - Encourage
    - Psychosocial assistance
    - Consultation with expert in chronic pain management

## ❖ Fatigue

### Recommendations

- Definition
  - Sense of tiredness
  - Lethargy, lack of energy that do **not** subside with risk
  - ↑ mental illness
    - ↑ alcohol use
  - ↓ quality of life (health-related)
  - ↓ sleep quality
- Demography
  - At time of diagnosis of IBD, ~50% of patients have fatigue



- Clinical associations
  - Associated with both active / inactive IBD
- At follow-up visits in patients with IBD
  - Ask about presence of fatigue (fatigue is common in IBD, and patients do **not** always mention it spontaneously)
  - If fatigue present, look for causes related / unrelated to IBD (active or inactive)
    - Fatigue, pain, stress, anxiety, and depression → ↓ quality of life (Agreement: 89%)
- Laboratory associations
  - Anemia, iron deficiency (OR, 2.5; 95% CI: 1.2 to 5.1)
  - ↓ Mg<sup>2+</sup>, ↓ serum vitamin D
  - Electrolyte disturbance (Agreement: 94%)
- Patient may benefit from correction of above associations  
If IBD-related causes of fatigue excluded, consider
  - Exercise program
  - Psychotherapy
  - Stress management
 (GRADE: weak recommendation, low-quality evidence. Agreement: 89%).
- Treatment
  - Address possible considerations, noted above
  - Consider that corticosteroids / immunomodulators may ↑ fatigue (rather than usually ↓ inflammation and thereby ↓ fatigue)

❖ IBD-associated arthropathy

- Give the differential diagnosis for Type II IBD-associated arthropathy.
  - Type 1 IBD-associated arthropathy  
Fluctuates with IBD activity, is often asymptomatic and  
Responds to IBD therapy / local injection of corticosteroids  
It is easy to distinguish from Type II IBD-associated arthropathy.

| Features                                             | Type I | Type II |
|------------------------------------------------------|--------|---------|
| ○ Effusion                                           | +      | -       |
| ○ Asymmetric, ≤ 4 joints                             | +      | -       |
| ○ Peripheral joints                                  | +      | (≥ 5)   |
| ○ Weight bearing lower limbs                         | +      | (axial) |
| ○ Inflammation of joints associated with IBD relapse | +      | -       |
| ○ Responds to                                        |        |         |
| – IBD treatment                                      | +      | -       |
| – Local injection of corticosteroids                 | +      | -       |



- Non-specific arthralgia
- Osteonecrosis (avascular necrosis)
- Osteopenia / osteoporosis
  - With/without use of corticosteroids
- Medications used to treat IBD
  - Corticosteroid withdrawal arthralgias
  - Azathioprine (AZA)-associated arthralgia (early onset when starting AZA, rapid resolution on stopping AZA)
  - Anti-TNF associated systemic lupus-like syndrome

#### Recommendations

- IBD-associated arthropathy
    - Related to active IBD (Type I)
      - Control of IBD-associated inflammation
      - Analgesia (non-narcotic)
        - Acetaminophen
        - NSAIDs, low dose
      - Physiotherapy (GRADE: strong recommendation, very low-quality evidence. Agreement: 100%)
    - Not related to active IBD (Type 2)
  - Safety
    - NSAIDs... short-term use is safe, particularly using low-dose where the IBD is well-controlled, with a relapse risk of about 2%
    - COX-2 inhibitors
      - Safe to use in IBD, with risk of flare of IBD while on COX-2 inhibitor no different from placebo (RR, 0.86; 95% CI: 0.39 to 1.88; low-quality evidence)
      - However, it is possible that COX-2 inhibitors may ↑ IBD inflammation that is already active.
  - There is no high-quality evidence that COX-2 inhibitors are safer than non-selective agents [in patients with IBD plus arthropathy (GRADE: weak recommendation, very low-quality evidence. Agreement: 81%).
- ❖ Miscellaneous
- There is **no** adequate data to recommend the use in IBD of pro- / pre- / symbiotics, fecal microbial transplantation (FMT), complimentary and alternate medications (CAMs), or cannabis extracts.
- Pre- / Pro-symbiotic
- UC
    - “... probiotic therapy may have modest benefits .... as an additional to standard therapy ... but should not be routinely used”
  - CD
    - “..... there is no evidence ... for [pre- / pro- / symbiotics] treatments”





- Fecal Microbial Transplantation (FMT)
  - FMT is "... an investigational treatment for use only in clinical trials in IBD"

#### Recommendation

- Do **not** use FMT except in a clinical trial until "... further high-quality evidence clarifies the potential for benefit and optimal administration protocol" (GRADE: weak recommendation, moderate-quality evidence. Agreement: 93%).
- Complimentary and Alternative Medications (CAMs)
  - ~40% of patents with IBD take CAMs
    - Fish oil and turmeric (contains curcumin) are of **no** proven benefit
- Cannabis
  - Cannabis extracts containing non-psychoactive cannabidiol (CBD) have **no** proven benefits on GI symptoms / inflammation in patients with IBD

#### ❖ Colorectal Cancer (CRC) in IBD

#### Recommendation

- Patients with any extent of UC, and patients with Crohn disease involving the colon or colon plus small bowel, should have ileocolonoscopy after the onset of their symptoms of IBD or diagnosis of IBD.
  - The extent of the IBD as well as the endoscopic and histological activity of the IBD is needed, so that other associations such as primary sclerosing cholangitis (PSC) or colectomy and ileostomy may be taken into account.  
(GRADE: strong recommendation, very low-quality evidence. Agreement: 89%).
- The severity and duration of inflammation (endoscopic, histological) determines the ↑ risk of CRC in patients with UC.
  - Even histological inflammation predisposes to colonic neoplasia
- Colonic post-inflammatory ("pseudopolyps") polyps are a marker for previous severe inflammation in UC
  - But, only some studies associate the presence of post-inflammatory polyps with the development of CRC.
- In the patient with pancolitis (UC)
  - Begin screening colonoscopy after 8 to 10 yr of known UC or of symptoms suggestive of UC.
  - Because the incidence of UC complicated by CRC is ~1% after 10 yr of IBD, initiation of endoscopic screening is recommended after 8-10 yr of disease.
  - The risk of CRC in UC doubles with about every decade of disease (active or inactive)
- Benefits of CRC screening in UC
  - Detection
    - Earlier tumour stage when first diagnosed
    - ↓ interval CRC
  - Prognosis better, with ↑ 5-yr survival



- Colonoscopy surveillance in patients with IBD to detect and manage dysplasia/neoplasia
- Commencement of colonoscopy surveillance:
  - 8 to 10 yr after IBD symptom onset
  - Immediately after diagnosis of associated primary sclerosing cholangitis (PSC)
- Next surveillance colonoscopy interval (summary of 2010 BSG update guidance):
  - Lower risk: next surveillance colonoscopy in 5 yr
    - If extensive colitis with *no* active endoscopic, or
    - Histological inflammation, or
    - Left sided colitis, or
    - Crohn colitis affecting <50% of colon
  - Intermediate risk: next surveillance in 3 yr if extensive colitis with
    - *Mildly* active endoscopic changes
    - Histological inflammation
    - Post-inflammatory polyps (often termed 'pseudopolyps')
    - Family history of colorectal cancer in first degree relative aged ≥50 yr
  - Higher risk: next surveillance colonoscopy in 1 yr if
    - Extensive colitis with *moderate/severely* active endoscopic or
    - Histological inflammation
    - Stricture/dysplasia in last 5 yr
    - Primary sclerosing cholangitis (including post-orthotopic liver transplant)
    - Family history of colorectal cancer in first degree relative aged <50 yr
  - In determining next colonoscopy surveillance interval, consider
    - Patient preference
    - Age
    - Comorbidity
    - Presence of multiple post-inflammatory polyps
    - Accuracy/completeness of examination
  - If previous
    - Colectomy and ileostomy, or
    - Colectomy and ileorectal anastomosis (IRA)
      - Retained rectum should undergo surveillance examination
      - Retained rectum after surgery is more difficult to inspect, and so
      - Proctectomy with/without pouch reconstruction should normally be considered
- Methods of detection:
  - Surveillance should be performed where possible during disease remission, though it may not be possible in some patients (chronic active disease is a risk factor for dysplasia)
    - It may be more difficult for pathologist to diagnose dysplasia in the presence of inflammation



## Recommendations

Statements published as part of 2015 SCENIC international consensus:

- When performing surveillance with
  - White-light colonoscopy
    - High definition is recommended rather than standard definition (strong recommendation, low-quality evidence)
  - Standard-definition colonoscopy
    - Chromoendoscopy is recommended rather than white-light colonoscopy (strong recommendation, moderate-quality evidence)
  - High-definition colonoscopy
    - Chromoendoscopy is suggested rather than white-light colonoscopy (conditional recommendation, low-quality evidence)
  - Standard-definition colonoscopy
    - Narrow-band imaging (NBI) is not suggested in place of white-light colonoscopy (conditional recommendation, low-quality evidence).
  - High-definition colonoscopy
    - NBI is not suggested in place of white-light colonoscopy (conditional recommendation, moderate-quality evidence).
  - Image-enhanced high-definition colonoscopy
    - NBI is not suggested in place of chromoendoscopy (conditional recommendation, moderate-quality evidence).
    - Colonoscopically targeted biopsies are recommended over random colonic biopsies.
    - If taking random biopsies, 2–4 biopsies should be taken every 10 cm.
    - Always take targeted biopsies from any endoscopically visualized lesion
- Management of dysplasia
  - After complete removal of endoscopically resectable
    - Polypoid dysplastic lesions,
  - After complete removal of endoscopically resectable
    - Non-polypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy (conditional recommendation, very-low quality evidence).
  - For patients with endoscopically invisible dysplasia (confirmed by a GI pathologist), referral is suggested to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy (conditional recommendation, very low-quality evidence).

If dysplastic lesions cannot be resected completely due to extent or multiplicity, refer the patient to a multidisciplinary team, regarding definitive management including surgical options should be arranged.

- \*Neither extensive systematic review nor consensus voting has been undertaken as part of the current guideline development process regarding subsequent surveillance intervals after initial surveillance colonoscopy, or methods to detect dysplasia.
  - Instead a summary is adapted/reproduced from the 2010 BSG and 2015 SCENIC guidance.



- Releasing risk
  - 5-ASA and thiopurines are protective for the development of high-grade dysplasia / CRC in UC (probably by ↓ amount / ↓ severity of inflammation over time).
    - In referral acute study, use of 5-ASA → ↓ risk of CRC (OR, 0.6; 95%CI: 0.4 to 0.9, P = 0.04)
    - The minimum effective dose of 5-ASA was 1.2 g to 2 g per day of 5-ASA to achieve this protective benefit
  - Data on use of anti-TNF therapy to ↓ risk of CRC is awaited
  - Antioxidants
    - No randomized prospective trials
  - RBC folate
    - ↓ RBC folate in some UC patients who develop CRC
      - Supplementing patients with folic acid does not ↓ risk of CRC

#### SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the postulated and plausible mechanisms by which 5-ASA may provide its protective effect on the development of CRC in patients with ulcerative colitis.
  - Cell cycle regulation-stabilized
  - Reactive oxygen species (ROS) / reactive nitrogen species (RNS) scavengers
  - Inhibitor/interference with proinflammatory / signalling pathways
    - TNF- $\alpha$ , NF- $\kappa$ B, TGF $\beta$  pathways
    - Wnt/beta-catenin
  - Antimicrobial activity

#### Gentle Reminder

- Prophylaxis for venothrombotic embolization (VTE) is usually necessary if the IBD patients is in hospital for active IBD.



## ❖ Pregnancy and Therapy of IBD

### • Anti-TNF drugs

- The reason for consideration
  - Infliximab (IFX) and adalimumab (ADA) are IgG1 monoclonal antibodies
  - IgG1 is actively transferred from the maternal to the fetal circulation, beginning at wk 13 of gestation, and progressing continuously until delivery
- Duration
  - The anti-TNF drugs last for some time in the circulation of the newborn infants
    - IFX, 28 wk
    - ADA, 11 to 16 wk
    - Rarely, low concentrations of IFX/ADA may be detected in the blood of infants for as long as 1 yr postpartum
- Concentration
  - The concentration of the anti-TNF drugs is 4x higher in the infant than in the mother
- To ↓ risk of exposure of fetus to mother's anti-TNF therapy, the following is suggested
  - If mother's IBD in remission
    - Stop anti-TNF therapy at end of T2 (second trimester, ~ 26 wk of gestation)
  - If mother's IBD is active at time of conception, or becomes active during pregnancy
    - There is ↑ risk adverse effects of active IBD on the fetus (delivering premature [OR, 2.64]. birth weight low [OR, 2.05] spontaneous abortion post-partum hemorrhage, but
    - There is ↑ risk of mother's IBD relapsing if anti-TNF therapy is stopped during pregnancy
- The benefit-risk ratio of continuing anti-TNF therapy during pregnancy
  - "...there is no evidence that continuing anti-TNF therapy during pregnancy has a negative impact on the pregnancy or neonatal outcomes"
  - However, the 2018 Evasion study noted ↑ maternal risk of using anti-TNF therapy in the first two trimesters of pregnancy (T1, T2)
    - Complications (OR, 1.49; 95%CI: 1.31 to 1.67)
    - Infections (OR, 1.31; 95%CI: 1.16 to 1.47)
  - Newborn complications
    - No ↑ risk of infection in newborns of mothers who used anti-TNF drugs pregnancy (OR, 0.89; 95%CI: 0.76 to 1.05)
- Note that continuing anti-TNF therapy beyond T2 and into T3 did not ↑ risk any further, but
  - Stopping treatment of anti-TNF in T3 → ↑ risk of relapse of IBD (OR, 1.98; 95%CI: 1.25 to 3.15)
- There may be ↑ risk of neonatal infections (bacterial, 5%; viral, 20%) if the anti-TNF is given combined with thiopurines (combination therapy versus monotherapy) (RR of infection 2.7; 95%CI: 1.07 to 6.48, P=0.02)



- ❖ Risks of newborn child from previous exposure to anti-TNF therapy drug gestation
- Kanis S, et al (Dutch study, 2017)
  - Neither anti-TNF nor purine exposure was associated with adverse birth outcomes, whereas
    - Use of steroids was associated with pre-term birth (Adjusted OR, 2.67; 95%CI: 1.59 to 4.47)
- TEDDY study
  - Exposure to anti-TNF, either during pregnancy or within 3 mon prior to conception
    - ↑ low birth weight of infant
    - ↑ ICU admission of infant
    - No ↑ risk of infection
- PIANO registry
  - Anti-TNF therapy during pregnancy
    - No ↑ risk of infection
    - No developmental delay at the time of conception

#### Recommendations

- Inform pregnant women with IBD about risks/benefits of anti-TNF therapy during pregnancy.
- For pregnant women who are on anti-TNF therapy at the time of conception and whose IBD is in remission
  - “... it may be reasonable to stop [anti-TNF therapy] at the start of the third trimester [of pregnancy, wk 22 to 24]
  - Note that in the discussion, IBD quiescence (remission) is defined as “...sustained remission for 12 mon prior to conception with endoscopic and radiological evidence”
  - It is also noted in the text that the patient needs to be part of the discussion about management, and that the first choice must be driven by strong patient preference.
- For pregnancy, women who are on anti-TNF therapy at the time of conception, but at that time had active disease, or have ↑ risk of developing active disease
  - “... it may be advisable to continue the drug throughout [the pregnancy]
 (GRADE: weak recommendation, very low-quality evidence. Agreement: 98%)



- ❖ Vaccination of infant who has been exposed to anti-TNF therapy during pregnancy (in utero)

#### Recommendation

- Non-live vaccinations may be given accordingly to standard vaccination schedules.
- The BCG vaccination against tuberculosis is given 6 mon after birth
- Rotavirus
  - For the mother on anti-TNF therapy during pregnancy, vaccination with the live rotavirus is normally not given until the infant  $\geq 6$  mon (GRADE: weak recommendation, very low-quality evidence. Agreement: 98%).
- ❖ Breastfeeding
  - "... breastfed infants of mothers receiving biologics [infliximab, adalimumab, certolizumab, natalizumab and ustekinumab], immunosuppression or combination therapy have similar risks of infection and similar milestone achievement at 12 mon to non-breastfed infants or infants unexposed to these drugs".
- ❖ Use of Vedolizumab, ustekinumab and tofacitinib in pregnancy
  - There is "...lack of data confirming safety and the consequences of withdrawing treatment with those 3 biologics.
  - For further consideration of the care of pregnancy and IBD, please see
    - ECCO Guidelines, van der Woude CJ, et al. J Crohn Colitis 2015; 9: 107-124
    - Toronto Guidelines, Nguyen GC, et al. Gastroenterology 2016; 150: 734-57
- ❖ The Traveller with IBD
  - If Traveller's diarrhea cannot be differentiated from a flare of IBD, do **not** stop the IBD therapy, and
  - If no fever or bloody stools
    - Use empirical ciprofloxacin 500 mg po b.i.d. (have a low threshold for recommending empirical antibiotics)
  - Use azathioprine
    - If no response to fluoroquinolone in 36 to 98 h
    - Fluoroquinolone resistance
    - Fluoroquinolone contraindications
      - Pregnant women
      - Child < 16 yr
  - Take stool cultures, if
    - Patient on immunosuppressants / biologics
    - Fever, bloody diarrhea
    - Non-response to empirical antibiotics



- Blood test
  - Complete blood count (CBC) for assessment for possible eosinophilia
- ❖ Genetic Testing
  - Children with
    - IBD diagnosis before 5 yr of age
    - “Aggressive, refractory IBD presentations”
  - Test for monogenic disorders, e.g., IL-10 receptor mutations / XIAP
- ❖ Delivery of patient care
  - Multidisciplinary teams (MDTs) composed of physicians and surgeons, nurses, nutritionists, pharmacists, mental health workers, and where appropriate obstetrician/pediatrician, ophthalmologists/rheumatologist, family physician, social workers, pathologists, diagnostic imager (GRADE: weak recommendation, very low-quality evidence. Agreement: 95%).
  - IBD nurse specialist
  - Protocol for
    - Urgent / rapid assessment
    - Family physician / other referrals
      - Triaging, with ↓ wait times
  - Access 24 h per day to on-call IBD nurse / IBD resident / physician
  - Audit / quality control and improvement measures
  - Agreement by IBD physicians to follow similar treatment guidelines for consistency / patient confidence, and for educational purposes
- ❖ Chronic Active UC

#### Recommendation

- Patients with chronic active UC, despite optimal medical therapy.
  - Offer total colectomy plus IPAA or ileostomy
  - The patient’s quality of life is similar with lack of these procedures, and the choice is up to the patient (GRADE: weak recommendation, very low-quality evidence. Agreement: 94%)
- ❖ Long-term complications of surgery in UC
  - Infertility after IPAA vs. medically treated UC, ~50% vs. 15%
    - Other fertility-related adverse effects after restoration proctocolectomy
      - ↑ time to conception
      - ↑ need for in vitro fertilization
      - ↑ need for caesarean section
  - Pouchitis
  - Adenocarcinoma in pouch





## Recommendations

- There is no ↓ fertility from colectomy plus ileorectal anastomosis (IRA; no removal of rectum, potentially scarring of Fallopian tube → ↓ fertility)
  - This may be an option for some patients
- Women with UC who require emergency subtotal colectomy and ileostomy may choose to subsequently request proctectomy plus IPAA but must be cautioned about risk of ↓ fertility.

### Surgical Alert

- The risk of colon cancer (in the rectum) remains in the UC patient who has had a colectomy plus IAA.
  - Surveillance of the IPAA must continue

## ➤ Differential

### ❖ Early

- Surgical complications
    - Sepsis, peri-pouch
    - Fistula
- } ■ May require stoma, defunctioning, pouch excision

### ❖ Late

- Idiopathic ~75%
- Infection
  - Candida
  - Clostridium difficile
- Immune disorder
- Ischemia
- Infiltration
  - Cancer
- Iatrogenic
  - NSAIDS
  - Radio-/chemotherapy
- Misdiagnosed Crohn Colitis, ~5%

## ➤ Investigations

- Digital rectal examination (DRE)
- MRI of pelvis
- Stool culture / sensitivity, O/P, C. difficile assay

## ➤ Endoscopy (pouchoscopy)

- Friability, ulceration, tumour



### Clinical Tip

- In patient with symptoms of pouch dysfunction, pay attention to careful digital examination of the stoma for
  - Stenosis
  - Squamous cell carcinoma of the stoma

### Recommendation

- Symptoms after colectomy, IPAA
  - Patient should have history and physical examination, including digital rectal examination (DRE), stool testing, pelvic MRI, pouchoscopy (using gastroscope or sigmoidoscope)
  - Pouchoscopy: inspect carefully (Agreement, 100%)
    - Anal transition zone
    - Rectal cuff
    - Pouch
    - Pre-pouch ileum
    - Afferent loop of pouch

### ➤ Scoring system

#### ❖ Pouchitis Disease Activity Index (PDAI)

| Variable                                   | Score                                                                                                                                   |
|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| ○ Clinical                                 |                                                                                                                                         |
| – Stool frequency (daily)                  | 0–2 (0=usual post-operative frequency, 1=1–2 stools more than post-operative frequency, 2=>3 stools more than post-operative frequency) |
| – Rectal bleeding                          | 0–1 (0=absent/rare, 1=present daily)                                                                                                    |
| – Urgency/abdominal cramps                 | 0–2 (0=absent, 1=occasional, 2=usual)                                                                                                   |
| – Fever (>37.8°C/100.5°F)                  | 0–1 (0=absent, 1=present)                                                                                                               |
| ○ Endoscopic inflammation                  | One point for each of: edema, granularity, friability, loss of vascular pattern, mucous exudate, ulceration)                            |
| ○ Histology                                |                                                                                                                                         |
| – Polymorphonuclear leucocyte infiltration | 1–3 (1=mild, 2=moderate + crypt abscesses, 3=severe + crypt abscesses)                                                                  |
| – Mean ulceration per low power field      | 1–3 (1 =<25%, 2=25–50%, 3 =>50%ulceration)                                                                                              |

Pouchitis, total score ≥7 points; Remission, score ≤2 with endoscopic subscore ≤1

Printed with permission: Lamb CT, et al, Gut 2019; 68: S1-S106 (Table 6)

- Modified PDAI – clinical plus endoscopy (no points for histopathology)



### Pouch Curiosities

- Staples
  - Staple-line ulcers, normal mucosa elsewhere
    - Is not pouchitis
- Suture-line
  - Pouchitis in half the pouch, sudden stopping at suture line (sharp demarcation)
    - Ischemia
- Afferent loop ulcers
  - NSAIDs
  - Crohn disease

- High risk of pouchitis after IPAA for UC
  - 1 yr, 40%
  - Long term, 50%
- Risk factors for pouchitis
  - PAA rather than IRA procedure
  - UC as the indication for IPAA
  - Extraintestinal manifestations (EIMs) of UC
- ↑ pANCA titres
- Pre-operative dysbiosis
- The ↑ risk is increased further if there is associated PSC
  - Requires 6-12 monthly surveillance colonoscopy plus multiple biopsies
- With UC plus PSC treated with total colectomy plus IPAA
  - Risk of pouchitis
    - 30 d ~40%
  - surgical treatment is
    - 6 yr ~65%
- Removal of pouch required, 3%

### ➤ Treatment

Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis (Nguyen N, et al. Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD001176. DOI: 10.1002/14651858.CD001176.pub5)

#### ❖ Acute pouchitis

- Ciprofloxacin (CIP) vs. metronidazole (MTZ)

|                        | CIP  | MTZ | RR, 95%CI                     | Certainty of evidence |
|------------------------|------|-----|-------------------------------|-----------------------|
| – Remission at 2 wk    | 100% | 33% | RR, 2.68; 95%CI: 1.13 to 6.35 | ▪ Very low            |
| – Adverse events (AEs) | 0%   | 33% | RR, 0.18; 95%CI: 0.01 to 2.98 | ▪ Very low            |



- Metronidazole (MTZ) vs. budesonide (BUD)
 

|                                | MTZ | BUD | RR, 95%CI                     |            |
|--------------------------------|-----|-----|-------------------------------|------------|
| - Achieved remission at 8 wk   | 43% | 50% | RR, 0.86; 95%CI: 0.37 to 1.96 | ▪ Very low |
| - Clinical improvement at 6 wk | 50% | 58% | RR, 0.86; 95%CI: 0.42 to 1.74 | ▪ Very low |
| - Adverse events (AEs)         | 57% | 25% | RR, 2.29; 95%CI: 0.78 to 6.73 | ▪ Very low |
  
- Rifaximin (RIF) vs placebo (PLA)
 

|                               | RIF | PLA | RR, 95%CI                     |            |
|-------------------------------|-----|-----|-------------------------------|------------|
| - Clinical improvement at wks | 38% | 30% | RR, 1.25; 95%CI: 0.34 to 4.60 | ▪ Very low |
| - Adverse events              | 75% | 50% | RR, 1.50; 95%CI: 0.72 to 3.14 | ▪ Very low |

## Recommendations

- Give ciprofloxacin po or metronidazole po for 2 wk (GRADE: strong recommendation, low-quality evidence).
- Ciprofloxacin may be better tolerated and have better efficacy than metronidazole (GRADE: weak recommendation, low-quality evidence. Agreement: 97%)
- Overall symptomatic response to antibiotics, 96%
- Prevention
  - Primary prevention (to ↓ initial development of pouchitis)
 

|                             |     |
|-----------------------------|-----|
| ▪ Probiotics                | 10% |
| ▪ Placebo                   | 40% |
| ▪ Sulfasalazine 2 g, 68 mon | 15% |
| ▪ Placebo                   | 65% |
  - Secondary prevention (↓ risk of recurrence)
    - Probiotics may be beneficial to ↓ risk of recurrence of pouchitis occurring after a previous episode of pouchitis which has been brought into remission with antibiotics.
- Fecal microbial transplant (FMT)
 

|                                                                      | Use FMT                   |
|----------------------------------------------------------------------|---------------------------|
| - UC plus C. difficile infection (CDI) not responding to antibiotics | Yes; use                  |
| - UC plus no CDI                                                     | No; do <b>not</b> use FMT |
- Antidiarrhea agents
  - No evidence of benefit for pouchitis



- Prevention

- No acute episodes of acute pouchitis

|                                                                                                                                       |    | DSF  | PL   | RR, 95%CI                     |                                          |
|---------------------------------------------------------------------------------------------------------------------------------------|----|------|------|-------------------------------|------------------------------------------|
| - At 12 mon                                                                                                                           | a. | 90%  | 60%  | RR, 1.50; 95%CI: 1.02 to 2.21 | ▪ Low                                    |
|                                                                                                                                       | b. | 100% | 92%  | RR, 1.10; 95%CI: 0.89 to 1.36 | ▪ Very low                               |
|                                                                                                                                       |    |      | BBL  | PL                            | RR, 95%CI                                |
| - At 6 mon, Bifidobacterium longum (BBL) vs PL                                                                                        |    |      | 86%  | 60%                           | RR, 1.43; 95%CI: 0.66 to 3.11 ▪ Very low |
|                                                                                                                                       |    |      | CB   | PL                            | RR, 95%CI                                |
| - At 24 mon,                                                                                                                          |    |      |      |                               |                                          |
| ▪ Clostridium butyricum MIYAIRI (CB) vs PL                                                                                            |    | 11%  | 50%  | RR, 0.22; 95%CI: 0.03 to 0.16 | ▪ Very low                               |
|                                                                                                                                       |    |      | ALLO | PL                            | RR, 95%CI                                |
| ▪ Allopurinol (ALLO) vs PL                                                                                                            |    | 46%  | 43%  | RR, 1.06; 95%CI: 0.76 to 1.46 | ▪ Low                                    |
| ○ The effects of antibiotics, probiotics and other interventions for treating and preventing pouchitis are uncertain.                 |    |      |      |                               |                                          |
| ○ Well designed adequately powered studies are needed to determine the optimal therapy for the treatment and prevention of pouchitis. |    |      |      |                               |                                          |

❖ Chronic/refractory pouchitis

Recommendation

- For persons with refractory pouchitis, use corticosteroids, immunomodulatory +/- biologics (GRADE: weak recommendation, very low-quality evidence. Agreement: 96%).
- Ensure adherence to pr and po therapy
- Exclude
  - Other rectal conditions
    - Constipation / rectal IBS-C
    - Solitary rectal ulcer syndrome (SRUS)
    - Rectal prolapse
  - Infection
    - Amebiasis
    - Giardia lamblia
    - Herpes simplex virus (HSV)
    - Lymphogranuloma venereum (LGV)
    - Neisseria gonorrhea
  - Injury/trauma to rectum
  - Immune
  - Iatrogenic
    - Psoriatic colitis
    - Chemical proctitis
    - Gold-/NSAID-associated UP



➤ Definition

- Symptom of pouchitis despite antibiotic therapy for 4 wk
- Ensure the diagnosis is pouchitis, and not some other causes of pouch dysfunction

Recommendation

- Failure of antibiotic / locally acting corticosteroids for chronic refractory pouchitis
  - Exclude other factors, then consider use of biologics (GRADE: weak recommendation, low-quality evidence. Agreement: 91%)

➤ Treatment

- Antibiotic combinations for 4 wk
  - Ciprofloxacin plus
    - Rifaximin, or
    - Tinidazole

- Patients who are antibiotic-dependent → rotate antibiotics
- Test coliform sensitivity to guide choice of antibiotics

- Budesonide 9 mg po / beclomethasone 10 mg po for 8 wks

- Failure of antibiotics/steroids

- Immunotherapy
- Biologics
  - Infliximab, adalimumab (pooled remission rate, 53%)
  - Vedolizumab (response rate 90%)

- De Simone formulation (DSF), probiotics vs placebo (PL), 9-12 mon

|                            | DSF | PL | RR, 95%CI                       |       |
|----------------------------|-----|----|---------------------------------|-------|
| – Maintenance of remission | 55% | 3% | RR, 20.24; 95%CI: 4.28 to 95.81 | ▪ Low |

- Adalimumab (ADA) vs PLA, 4 wk

|                                 | ADA | PL  | RR, 95%CI                    |       |
|---------------------------------|-----|-----|------------------------------|-------|
| – Achieved clinical improvement | 50% | 40% | RR, 1.7; 95%CI: 0.36 to 3.76 | ▪ Low |

- Glutamine (Glu) vs butyrate (But), 3 wk

|                                                 | Glu | But | RR, 95%CI                    | Certainty of evidence |
|-------------------------------------------------|-----|-----|------------------------------|-----------------------|
| – Bismuth carbomer foam enema (BFE) vs PL, 3 wk | 45% | 45% | RR, 1.0; 95%CI: 0.50 to 1.98 | ▪ Very low            |

➤ Demography

- Risk of pouch neoplasia
  - 20/10<sup>5</sup> over 20 yr



- Location
  - Pouch
    - Adenomatous cancer
  - Skin/anus
    - Squamous cell carcinoma
- Risk factors
  - IPAA for UC +/- PSC
  - Long rectal cuff
  - Family history of CRC
  - Histopathology
    - Severe pouchitis coming rapidly after formation of pouch
    - Severe villous atrophy of ileal pouch mucosa

#### Recommendation

- Person with UC who have restorative proctocolectomy with IPAA plus ↑ risk factors for neoplasia (please see below) should have proctoscopy q1yr (GRADE: weak recommendation, very low-quality evidence. Agreement: 94%)

Abbreviations: <sup>14</sup>C, carbon 14; 5-ASA, 5-aminosalicylic acid; 6-MP, 6 mercaptopurine; A, ascending; ACTH, adrenocortical thyrotropic hormone; ADA, adalimumab; ADA, anti-drug antibodies; aOR, adjusted odds ratio; ASUC, acute severe ulcerative colitis; ATI, antibodies to infliximab; AZA, azathioprine; b.i.d., twice in a day; BMD, bone mineral density; BMDP, beclomethasone dipropionate; BMI, body mass index; BSG, British Society of Gastroenterology; C4, 7-alpha-hydrocholestenone; Ca<sup>2+</sup>, serum calcium concentration; CAMs, complimentary and alternative medicines; CBC, complete blood count; CBD, cannabidiol; CC, Crohn colitis; CD, Crohn disease; CDA, Crohn disease activity index; CDGIS, Crohn Disease Endoscopic Index of Severity; CDI, Clostridium difficile infection; CDPC, Centre for Disease Prevention and Control; CI, confidence interval; CMV, cytomegalovirus; CNS, central nervous system; COX, coxib; CRC, colorectal cancer; CRP, C-reactive protein; Cr<sub>s</sub>, serum creatinine; CS, corticosteroids; CT, computed tomography; CTE, CT enterography; CyA, cyclosporin; d, day; D, descending; DHGB, Department of Health Green Book; DRE, digital rectal examination; E. coli, Escherichia coli; EBD, endoscopic balloon dilation; EBV, Epstein Barr virus; ECF, enterocutaneous fistula; EGD, esophagogastroduodenoscopy; EIM, extraintestinal manifestation (of inflammatory bowel disease); EMS, Extended Modified score; EN, enteral nutrition; ESPEN, European Society of Parenteral and Enteral Nutrition; FBG, fasting blood sugar; fCal, fecal calprotectin; FGF-19, fibroblast growth factor-19; FMT, fecal microbial transplantation; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide and polyols; FRAT, fracture risk assessment tool; GFR, glomerular filtration rate; GI, gastrointestinal; GRADE, Grading of Recommendations, Assessments, Development, and Evaluation; GU, genitourinary; HAT, hepatic artery thrombosis; HBI, Harvey Bradshaw Index; HBV, hepatitis B virus; HCG, human chorionic gonadotropin; HCV,



hepatitis C virus; HgA1C, hemoglobin A1C; HLA, human leucocyte antigen; HR, hazard ratio; HSV, herpes simplex virus; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease – undiagnosed; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome, constipation predominant; ICS, ileocolonoscopy; ICV, ileocecal valve; IFX, infliximab; IGRA, interferon gamma release assay; IL, interleukin; IPAA, ileal pouch anal anastomosis; IV, intravenous; kg, kilogram; K<sub>s</sub><sup>+</sup>, serum potassium; L, litre; LEs, liver enzymes; LFTs, liver function tests; LGV, lymphogranuloma venereum; LIFT, ligation of intersphincter tract; LMWH, low molecular weight heparin; LT, liver transplant; MAdCAM-1, mucosal addressin cell adhesion molecule 1; MCMAP, methyl mercaptopurine; MDT, multidisciplinary teams; mg, milligram; Mg<sub>s</sub><sup>2+</sup>, serum magnesium concentration; MMES, Modified Mayo Endoscopic Score; mon, month; MRI, magnetic resonance imaging; MTWC, modified Truelove and Witt's criteria; MTX, methotrexate; NFkB, nuclear factor kB; NNT, number needed to treat; NPV, negative predictive value; NSAID, non-steroidal anti-inflammatory drug; NSAIDs, non-steroidal anti-inflammatory drugs; °C, degree centigrade; od, once in a day; OFG, orofacial granulomatous; OR, odd ratio; P, probability; PCJ, pneumocystic jirovecii; PCR, polymerase chain reaction; PCV, pneumococcal virus; PDAI, pouchitis disease activity index; PEG, polyethylene glycol; PEO, Population Exposure Outcome; po, per os (by mouth); PO<sub>4</sub><sup>2-</sup>, phosphate; PPI, proton pump inhibitor; pr, per rectum; PROMs, Patient Reported Outcome Measures; PSC, primary sclerosing cholangitis; QFT-6, QuantiFERON TB gold; R, rectum; RBC, red blood cell; RES, resection; RNS, reactive nitrogen species; ROS, reactive oxygen species; RR, relative risk; S, sigmoid; SB, small bowel; SBUS, small bowel ultrasound; SC, subcutaneous; SES-CD, Simplified Endoscopic Activity Score for Crohn Disease; SIBO, small intestinal bacterial overgrowth; Sn, sensitivity; SNRI, serotonin and norepinephrine reuptake inhibitor; Sp, specificity; SRUS, solitary rectal ulcer syndrome; SSRI, selective serotonin reuptake inhibitor; T, transverse; T1, first trimester of pregnancy; T2, second trimester of pregnancy; T3, third trimester of pregnancy; TB, tuberculosis; TCA, tricyclic antidepressants; TDM, therapeutic drug monitoring; TG, thioguanine; TGFβ, transforming growth factor β; TI, terminal ileum; TNF, tumor necrosis factors; TPMT, thiopurine methyl transferase; TPN, total parenteral nutrition; TS, transferrin saturation; TST, tuberculin skin test; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; UK, United Kingdom; ULN, upper limit of normal; UP, ulcerative proctitis; USA, United States of America; VCE, video capsule endoscopy; VEDO, vedolizumab; VTE, venous thromboembolism; VZV, variceal zoster virus; wk, week; yr, year; Zn, zinc





## Assessment of Disease Activity: Ulcerative Colitis (UC)

Walsh AJ, et al. Nat Rev Gastroenterol Hepatol 2016; 13; 567-79.

- There is a spectrum of targets used for the assessment of the IBD patient's quality of life (QoL) and of underlying disease activity.
- It is now appreciated that treating targeted to response of clinical symptoms results in a poorer short to long-term outcome for the patient.
  - Beyond symptoms is the endoscopic or histological assessment of IBD activity, as well as diagnostic imaging even beyond the bowel, for example to the mesentery.
- The number of Ulcerative Colitis (UC) assessment indices are shown below; for details on the strengths and weakness of each, please refer to Table 2 of the above publication.
- The number of ulcerative colitis (UC) disease activity assessment indices are shown below: for details on the strengths and mechanisms of each, please refer to the above publication.

### ➤ Disease activity Assessment Indices

|                      |                                   |                                                                          | Threshold for<br>Remission<br>(Range) |
|----------------------|-----------------------------------|--------------------------------------------------------------------------|---------------------------------------|
| ○ Clinical           | – SCCAI                           | ▪ Simple Clinical Colitis Activity Index                                 | ≤ 2 (0-19)                            |
|                      | – PMI                             | ▪ Partial Mayo Index                                                     | ≤ 1 (0-9)                             |
|                      | – PUCAI                           | ▪ Pediatric Ulcerative Colitis Activity Index                            | < 10 (0-85)                           |
|                      | – TWS                             | ▪ Truelove Witts Severity Index                                          | -                                     |
|                      |                                   |                                                                          |                                       |
| ○ Endoscopic         | – UCEIS*                          | ▪ Ulcerative Colitis Endoscopic Index of Severity                        | ≤ 1 (0-8)                             |
|                      | – Mayo Clinic                     | ▪ Mayo Clinic Index: Endoscopic Sub-score                                | ≤ 1 (0-3)                             |
| ○ Histopathology     | – Riley Score                     |                                                                          | 0-18                                  |
|                      | – Geboes Score                    |                                                                          | < 3.1 (0-5.4)                         |
|                      | – Nancy Histologica Index         |                                                                          | 0 (0-4)                               |
|                      | – RHI                             | ▪ Robarts Histopathological Index                                        | ≤ 6 (0-12)                            |
| ○ Diagnostic imaging | – Bowel Ultrasound Severity Score |                                                                          | 0 (0-3)                               |
|                      | – MRC-S                           | ▪ Magnetic Resonance Colonography Simplified Index (requires bowel prep) | 0 (0-4)                               |
|                      | – MR-score-S                      | ▪ Segmental Magnetic Resonance Score (no bowel prep required)            | 0 (0-6)                               |
|                      |                                   |                                                                          |                                       |



|                         |                                                  | Threshold for Remission<br>(Range)    |
|-------------------------|--------------------------------------------------|---------------------------------------|
| ○ Biomarkers            |                                                  |                                       |
| – CRP                   | ▪ C-reactive protein                             | ≤ 5 mg/L (0 to > 200 mg/L)            |
| – FCP/fCal              | ▪ Fecal calprotectin                             | < 50 to < 250 µg/g (0 to > 1000 µg/g) |
| ○ Quality of life (QoL) |                                                  |                                       |
| – IBD-Control 8         |                                                  | 0-16 (16 = best QoL)                  |
| – CUCQ-8                | ▪ Crohn Ulcerative Colitis Questionnaire - 8     | 0-8 (0 = best QoL)                    |
| – SIBDQ                 | ▪ Short Inflammatory Bowel Disease Questionnaire | 10-70 (70 = best QoL)                 |

\*UCEIS is the only validated endoscopic index of UC

Printed with permission: Walsh AJ, et al. Nat Rev Gastroenterol Hepatol 2016; 13; 567-79.

- Subjective
  - ↓ interobserver agreement
  - No definition of mucosal healing
  - Does not account for UC activity
- Endoscopic mucosal healing
  - Ultimate therapeutic goal (because UC is confined to mucosa)
    - No validated definition of mucosal healing
- Mayo Clinic endoscopy subscore (MCSC) < 1 (remission)
  - Predicts low risk for colectomy

Tip on Clinical Examination for Canadian Residents

- Be prepared to provide Mayo Clinic Index Endoscopic Sub-score from a digital image, and to suggest appropriate therapeutic options based on your interpretation of the severity of the endoscopic score.

- Benefits of mucosal healing in UC
  - ↓ corticosteroids, hospitalization, surgery (↓ colectomy)
    - ↓ risk of colorectal cancer (CRC)
  - ↑ length of clinical remission



- Histopathology
  - Persistent histological inflammation associated with ↑ risk of
    - Relapse
    - Hospitalization
    - Colorectal cancer
    - Colectomy
  - Only the Geboes Score and, the Riley histopathology scores are partially validated
  - Biopsies may show inflammation, even when endoscopy is normal
  - “Complete” / deep remission is histological in UC, and may become the therapeutic target in the future
- Diagnostic imaging (DI)
  - “...resolution of radiological abnormalities in ulcerative colitis is not considered [to be] a therapeutic target in clinical practice”
  - Indicators of severe ulcerative colitis on DI:
    - Lumen
      - Fecal residue, extent
    - Wall
      - Dilation (megacolon, > 5.5 cm diameter in transverse colon)
      - Mucosal islands (normal mucosa surrounded by ulcerated mucosa)
  - Purposes
    - Diagnose
      - Extent
      - Severity (megacolon)
      - Stenosis/mass
      - Ileal disease (suggesting different diagnosis of Crohn disease)
  - Features to look for
    - Simplified magnetic resonance colonography index (MRC-S)
      - Uptake of contrast (gadolinium)
      - Edema
      - ↑ vascularity of mesentery (“comb sign”)
      - Lymphadenopathy
    - MRC-S-1
      - Performance characteristics: approximate indexes
        - Sensitivity 87%
        - Specificity 88%
  - CT of the colon has low sensitivity (74%) compared to colonoscopy to assess the activity of UC (MRI, and bowel US [BUS] is more sensitive, than CT to detect both activity and extent)
  - Bowel ultrasound (BUS)
    - Correlates with colonoscopy to assess activity of moderate-severe UC (weighted kappa value of 0.76 – 0.90)
    - Predicts UC outcome at 15 mon after corticosteroid-induced remission



➤ Biomarkers

- C-reactive protein (CRP)
  - Prediction of disease outcome / need for colectomy (rescue treatment)
    - Use at diagnosis, with Truelove-Witts Oxford criteria
    - With development of severe UC, CRP has weaker correlation with endoscopy)
    - Remember that, some persons do **not** make CRP
    - ↑ CRP in pregnancy, so may be falsely positive to predict active UC at that time
  - Oxford (Tradone-Will) criteria for severely active UC
    - BM > 8/d, or
    - BM 3-8/d plus CRP > 45 mg/L

}

    - After 3 d of IV corticosteroids, this predicts 85% of persons at risk of colectomy
- Fecal calprotectin (fCal)
  - Best use is to
    - Monitor disease activity by detecting a change in fCal (detect response to therapy)
    - Predict
      - Risk of relapse
      - Persistent inflammation
  - Quality of life (QoL)
    - Patient-oriented, important, but time-consuming to use, and may require payment for use/reuse.

Abbreviations: CD, Crohn disease; CRP, c-reactive protein; CT, computed tomography; DI, diagnostic imaging; fCal, fecal calprotectin; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; QoL, quality of life; UC, ulcerative colitis



## Use of Biomarkers for Patients with Ulcerative Colitis (UC): AGA Clinical Practice Guideline (2023)

Singh S and Ananthakrishnan AN. Gastroenterol 2023; 164: 344-372.

### ➤ Background

- The therapeutic target for patients with UC include symptoms, laboratory markers, endoscopic and appearance
- In UC, endoscopic remission or improvement is associated with
  - ↓ relapse
  - ↓ need for
    - Corticosteroids
    - Hospitalization
    - Colectomy
  - ↓ development of colorectal cancer
- The target of endoscopic improvement is Mayo Endoscopic Score (MES) 0 or 1 (some guidelines suggest MES or “equivalent”)
- In hospitalized patients with severe acute UC endoscopic, assessment is of use to
  - Guide treatment
  - Give prediction of prognosis
- In patients with Crohn disease, there is also non-RCT evidence that “...a tight control strategy based on a combination of symptoms biomarkers [is] more effective than a usual care strategy targeting symptoms alone in achieving deep remission”
  - The guideline considered only patients with UC
- While endoscopic healing is an important target in UC, biomarkers are also useful and, in some circumstances, can be surrogate markers for the presence or absence of active inflammation.

### ➤ Biomarkers

- C-reactive protein (CRP)
  - ↑ CRP in
    - Inflammatory conditions, including UC (idiopathic, infection, drug-associated)
    - Coexisting systemic conditions
- Fecal calprotectin (fCal), fecal lactoferrin (fLAC)
  - Useful to follow patients in remission (q6-12 mon)
    - To predict future relapse
  - Because fecal infection with pathogens can ↑ fCal / ↑ fLAC, and because enteric infections occur in ~30% of patients with active UC: always do stool testing for stool pathogens when requesting these fecal markers of UC activity.
  - Be aware of high variability in testing fCal
    - Use same assay in a given patient, if reported value in “grey area”, repeat test
  - fCal predicts extent of UC better than severity
  - Less effective to predict active proctitis, but
  - Is effective in proctitis to follow therapeutic response to treatment response to treatment with medicated suppositories.



- Note
    - These biomarkers do **not** detect endoscopic remission (MES 0)
      - Histopathological remission
      - MES 1 in patient with mild symptoms
    - Only colonoscopy is indicated to assess for mucosal dysplasia / surveillance obtaining biopsies for possible cytomegalovirus (CMV) infection
  - It is important to appreciate the importance of the value of false positive (FP) and false negative (FN) values of these biomarkers
    - High FP → perform unnecessary number of colonoscopies in response to the positive biomarker test
    - High FN → under treat the patient because dose modifications not performed to ↓ risk of future relapse
- Diagnostic Performance
- The diagnostic performance is influenced by the pretest probability of the test
    - The pretest probability can be estimated from the patient's symptoms of UC
    - The cut-off value

| Pretest Probability | Symptoms        | Rectal Bleeding Score | Stool Frequency Score | Prevalence of Moderate to Severe Inflammation |
|---------------------|-----------------|-----------------------|-----------------------|-----------------------------------------------|
| Low                 | Asymptomatic    | 0                     | 0-1                   | 15%                                           |
| Intermediate        | Mild            | 1                     | 2-3                   | 50%                                           |
| High                | Typical "flare" | 2-3                   | 2-3                   | 85%                                           |

❖ Diagnostic Accuracy for detecting moderate to severe endoscopic inflammation (MES 2-3)

• fCal

| 50 +/- cut-off value, µg/g                        | Sensitivity | Specificity                                                                                   | To detect endoscopic inflammation                                                          |
|---------------------------------------------------|-------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| 50 +/- 50                                         | 78%         | 57%                                                                                           |                                                                                            |
| 150 +/- 50                                        | 71%         | 69%                                                                                           |                                                                                            |
| 250 +/- 50                                        | 67%         | 73%                                                                                           |                                                                                            |
| Pretest Probability (please see definition above) | fCal        | False negative (FN)                                                                           | False positive (FP)                                                                        |
| ○ Low                                             | < 50        | 3.3%                                                                                          | 37%                                                                                        |
|                                                   | < 150       | 4.3%                                                                                          | 26%                                                                                        |
|                                                   | < 250       | 5.5%                                                                                          | 23%                                                                                        |
|                                                   |             | Misclassified as having endoscopic improvement of MES 0 or 7, when they actually have MES 2-3 | Misclassified as having endoscopic improvement of MES 2-3, when they actually have MES 0-1 |



| Pretest Probability (please see definition above) | fCal  | False negative (FN)                                                                             | False positive (FP)                                          |
|---------------------------------------------------|-------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| ○ Intermediate                                    | < 50  | 11                                                                                              | 21.5%                                                        |
|                                                   | < 150 | 14.5                                                                                            | 15.5%                                                        |
|                                                   | < 250 | 18.5                                                                                            | 13.5%                                                        |
|                                                   |       | – Incorrectly classified as having endoscopic improvement of MES 0-1, but actually have MES 2-3 |                                                              |
|                                                   |       |                                                                                                 | Incorrectly classified as MES 2-3, but actually have MES 0-1 |

- fLAC

|          | Cut-off value, µg/g | Summary Sensitivity | Specificity |                                   |
|----------|---------------------|---------------------|-------------|-----------------------------------|
| Positive | > 7.25              | 83%                 | 75%         | To detect endoscopic inflammation |
| Normal   | < 7.25              |                     |             |                                   |

## Recommendations

- Asymptomatic, remission
  - Patient wishes/situation allows for alternate approaches to those who are noted
  - After treatment within the past 1-3 mon, perform follow ups of symptoms plus serum/fecal biomarkers q6-12 mon (Strength of recommendation, conditional; certainty of evidence, moderate)
    - fCal < 150 µg/g, normal → rules out active UC (no need to do colonoscopy to assess endoscopic evidence of active UC MES 0-1)
    - CRP previously ↑ but currently normal
 (Strength of recommendation, conditional; certainty of evidence (low for fCal/fLAC; very low for CRP))
  - fCal > 150 µg/g, ↑ fLAC, ↑ CRP
    - Perform endoscopy, not empiric therapy
 (Strength of recommendation, conditional; certainty of evidence, very low)
- Symptomatic, active UC
  - Mild symptoms
    - fCal > 150 µg/g, ↑ fLAC, ↑ CRP
    - fCal < 150, normal fLAC/CRP
 } → Endoscopy (not empirical treatment)
  - Moderate/severe symptoms
    - fCal > 150 µg, ↑ fCal, ↑ CRP → rules in active UC → empirical treatment change
 (Strength of recommendation, conditional; certainty of evidence, very low)



**Probiotics for Induction of Remission in Ulcerative Colitis: Cochrane Review (2020)**

Kaur L, et al. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD005573.  
DOI: 10.1002/14651858.CD005573.pub3)

❖ Induction and maintenance of remission

• Probiotics in UC

|                                                                                                                                                                                                          | RR, 95%CI                     | Certainty of Evidence                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------------------------------|
| ○ Active UC                                                                                                                                                                                              |                               |                                                    |
| – Induction of remission                                                                                                                                                                                 | RR, 1.73; 95%CI, 1.19 to 2.54 | ▪ Low                                              |
| – Probiotics vs placebo                                                                                                                                                                                  |                               |                                                    |
| ▪ Improvement in clinical disease score                                                                                                                                                                  | RR, 2.29; 95%CI, 1.13 to 4.63 | ▪ Downgraded due to “risk of bias and imprecision” |
| – Probiotics vs 5-ASA                                                                                                                                                                                    |                               |                                                    |
| ▪ Induction of remission                                                                                                                                                                                 | RR, 0.92; 95%CI, 0.73 to 1.16 | ▪ Low (also downgraded)                            |
| – Probiotics plus 5-ASA vs 5-ASA                                                                                                                                                                         |                               |                                                    |
| ▪ Induction of remission                                                                                                                                                                                 | RR, 1.22; 95%CI, 1.01 to 1.47 | ▪ Low (downgraded)                                 |
| ○ Low certainty evidence suggests that probiotics may induce clinical remission in active ulcerative colitis when compared to placebo.                                                                   |                               |                                                    |
| ○ There may be little or no evidence when patient is in a clinical remission using probiotics alone compared to 5-ASA.                                                                                   |                               |                                                    |
| ○ There is limited evidence from a single study, which failed to provide a definition of remission, that probiotics may slightly improve the induction of remission when used in combination with 5-ASA. |                               |                                                    |





## Oral JAK-kinase inhibitors (Tofacitinib) for maintenance of remission in UC (2020)

Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis (Davies SC, et al. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD012381. DOI: 10.1002/14651858.CD012381.pub2)

|                                                                                                                                                                                                    | Placebo | Tofacitinib                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------------------|
| ○ Failure to maintain clinical remission                                                                                                                                                           | 89%     | – 63% (RR, 0.70; 95%CI, 0.64 to 0.77; high certainty evidence) |
| ○ Failure to maintain clinical response at 52 wk                                                                                                                                                   | 80%     | – 43% (RR, 0.54; 95%CI, 0.64 to 0.77; high certainty evidence) |
| ○ Failure to maintain endoscopic remission                                                                                                                                                         | 84%     | – 96% (RR, 0.88; 95%CI, 0.83 to 0.92; high certainty evidence) |
| ○ High certainty evidence suggests that tofacitinib is superior to placebo for maintenance of clinical and endoscopic remission at 52 wks in participants with moderate-to-severe UC in remission. |         |                                                                |
| ○ The optimal dose of tofacitinib for maintenance therapy is unknown.                                                                                                                              |         |                                                                |
| ○ High certainty evidence suggests that there is no increased risk of AEs with tofacitinib compared to placebo.                                                                                    |         |                                                                |

Abbreviations: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AA, alcoholic anonymous; ADA, adalimumab; AEs, adverse events; ALLO, allopurinol; AUD, alcohol use disorder; AWS, alcohol withdrawal syndrome; BBL, Bifidobacterium longum; BF, biofeedback; But, butyrate; CB, Clostridium butyricum; CBT, cognitive behaviour therapy; CD, Crohn disease; CI, confidence interval; CRC, colorectal cancer; DSF, De Simons formulation; FAPD, functional abdominal pain disorder; Glu, glutamine; HAV, hepatitis A virus; HE, hepatic encephalopathy; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IV, intravenous; IVC, inferior vena cava; LPA, longest period of abstinence; M, metastases; MDs, mean differences; MSM, men who have sex with men; MTZ, metronidazole; N, nodes; NPV, negative predictive value; PDA, percent days abstinence; PDHD, percent days heavy drinking; PEP, post-exposure prophylaxis; PFR, paracentesis plus fluid replacement; PL, placebo; PML, progressive multifocal leukoencephalopathy; PPV, positive predictive value; PV, portal vein; PWID, people who inject drugs; RCT, randomized controlled trial; RIF, rifaximin; RR, relative risk; SBP, spontaneous bacterial peritonitis; SC, subcutaneous; SEMs, self expandable metal stents; SMDs, standardized mean differences; ST, standard therapy; SVC, superior vena cava; T, depth; TIPS, transcutaneous intrahepatic portocaval shunt; TSF, twelve step facilitating program; UC, ulcerative colitis; UST, ustekinumab; VAG, neodymium-yttrium aluminium-garnet; wk, week; yr, year



## Medical and Surgical Management of Patients with Ulcerative Colitis (UC): BSG and CSSG Guidelines (2019)

Lamb CT, et al, Gut 2019; 68: S1-S106.

### ➤ Background

- Frequency of having  $\geq 1$  relapse after diagnosis of ulcerative colitis,  $> 90\%$ 
  - Early relapse in the first 2 yr after diagnosis associated with a worse subsequent disease course
    - Patients who have UC diagnosed initially by sigmoidoscopy should have an ileocolonoscopy (ICS) within a year of diagnosis of left sided disease to determine the extent of the UC.
- Rectal sparing is seen in  $\sim 3\%$  of patients with UC
  - This may be a true finding in persons who have had suppository/enema therapies recently, or
  - May represent a misdiagnosis, such as Crohn Colitis (CC)
- Backwash ileitis is seen in  $\sim 20\%$  of patients with UC
  - Usually in patients with severe UC
- Periappendiceal inflammation (“cecal patch”) may occur with/without associated UC.

### ➤ Histopathology

- The diagnosis of UC is made histological by the presence of some features, and the absence of others.
- Features suggestive of UC include
  - Villous surface
    - Irregular
    - Mucus depletion
  - Crypt
    - Distortion/branching
    - Diffuse atrophy / abscesses
  - Basal
    - Plasmacytosis
- About 10% of persons with idiopathic colitis may have histopathological features of both UC and CC
  - The clinical setting determines the terminology
    - No colectomy (biopsies at endoscopy)
    - IBD unidentified (IBS-U)
    - Colectomy (biopsies obtained from resected colon; deep and multiple biopsies possible)
    - Indeterminant colitis



➤ Phenotypes: Montreal Classification

❖ Use of phenotype: Extent

- The classification of “extent” of UC for purposes of screening for colorectal cancer
  - The maximal extent for the patient classified initially as “E”
  - The UC regresses to E1, then for purposes of CRC screening, they are considered to be E1
  - Once extensive UC, then for purposes of screening for CRC, patient is classified as “extensive”, even if over time the extent of the UC becomes less (regresses)
  - Take mucosal biopsies even from normal-appearing mucosa to determine the true extent of the UC (i.e., determined histologically).
  - May progress over time from distal to pancolitis
- Even if the mucosal appears normal on colonoscopy, during determination of extent of disease, take colonic mucosal biopsies from endoscopically normal mucosa.
- Extensive UC / pancolitis is often
  - ↑ severity
  - ↑ risk of
    - Colectomy within 10 yr
    - Colorectal cancer (CRC)
    - Associated primary sclerosing cholangitis (PSC), and backwash ileitis
- Risk factors for colectomy
  - Colon
    - Backwash ileitis
    - Long duration of disease, even if usually in remission
    - Pancolitis/severe disease activity
    - UC with PSC (development of CRC)
  - Patient
    - Young male
    - ↑ CRP at timing of diagnosis

Recommendation

- If UC diagnosed with sigmoidoscopy, within a year perform an ileocolonoscopy to determine
  - Extent of inflammation
    - Activity/severity of inflammation
    - Exclude Crohn disease (GRADE: strong recommendation, very low-quality evidence. Agreement: 100%)

➤ Scoring systems

❖ Clinical

- Mayo Score (for UC)
  - Components
    - Patient's stool frequency, rectal bleeding
  - Physician
    - Global assessment (mild, moderate, severe)
  - Endoscopy
    - Redness, feasibility, vascular pattern



➤ Terminology

- Partial Mayo Score
  - Mayo Score minus/without endoscopic changes
    - “...correlates well to patient perceptions of response to therapy”
- Mayo Score
  - Each of the four variables (stool frequency, rectal bleeding, endoscopic subscore and physician’s global assessment) is given 0 to 3 points, with a maximum of 4x3 (12) points
  - Disease activity (Mayo score)
    - Mild 3-5
    - Moderate 6-10
    - Severe 10-12

❖ Mayo score for ulcerative colitis

| Mayo Index                               | 0                          | 1                                                                    | 2                                                                                  | 3                                                 |
|------------------------------------------|----------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------|
| ○ Stool frequency                        | Normal                     | 1–2/day more than normal                                             | 3–4/day more than normal                                                           | 5/day more than normal                            |
| ○ Rectal bleeding                        | None                       | Streaks of blood with stool <50% of the time                         | Obvious blood with stool most of time                                              | Blood passed without stool                        |
| ○ Mucosa (Mayo endoscopic subscore, MES) | Normal or inactive disease | Mild disease (erythema, decreased vascular pattern, mild friability) | Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) | Severe disease (spontaneous bleeding, ulceration) |
| ○ Physician’s global assessment          | Normal                     | Mild disease                                                         | Moderate disease                                                                   | Severe disease                                    |

- Mayo score = sum of scores for each of the four variables (maximum score 12).
- Clinical response: reduction of baseline Mayo score by  $\geq 3$  points and a decrease of 30% from the baseline score with a decrease of at least one point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.
- Clinical remission: defined as a Mayo score  $\leq 2$  and no individual subscore  $> 1$ .
- Mucosal healing: defined as a mucosa subscore of  $\leq 1$ .
- Disease activity: Mild 3–5; Moderate 6–10; Severe 11–12

Printed with permission: Lamb CT, et al, Gut 2019; 68: S1-S106. (Table 2)

❖ Endoscopic: Mayo endoscopic subscore (MES)

- Please see table above
- Look at the endoscopically most inflamed part of the colonic segments: ascending (a), transverse (t), descending (d), sigmoid (s), rectum (r), and use Mayo Endoscopic subscore from the table above.



- Measure in decimeters the maximal score (MES)
  - Calculate Modified Mayo Endoscopic Score (MMES)
    - $MMES = MES \times \text{number of bowel segments which had a score} > 0$

❖ Modified Mayo Endoscopic Score (MMES)

Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

| Descriptor (score most severe lesions) | Likert scale                                                                                                                              | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Vascular pattern*                    | <ul style="list-style-type: none"> <li>– Normal</li> <li>– Patchy obliteration</li> <li>– Obliterated</li> </ul>                          | <ul style="list-style-type: none"> <li>▪ Normal vascular pattern</li> <li>▪ Arborization of capillaries clearly defined, or</li> <li>▪ Blurring or patchy loss of capillary margins</li> <li>▪ Patchy obliteration of vascular pattern</li> <li>▪ Complete obliteration of vascular pattern</li> </ul>                                                                                                                                                                                        |
| ○ Bleeding*                            | <ul style="list-style-type: none"> <li>– None</li> <li>– Mucosal</li> <li>– Luminal mild</li> <li>– Luminal moderate or severe</li> </ul> | <ul style="list-style-type: none"> <li>▪ No visible blood</li> <li>▪ Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, that can be washed away</li> <li>▪ Some free liquid blood in the lumen</li> <li>▪ Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or</li> <li>▪ Visible oozing from a hemorrhagic mucosa</li> </ul>                                                               |
| ○ Erosions and ulcers*                 | <ul style="list-style-type: none"> <li>– None</li> <li>– Erosions</li> <li>– Superficial ulcer</li> <li>– Deep ulcer</li> </ul>           | <ul style="list-style-type: none"> <li>▪ Normal mucosa, no visible erosions or ulcers</li> <li>▪ Tiny (<math>\leq 5\text{mm}</math>) defects in the mucosa, of a white or yellow colour with a flat edge</li> <li>▪ Larger (<math>&gt; 5\text{mm}</math>) defects in the mucosa, which are</li> <li>▪ Discrete fibrin-covered ulcers when compared with erosions, but</li> <li>▪ Remain superficial</li> <li>▪ Deeper excavated defects in the mucosa, with a slightly raised edge</li> </ul> |

UCEIS score=sum of all three descriptors in the worst affected area of the colon visible at endoscopy.

Remission, score  $\leq 1$ .

\*These three features account for 90% of variability in assessment of severity

Printed with permission: Lamb CT, et al, Gut 2019; 68: S1-S106. (Table 3)

- The basic problem with these scoring systems is their
  - Subjective nature
  - High inter-observer variation
  - Lack of patient reported outcome measures (PROMs)



## Recommendation

- Target therapy to symptomatic remission plus [endoscopically determined] mucosal healing (GRADE: weak recommendation, very low-quality evidence. Agreement: 96%)
- Clinical response
  - Baseline Mayo Score
    - ↓ by  $\leq 3$  points, and
    - 30% from baseline, with  $\geq 1$  point ↓ bleeding score 0 to 1
- Clinical remission
  - Mayo  $\leq 2$ , plus no individual subscore  $> 1$
- Mucosal healing endoscopic score (“mucosal healing”)  $\leq 1$

## ➤ Treatment

- Targets debated
  - Patient/physician related
    - Laboratory/endoscopic/histological
- “Growing consensus” of target of treatment
  - Clinical
    - Reasons for extensive outcome measures
    - Endoscopic +/- histological remission (MES  $\leq 1$ )
- Reasons for extensive defecation
  - In patients with clinical remission, only 35% will have endoscopic remission
  - Of patient with clinical plus endoscopic remission, only 16% have histological remission
  - Advantages of adding endoscopic plus histological remission to clinical remission predicts benefits, and may be important to
    - ↓ future
      - Flares
      - ↓ length of remission
    - ↓ need for
      - Corticosteroids
      - Colectomy

## ❖ 5-aminosalicylic acid (5-ASA)

- Acute UC
  - Induction therapy
    - Mild to moderate activity



## Recommendation

- Use 5-ASA po 2-3 g/d plus 5-ASA enemas, rather than only 5-ASA po (GRADE: strong recommendation, high-quality evidence. Agreement: 96%)
  - If patient on maintenance 5-ASA 2-3 g/d po has a flare of UGI → ↑ 5-ASA dose to 4-4.8 g/d plus 5-ASA enemas (GRADE: weak recommendation, low-quality evidence. Agreement: 82%)
  - Dose
    - 4.8 g/d po, superior to 2.4 g/d po for moderately active flare of UC (Accent II; 72% vs. 59%,  $p=0.0036$ )
    - In UC patients with no symptoms but ↑ fCal (fecal calprotectin > 50 µg/g) - ↑ dose from 0 to 1.2 to 2.4 g/d or 2.4 g/d → 4.8 g/d maintained clinical remission and within 6 wk reduced fCal to < 50 µg/g (DEAR trial)
    - 5-ASA has similar beneficial effects as sulfasalazine, but with fewer adverse effects (RR for adverse events 0.48, 95% CI 0.36 to 0.63)
  - Combination therapy of 5-ASA po plus pr
    - The combination of 5-ASA po plus pr is superior to monotherapy, even in patients with pancolitis (E3)
      - RR of no remission, comparing 5-ASA po plus pr vs. po alone, 0.65 (95% CI: 0.47 to 0.91)
  - Nephrotoxicity of 5-ASA
- Demography (5-ASA nephrotoxicity)
- 1/4000 patient yr on 5-ASA
  - Median time on 5-ASA until renal impairment 3 yr
  - Patients with 5-ASA associated renal impairment improvement upon stopping 5-ASA, 30%
- Give the nephrotoxicity disorders associated with the use of 5-ASAs.
    - Glomerulonephritis
      - Calculi
    - Nephritis, tubulointerstitial (deosyncratic)
      - Obstruction (obstructive nephropathy) fistulization
    - Nephropathy
      - Minimal change (nephrotic syndrome)
      - Patient losing neuropathy
      - Renal failure

## Recommendation

- "...patients on long-term 5-ASA therapy should have renal function checked, including eGFR before starting [5-ASA], after 2-3 mon, and then annually long term..."



❖ Corticosteroids (CS)

- Acute UC; induction therapy

Recommendations

- For patients with mild to moderate UC, in whom 5-ASA induction therapy failed / was not tolerated
  - Treat with prednisolone po (GRADE: strong recommendation, high-quality evidence), or
  - Budesonide MMX (GRADE: strong recommendation, moderate-quality evidence), or
  - Beclomethasone dipropionate (Agreement: 93%)
- Budesonide MMX (BMMX)
  - MMX 9 mg/d po vs placebo clinical and endoscopic remission at wk 8 (CORE I/II); 8% vs. 2% ( $p = 0.0002$ )
  - Cochrane systemic review
    - Benefit for left-sided / distal UC (vs placebo)
      - Endoscopic healing 28% vs. 17% ( $p = 0.009$ )
    - Clinical and histological healing BMMX 9, but not BMMX 6
  - Do **not** use ileal-release budesonide (Entocort®)
  - Comparing locally acting budesonide with systemic corticosteroids
    - ↓ adverse effects (33% vs. 55%)
    - No ↓ bone mineral density (BMD on DEXA Scan)
- Beclomethasone dipropionate (BMDP)
  - BMDP 5 mg/d po
    - Equivalents to 5-ASA 2.4 mg po
  - BMDP plus 5-ASA
    - Superior to 5-ASA alone

Therapeutic Thought

- BMDP is an alternate to corticosteroids in patients with mild/moderate UC and who have failed escalation of dose 5-ASA po/pr.

- For moderate to severe UC activity
  - Use oral corticosteroids (e.g., prednisolone 40 mg/d, missing dose over 6-8 wks (GRADE: strong recommendation, high-quality evidence. Agreement: 100%
- Indications
  - 5-ASA failure on dose escalation
  - Remission of severe UC achieved with IV corticosteroids → switch from IV to po, then wean off steroids while placing patient on maintenance therapy (5-ASA, immunosuppression, biologics)





- Corticosteroids (CS) superior to placebo for induction of remission of UC (RR of no remission, 0.65; 95% CI, 0.45 to 0.93)
    - Dose 40-60 mg/d, if improvement
      - Do **not** use longer than 3 mon
      - Begin dose taper after 6-8 wk
    - Improvements in symptoms/endoscopy within 2 wks
  - Dosing
    - Use once per day (↓ adrenal suppression)
  - If patient fails CS po, by symptoms/endoscopy within 2 wk, consider hospitalization for IV CS
  - If patient presented with severe acute ulcerative colitis (SAUC)
    - Start on solumedrol 40-60 mg/d IV for 3-5 d, reassess at that point if < 50% improvement → rescue therapy with infliximab or cyclosporine (Toronto Guidelines)
    - Development of megacolon on SAUC (toxic patient) → urgent surgical consultation for possible immediate colectomy / total colectomy.
- ❖ Maintenance therapy for UC in remission
- 5-ASA
- Recommendations
- Use 5-ASA po for maintenance therapy (maintenance if remission) in UC (GRADE: strong recommendation, high-quality evidence)
  - The maintenance dose of 5-ASA is
    - Useful 2.0 to 2.4 g/d po, od but once daily dosing recommended
    - “No difference between the various 5-ASA formulations in efficacy (Cochrane analysis)
    - 5-ASA pr also effective maintenance therapy for distal colitis
    - Use od (once daily dosing) (GRADE: strong recommendation, high-quality evidence), which may improve adherence (Agreement: 100%)
  - Note that some patients will have ↑ adverse effects (AEs) on: a daily dose of 5-ASA taken once, and these AEs may be less or resolve if the same total dose is taken several times a day (e.g., b.i.d., q.i.d.)
- ❖ Therapeutic escalation of maintenance therapy after failed 5-ASA
- Definition of failure of high-dose 5-ASA for maintenance therapy in UC
    - Need to use ≥ 2 courses of corticosteroids in last year for acute/relapse of UC
    - Corticosteroid-dependent refractory



- Need to add
  - Thiopurine (GRADE: strong recommendation, moderate-quality evidence)
  - Anti-TNF (GRADE: strong recommendation, high-quality evidence)
  - Vedolizumab (GRADE: strong recommendation, high-quality evidence)
  - Tofacitinib (GRADE: strong recommendation, high-quality evidence)
- “The choice of drug [for escalation] should be determined by
  - Clinical factors
  - Likely patient adherence
  - Patient choice
  - Local infusion capacity
  - Cost
 (Agreement: 97%)
- ❖ Treatment options for UC patient after 5-ASA failure
- Thiopurine
  - Thiopurine vs. placebo for maintenance (OR, 2.5; 95% CI: 1.26 to 5.3; ARR 23%; to prevent 1 recurrence, NNT = 5)
- Infliximab (IFX)
  - 5 mg/kg pooled data (ACT ½) vs. placebo clinical response after failed therapy
    - wk 8, 67% vs. 33%
    - wk 30, 30% vs. 18%
  - CS failure
    - IFX plus azathioprine (AZA; IFX-AZA) vs. IFX wk 16 (UC success study - 40% vs. 22%)
  - Corticosteroid-dependent UC, IFX
    - Steroid-free remission at 1 yr 47%; colectomy-free at 42 mon, 77%
  - Clinical remission in anti-TNF naïve subgroups (ULTRA3) vs. placebo wk 52, 14% vs. 6%
  - Active UC patients, anti-TNF naïve failure to respond (5-ASA, CS, AZA, mercaptopurine) or CS-dependent, golimumab vs. placebo response, 55% vs. 30%, and wk 6 remission 18%, vs. 6% (PURSUIT-SC).
  - Comparison of infliximab, adalimumab, and golimumab in UC
    - Network meta-analysis conflicting results regarding relative efficacy
- Vedolizumab
  - Vedolizumab vs. placebo, acute UC, anti-TNF naïve, induction therapy (GEMINI 7), 6 wk response, 53% vs. 26%; remission, 23% vs. 7%
    - Maintenance (durable clinical response) at wk 52, 61% vs. 27%
  - Prior response to anti-TNF therapy ↓ possibility of achieving clinical remission on vedolizumab (VICTORY)
  - Clinical HR, 0.53; 95% CI: 0.38 to 0.75



- Endoscopic HR, 0.51; 95% CI 0.29 to 0.88
- Head-to-head comparison of vedolizumab to
  - Adalimumab, UC moderate/severe, failed previous conventional therapy (VARSITY trial) 52 wk
    - Clinical remission (Mayo  $\leq 2$ ) 31% vs. 23%
    - Mucosal healing, 40% vs. 28%

#### Recommendation

- “..vedolizumab can be used in the induction and maintenance of remission of ulcerative colitis in patients when anti-TNF therapy has failed” (GRADE: strong recommendation, high-quality evidence. Agreement: 98%)

#### • Tofacitinib (oral JAK-kinase inhibitor)

Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis (Davies SC, et al. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD012381. DOI: 10.1002/14651858.CD012381.pub2)

|                                                                                                                                                                                                    | Placebo | Tofacitinib                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------------------------------------------------------|
| ○ Failure to maintain clinical remission                                                                                                                                                           | 89%     | 63% (RR, 0.70; 95%CI, 0.64 to 0.77; high certainty evidence) |
| ○ Failure to maintain clinical response at 52 wk                                                                                                                                                   | 80%     | 43% (RR, 0.54; 95%CI, 0.64 to 0.77; high certainty evidence) |
| ○ Failure to maintain endoscopic remission                                                                                                                                                         | 84%     | 96% (RR, 0.88; 95%CI, 0.83 to 0.92; high certainty evidence) |
| ○ High certainty evidence suggests that tofacitinib is superior to placebo for maintenance of clinical and endoscopic remission at 52 wks in participants with moderate-to-severe UC in remission. |         |                                                              |
| ○ The optimal dose of tofacitinib for maintenance therapy is unknown.                                                                                                                              |         |                                                              |
| ○ High certainty evidence suggests that there is no increased risk of AEs with tofacitinib compared to placebo.                                                                                    |         |                                                              |

#### Recommendation

- Use tofacitinib for induction and maintenance of remission of UC in patients when anti-TNF has failed (GRADE: strong recommendation, high-quality evidence. Agreement: 91%)
- Acute UC, induction therapy
  - Anti-TNF naïve, tofacitinib vs. placebo, 24% vs. 13%
  - 1 yr remission tofacitinib 5/10 mg b.i.d. vs. placebo, 34% vs. 11% (OCTANE sustain trial)
- HZV vaccination before starting tofacitinib
  - Age > 70 yr
  - Any age with recurrent HZV



- Adverse effects
  - Tofacitinib associated with ↑ risk of infection, especially HZV infection
    - ↑ risk of pulmonary embolus vs. anti-TNF therapy
  - HZV vaccination timing
    - 3 mon after stopping biologics
    - 1 mon before starting tofacitinib
- Ustekinumab
  - Induction and maintenance therapy in moderate to severe UC, failed response/ tolerance to CS, IN, anti-TNF, vedolizumab (UNITI UC trial) ustekinumab vs. placebo
    - Clinical remission, wk 8: 16% vs. 5% ( $p = 0.001$ )
    - Endoscopic healing: 27% vs. 14% ( $p < 0.001$ )
    - Clinical response: 51% to 62% vs. 31%
    - Maintenance, clinical remission wk 44: 38% to 44% vs. 24%
- Methotrexate
  - No role in the maintenance of remission of UC (e.g., MERIT study)
- Probiotics in UC

|                                                                                                                                                                                                         | RR, 95%CI                     | Certainty of Evidence                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------|
| ○ Active UC                                                                                                                                                                                             |                               |                                                  |
| – Induction of remission                                                                                                                                                                                | RR, 1.73; 95%CI, 1.19 to 2.54 | Low                                              |
| – Probiotics vs placebo <ul style="list-style-type: none"> <li>▪ Improvement in clinical disease score</li> </ul>                                                                                       | RR, 2.29; 95%CI, 1.13 to 4.63 | Downgraded due to “risk of bias and imprecision” |
| – Probiotics vs 5-ASA <ul style="list-style-type: none"> <li>▪ Induction of remission</li> </ul>                                                                                                        | RR, 0.92; 95%CI, 0.73 to 1.16 | Low (also downgraded)                            |
| – Probiotics plus 5-ASA vs 5-ASA <ul style="list-style-type: none"> <li>▪ Induction of remission</li> </ul>                                                                                             | RR, 1.22; 95%CI, 1.01 to 1.47 | Low (downgraded)                                 |
| ○ Low certainty evidence suggests that probiotics may induce clinical remission in active ulcerative colitis when compared to placebo.                                                                  |                               |                                                  |
| ○ There may be little or no evidence in a clinical remission with probiotics alone compared to 5-ASA.                                                                                                   |                               |                                                  |
| ○ There is limited evidence from a single study which failed to provide a definition of remission, that probiotics may slightly improve the induction of remission when used in combination with 5-ASA. |                               |                                                  |



## INFLAMMATORY BOWEL DISEASE (IBD)

### Clinical Nutrition in Patients with Inflammatory Bowel Disease: Guidelines (2017)

Forbes A, et al. Clin Nutrition 2017; 36: 321-47

#### ➤ Diet

##### Recommendations

- Consume a diet with ↑ n-3 / ↓ n-6 fatty acid to ↓ risk of developing IBD (Crohn disease, [CD]) and ulcerative colitis [UC]) (Grade of recommendation 0 – Strong consensus, 90% agreement)
- Breastfeeding (for 6-12 mon)
  - Protective against IBD, and
  - Optimal food for infants (Grade of recommendation B – Strong consensus, 93% agreement)
- Fluids
  - Maintain hydration / avoid dehydration → ↓ risk of thromboembolism (Grade of recommendation GPP – Strong consensus, 100% agreement)

#### ➤ Assessment

- Perform dietary assessment for persons diagnosed with IBD, and regularly thereafter (Grade of recommendation GPP – Strong consensus, 96% agreement)
- Treat documented malnutrition (Grade of recommendation GPP – Strong consensus, 96% agreement)
  - This includes micronutrient assessment and correction (Grade of recommendation GPP – Strong consensus, 100% agreement)

#### ➤ Diet

- Use energy/calorie requirement estimates for IBD similar to healthy non-IBD persons
- Protein requirements in IBD
  - Active IBD
    - 1.2 to 1.5 g/kg per day (Grade of recommendation GPP – Strong consensus, 96% agreement)
  - Inactive IBD
    - 1 g/kg per day (Grade of recommendation GPP – Strong consensus, 96% agreement)
- Iron
  - Assess persons with IBD for iron deficiency / iron deficiency anemia
  - Treat to correct concentration of hemoglobin (Hg), transferrin saturation and ferritin (Grade of recommendation A – Strong consensus, 100% agreement)
    - Oral iron
      - Anemia / deficiency mild
      - When activity of IBD is low
      - No known intolerance to iron po (Grade of recommendation A – Strong consensus, 100% agreement)



### Meta-analysis

- IV vs. po iron
  - ↑ hemoglobin (Hg) rise of  $\geq 2$  g/dL (OR, 1.57; 95% CI, 1.13-2.18)
  - ↓ rate of discontinued iron therapy (OR, 0.27; 95% CI, 0.10-0.59), but
  - ↑ risk of severe adverse effects (OR, 4.59; 95% CI, 6.11-18.8).

- IV iron
  - Anemia/deficiency, moderate/severe Hg < 100 g/L
  - When activity of IBD is high
  - Intolerance to po iron
  - Need for erythropoiesis
    - Stimulatory drugs (Grade of recommendation A – Strong consensus, 93% agreement)
- Target Hg to IBD patients' gender/pregnancy
- Retreat when ferritin < 100 µg/L, Hg < 12-13 g/dL

### ❖ Specific Considerations

### Recommendations

- Active IBD
  - There is no such thing as an “IBD diet” (Grade of recommendation GPP – Strong consensus (96% agreement))
  - ↑ po intake, and if necessary, give IV infusion of fluids /electrolytes
    - Correct volume depletion and electrolyte disturbances
  - If large losses (e.g., high output stoma [HOS])
    - Monitor and respond to
      - Fluid output
      - Urinary Na<sup>+</sup> concentration (Grade of recommendation 0 – Strong consensus, 96% agreement)
- Strictures/Stenosis plus obstructive symptoms
  - Pharmacotherapy, balloon dilation, surgery
  - Modified diet
  - Enteral nutrition (EN) delivered distally to proximal stricture of small intestine (post-stenotic infusion) (Grade of recommendation 0 – Strong consensus, 96% agreement)
    - Single study results promising for “exclusive enteral nutrition (EEN) in patients with IBD strictures.



- Metabolic Bone Disease
  - Give calcium and vitamin D supplements to IBD patients with
    - Active disease
    - Corticosteroid treatment (Grade of recommendation B – Strong consensus, 96% agreement)
    - Abnormal DEXA Scan ( $\downarrow$  bone mineral density)
- Bile acid diarrhea (BAD) / malabsorption (BAM)
  - Bile acid sequestrants, e.g., cholestyramine
  - No nutrient changes needed (Grade of recommendation GPP – Strong consensus, 88% agreement)
    - Some authorities have previously recommended monitoring for possible deficiency of fat-soluble vitamins.
    - Request assistance of pharmacist to schedule intake of cholestyramine at a time so as to manage interaction with other drugs the patient may be taking
- High output / proximal
  - Use only enteral nutrition (EEN) or total parenteral nutrition (TPN) (Grade of recommendation B – Strong consensus, 96% agreement)
  - Give low output / distal EEN by nasogastric tube (Grade of recommendation – Strong consensus, 100% agreement)
- Refeeding syndrome
  - After several days of nutritional deprivation
    - Monitor and correct  $\downarrow K_s^+$ ,  $PO_4^{2-}$ ; give thiamine (Grade of recommendation B – Strong consensus, 100% agreement)
- Ulcerative Colitis (UC)
  - Use EN in patients with severe UC
    - “...according to standard nutritional practice (Grade of recommendation GPP – Strong consensus, 100% agreement)
  - Do **not** use parenteral nutrition (PN) in UC unless patient has intestinal failure (Grade of recommendation, Strong agreement)
- Hyperoxaluria ( $\uparrow$  risk of oxalate renal calculi)
  - With extensive ileal Crohn disease / ileal resection  $\rightarrow \uparrow$  risk of steatorrhea /  $\uparrow$  risk of hyperoxaluria  $\rightarrow \uparrow$  risk of renal oxalate stones.
  - These patients may benefit from  $\downarrow$  intake of
    - Oxalate-high foods (fruit, tea) (Grade of recommendation GPP– Strong consensus, 88% agreement)
    - Some patients will benefit from  $\uparrow$  intake of calcium citrate  $Ca^{2+}$  binds to oxalate in the intestinal lumen  $\rightarrow \downarrow$  oxalate absorption in colon



- ❖ Special diets
- Exclusion diets
  - Do **not** use exclusion diets (Grade of recommendation GPP– Strong consensus, 88% agreement)
- Probiotics
  - Use Escherichia coli Nissle 1917 for
    - Induction of remission in mild moderate UC (Grade of recommendation 0 – Strong consensus (92% agreement))
    - Use VSL #3 for pouchitis, for maintenance of remission (only VSL #3) (Grade of recommendation B – Strong consensus, 95% agreement)
  - Induction of remission
  - Maintenance of remission
    - UC (Grade of recommendation B – Strong consensus, 96% agreement)
    - UC (pouchitis, VSL #3) (Grade of recommendation B – Strong consensus, 96% agreement)
    - Not in CD (Grade of recommendation 0 – Strong consensus, 100% agreement)
- Nutrient supplements
  - Oral enteral nutrition (EN) to ↑ energy/protein intake when oral inadequate (Grade of recommendation 0 – Strong consensus, 92% agreement)
  - Parenteral nutrition (PN) when
    - Po/tube EN not appropriate/sufficient
    - Short bowel
    - Obstructed bowel
    - High output fistula (HOF) (Grade of recommendation B – Strong consensus (96% agreement))
    - Pseudo-obstruction, chronic
- Tube feeding

#### Recommendations

- Use NG or percutaneous endoscopic gastrostomy (PEG) / percutaneous endoscopic jejunostomy (PEJ) tube feeding, where indicated (Grade of recommendation B – Strong consensus, 96% agreement)
  - Administer tube feeding by enteral feeding pump (often at night), rather than giving boluses of EN (Grade of recommendation B – Strong consensus, 92% agreement)





- Enteral Nutrition (EN)
  - EN for primary/supportive therapy in active IBD, no specific recommendation of product (Grade of recommendation 0 – Strong consensus, 96% agreement)
    - Do **not** use specific formulations / substrates (e.g., glutamine, omega-3-fatty acids) in EN/PN in IBD patients (Grade of recommendation B – Strong consensus, 96% agreement)
- ❖ Surgical aspects of nutrition in patient with IBD
- Preoperative
  - Elective Surgery
    - Use enhanced recovery after surgery protocol (ERAS) to accelerate functional recovery after surgery
    - Do **not** use preoperative fasting (from midnight) (Grade of recommendation B (see surgery guideline) – Strong consensus, 100% agreement)

Point to ponder

- ↓ preoperative nutrient intake → ↑ risk of surgical complications

Abbreviations: BAD, bile acid; BMI, body mass index; CD, Crohn disease; EEN, exclusive enteral nutrition; EN, enteral nutrition; ERAS, enhanced recovery after surgery; Hg, hemoglobin; HOF, high output fistula; IBD, inflammatory bowel; IV, intravenous; K<sup>+</sup><sub>s</sub>, serum potassium concentration; mon, month; NG, naso-jejunal; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; PN, parenteral nutrition; po, by mouth; UC, ulcerative colitis

- Peri-operative
- ❖ Early after surgery

Recommendations

- Early nutrition (within 24 h)
  - CD
    - Any surgery
      - Food (Grade of recommendation 0 (see surgery guideline) – Strong consensus, 100% agreement)
    - Prolonged intestinal failure / early with short bowel syndrome
  - UC
    - Any surgery
      - Food/EN
    - Monitoring / treat water/electrolyte disorders (Grade of recommendation A (see surgery guideline) – Strong consensus, 96% agreement)



❖ Maintenance of remission

Recommendations

- Multidisciplinary team (MDT)
- Standard diet (Grade of recommendation: Good practice point (GPP) – Strong consensus, 95% agreement) plus
  - Monitoring by registered dietitian monitoring (Grade of recommendation GPP – Strong consensus, 100% agreement)
- Exercise
  - Physical activity, including endurance training (Grade of recommendation GPP – Strong consensus, 100% agreement)
- Stop smoking forever
- IBD patients who are malnourished (inadequate intake of energy/protein) → intensive artificial feeding for 7-14 d (to ↓ rate of complications, including mortality) (Grade of recommendation A – Strong consensus, 96% agreement)
  - ESPEN Working Group definition of severe nutritional risk, as related to perioperative care of IBD patients
    - Weight loss > 10-15% within 6 mon
    - BMI < 18.5 kg/m<sup>2</sup>
    - Serum albumin < 30 g/L (with no evidence of hepatic or renal dysfunction)
- If EN inadequate (> 60% of energy needs cannot be met) → add PN (Grade of recommendation A (see ESPEN surgery guideline – Strong consensus, 100% agreement)
  - PN given in the perioperative period should be supplemented to EN
- If EN cannot be given, use PN (Grade of recommendation A – Strong consensus, 96% agreement)
  - EN access
    - No access
    - Vomiting
    - Diarrhea
  - Contraindication
    - Patient in shock
    - Hemorrhage, severe
    - Obstruction/ileus
    - Perforation / high output fistula
- Give EN in CD patients who are malnourished but “...cannot be treated sufficiently by dietary counseling (Grade of recommendation GPP – Strong consensus, 100% agreement)



- Vitamin B12 supplementation
  - B12 deficiency, clinical (use of po vitamin B12 in this setting requires further study)
    - 1000 µg IM q2d for 1 wk, then q1mon for life
  - > 20 cm ileum resected
    - 1000 µg IM q1mon for life (Grade of recommendation A – Strong consensus, 100% agreement)
- Specific diets
  - No specific diets (Grade of recommendation 0 – Strong consensus, 96% agreement)
  - No omega-3 supplemented diet (Grade of recommendation B – Strong consensus (100% agreement)
  - No non-specific high fibre diets (Grade of recommendation 0 – Strong consensus, 96% agreement)
  - No routine use of EN or PN (Grade of recommendation GPP – Strong consensus, 100% agreement)
- Folic acid / vitamin B9
  - Treatment with sulfasalazine or methotrexate (Grade of recommendation B – Strong consensus, 100% agreement)

#### Meta-analysis

- Using folic acid plus vitamin B9 supplementation in IBD patients protects against development of colorectal cancer (pooled HR, 0.58; 95% CI, 0.37-0.80)

- Pregnancy and IBD
  - Monitor pregnant mother for iron/folate levels, and supplement as appropriate (Grade of recommendation GPP – Strong consensus, 95% agreement)
  - Monitor breastfeeding mother's nutritional status, and treat appropriately (Grade of recommendation GPP– Strong consensus, 100% agreement)
- Obesity
  - Active IBD
    - No low-calorie diets
  - Inactive IBD (stable remission)
    - “According to current obesity guidelines” (Grade of recommendation GPP – Strong consensus, 100% agreement) overweight / obesity is more prevalent in UC than CD

|      | IBD | Overweight | Obesity |
|------|-----|------------|---------|
| – UC |     | 4.9%       | 8.5%    |
| – CD |     | 2.5%       | 2.0%    |



## Inflammatory Bowel Disease in Pregnancy: AGA Critical Care Pathway (2018)

Mahadevan U, et al. Gastroenterology 2019;156(5):1508-1524.

- Multidisciplinary team (MDT)
  - Maternal-fetal specialist
  - High risk obstetrician
  - Clinical geneticist
  - General surgeon
  - Registered dietitian
- Pre-conception
  - Conception plan for when mother is in remission from her Crohn disease (CD) or ulcerative colitis (UC)
    - Avoid entering pregnancy with active disease →
      - ↑ risk of continued active disease in pregnancy (risk ratio of 2.0 in CD/UC)
      - 2x ↑ risk of preterm birth
      - Patients in remission at conception and having active disease flare during pregnancy, 14%
      - Patients with active disease at conception, and having active disease continue during pregnancy, 26%
  - Contraception
    - Intrauterine device
      - Hormonal
      - Non-hormonal
    - Contraceptive implant
    - Low-dose estrogen oral contraceptive pills (OCP) if woman has low risk of thromboembolism

### ❖ Genetic counseling – preconception

- Family history
  - Twins, monozygotic
    - CD
    - UC

|  |    | Concordance Rates |  |
|--|----|-------------------|--|
|  | CD | ~20% to 50%       |  |
|  | UC | ~5% to 20%        |  |

|                |      | Incidence rate ratio | Absolute risk of IBD in child |
|----------------|------|----------------------|-------------------------------|
| – Maternal IBD | ▪ CD | 6.3                  | 2.7%                          |
|                | ▪ UC | 3.7                  | 1.6%                          |

  - Mother plus father have IBD
    - Risk of IBD in child, 30%



❖ Fertility

- Risk of ↓ fertility
  - Mother with CD > 30 yr
  - Active disease
  - Intestinal surgery
    - Ileal pouch anal anastomosis (IPAA)
    - Proctectomy
    - Ostomies, permanent
  - Do **not** plan conception until after 6 mon of intestinal surgery
- Assisted reproductive technology (ART)
  - ↓ effectiveness compared with non-IBD population
    - "...likely due to a lesser chance of achieving a chemical pregnancy (positive human chorionic gonadotropin [HCG] 2 weeks after embryo transfer"
  - No adverse effect on ART
    - IBD medications
  - No effect on IBD activity
    - Hormones used for ART

❖ Usual preconception care

- Discontinue during pregnancy/lactation
  - Alcohol
  - Smoking
  - Opioids
  - Recreational drugs, including marijuana
- Vaccinations up to date, age appropriate
- Papanicolaou ("Pap") smear
- Dietary/nutritional counselling
  - Avoid excess weight gain
  - Achieve target gestational weight gain (GWG) for body mass index category

❖ Maintenance of IBD remission

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the reason for the need to ↓ the increased risk of poor gestational weight gain (GWG) in pregnant women with IBD.
  - ↓ GWG in IBD → 2x ↑ risk of small-for-gestational age infants  
→ ↑ IBD activity in mother



- Drugs to discontinue
  - 5-ASA drugs
    - Avoid phthalate in sulfasalazine (Asacol® may contain phthalate, but not in Canada)
  - Immune modulators
    - Stop  $\geq 3$  mon before conception (teratogenic)
    - Azathioprine (AZA)
      - If already on AZA, consider prophylactic drug monitoring
- Drugs **not** to start in pregnancy
  - AZA:  $\uparrow$  risk of
    - Leucopenia
    - Pancreatitis
    - Slow onset of action
  - Biologics
    - Safe in pregnancy
      - $\downarrow$  number of flares
      - $\downarrow$  disease activity
        - $\downarrow$  adverse outcomes of pregnancy
    - Monitor trough levels before and during pregnancy and during breastfeeding
    - Do **not** interrupt anti-TNF therapy during pregnancy (including the third trimester [T3])
    - If possible, use monotherapy AZA alone, and  $\alpha$  TNF alone (combination  $\rightarrow \uparrow$  infection in infant)

Therapeutic Alert

- Do **not** use tofacitinib in pregnancy
  - Washout period is usually for  $\sim 2$  mon

- Plan post-partum dosing of biological therapy before delivery
- Give prenatal vitamins, folic acid, possibly vitamin B12, iron, vitamin D

❖ Relapse / active disease

- Laxatives to prevent constipation
  - Stool softeners, PEG300, senna, docusate
  - Do **not** use castor oil ( $\uparrow$  contractions of uterus)
- Corticosteroids only for flares
  - Do **not** use higher than necessary doses  $\rightarrow \uparrow$  risk of
    - Mother with gestational diabetes
    - Fetus with  $\downarrow$  birth weight



- Diagnosis
  - Clinical
  - Laboratory: be aware of changes which occur naturally in pregnancy, and thus ↓ accuracy in pregnancy to assess ↑ disease activity
    - ↑ white blood cell count (WBC)
    - ↑ C-reactive protein (CRP)
    - ↓ hemoglobin (Hg)
  - No colonoscopy
  - ↑ risk of fetal distress / need for cesarian section
  - MRI (no gadolinium), CT scans, ultrasound

❖ Perianal disease

➤ Types

- |                        |                         |                                                                                                                                                                                                        |
|------------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Anus                 | - Fissure<br>- Stenosis | } <ul style="list-style-type: none"> <li>▪ When active CD is present, may be an indication for cesarian delivery (10x ↑ risk of fourth degree laceration)</li> <li>▪ ↓ risk of incontinence</li> </ul> |
| ○ Anorectum            | - Fistula<br>- Abscess  |                                                                                                                                                                                                        |
| ○ Rectovaginal fistula |                         |                                                                                                                                                                                                        |

➤ Clinical significance

- 4x ↑ risk of fourth-degree laceration developing during vaginal childbirth

➤ Delivery

- Usual obstetrical indications for vaginal delivery for IBD patient
- Perform examination between 37 wk to time of delivery to determine extent of perianal disease
- Anti-coagulation prophylaxis against thromboembolic disease
  - Use compression ambulation
  - Peri-delivery
  - Post-operatively for 3 to 6 wks if cesarian delivery performed
- Choices
  - Heparin
    - Unfractionated
    - Low-molecular-weight
    - Warfarin

Therapeutic Alert

- Do **not** use anticoagulants with
  - Direct thrombin inhibitor, or Xa inhibitors



- Mother with ileal pouch anal anastomosis (IPAA)
  - Cesarean section may be considered to ↓ risk of injury to anal sphincter and resulting fecal incontinence
  - Recommended to have general surgeon present at time of delivery in the event that adhesions in the abdomen may interfere with the cesarian delivery
- Treat any complication of delivery
  - Infection of wound
  - Ileus
- IBD medications
  - Continue as per preoperatively
  - Continuation of biologic therapy in pregnancy has been associated with
    - ↓ flares in pregnancy and postpartum
    - ↓ disease activity
    - ↓ adverse outcomes of pregnancy
  - Restart biologics after delivery
    - Vaginal, 24 h
    - Cesarean, 48 h
    - Monotherapy is preferred
    - For dosing purposes, use base weight on prepregnancy weight
    - Monitor drug levels to assist in dosing
    - Do **not** use biologics plus thiopurine during pregnancy because of ↑ risk of infection in the infant
    - Do **not** start thiopurine therapy for the first time in pregnancy
- Pain control
  - Avoid use of codeine/tramadol
  - Ideally, no NSAIDs
- Bowel routine
  - Dietary, stool softeners, osmotic agents
- Ostomy care
  - Consult ostomy nurse/surgeon
  - Anticipated problems
    - Prolapse/retraction
    - Stenosis/enlargement
    - Displacement
- Breastfeeding
  - ↑ calorie intake by 450 to 500 kcal/d
  - Add omega-3 fatty acids, 200-300 mg/d
  - Ensure intake of adequate fluids
  - Milk supply
    - **No** fenugreek (galactagogue) to ↑ milk supply
    - **No** high dose IV corticosteroids, if possible (may ↓ milk supply)
    - Corticosteroids po/pr and all other IBD drugs do **not** ↓ milk supply





- Safety
  - 5-ASAs
    - Avoid sulfasalazine because the sulfapyridine is excreted in large amounts into mother's milk and may cause
      - Hemolysis/jaundice
      - Antimicrobial effects
  - Immunosuppressants
  - Biologics
    - No negative impact on breastfeeding or infant health
    - No need to "pump and dump" milk
- Vaccinations for baby
  - 2 and 4 mon: rotavirus
    - Exception: if mother was taking biologics after 27 wk gestation (T3): do **not** give infant live vaccines until after 6 mon (give rotavirus then after mon 6)
  - 1 yr
    - Live vaccines (safe if still breastfeeding)
      - Measles, mumps, rubella (MMR)
      - Varicella

Abbreviations: AGA, American Gastroenterology Association; ART, assisted reproductive technology; AZA, azathioprine; CD, Crohn disease; CRP, C-reactive protein; d, day; GWG, gestational weight gain; Hg, hemoglobin; IBD, inflammatory bowel disease; IPAA, ileal pouch anal anastomosis; IV, intravenous; MGG, multidisciplinary group; MMR, measles, mumps, rubella; mon, month; NSAIDs, anti-inflammatory drugs; Pap, papanicolaou; PEG, polyethylene glycol; T3, third trimester of pregnancy; UC, ulcerative colitis; WBC, white blood cell; wk, week



## IBD and Pregnancy

Nguyen GC, et al. Seon CH, et al. Gastroenterol 2016; 100: 734-57; and Bressler B, Marshall JK, et al. Gastroenterol 2015; 148: 1035-58.

### ❖ Antipartum

#### Recommendations

- Women with UC/CD who are considering pregnancy
  - Preconception counseling (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 83%; agree, 17%), including by gastroenterologist
  - Disease evaluation, “objective” (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 0%; agree 75%; uncertain, 25%)
  - Care throughout pregnancy with gastroenterologist
  - If complicated/active IBD, high-risk obstetrician
  - Medication review: during pregnancy, safe to
    - Continue po/pr 5-ASA maintenance therapy (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 58%; agree, 42%, uncertain, 25%), but
      - Stop 5-ASA formulation containing dibutyl phthalate (some formulations of Asacol® [not in Canada]) (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 0%; agree, 75%, uncertain, 25%)
    - Discontinue maintenance thiopurine ≥ 3 mon before pregnancy (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%)
    - Continue anti-TNF therapy
      - If anti-TNF to be stopped, give last dose at gestation wks 22 to 24
    - Stop use of methotrexate 3 mon before trying to become pregnant (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 17%; agree, 75%, uncertain, 8%)
    - If patient on anti-TNF plus MTX, individualize stopping of MTX (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 67%)

### ❖ Peripartum

#### Recommendations

- If methotrexate maintenance not already stopped 3 mon before pregnancy, stop now and refer woman for counselling with obstetrician (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 50%, uncertain, 8%)
- In selected pregnant women at low risk of a relapse of IBD who have a compelling reason to discontinue anti-TNF therapy to minimize fetal exposure, administer the last dose at 22 to 24 wk gestation (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 8%; agree, 67%, uncertain, 8%; disagree, 8%; strongly disagree, 8%)



- Women with
  - Mild-moderate UC flare while on 5-ASA maintenance → use po plus pr 5-ASA
  - Severe flare, use non-stress doses of corticosteroids (↑ dose from maintenance to active 2 g → 4 g po per day)
- Women with CD with perianal sepsis → methotrexate +/- ciprofloxacin
  - Complicated/active IBD consult high risk obstetrician (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 50%, uncertain, 8%)
- Women with UC/CD with
  - Flare despite 5-ASA (UC) or thiopurine (UC or CD) maintenance therapy → systemic corticosteroids or anti-TNF (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 58%, disagree, 8%)
  - If corticosteroid-resistant → anti-TNF (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 33%; agree, 67%)
  - If on thiopurines and require anti-TNF → use combination therapy
  - If thiopurine naïve and require anti-TNF → use monotherapy with anti-TNF (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 0%; agree, 83%, uncertain, 17%)
- In pregnant women hospitalized for UC/CD
  - Use anticoagulant thromboprophylaxis (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%)
  - Use tertiary centre, high risk obstetrician, gastroenterologist (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 58%; agree, 42%)
- Investigation for flare of UC/CD during pregnancy
  - Flexible sigmoidoscopy/colonoscopy
    - “...if the results will affect the ...management” (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 75%; agree, 25%)
  - Ultrasound or MRI, avoid barium or CT imaging (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%)
- Treatment
  - If urgent surgery necessary for IBD complications
    - Proceed on basis of surgical / GI indication (e.g., not solely on the consideration of the pregnancy (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%).



- The decision for cesarian delivery should be made on the basis of obstetrical and not just the IBD considerations (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%), except for
  - Cesarian delivery
    - Active perianal disease (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 50%; agree, 50%)
    - Previous IPAA (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 8%; agree, 92%)
- If not yet anticoagulated before cesarian section, do so after cesarian delivery (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 67%; agree, 33%).
- Do **not** use methotrexate or cyclosporine during pregnancy/lactation
  - Use 5-ASA, thiopurine, corticosteroids, anti-TNF drug approved for use during pregnancy
- 5-ASA systemic corticosteroid, thiopurine, or anti-TNF therapy are safe to use in pregnancy and during lactation.
  - Breast-feeding should not influence the decision to use these medications (GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%)
- Vaccinations of newborn
  - **No** live vaccines for 6 mon postpartum (GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 58%)



## Biosimilars in Inflammatory Bowel Disease

Buchner AM, et al. Am J Gastroenterol 2021; 116: 45-56

### ➤ Definitions

- "...biological agents that are highly similar to an existing FDA-approved reference biological agent for purity, chemical activity, and bioactivity, with no clinically meaningful difference".
- FDA definition
  - "...highly similar to the reference predict not withstanding minor differences in clinically inactive components"
- To be approved by the FDA, product must have similar
  - Function and structures
  - Pharmacokinetics
  - Safety/efficacy
  - Development of antibodies

### MCQ Gem

- Anti-TNF biosimilar for infliximab/adalimumab are not interchangeable.

### Test Question

| Differences                                                                           | Biologics | Small Molecules |
|---------------------------------------------------------------------------------------|-----------|-----------------|
| ○ Protein, parenteral                                                                 | +         | -               |
| ○ Organic, oral                                                                       |           | +               |
| ○ 3-D structure, variable                                                             | +         |                 |
| ○ Catabolism                                                                          |           |                 |
| – Metabolism                                                                          | +         | +               |
| ○ Blockers                                                                            |           |                 |
| – Enzyme inhibitors                                                                   | +         | +               |
| ○ "Cross-switching or multiple switching among biosimilars should not be recommended" |           |                 |
| ○ Clinical use of biologics                                                           |           |                 |
| ○ Patients in remission who are suitable from original to biosimilar                  |           |                 |
| ○ Switch during the active phase                                                      |           |                 |
| ○ Safe non-medical switching of original infliximab to infliximab biosimilar          |           |                 |
| ○ IBD naïve to anti-TNF                                                               |           |                 |
| ○ No differences between biosimilar to reference agent in CD/UC                       |           |                 |



## CLOSTRIDIUM DIFFICILE\* INFECTION (DCI)

### Prevention, Diagnosis, and Treatment of Clostridium difficile Infection (DCI): ACG Guidelines (2021)

Kelly CR, et al. Am J Gastroenterol 2021; 116: 1124-1147.

- “These guidelines are intended to be complimentary to the recently updated Infectious Disease Society of America (IDSA) and Society of Healthcare Epidemiologists of America (SHEA) (McDonald LC, et al. Clin Infect Dis 2018; 66: 21-48; Crobach MJ, et al. Clin Microbiol Infect 2016; 11(Suppl 4): S63-S81); and DeBast SB, et al., Clin Microbial Infect 2014; 20 (Suppl 2); 1-26.

#### ➤ Demography

- Incidence of CDI in US, 453,000/yr
  - Community-associated CDI accounts for ~40% of cases
    - Risk factors
      - Caucasian
      - Use of antibiotics
      - Chronic renal disease
      - Inflammatory bowel disease (IBD)
- Deaths (from CDI), ~14,000/yr
- Colonization
  - Definition: detection of Clostridium difficile (CD) organism in the absence of symptoms
    - Healthy adults, ~10%
    - Hospitalized adults facilities
    - Residents in long-term care
- Risk of CDI
  - Age  $\geq$  65 yr
  - Use of antibiotics
  - Colonization with CD at time of hospitalization ( $\uparrow$  6x)
  - Contact with healthcare environment
  - Infection with NAP1 strain (North America pulsed field electrophoresis type one strain)

} ~20%

#### ➤ Prevention of CDI

##### ❖ Probiotics

- Definition: “...live organisms that, when administered in adequate amounts, confer to a health benefit on the host”

\*now called “Clostridium difficile”



## Recommendation

- Do **not** use probiotics for
  - Primary prevention
    - Prevention of CDI in persons treated with antibiotics (primary prevention) (conditional recommendation, moderate quality of evidence)
  - Secondary prevention
    - Prevention of recurrent of CDI (secondary prevention) (strong recommendation, very low quality of evidence).
- There is **not** sufficient evidence to ↓ risk of CDI by using probiotics for prevention (primary/ secondary)
  - There may be possible benefits of probiotics in some persons with a baseline risk of
    - CDI of > 5%, but the Cochrane review has been criticized:
    - While combining *Saccharomyces boulardii* with metronidazole or vancomycin is useful vs. placebo to ↓ risk of recurrent CDI (RR, 0.43; 35% vs. 65%), there was no comparator study of just the protease inhibitor or just the antibiotic.

## ➤ Diagnosis

- Clinical suspicion of CDI
  - Unexplained and new-onset diarrhea with ≥ 3 unformed stools in 24 h
  - Stools must be unformed / liquid
- Give why it is **not** recommended to test routinely for elimination of CD.
  - Even in persons with diarrhea from CDI who are treated and become asymptomatic (resolution of diarrhea), shedding of CD may continue for 4 wk in ~55% of persons
  - If the mucosa of the colon is normal endoscopically and histologically
    - *C. difficile* is unlikely to be the source of diarrheal symptoms
  - Laboratory
    - “gold standards”
      - Toxigenic stool culture
      - Cell cytotoxicity neutralization (CCN) assays
    - High specificity
      - Enzyme immunoassays (EIAs) – rapid detection of toxin A/B produced by CD
    - High sensitivity
      - Nucleic acid amplification testing (NAAT) such as
        - Polymerase chain reaction (PCR)
        - Loop-mediated isothermal amplification (LMIA)
        - Glutamate dehydrogenase (GDH)
          - Must be confirmed by NAAT/EIA

▪ Detects the gene which codes the toxin



### MCQ Trick

- Give the drawbacks of nucleic acid amplification testing (NAAT) to diagnosis of CDI.
  - Asymptomatic persons who are colonized by CDI may not test positive by NAAT
    - NAAT may be falsely positive for CDI, and non-CDI causes may be responsible for the diarrhea, e.g.,
      - Microscopic inflammatory bowel disease (IBD)
      - Irritable bowel syndrome (IBS)

### • CDI Testing Modalities

| Test                     | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Distinguishes colonization from active infection | Other considerations                                                                       |
|--------------------------|-----------------|-----------------|-------------------------------|-------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------------|
| ○ Toxigenic culture      | 94              | 99              | -                             | -                             | No                                               | – Detects toxin producing <i>C. difficile</i> strains in culture.<br>– Not used clinically |
| ○ CCNA                   | 93              | 98              | -                             | -                             | Yes                                              | – Demonstrates presence of free toxin Bm<br>– Not used clinically                          |
| ○ GDH                    | 94-96           | 90-96           | 34-38                         | 100                           | No                                               | – Does not distinguish non-toxigenic from toxigenic strains                                |
| ○ NAAT (PCR or LAMP)     | 95-96           | 94-98           | 46                            | 100                           | No                                               | – Detects gene for toxin B                                                                 |
| ○ EIA for toxins A and B | 57-83           | 99              | 69-81                         | 99                            | Yes                                              | – Detects presence of free toxin                                                           |

Abbreviations: ACG, American College of Gastroenterology; CCNA, cell cytotoxicity neutralization assay; CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; IBD, inflammatory bowel disease; LMIA, loop-mediated isothermal amplification assay; NAAT, nucleic acid amplification testing; PCR, polymerase chain reaction; US, United States

Printed with permission: Kelly CR, et al. Am J Gastroenterol 2021; 116: 1124-47.





### Know the Interpretation of Laboratory Results

- Give why PCR-only testing is insufficient to diagnose/exclude diagnosis of CDI in patients with IBD.
  - PCR is useful to establish the presence of colonization with CDI, but colonization with CD does **not** mean that toxin is necessarily being produced (no toxin, no CDI).
    - Thus, if PCR test is negative for CD, then there is no CDI
    - If PCR-positive for CD, then do NAAT testing for CD toxin (CDI)

### ➤ Clinical prediction rules (CPRs)

- Classification of CDI at the time of diagnosis

|             | Laboratory value                                                                                                                                                                |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| - Severe    | <ul style="list-style-type: none"><li>▪ WBC <math>\geq 15,000</math> cells/mm<sup>3</sup>, or</li><li>▪ Serum creatinine (Cr<sub>s</sub>) <math>\geq 1.5</math> mg/dL</li></ul> |
| - Fulminant | <ul style="list-style-type: none"><li>▪ Hypotension <math>\pm</math> use of vasopressors, or</li><li>▪ Ileus, or megacolon</li></ul>                                            |

- Performance characteristics: sensitivity

|              |      |   |                                        |
|--------------|------|---|----------------------------------------|
| - Setting    |      |   |                                        |
| ▪ Ambulatory | 0.48 | } | NPV (negative predictive value) > 0.80 |
| ▪ Hospital   | 0.73 |   |                                        |

- Other predictors of severe CDI

- Clinical
  - Fever > 38.5°C
  - Abdominal tenderness
- Endoscopy
  - Pseudomembranes
- Laboratory
  - ↓ albumin (gut secretes albumin to bind toxin A/B → ↑ proteolytic cleavage outside gut epithelium (thereby ↓ cytotoxic effects on mucosa)
  - ↓ eosinophils (peripheral blood)
  - ↑ fCal (fecal calprotectin) > 2000 µg/g
  - Hypervirulent strains (e.g., NAP/27 / B1 (North America pulsed-field electrophoresis type one strain)

### MCQ Pearl

- Give the mechanism of action which is common to cholestyramine and to serum albumin (exuded across the colonic wall) in the treatment of CDI.
  - Binding of CD toxin A or B
  - ↑ proteolytic cleavage in gut lumen



## ➤ Treatment

### ❖ Medical

#### ○ Non-severe CDI (initial treatment)

- Considerations
  - Treating active CDI       $V = F > M$        $V, F = \sim 85\%, M = \sim 72\%$
  - ↓ risk of recurrence       $F > V > M$        $F > V, 8\%, 13\% \text{ vs. } 27\%$   
- 33%,  $P = 0.02$
  - Mortality rates, 180 d       $V = F, 29\%$
  - Older hospitalized patients with CDI, extended pulse  $F = V$  for 10 d

Abbreviations: F, fidaxomicin; M, metronidazole; V, vancomycin

- Summary
    - "...all 3 agents (V, F, M) have a role in first-line treatment of initial non-severe CDI"
  - Other agents
    - Rifaximin
    - Tigecycline
    - Anti-motility agent
    - Cholestyramine
    - Psyllium
- } - Further data required (use "...**not** currently supported by the evidence [Cochrane Review, 2017])
- Use safe in mild CD, after initiation of anti-CDI antibiotics
  - Do **not** use in untreated or fulminant CDI
  - Little evidence
  - May ↓ diarrhea during the recovery phase

### Recommendations

- For initial treatment of non-severe CDI, use for 10 d
  - Vancomycin, 125 mg po q.i.d. (strong recommendation, low quality of evidence)
  - Fidaxomicin, 200 mg po b.i.d. (strong recommendation, moderate quality of evidence)
  - Metronidazole, 500 mg po t.i.d. (strong recommendation/moderate quality of evidence)
- Severe CDI
  - Consideration
    - $V = F$ , day 10, cure rate 60-64%;  $V = F$  for recurrence of CDI, mortality
    - ↑ dose of vancomycin **not** useful
  - Caution
    - Do **not** use monotherapy with metronidazole (inferior to vancomycin)
    - Giving vancomycin after failed metronidazole is less effective than with no previous exposure to metronidazole
      - ↑ acute kidney injury (AKI)
      - ↑ length of hospital stay (LHS)
      - ↑ mortality



## Recommendations

- For initial treatment of severe CDI, use same treatment as for non-severe CDI (for 10 d)
  - Vancomycin, 125 po q.i.d. (strong recommendation, low quality of evidence)
  - Fidaxomicin, 200 mg po b.i.d. (conditional recommendation, very low quality of evidence)
- Fulminant CDI
  - Limited data from clinical trials: recommendations based on expert opinion (1 study positive, 1 negative) [p = 0.03]
    - No data for fidaxomicin in fulminant CDI
      - No benefit for immunoglobulin IV
      - No benefit for adding metronidazole (M) to vancomycin (V)
  - Combination therapy

| Treatment                             | Mortality Rate |
|---------------------------------------|----------------|
| – Vancomycin monotherapy (V)          | 36%            |
| – Vancomycin plus metronidazole (V+M) | 16%            |

## Recommendations

- Multidisciplinary team (MDT) (e.g., Gastroenterology, Infectious Disease, Surgery)
- Volume resuscitation
  - IV fluids, electrolyte balance
- No ileus (if patient responds, ↓ vancomycin to 125 mg q6h)
  - Vancomycin 500 mg po q6h for initial 48-72 h (strong recommendation, very low quality of evidence), or
  - Vancomycin plus metronidazole 500 mg IV q8h (conditional recommendation, very low quality of evidence)
- Ileus
  - Vancomycin enemas 500 mg q6h pr may be added to po V / V+M noted above (add on) (conditional recommendation, very low quality of evidence)
- Surgical Treatment
  - In severe/fulminant patients with serious CDI, total colectomy plus construction of an end ileostomy plus stapled rectal stump may give ↓ mortality as compared to continued medical treatment
  - ↑ mortality with total colectomy in persons with
    - Preoperative acute renal failure
    - Mechanical ventilation required for respiratory failure
    - Need for vasopressors
  - Partial colectomy



- Diverting loop ileostomy, plus intraoperative antigrade need for vassopressive irrigation of colon, plus 8 L PEG through the distal limb of the ileostomy, plus 10 d preoperative intraluminal vancomycin for 10 d (↓ mortality rate vs. total colectomy, 19% vs. 50%;  $P = 0.006$ )

#### Recommendation

- For patients with CDI who require surgery, the ACG guidelines supported the recommendation of surgical societies\*, using
  - Total colectomy, with an end ileostomy and a stapled rectal stump, or
  - Diverting loop ileostomy plus intraluminal vancomycin and colonic lavage
    - "...depending on clinical circumstances, the patient's estimated tolerance to surgery, and the surgeon's best judgement"

\*WSES guidelines, Sartelli M, et al., World J Emerg Surg 2019; 14: 8; Steele SR, et al. Dis Colon Rectum 2015; 58: 10-24.

- Fecal Microbiota Transplantation (FMT)
  - For severe/fulminant CDI, non-irresponsive to 48-72 h of standard medical therapy.
  - Patient may require multiple FMTs in short succession, especially if pseudomembranes are present.
    - Example of pseudomembrane-driven protocol for patients with severe/fulminant CDI who fail vancomycin po+/- metronidazole IV for 5 d
      - FMT delivery by colonoscopy
      - Restart vancomycin within 24-48 h, and continue until pseudomembranes disappear
      - Repeat FMTs q3-5 d, until symptoms resolved; then once pseudomembranes disappeared, do one more FMT
    - Benefits
      - ↑ rate of cure
      - ↑ survival (↓ 90 d mortality from 42% to 12%,  $P < 0.0001$ )
      - ↓ colectomy
      - ↓ sepsis
  - Assess response to FMT
    - Clinical
      - Frequency/form of stool
      - Presence/absence of pseudomembranes
    - Laboratory
      - ↓ leucocytes
      - ↓ CRC (C reactive protein)

#### Recommendation

- Consider FMT for patients with severe/fulminant CDI which fails to respond to [48-72 h of] antibiotic therapy [standard medical care], particularly when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence).



- Recurrent CDI (rCDI)

- Definition

- "...recurrence of diarrhea and a confirmatory positive test (NAAT or EIA) within 8 wks [some authorities suggest within 8 to 12 wk] after [successful] treatment of an initial episode of CDI:
  - Recurrent CDI (rCDI):  $\geq 3$  confirmed episodes of CDI

- Demography

- Risk of one (first) recurrence ~20%
- $\uparrow$  likelihood of further recurrence with each recurrence (i.e., risk of second recurrence is higher after first recurrence; risk of third recurrence is even higher after second recurrence)
- Symptomatic cure
  - "...initial resolution of the diarrhea and no evidence of recurrence of diarrhea to CDI"
- Bacteriological
  - "...confirmed negative stool test [for CDI], and no recurrence of diarrhea" [window of recurrence between 8 to 12 wk]

- Treatment

- Fidaxomicin and vancomycin have approximately similar beneficial rates of response to initial treatment of CDI, but
  - Fidaxomicin is superior to vancomycin in preventing a second recurrence within 28 d (20% vs. 36%;  $P = 0.045$ )
    - Benefit of fidaxomicin to  $\downarrow$  rate of recurrence is greater for the second as compared with the initial episodes

| Recurrence of CDI | Recurrence rate after fidaxomicin |
|-------------------|-----------------------------------|
| #1                | 23%                               |
| #2                | 29% ( $P = 0.005$ )               |

- Fidaxomicin may be given as an "extended-pulsed" regimen (EPR)
  - EPR fidaxomicin vs. vancomycin, 30 d sustained clinical care, 70% vs. 59% ( $P = 0.03$ )

## Recommendations

- rCDI (recurrence of CDI) after initial treatment of CDI with vancomycin, fidaxomicin or metronidazole
  - Use tapering/pulsed dose vancomycin (strong recommendation, very low quality of evidence)
- rCDI after initial treatment with vancomycin or metronidazole
  - Use fidaxomicin (strong recommendation, moderate quality of evidence)



- Prevention of rCDI

- ❖ FMT (to ↓ risk of rCDI)

- Efficacy of FMT for treating rCDI is ~85%, with NNT (number needed to treat) of 3
  - Delivery of FMT by colonoscopy is superior to using naso-gastric, duodenal, jejunal tubes
    - Delivery of FMT by enema have ↓ effectiveness, ~50%
    - Capsules of stool taken po are also effective (~85%)
- FMT failure (recurrence of diarrhea, with a confirmatory test for *C. difficile* [being negative])
  - Rate of failure for 1 FMT treatment ~15% in 4-8 wk (rCDI)
- Predictors of failure of FMT
  - Outpatients
    - Previous hospitalization for CDI
  - Inpatients
    - Previous hospitalization for CDI
    - Inpatient status, severe/fulminant CDI
- Because of possible rCDI after FMT, evaluate regularly for possible recurrences
  - Once failure of FMT is diagnosed, begin anti-CDI antibiotics to control symptoms before repeating FMT (preferably administered by colonoscopic delivery)

#### Recommendations

- In patients with ≥ 2 recurrence of CDI, give FMT to prevent further recurrences (strong recommendation, moderate quality of evidence)
  - Ranking of choice of delivery for FMT
    - Colonoscopy (strong recommendation, moderate quality of evidence)
    - Capsules (strong recommendation, moderate quality of evidence)
    - Enema (conditional recommendation, low quality of evidence).
  - Repeat FMT if rCDI within 8 wk of initial FMT (conditional recommendation, very low quality of evidence)
- ❖ Oral Vancomycin (VAN) prophylaxis
  - For suppression/prophylaxis against rCDI (extended antimicrobial treatment)
    - Dose of maintenance of suppression
      - Vancomycin 125 mg po od, b.i.d.
      - Long term use of vancomycin to ↓ risk of rCDI does not ↑ risk if vancomycin-resistant enterococci (VRE)
  - In patients with previous episodes of CDI, who require use of systemic antibiotics for other reasons, vancomycin (VAN) po may ↓ risk of CDI from the systemic antibiotic (not targeted against CDI).
    - 5x ↑ risk of rCDI in patient who has had previous episode of CDI, and then requires use of systemic antibiotics for any indication



- ↑ risk especially if
  - Patient ≥ 65 yr
  - Previous episode of CDI was severe
- } ■ CDI, 87%
- Previous history of CDI
- Benefit of VAN to ↓rCDI (second recurrence, third episode of CDI)
  - Recurrence of CDI within 90 d after antibiotics, VAN vs. no oral vancomycin prophylaxis (OVP): 55% vs. 70% (P < 0.0001) [small retrospective non-randomized studies, variable doses/durations of VAN]
- VAN and fidaxomicin are useful primary prophylaxis of CDI in patients who are immunocompromised.
  - Hematopoietic stem cell recipients
    - Primary/secondary prophylaxis
  - Postrenal transplantation (secondary prophylaxis)
- In high-risk patients (> 65 yr, hospitalized for severe CDI within the past 3 mon, and immunocompromised) who have been recently treated for CDI and now require antibiotics for some other reason
  - Give VAN 125 mg po od until five days after completion of other antibiotic

#### Recommendations

- Use long term oral vancomycin prophylaxis (125 mg po od)
  - FMT
  - CDI after FMT
  - Need for frequent course of antibiotics, especially systemic antibiotics for non-CDI indications (use vancomycin for 5 d after completion of systemic antibiotics (conditional recommendation, very low quality of evidence)
  - History of CDI who are at ↑ risk of rCDI
    - ≥ 65 yr
    - Hospitalized for CDI within the last 3 mon
    - Immunosuppression, “significant”
    - Suggestion to use VA (conditional recommendation, low quality of evidence)
- Bezlotoxumab
  - Monoclonal antibody which binds to toxin B
  - ↓ passage of toxin B across intestinal epithelium
  - Effective against high virulence strains of CDI
  - Greatest benefit
    - ≥ 65 yr
    - Severe CDI
    - Previous CDI (second episode, i.e., rCDI within the past 6 mon)
    - Immunocompromised
      - The more high-risk factors listed above the greater the response



- Contraindications
  - Do **not** use in persons with
    - Heart failure
    - “...severe underlying cardiovascular comorbidities”

#### Recommendation

- Use bezlotoxumab to ↓ risk of rCDI in persons with risk factors for rCDI (conditional recommendation, moderate quality of evidence)
- Proton pump inhibitors (PPIs)
  - Persons with CDI and taking PPIs should be assessed for the continued need to use PPIs
    - Stop PPIs if not indicated absolutely

#### Recommendation

- If appropriateness of continued use of PPI is confirmed, do **not** stop PPI therapy in patient with CDI (strong recommendation, very low quality of evidence)

- CDI in patients with inflammatory bowel disease (IBD)

#### ➤ Demography

- 0.48x ↑ risk of CDI in patients with IBD
- Risk factors
 

|                                                                                                                                                                                                      |   |                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>– Short duration of IBD</li> <li>– Younger age</li> <li>– Hospitalizations</li> <li>– Comorbidities</li> <li>– Use of corticosteroids, biologicals</li> </ul> | } | <ul style="list-style-type: none"> <li>↑rCDI</li> <li>↑ER visits</li> <li>↑ need to ↑ (escalate) IBD therapy</li> <li>↑ mortality when hospitalized</li> <li>↑ long term colectomy rate (CDI is marker of severe IBD)</li> </ul> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
- IBD + CDI in IBD, aOR, 4.7; 95% CI: 2.9-7.9
- IBD +CDI vs. CDI, aOR, 2.2; p5% CI, 1.4-3.4
- Ulcerative colitis (UC) > Crohn disease (CD) mortality rate

#### ➤ Treatment

- Patients with IBD + CDI benefit from treatment of CDI
  - Clinical course
    - ↓ readmissions
    - ↓ length of hospital stay (LOS)
    - ↓ rate if colectomy





### MCQ Teaser

- Give the similarities and differences of patients with ulcerative colitis (UC) vs. Crohn disease (CD) with regards to CDI.
  - Evidence of CDI, UC=CD
  - Mortality of IBD+CDI, UC >CD

### Point and Counterpoint

- Give why it may not be appropriate to perform sigmoidoscopy in a patient with severe acute UC to determine if there is associated CDI.
  - CDI in IBD does not usually have pseudomembranes
  - If pseudomembranes present, may be only on right side of colon, beyond reach of sigmoidoscope.
  - Risk of possible perforation from sigmoidoscopy in unprepared bowel
  - Empirical use of vancomycin po is safe, and can be stopped if laboratory tests for CDI are negative

### Recommendations

- Test for *C. difficile* toxins A/B in patients with IBD who present with an IBD flare (strong recommendation, low quality of evidence)
- Treat CDI in IBD with vancomycin 125 mg po q.i.d. for 14 d (not the usual 10 d vancomycin with DI without IBD) (strong recommendation, very low quality of evidence)

Abbreviations: AKI, acute kidney injury; C, centigrade; CCN, cell cytotoxicity neutralization; CD, Crohn disease; CDI, *C. difficile* infection; CI, confidence interval; CPRs, clinical prediction rules; CRC, C-reactive protein; Cr<sub>s</sub>, serum creatinine; d, day; EIA, enzyme immunoassay; F, fidaxomicin; fCal, Fecal calprotectin; FMT, fecal microbiota transplantation; GDH, glutamate dehydrogenase; h, hour; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IDSA, Infectious Disease Society of America; L, litre; LMIA, loop-mediated isothermal amplification; LOS, length of hospital stay; M, metronidazole; mg, milligram; mon, month; NAP, North America pulsed-field electrophoresis; OR, odds ratio; OVP, oral vancomycin prophylaxis; P value, probability; PCR, polymerase chain reaction; PEG, polyethylene glycol; po, per os (by mouth); PPI, proton pump inhibitor; rCDI, recurrent *C. difficile* infection; RR< relative risk; SHEA, Society of Healthcare Epidemiologists of America; US, ulcerative colitis; USA, United States of America; V, vancomycin; WBC, white blood cell; yr, year



## **Refractory Clostridium Difficile\* Infection (CDI) Treated with Fecal Microbiota Transplant (FMT): BSG Guidelines (2018)**

Mullish BH, et al. Gut 2018 ;67(11):1920-1941.

- Name change
  - Clostridioides difficile now replaces Clostridium difficile, but the abbreviation remains the same, CDI.
- Pathogen testing for donors of feces for FMT
  - Recommended for donor screening
    - Multi-drug-resistant organisms (MDRO) e.g.,
      - Extended-spectrum beta-lactamase organism
      - Methicillin-resistant Staphylococcus aureus (MRSA)
      - Carbapenem-resistant Enterobacteriaceae
      - Shiga A toxin producing E. Coli (STEC); positive by stool nucleic acid amplification testing (NAAT)
  - Not yet recommended, but concern expressed
    - Enteropathogen E. Coli
    - COVID-19 virusNot widely available  
“..as the July 23, 2020, the US FDA has required a clinical hold of all investigational new drug applications (IND) for FMT using stool bank (OpenBiome) material
  - Area of possible future use are premature to use clinically
  - For obtaining patient consent, use local requirements, and consider referring to Table 2 of the above publication.

Gupta S, et al. Am J Gastroenterol 2021; 116: 647-56.

- Pathogenesis of Clostridium difficile Infection (CDI)
  - Antibiotics which more commonly will change microbiota in a manner which predisposes to C. difficile infection in small intestine/colon
    - Carbapenem (especially 3<sup>rd</sup>, 4<sup>th</sup> generation)
    - Cephalosporins
    - Clindamycin
    - Fluoroquinolones
  - Only some patients with CDI have identifiable risk factors
    - Old age
    - Use of a
      - Antibiotics
      - Chemotherapy
      - Enemas (bowel cleansing)
    - IBD
    - Chronic renal disease (CRD)



- The low risk of CDI in children < 2 yr, despite C. difficile colonization rates (25% to 80%)
  - It is speculated that the CDI occurs when there is toxin present at age < 2 yr
  - Bind to host membrane receptors → receptors → receptor-mediated endocytosis
    - Formulation of pores
    - Activation of intrinsic strains
- C. difficile toxins in pathogenesis strains
- Exotoxins (virulence factors)
  - A                      ■ Pathogenicity locus for      ↗ Encoding toxin A (ted A)
  - B                                                           ↘ Encoding toxin B (ted B)      } ■ Common N-terminal DXD causes toxicity
  - C (ted C)                      } ■ Regulatory                      ↓ production of toxin
  - D (ted D)                      }                                      ↓
  - E                                      ■ Mediates secretion of toxin across outer membranes of C. difficile
    - ↑ production of toxin → complexes RNS polymerase → binds promotor regions of Ted A / Ted B
  - Binary toxin                      ■ May ↑ toxicity of toxins A/B
- Toxins enter host cells (small intestine / colon) through pores in the bacterial membrane
  - The toxin is released
  - Glycosylation of guanosine triphosphate-binding protein rho proteins →
    - Rap, substrate for toxin A
    - RhoA, Rac, Cdc Y2, substrate for toxin A/B
  - ↓
  - Abnormal
    - Cytoskeleton
    - Protein synthesis
    - Signaling
  - ↓
  - Cell death
- Immune Responses
  - ↑ antitoxin antibody → protection against recurrent CDI
- Fecal microbiota transplant (FMT)
  - "...fecal microbiota transplant (FMT) is an efficacious treatment for recurrent Clostridium difficile infection (CDI)"
    - FMT is an "unlicensed medicine"
    - Refractory CDI
      - No consensus on the definition of this term



- Factors associated with ↓ cure ratio (1 mon failure rates) using FMT
  - CDI with ribotype O27
  - Hospitalized patients (surrogate marker of severity)
  - Definition of complicated, including
    - Hospitalization into ICU
    - Abnormal signs
      - End organ damage
      - ↑ temperature (fever)
      - ↓ systemic blood pressure (hypotension)
      - Altered mental status
      - Ileus
      - WBC > 30x10<sup>9</sup> /L
      - Lactate > 2.2 mmol/L
- Other “newer” agents for refractory CDI
  - Fidaxomicin
  - Bezlotoxumab

## Recommendations

- Overall cure rate of CDI at 12 wk with FMT is 89%, with a rate of adverse effects of 15%.
- Initial treatment of CDI
  - Do **not** use FMT for the initial treatment of CDI (GRADE of evidence: low; strength of recommendation: strong) (only small studies with equivocal results)
- Refractory CDI
  - Use FMT for patients with refractory CDI
    - ≥ 2 recurrences, or
    - 1 recurrence plus risk factors for further episodes, such as
      - Severe or severe complicated CDI
 (Grades of Recommendation Assessment, Development and Evaluation (GRADE) of evidence: high; strength of recommendation: strong)
- Reduction of risk of CDI recurrences
  - Recurrence rate with
    - Vancomycin 27-33%
    - Fidaxomicin 8-13%
    - Bezlotoxumab plus standard of care antibiotics (SCA) vs. SCA alone 11% vs. 20%
  - Current approaches to ↓ recurrences of CDI
    - Vancomycin
      - Pulsed/tapered dosing
    - Fidaxomicin
      - Standard or pulsed dosing
    - Bezlotoxumab



## Recommendations

- Use FMT for
  - Recurrence of symptoms after reduction of an episode of CDI treated with appropriate antimicrobials (standard of care antibiotics) for  $\geq 10$  d (GRADE of evidence: low; strength of recommendation: strong).
- Use extended/pulsed vancomycin +/- fidaxomicin before FMT in patients with recurrent CDI (GRADE of evidence: low; strength of recommendation: strong).
- Use fidaxomicin and bezlotoxumab before FMT in patients with severe/complicated CDI (associated with  $\downarrow$  cure rates) (GRADE of evidence: low; strength of recommendation: strong).
- Failure of FMT
  - Numerous possible approaches
    - Repeat FMT
    - Repeat vancomycin plus repeat FMT
    - Several repeats of vancomycin, then FMT
    - IV immunoglobulins

## Recommendations

- If first FMT fails, then repeat FMT (in 1 to 5 d) (GRADE of evidence: high; strength of recommendation: strong).
- Follow-up after FMT
  - Provide follow-up for patient receiving FMT
    - For long enough "...to fully establish efficacy/adverse events, and
    - For at least 8 wks in total(GRADE of evidence: low; strength of recommendation: strong).
- C. difficile toxin negative diarrhea may also occur
  - Use regular endoscopy unit
    - Protocols
      - Post-procedure protocols
      - Infection control protocols
  - Rare severe symptoms of
    - Mucosal tears, microperforation
    - Aspiration
    - Recurrence of severe CDI

▪ These may be associated with mortality



- Inform patients coming for FMT the possibility of
  - Self-limited GI symptoms
  - Rate occurrence of severe adverse effects (inducing death)
 (GRADE of evidence: very low; strength of recommendation: strong)
- When FMT administered by colonoscopy
  - Follow standard post-endoscopy protocol
 (GRADE of evidence: very low; strength of recommendation: strong)
- When FMT administered by FMT
  - Remove enteral tube and offer patient a drink of water 30 min after tube administration of FMT
 (GRADE of evidence: very low; strength of recommendation: strong)
- Cure for CDI with FMT
  - A recommendation from the US for post-FMT cure
  - The definition of success/failure of FMT is based upon the patient's symptoms, not the presence of CDI (e.g., sepsis)
    - Asymptomatic patients at 4 wk post-FMT have very low rate (3%) of CDI on PCR
    - Endpoints
 

|           |                                        |
|-----------|----------------------------------------|
| Primary   | Resolution of symptoms                 |
| Secondary | Absence of symptoms within 8 wk of FMT |
 (Bakken JS, et al. Clin Gastroenterol Hepatol 2011; 9: 1044-9)

#### Recommendations

- No “uniformly agreed definition” of CDI cure, but
  - Record time when patient considered and recorded to be “cured” (i.e., case-by-case)
 (GRADE of evidence: very low; strength of recommendation: strong)
- Define treatment failure / CDI recurrence on a case-by-case basis [by symptoms]
  - Do **not** do routine testing for C. difficile toxin post-FMT, but consider doing toxin testing on a case-basis, e.g.,
    - Persistent CDI symptoms
    - Suspected CDI relapse
 (GRADE of evidence: very low; strength of recommendation: strong)

#### ➤ Modifiers of FMT Outcomes

- Recipient factors

#### Recommendations

- Recipients with anaphylactic food allergy and CDI
  - Do **not** use FMT
 (GRADE of evidence: very low; strength of recommendation: strong)



- Recipients who are immunocompromised
  - “...in whom FMT appears efficacious without significant additional adverse effects (GRADE of evidence: moderate; strength of recommendation: strong)
  - “...at risk of severe infection if exposed to EBV or CMV
    - Do **not** use FMT from donors who are positive for EBV and CMV (GRADE of evidence: very low; strength of recommendation: strong)
- Recipients with decompensated chronic liver disease and CDI
  - Use FMT with caution (GRADE of evidence: very low; strength of recommendation: weak)
- Recipients with IBD and CDI
  - Use FMT, but inform patient that there is a small risk of an exacerbation of their IBD (GRADE of evidence: moderate; strength of recommendation: strong)
- Recipients with other comorbidities other than those listed above
  - Use FMT for CDI, using previous recommended criteria [and lack of above considerations] (GRADE of evidence: moderate; strength of recommendation: strong)
- Donor factors
  - Source
    - May use related or unrelated donors for FMT, but
      - Ideally the stool donor should be healthy unrelated donor, with donation from a centralized stool bank (GRADE of evidence: low; strength of recommendation: strong)
  - Age and BMI
    - Some stool bacterial phylum changes with age, but stool donations from young and old have comparable efficacy
    - Single case of ↑ BMI developing in recipient of a stool from an overweight donor

#### Recommendation

- Criteria for consideration of being a donor for FMT
  - Age,  $\geq 18$  and  $\leq 60$  yr
  - BMI,  $\geq 18$  and  $\leq 30$  kg/m<sup>2</sup> (GRADE of evidence: low; strength of recommendation: weak)
- Donor screening and possible exclusion
  - Recommended donor history/questionnaire
    - Receipt of antimicrobials within the past 3 mon.
    - Known prior exposure to HIV and/or viral hepatitis, and known previous or latent tuberculosis.
    - Risk factors for blood borne viruses, including high risk sexual behaviours, use of illicit drugs, any tattoo/body piercing/needlestick injury/blood transfusion/acupuncture, all within the previous 6 mon.
    - Receipt of a live attenuated virus within the past 6 mon.



- Underlying GI conditions/symptoms (e.g., history of IBD, irritable bowel syndrome (IBS), chronic diarrhea, chronic constipation, coeliac disease, bowel resection or bariatric surgery), also including acute diarrhea/GI symptoms within the past 2 weeks.
- Family history of any significant GI conditions (e.g., family history of IBD or colorectal cancer).
- History of atopy (e.g., asthma, eosinophilic disorders).
- Any systemic autoimmune conditions.
- Any metabolic conditions, including diabetes and obesity.
- Any neurological or psychiatric conditions, or known risk of prion disease.
- History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.
- History of any malignancy.
- Taking particular regular medications, or such medications within the past 3 mon—that is, antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy.
- History of receiving growth hormone, insulin from cows or clotting factor concentrates.
- History of receiving an experimental medicine or vaccine within the past 6 mon.
- History of travel to tropical countries within the past 6 mon.

\*A positive response to any of these questions would usually result in exclusion from further consideration as a donor, although this would depend upon on the particular circumstances/answers given

- Recommended blood screening for stool donors
  - Pathogen screening:
    - Cytomegalovirus IgM and IgG\*
    - *Entamoeba histolytica* serology
    - Epstein–Barr virus IgM and IgG\*
    - Hepatitis A IgM
    - Hepatitis B (HBsAg and HBcAb)
    - Hepatitis C antibody
    - Hepatitis E IgM
    - HIV-1 and HIV-2 antibodies
    - HTLV-1 and HTLV-2 antibodies
    - *Strongyloides stercoralis* IgG
    - *Treponema pallidum* antibodies (TPHA, VDRL)
  - General/metabolic screening:
    - Full blood count with differential
    - Creatinine and electrolytes
    - Liver enzymes (including albumin, bilirubin, aminotransferases, gamma-glutamyltransferase and alkaline phosphatase).
    - C reactive protein

\* Epstein – Barr virus (EBV) and cytomegalovirus (CMV) testing is only recommended where there is the potential that the fecal microbiota transplant prepared from that donor will be administered to immunosuppressed patients at risk of severe infection

Source: Mullish BH, et al. Gut 2018 ;67(11):1920-1941





- Recommended stool screening for stool donors
  - Acid fast stain for *Cyclospora* and *Isospora*
  - *Campylobacter*, *Salmonella*, and *Shigella* by standard stool culture and/ or PCR
  - *Clostridium difficile* PCR
  - Fecal antigen for *Cryptosporidium* and *Giardia*
  - *Helicobacter pylori* fecal antigen
  - Multi-drug resistant bacteria, at least CPE and ESBL\*
  - Norovirus, rotavirus PCR
  - Shiga toxin-producing *Escherichia coli* by PCR
  - Stool ova, cysts and parasite analysis, including for Microsporidia

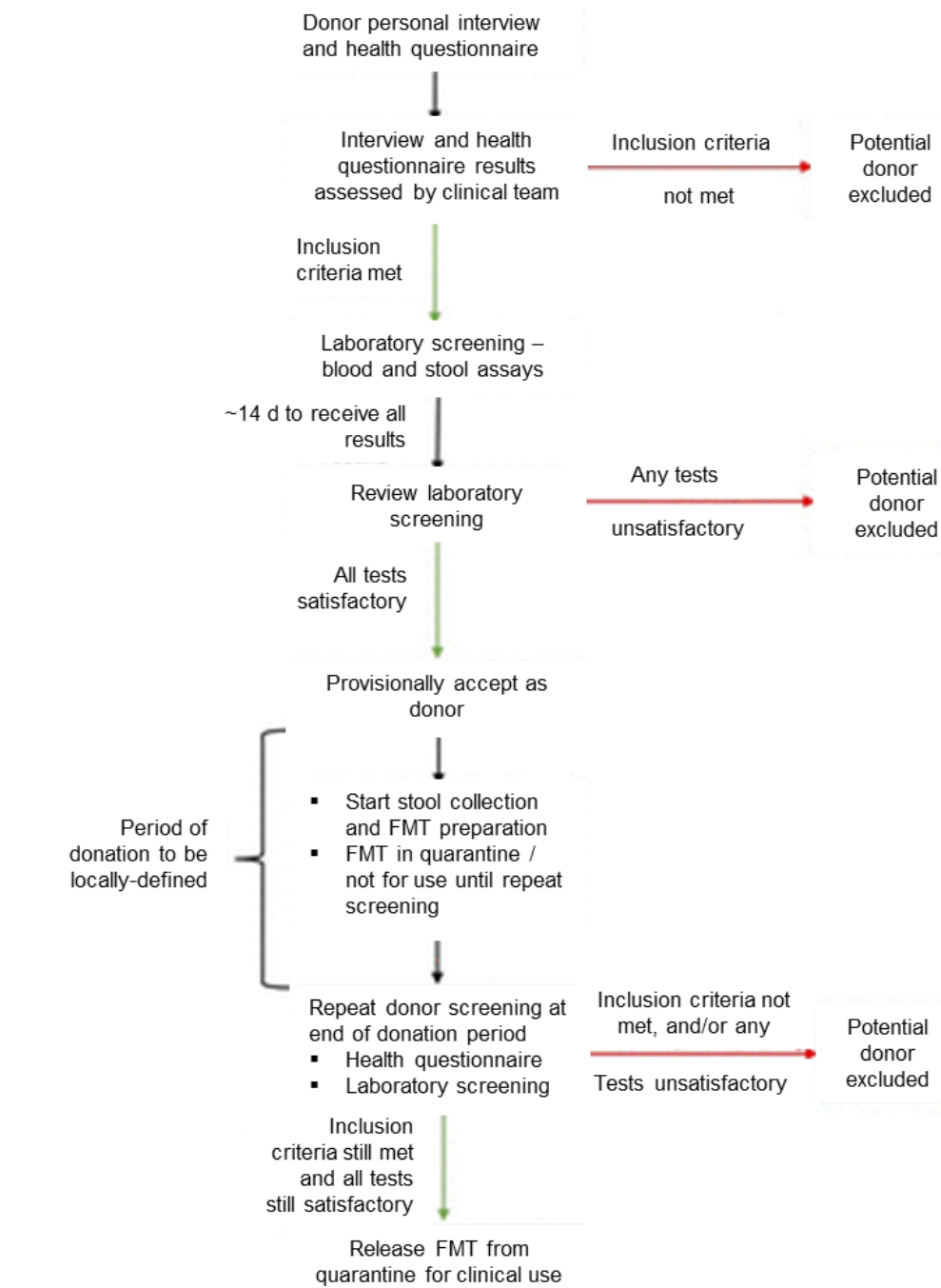
\* While carbapenemase-producing Enterobacteriaceae (CPE) and extended spectrum beta-lactamases (ESBL) are the only multi-drug resistant bacteria that are recommended to be screened for universally, consider testing for other resistant organisms (including vancomycin resistant Enterococci (VRE) and/or methicillin resistant *Staphylococcus aureus* (MRSA)) based on risk assessment and local prevalence

- Criteria for stool collection
  - Clear instructions should be given to donors regarding hand hygiene.
  - Collect stool donations in a sealable clean container. A number of specifically designed devices are available commercially.
  - Stool should ideally be passed directly into the clean container for collection; alternatively, it may be collected in clean tissue and transferred to the clean container.
  - Stool should be transported to the FMT production site as soon as possible post defecation (and within 6 hrs); however, if a short period of storage is necessary, this should be at 4°C.

Source: Mullish BH, et al. Gut 2018 ;67(11):1920-1941



- Proposed summary pathway for donor screening for centres preparing frozen fecal microbiota transplant (FMT) from recurring donors.



Used with permission of: Mullish BH, et al. Gut 2018 ;67(11):1920-1941



- Screening for colorectal cancer
  - “...potential donors living in countries with bowel cancer screening programs that start before age 60 yr ( $\geq 45$  yr in US) should have therefore completed appropriate screening with negative/normal tests before they are considered as donors”

#### Recommendations

- Screening is meant to ↓ risk to recipients from stool provided by donors
- Consideration of specific antibiotics
- “...screen potential donors by questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota (Box 1) (GRADE of evidence: low; strength of recommendation: strong)
- Screen blood and stool of donors (Box 2,3) (GRADE of evidence: low; strength of recommendation: strong)
- The screening is different for frozen vs. fresh stool for FMT
  - Centres using frozen FMT, the donor should complete donor health questionnaire plus laboratory screening before and after the period of the stool donation. (GRADE of evidence: low; strength of recommendation: strong)
  - Centres using fresh FMT, the donor should
    - Complete the health questionnaire and laboratory screening at the time of each stool donation
    - This should be repeated regularly (GRADE of evidence: low; strength of recommendation: strong)

Abbreviations: CPE, carbapenemase producing Enterobacteriaceae ESBL, extended spectrum beta-lactamase producing organisms; multidrug resistance; VRE, vancomycin-resistant Enterococci

#### Recommendations (for stool collection)

- Use a standard protocol for the collection of donor stool (GRADE of evidence: low; strength of recommendation: strong)
- Process stool within 6 h of defecation (GRADE of evidence: low; strength of recommendation: strong)
- Use both aerobically and anaerobically prepared FMT for treatment (GRADE of evidence: moderate; strength of recommendation: strong)
- Use 0.9% saline as a diluent
  - If stool for FMT to be frozen
    - Use cryoprotectant such as glycol
 (GRADE of evidence: moderate; strength of recommendation: strong)
- Use  $\geq 50$  g of stool for each FMT preparation (GRADE of evidence: moderate; strength of recommendation: strong)
- Make the initial stool emulsion with 1:5 ratio of stool to diluent (GRADE of evidence: low; strength of recommendation: weak)
- Use closed disposable system to homogenize and filter the FMT (GRADE of evidence: low; strength of recommendation: weak)



- Use banked frozen FMT in preference to fresh (GRADE of evidence: high; strength of recommendation: strong)
- Thawing FMT preparation
  - Do **not** store frozen FMT at -80°C for > 6 mon ("shelf-life) from time of preparation (GRADE of evidence: low; strength of recommendation: strong)
  - Thaw frozen FMT at ambient (room) temperature, thawing over 6 h (GRADE of evidence: low; strength of recommendation: weak)
  - Do **not** use warm water bath (GRADE of evidence: low; strength of recommendation: weak)
- Administration of FMT
  - Use bowel lavage (preferably with polyethylene glycol (PEG) pr prior to giving FMT po/pr (GRADE of evidence: low; strength of recommendation: strong)
  - If giving FMT by upper route, give
    - PPI the evening and then the morning before FMT (GRADE of evidence: low; strength of recommendation: weak)
    - Prokinetic (e.g., metoclopramide) (GRADE of evidence: low; strength of recommendation: weak)
    - If giving FMT by upper GI route, giving anti-motility drug such as loperamide after lower GI FMT delivery (GRADE of evidence: low; strength of recommendation: weak)
  - Follow best practice protocols when giving FMT for CDI (GRADE of evidence: high; strength of recommendation: strong)
  - Use an antimicrobial (e.g., fidaxomicin, metronidazole, vancomycin) at least 72 h before the FMT (GRADE of evidence: low; strength of recommendation: strong).
    - This washout interval between pre-FMT antibiotics and FMT should be a minimum of 24 h (GRADE of evidence: low; strength of recommendation: strong)
    - For patients scheduled to receive FMT who have an indication for
      - Long term antibiotics, or
      - Non-CDI antibiotics within 8 wk of FMT
- Upper GI administration of FMT
  - Use upper GI route for recurrent/refractory CDI, where clinically appropriate (GRADE of evidence: high; strength of recommendation: strong)
    - When upper GI administration of FMT most appropriate, use
      - Naso-gastric, -duodenal, jejunal tube, or
      - Esophagogastroduodenoscopy (EGD), or
      - Permanent feeding tube e.g., PEG/PEJ (percutaneous endoscopic gastroscopy/jejunostomy) tube



- Limit the volume of FMT given by upper GI tract to  $\leq 100$  mL (GRADE of evidence: low; strength of recommendation: strong)
- Use upper GI route for FMT administration with caution in any patient with
  - Regurgitation
  - Swallow disorder
 }  $\uparrow$  risk of aspiration (GRADE of evidence: low; strength of recommendation: strong)
- Lower GI tract administration of FMT
  - Use lower GI tract administration of FMT by colonoscopy for recurrent/refractory CDI (GRADE of evidence: high; strength of recommendation: strong)
    - Deliver FMT by colonoscopy into cecum/ terminal ileum (GRADE of evidence: low; strength of recommendation: weak)
  - If delivery via colonoscopy/sigmoidoscopy not possible
    - Use FMT via enema (GRADE of evidence: high; strength of recommendation: strong)
- ❖ Capsulized FMT
  - Each capsule contains 1.6 g original crude stool;
    - Give 15 capsules per day for 2 d (30 capsules, 48 g original crude stool)
      - Remission rate at 12 wk, 96%

#### Recommendation

- Use capsulized FMT where available ('...holds promise as a treatment option for recurrent CDI'), using standard protocol (GRADE of evidence: high; strength of recommendation: strong)
- Possible future use of FMT
  - Mild/moderate ulcerative colitis
    - FMT vs. placebo

|           | Pooled rate of combined clinical / endoscopic remission | Pooled risk ratio for failed FMT | Histological Deep Remission |
|-----------|---------------------------------------------------------|----------------------------------|-----------------------------|
| - FMT     | 28%                                                     | 0.8, 95%                         | 18%                         |
| - Placebo | 10%                                                     | CI: 0.7 to 0.9                   | 3%                          |
  - Functional bowel disease (irritable bowel syndrome [IBS])
    - IBS-D / IBS-D/C
      - Improved IBS severity score at 3 mon after 1 treatment of FMT (P=0.049)
    - IBS-C
      - $\uparrow$  mean of  $\geq 3$  spontaneous bowel movements per wk, 53% vs. 20% (P=0.009)

#### Recommendations

- Do **not** use for treatment of IBD, IBS, hepatic encephalopathy,  $\uparrow$  BMI / metabolic syndrome, or for "... any other gastrointestinal or non-gastrointestinal disease" (GRADE of evidence: moderate; strength of recommendation: strong)



- FMT recipients
  - Indications in patients with CDI and indications for FMT, proceed with FMT “...regardless of other co-morbidities (GRADE of evidence, moderate; strength of recommendation, strong)
    - This includes recipient with chronic liver disease (GRADE of evidence, very low; strength of evidence, weak)
- FMT Donors
  - Donors of fresh stool for FMT must complete a questionnaire as well as stool screening at the time of each stool donation (GRADE of evidence, low; strength of recommendation, strong)
  - Contraindications/cautions
    - Should not have an anaphylactic food allergy (GRADE of evidence, very low; strength of recommendation, strong)
  - Use cautiously in recipients who are immune suppressed (GRADE of evidence, moderate; strength of recommendation, strong)
  - In recipients who are immune suppressed and are therefore at ↑ risk of CMV and negative for EBV (GRADE of evidence, very low; strength of recommendation, strong)
  - Recipients with IBD plus CDI who are given FMT.
  - Optimal
    - FMT donors
    - Central stool bank
    - Healthy unrelated donors (GRADE of evidence, low; strength of recommendation, strong)
    - ≥ 18 yr and ≤ 60 yr of age
    - BMI ≥ 18, and ≤ 30 kg/m<sup>2</sup> (GRADE of evidence, low; strength of recommendation, weak)
- FMT preparation
  - Use a standard protocol for the stool collection (GRADE of evidence, low; strength of recommendation, strong)
  - Process the donor stool within 6 h of defecation (GRADE of evidence, low; strength of recommendation, strong)
  - Use both aerobically and anaerobically prepared FMT for the treatment of recurrent CDI (GRADE of evidence, moderate; strength of recommendation, strong)
  - Use sterile 0.9% saline (NaCl) to dilute the FMT, as well as using glycerol as a cryoprotectant (GRADE of evidence, moderate; strength of recommendation, strong)
  - Mix the stool 1:5 with diluent to make the initial fecal emulsion (GRADE of evidence, low; strength of recommendation, weak).



- Use  $\geq 50$  g of stool for each preparation for FMT (GRADE of evidence, moderate; strength of recommendation, strong)
- Homogenization and filtration of the FMT should be done in a closed disposable system (GRADE of evidence, low; strength of recommendation, weak)
- Use banked frozen FMT rather than fresh preparations (GRADE of evidence, high; strength of recommendation, strong)
  - Store the frozen FMT at  $-80^{\circ}\text{C}$  for no more than 6 mon (shelf-life) (GRADE of evidence, low; strength of recommendation, strong)
  - Thaw the frozen FMT material at room (ambient) temperature, and use within 6 h (GRADE of evidence, low; strength of recommendation, weak)
  - Do **not** thaw frozen FMT material in warm water baths
    - $\uparrow$  risk of cross contamination (GRADE of recommendation, very low; strength of recommendation, weak)
- FMT administration
  - Before planned patient recipient is given FMT by either the upper or lower GI route (po or pr), given the patient a bowel lavage with polyethylene glycol (PEG) solution (GRADE of evidence, low; strength of recommendation, strong)
  - Given by mouth / upper GI tract
    - When using po (upper GI tract) administration of FMT, give the recipient
      - PPI (proton pump inhibitor) the evening before and the morning of their receiving the FMT (GRADE of evidence, low; strength of recommendation weak)
      - A prokinetic (GRADE of evidence, low; strength of recommendation, weak)
  - Use po (upper GI tract) administration of FMT for recurrent CDI when appropriate (GRADE of evidence, high; strength of recommendation, strong)
    - Use upper GI route to administer FMT in patients with risk of aspiration, e.g., swallowing disorder (GRADE of evidence, low; strength of recommendation, strong)
  - Route of upper GI administration via tube
    - Nasogastric tube (NG)
    - Nasoduodenal (ND)
    - Nasojejunal (NJ)
    - Upper GI endoscopy (EGD)
    - Permanent feeding tube

(GRADE of evidence, high; strength of recommendation, strong)
  - After oral administration
    - By tube (GRADE of evidence, very low; strength of recommendation, low)
      - Remove the after FMT, and give water po after 30 min
    - By endoscope (EGD) (GRADE of evidence, very low; strength of recommendation, strong)
      - Follow the protocol of the endoscopy unit



- Given per rectum / lower GI tract
    - When using the pr (low GI) administration of FMT, give the FMT pr then loperamide / any antidiarrhea / antimotility agent (GRADE of evidence, low; strength of recommendation, weak)
  - Use pr (per rectum) administration of FMT for recurrent / refractory CDI when appropriate (GRADE of evidence, high; strength of recommendation, strong)
    - For greatest efficacy from colonoscopically delivered FMT, administer into terminal ileum/cecum (GRADE of evidence, low; strength of recommendation, weak)
    - If FMT delivery by colonoscopy or by sigmoidoscopy is not possible, give the pr FMT by enema (GRADE of evidence, high; strength of administration, strong)
  - Clinical effectiveness of FMT
    - CDI, generally adequate data
    - IBD, currently inadequate data to recommend (GRADE of evidence, moderate; strength of recommendation, strong)
  - Implementing a FMT service
    - Encourage development of FMT criteria (GRADE of evidence, very low; strength of recommendation, strong)
    - FMT centres should raise awareness of use of FMT in CDI, and provide training for health professionals to deliver FMT service (GRADE of evidence, very low; strength of recommendation, weak)
  - Definition of cure or treatment failure
    - Cure
      - No uniformly agreed duration
      - Define on a case-by-case basis (Grade of evidence, very low; strength of recommendation, strong)
    - Treatment failure
      - No uniformly agreed definition
      - Define on a case-by-case basis
      - Testing for C. difficile toxin after FMT
        - Routinely, no
        - Persistent symptoms/suspected relapse, yes
- (Grade of evidence, low; strength of recommendation, strong)
- Administer the FMT using best practise to ↓ the risk of further transmission of CDI (e.g., enteric precautions, sporicidal treatment of endoscopic / NG tube (GRADE of evidence, high; strength of recommendation, strong)
  - Allow a 24 h interval between the last dose of antibiotics and the administration of the FMT (GRADE of evidence, low; strength of evidence, strong)





- When patients having a FMT and who requires
  - Long term antibiotics
  - Antibiotics for a non-CDI indication, within 8 wk of FMT

▪ Consult infectious disease expert

(GRADE of evidence, very low; strength of recommendation, weak)

- Develop appropriate infrastructure including production of FMT (GRADE of evidence, very low; strength of recommendation, strong)
- Establish traceability of supply (donors, and their characteristics (GRADE of evidence, very low)
- Establish quality control for production, indications, donor and recipient demographic and clinical characteristics, adverse effects and reactions (GRADE of evidence, very low; strength of recommendation, strong)

#### ➤ Treatment using FMT

- Initial therapy for CDI
  - FMT is "...currently an unlicensed medicine with poorly studied long term sequelae resolution of CDI.
  - Results of initial therapy
    - Vancomycin (Van), 89%
    - FMT x1, 57%
    - FMT x2, 71%

#### Recommendations

- Do **not** use FMT for initial treatment of CDI (GRADE of evidence, low; Strength of recommendation, strong)

#### • Recurrent CDI

#### ➤ Definitions used in the analysis of data

- Clinical symptoms  $\geq 3$  uniformed bowel movements within 24 h, for  $\geq 2$  consecutive days. Following previously successful CDI treatment, +/- positive microbiological test
- Severe CDI
  - $\uparrow$  WBC,  $\downarrow$  serum albumin, abdominal tenderness



- Severe complicated CDI
  - Patient with CDI
    - Clinical
      - Admitted to ICU
      - Fever
      - Altered mental status
      - Hypotension
      - End organ damage
    - Laboratory
      - $\uparrow$  WBC  $> 30 \times 10^9$  /L
      - Lactate  $\geq 2.2$  mmol/L
  - C. difficile ribotype O27 was not a condition for severe/complicated CDI

#### ➤ Prognosis

- 1 mon failure rates
  - Recurrent, 12%
  - Severe, 72%
  - Severe complicated, 53%
- Failure rate of FMT 4x higher given for inpatients than for outpatients
- Rates of recurrence after treatment of severe CDI
  - Vancomycin (VAN), 27% to 33%
  - Fidaxomicin (FID), 8% to 18%
  - VAN or FID vs VAN/FID plus bezlotoxumab (BEZ), 20% vs. 11%
- Pulsed/tapered dosing of VAN/FID results in  $\downarrow$  recurrence vs. standard doses administration of these antibiotics.

#### Recommendations

- Use FMT for the recurrent CDI if
  - $\geq 2$  previous recurrences, or
  - 1 previous recurrence plus risk factors for further recurrences
    - Severe/complicated CDI (GRADE of evidence, high; strength of recommendation, strong)
  - If CDI treated with vancomycin or fidaxomicin for  $\geq 10$  d (GRADE of evidence, low; Strength of recommendation, strong)
  - If recurrent CDI occurs after pulsed dose VAN/FID
- Use FMT for severe/complicated CDI only after treatment of FID plus BEZ (GRADE of evidence, low; strength of recommendation, strong)



- Refractory CDI

- Definitions

- "...there is little consensus on the definition of refractory CDI"
    - Some studies use the terms "recurrent" and refractory" interchangeably, while some studies use the term "salvage therapy" instead of refractory"
    - Examples of definitions of refractory CDI
      - ≥ 3 wk of continued severe symptoms despite the use of standard anti-microbial therapy for CDI", or
      - Worsening diarrhea plus one of the following
        - Abdominal pain
        - Fever
        - WBC > 15x10<sup>9</sup>/L
- } Despite vancomycin 500 mg po q.i.d. x5d

#### Recommendation

- Use FMT for refractory CDI (GRADE of evidence, moderate; strength of recommendation, strong)
- Failure of initial FMT
  - Repeat FMT has been studied after failure of the first subsequent repeated and failed FMT.
    - The working committee "...were not able to recommend a specific protocol for administering repeat FMT and/or maximum number of FMTs, given the heterogeneity of approach disclosed within the reviewed literature".

#### ❖ Other Possible Disorders in which Patients may Benefit from FMT, but Death is Limited

- Ulcerative colitis (UC)

- For RCTs performed in patients with mild and moderate UC (Mayo score, 3 to 11, endoscopy subscore ≥ 1) and stable immune suppressive therapy were given FMT
  - Pooled rate of
    - Clinical plus endoscopy remission is placebo, 30% vs. 10% at 7 to 10 wk
    - Histological remission, 18% vs. 3%
  - No significant difference in adverse events

- Irritable bowel syndrome (IBS)

- IBS-D / IBS-D/-C
  - Symptom relief at 3 mon, FMT x1 by colonoscopy
    - ↑ FMT superior to placebo, p=0.049
- IBS-C
  - FMT super to placebo, 53% vs. 20%, P = 0.009

- Hepatic Encephalopathy

- Limited/mixed data
  - ↑ MELD (Model for End Stage Liver Disease)
  - ↑ cognition, and
  - ↓ severe adverse events



## Fecal Microbiota Transplant (FMT): *Clostridium difficile* Infection (CDI)

Gupta S, et al. Am J Gastroenterol 2021; 116: 647-656.

- Name change
  - *Clostridioides difficile* now replaces *Clostridium difficile*, but the abbreviation remains the same, CDI.
- Pathogen testing for donors of feces for FMT
  - Recommended for donor screening
    - Multi-drug-resistant organisms (MDRO) e.g.,
      - Extended-spectrum beta-lactamase organism
      - Methicillin-resistant *Staphylococcus aureus* (MRSA)
      - Carbapenem-resistant Enterobacteriaceae
      - Shiga A toxin producing *E. Coli* (STEC); positive by stool nucleic acid amplification testing (NAAT)
    - Use sensitive method, nucleic acid amplification testing (NAAT)
  - Not yet recommended, but concern expressed
    - Enteropathogen *E. Coli*
    - COVID-19 virus
      - Not widely available
      - “..as the July 23, 2020, the US FDA has required a clinical hold of all investigational new drug applications (IND) for FMT using stool bank (OpenBiome) material
  - Book-end testing of donor stool
- Use of FMT in non-CDI GI/liver disorders\*
  - GI tract
    - Inflammatory bowel disease (IBD)
      - **Not** sufficient evidence to recommend use in
      - Ulcerative colitis or Crohn disease induction/maintenance
      - Emerging evidence of FMT using single “super donor”
    - Irritable bowel disease (IBS)



- Liver
  - Hepatic encephalopathy (HE)
    - Evidence emerging for FMT by enema or capsule
  - Primary sclerosing cholangitis (PSC)
    - 30% of PSC patients experienced 50% ↓ alkaline phosphatase (AP)
  - Non-alcoholic fatty liver disease (NAFLD)
    - **No** change in hepatic fat +/- insulin resistance when FMT given from thin donor / healthy donor, by duodenoscopy
  - Alcoholic hepatitis (AH)
  - Alcohol-related cirrhosis, alcohol dependence, decreased craving and better cognitive and cognition psychosocial quality of life
  - Hepatitis B virus (HBV) infection
    - Possibly ↑ clearance of HBeAg
  - Graft-versus-host disease (GVHD)
    - Chemical response, ↑ survival, ↑ diversity of gut microbiota
  - Chemotherapy-inducing diarrhea (tyrosine-kinase inhibitor)
    - ↓ diarrhea with FMT by colonoscopy
  - Immune checkpoint inhibitor colitis, refractory to corticosteroids
    - Resolution of colitis in two patients after FMT from healthy donor

\*For further detail and references, please see Gupta S, et al. Am J Gastroenterol 2021; 116: 647-656 (Table 1)



## COLORECTAL POLYPS

### Adenomatous Polyposis Syndromes (APS)

#### ➤ Indications for screening for APS

- FAP, AP, MUTHYH-associated Adenomatous Polyposis Syndromes (MAP)

- Personal history
  - 10 cumulative colorectal adenomas
  - Adenomas plus FAP-type extracolonic associations
- Family history

| Findings  |                                                                    |
|-----------|--------------------------------------------------------------------|
| – GI      | ▪ Duodenal, ampullary adenomas                                     |
| – Eye     | ▪ Congenital hypertrophy of the retinal pigment epithelium (CHRPE) |
| – Skin    | ▪ Epidermal cysts                                                  |
| – Thyroid | ▪ Papillary cancer                                                 |
| – Bone    | ▪ Osteomas                                                         |



- Genetic testing

- |                                                                       |   |                                                                                                  |
|-----------------------------------------------------------------------|---|--------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>○ APC</li><li>○ MUTYH</li></ul> | } | ▪ Gene mutational analysis in persons with suspected FAP, AFAP, MUTYH-associated polyposis (MAP) |
|-----------------------------------------------------------------------|---|--------------------------------------------------------------------------------------------------|

#### ➤ Malignant lesions

- Colon

- Screening/surveillance
  - Persons at risk for or with
    - FAP, colonoscopy
    - AFAP/MAP, colonoscopy
- Indications for colorectal surgery
  - Absolute, immediate CRC present/suspected
  - Relative
    - Multiple adenomas > 6 mm
  - Any adenoma with high grade dysplasia (HGD)
    - ↑ adenomas over time
    - Inadequate possibility for adequate screening/surveillance – multiple small polyps
    - Post-surgical endoscopic surveillance
      - Rectal pouch, q1yr
      - Ileostomy, q2yr
      - Ileoanal anastomosis



- Gastroduodenum

- Screening/surveillance

- EGD side-viewing duodenoscope

- Screen at age 25 to 30 yr
      - Surveillance interval depends upon Spiegelman stage of duodenal polyposis:

| Stage | Interval of repeat EGD |
|-------|------------------------|
| 0     | q4yr                   |
| I     | q2-3yr                 |
| II    | q1-3yr                 |
| III   | q6-12mon               |

- Biopsy results of fundic gland polyp (FGP)

- Surgery for FGP which show high grade dysplasia (HGD) or cancer

- Thyroid

- Perform thyroid ultrasound q1yr

- Skin

- JPS (SMAD4 mutation carriers) is associated with hereditary hemorrhages telangiectasis (HHT)

- HHT may be associated with arteriovenous / cardiovascular abnormalities
- Conditional recommendation, very low quality of evidence



## Hamartomatous Polyposis Syndromes

- Peutz-Jeghers syndrome (PJS)
  - Genetic testing
    - STK11 mutations
    - Perform testing if
      - Family history of PJS
      - Personal history of
        - Buccal pigmentation +/-
        - $\geq 2$  PJS-like hamartomatous polyps
  - Surveillance
    - Family history of PJS / PJS patient
    - Known evidence-based guidelines directed recommendations for cancers
      - Lung
      - GI
        - Stomach, small bowel, colon, pancreas
      - GU
        - Uterus, cervix, ovary
      - Breast
    - If there is a family history of one of these cancers, e.g., pancreatic cancers then do early screening
      - MRI, EUS
      - Start surveillance at age 35 yr
      - Family: age 50 yr, or 10 yr less than earliest pancreatic cancer in the family

“It is wise to “...consider annual chest radiograph or CT in smokers [with PJS] because of their  $\uparrow$  risk of lung cancer”

- Juvenile polyposis syndrome (JPS)
  - The cancer risk in JPS hamartomatous polyps arises from adenomatous tissue within the juvenile polyp
- Genetic testing

### Recommendation

- SMAD4 (aka MADH4 gene), BMPR1A mutations
- Perform testing if
  - Juvenile polyps
    - $\geq 5$  in colorectum
    - $\geq 1$  in other parts of GI tract





- Conditions associated with JPS
  - Cowden syndrome (CS)
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS)

➤ Surveillance

- Affected / at risk JPS patients
    - Stomach, small intestine, colon
    - Method, mutation, frequency not recommended
- Strong recommendation, very low quality of evidence

➤ Treatment

Recommendation

|                                                            | Indication                                                                                                                                                                         |
|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Proctocolectomy plus ileal pouch anal anastomosis (IPAA) | <ul style="list-style-type: none"> <li>- When polyp-related symptoms develop</li> <li>- When polyps cannot be managed by endoscopy (strong recommendation, low quality)</li> </ul> |
| ○ Colectomy plus ileorectal anastomosis (IRA)              |                                                                                                                                                                                    |

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the reason why examination of the perioral skin and buccal mucosa is associated in the patient with JPS.
  - Wrong
    - Pigmentation in those areas is associated with PJS
  - Correct
    - JPS (SMAD4 mutation carriers) is associated with hereditary hemorrhages telangiectasis (HHT)
      - HHT may be associated with arteriovenous / cardiovascular abnormalities

Conditional recommendation, very low quality of evidence

- Cowden Syndrome (CS; aka PTEN Hamartoma Tumour Syndrome)

➤ Genetic testing

- PTEN mutations
- Perform testing if multiple GI
  - Hamartomas
  - Ganglioneuromas



➤ Surveillance

Recommendation

- Affected / at risk CS patients
- No specific recommendations for screening/surveillance

| Cancer  |                               |
|---------|-------------------------------|
| – Chest | ▪ Breast, thyroid             |
| – GI    | ▪ Stomach, small bowel, colon |
| – GU    | ▪ Uterus, kidney              |
| – Skin  | ▪ Melanoma                    |

Conditional recommendation, low quality of evidence

❖ Sessile Serrated Syndrome (SSP)

➤ Clinical suspicion

- Throughout the colon  $\geq 20$  SPs, any size

➤ Genetic testing

- Not recommended
  - Exception
    - If patient with SPS also has colonic adenoma +/- family history of adenomas → also test for MUTYH mutations

➤ Surveillance

- At screening, remove all polyps  $> 5$  mm
- Surveillance colonoscopy q1-3 yr with removal of all polyps  $> 5$  mm (Conditional recommendation, low quality of evidence)

➤ Treatment

- Colorectal
  - Indications
    - ↑ risk of metachronous neoplasia colectomy plus IRA might perform even when above two outcomes not met (Conditional recommendation, low quality of evidence)



## ❖ Serrated Polyposis Syndrome (SPS)

### ➤ Definition

- A hyperplastic polyposis syndrome
- $\geq 5$  serrated polyps (SP) proximal to sigmoid colon, with  $\geq 2$  of these  $> 10$  mm in diameter; or
- Any number SP proximal to sigmoid in a patient who has a first degree relative with SPS, or
- $> 20$  SP, any size, throughout colon
  - Sometimes patients with SPS also have adenoma themselves +/- a family history of SPS

### ➤ Genetic testing

- Exception, MUTYH not recommended only in SRS patients with concurrent adenomas and/or a family history of adenomas

### ➤ Surveillance

- Colonoscopy q1 to 3 yr, with polypectomy for lesions  $\geq 5$  mm
- Pending guidelines for extracolonic cancers and for family members

### ➤ Treatment

- Surgery
  - Colectomy plus ileorectal anastomosis (IRA), if
    - Inability to control the growth of serrated polyps, or
    - Development of CRC

Abbreviations: AFAP, attenuated familial adenomatous polyposis; APS, adenomatous polyposis syndrome; ASA, aspirin; CHRPE, congested hypertrophic of the retinal pigment epithelium; CRC, colorectal cancer; CS, Cowden syndrome; EUS, endoscopic ultrasound; F, female; FAP, familial adenomatous polyposis; HDGC, hereditary diffuse gastric cancer; HNPCC, hereditary non-polyposis colon cancer; HPC, hereditary pancreatic cancer; IPAA, ileal pouch duodenoscopy; IRA, ileorectal anastomosis; IRA, ileorectal anastomosis; JP, juvenile polyp; JPS, juvenile polyposis syndrome; LS, Lynch syndrome; M, male; MRI, magnetic resonance imaging; MSI, microsatellite instability; NSAID, non-steroidal anti-inflammatory drug; PJS, Peutz Jeghers syndrome; SPS, serrated polyposis syndrome; yr, year (of age)



## **Biallelic Mismatch Repair Deficiency (BMMRD) Syndrome and Colorectal Cancer (CRC): USMSTF\* Consensus (2017)**

Durno C, et al. Am J Gastroenterol 2017; 112: 682-690.

### ➤ Terminology

- BMMRD syndrome, aka Constitutional Mismatch Repair Deficiency (CMRD) Syndrome
  - Please also see Giardiello FM, et al. Gastroenterology 2014; 147: 502-526

### ➤ Background

- Lynch syndrome (LS)
  - Most common cause of inherited CRC
  - Cause: the autosomal-dominant disease caused by “...a monoallelic germline mutation in a DNA-mismatch repair (MMR) or EPCAM gene”
    - Heterogenous germline mutations in MLH1, MSH2, MSH6, PMS2, EPCAM
    - The tumour DNA is characterised by microsatellite instability (MSI-H, microsatellite instability-high, aka MSI)
    - The most common mutation in BMMRD patients in PMS2
    - MLH1, MSH2, MSH6, 40-70%
    - PMS2, 10-20%
    - MLH1, MSH2 in women, endometrial cancer, 40%
  - Only one wild-type allele; requires a “second hit” to inactivate the wild-type allele from the unaffected parent
  - Penetrance incomplete: infection risk for CRC
  - Less common than LS
- Biallelic MMR deficiency (BMMRD)
  - From birth, no DNA MMR activity in any tissue → early somatic mutations in polymerase proofreading genes DNA polymerase  $\epsilon$  and  $\delta$  → ultrahypermutated tumours → rapid progression of tumours
  - Requires each parent to have LS from the same gene → mutations are homozygous or compound heterozygous → clinical pleiotropy
  - Childhood development of adenomas as well as extraintestinal tumours
  - Clinical feature
    - Café-au-lait macules (like fibroneuromas)

\* US Multi-Society Task Force (USMSTF)



➤ Clinical suspicion

- Child/young adult with cancer, plus
  - Parental consanguinity, or
  - Clinical features of neurofibromatosis (NF), without the NF mutations

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give why most patients with BMMRD do **not** have a family history of LS / LS-associated tumours.
  - "...because their parents are young and **not** yet phenotypically affected despite harbouring a mono-allelic mutation in a DNA-MMR gene"
  - "Small family sizes make autosomal-recessive appear to be sporadic"
  - Low penetrance of LS-associated cancers if the parents carry mutations in PMS2
  - MSH6-LS, the biallelic child with MMR mutations develops cancer before the parents, so the child does **not** appear to have a family history

Clinical and Laboratory Features to Raise Suspicion for Possible BMMRD

- Child or young adult with a Lynch syndrome cancer (colorectal, small bowel, ureter, endometrial, and so forth)
- Child or young adult with colonic adenomatous polyposis not explained by a known polyposis syndrome mutation (familial adenomatous polyposis, MUTYH-associated polyposis)
- Any child or young adult with cancer plus parenteral consanguinity, café-au-late macules, or features of neurofibromatosis, not explained by other confirmed germline mutation (i.e., neurofibromatosis)
- Any cancer with abnormal immunohistochemistry for the DNA-MMR proteins in normal and tumour tissue
- History of brain cancer, lymphoma, or leukemia without history of radiation
- Any child or adult with hypermutated tumour



Recommendations on Surveillance and Management of Biallelic Mismatch Repair Deficiency (BMMRD) Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer

| Intervention                                   | Recommendation                  | Alternative Approach                                       |
|------------------------------------------------|---------------------------------|------------------------------------------------------------|
| ○ Upper Endoscopy and capsule endoscopy        | Annually beginning at 8 yr      | -                                                          |
| ○ Colonoscopy                                  | Annually beginning at 6 yr      | -                                                          |
| ○ Brain MRI                                    | q6mon beginning at 2 yr         | Head ultrasound starting at 6 mon until fusion of fontanel |
| ○ Complete blood count                         | q6mon beginning at 1 yr         | -                                                          |
| ○ Pelvic examination with endometrial sampling | Annually beginning at age 20 yr |                                                            |
| ○ Urinalysis                                   | Annually beginning at age 10 yr | MRI                                                        |
| ○ Total-body MRI                               | Uncertain                       |                                                            |

Printed with permission: Durno C, et al. Am J Gastroenterol 2017; 112: 682-690 (Table 3)

➤ Diagnostic Precaution/Recommendations

- "...recommend universal testing for immunohistochemistry and MSI on all small- and large-bowel cancers in children.

➤ Surveillance

- In patients with BMMRD, perform surveillance for possible tumours
  - Small/large bowel
    - Begin annual colonoscopy at age 6
    - Once polyps found, perform colonoscopy q6mon (weak recommendation, low-grade evidence)
    - Begin EGD / videocapsule endoscopy (VCE) and measurement of hemoglobin concentration at age 8 (weak recommendation, very low quality evidence)
  - Brain
    - Begin brain MRI at age 2, and repeat q6mon (weak recommendation, low quality evidence)
  - Leukemia/lymphoma
    - Begin complete blood count (CBC) at age 1 yr and repeat q6mon (weak recommendation, very low-quality evidence)



- Endometrial cancer
  - Annual pelvic examination, transvaginal ultrasound, and endometrial sampling, beginning at 20 yr (weak recommendation, very low-quality evidence)
- Urinary tract cancers
  - Annual urinalysis beginning age 10-20 yr
- Hepatic adenomas
  - No routine surveillance recommended (weak recommendation, very low-quality evidence)
- Asymptomatic relative
  - Screen for LS-associated cancers
    - First-degree relative of affected patients
    - Person with LS
 (weak recommendations, moderate-quality evidence)
- Management
  - GI / extra-GI tumours in 20% (from 2 to 10 cancers)
    - Synchronous
    - Metachronous
    - Common, (after partial colectomy, ~2% per yr), but data may be biased
  - Aspirin (ASA) 600 mg/d for  $\geq 2$  yr
    - Median age of CRC, 45 yr
    - $\downarrow$  CRC by > 60%
 (Burn J, et al. Lancet 2011; 378: 2081-2087)



## HEREDITARY CANCERS

- Hereditary Gastric Cancer (HDGC)
  - Clinical suspicion
    - Associated with lobular breast cancer as well as stomach/colon cancer
      - Require surveillance of stomach, colon, and breasts
  - Genetic testing if
    - Personal history
      - Diffuse gastric cancer age < 40 yr
    - Family history
      - ≥ 3 family members with documented diffuse gastric cancer in first- or second-degree relatives of any age
      - ≥ 2 family members if diffuse gastric cancer, with ≥ 1 diagnosed when < 50 yr
  - Surveillance
    - Stomach
      - Diffuse gastric cancer, age < 40 yr
    - Colon
      - Colonoscopy after 40 yr if family member with CRC
    - Breast
      - Examination at age 35 yr (clinical q6mon, mammography q1yr, and MRI q6mon)  
(Conditional recommendation, low quality evidence)

Abbreviations: AFAP, attenuated familial adenomatous polyposis; APS, adenomatous polyposis syndrome; ASA, aspirin; CHRPE, congested hypertrophic of the retinal pigment epithelium; CRC, colorectal cancer; CS, Cowden syndrome; EUS, endoscopic ultrasound; F, female; FAP, familial adenomatous polyposis; HDGC, hereditary diffuse gastric cancer; HNPCC, hereditary non-polyposis colon cancer; HPC, hereditary pancreatic cancer; IPAA, ileal pouch duodenoscopy; IRA, ileorectal anastomosis; IRA, ileorectal anastomosis; JP, juvenile polyp; JPS, juvenile polyposis syndrome; LS, Lynch syndrome; M, male; MRI, magnetic resonance imaging; MSI, microsatellite instability; NSAID, non-steroidal anti-inflammatory drug; PJS, Peutz Jeghers syndrome; SPS, serrated polyposis syndrome; yr, year (of age)





- Hereditary pancreatic and colon cancer
- Genetic testing if
  - Known mutation carriers
    - APC-associated, ATM, BRCA 1/2, CDKN 2A, PALB2, FAMMM (familial atypical multiple melanoma and mole) syndrome, HB-OC (hereditary breast-ovarian cancer) syndrome, LS, PJS
  - Personal family history
    - Personal history of  $\geq 2$  attacks of acute idiopathic pancreatitis
    - Family history of pancreatitis: 1, 2, 3 first-degree relatives
    - Early-age onset of chronic pancreatitis
    - Associated hereditary syndromes
      - Familial
        - Atypical melanoma and mole
        - Breast and ovarian cancer
        - Adenomatous polyposis
        - Pancreatic cancer
      - GI
        - Lynch syndrome (LS)
        - Peutz-Jeghers syndrome (PJS)
      - Fanconi anemia / breast cancer
      - Ataxia
      - Li-Fraumeni
- Surveillance
  - Surveillance in those who are carriers of a mutation, plus first- or second degree relative affected pancreatic cancer.
  - Age  $> 50$  yr, or 10 yr younger than the earliest age of affected family member
    - EUS, MRI (conditional recommendation, very low quality evidence)
  - Exception
    - PJS patients seen at 35 yr (conditional recommendation, very low quality evidence)
- Treatment
  - Stop smoking
  - Low fat diet for those with
  - Surgical team, multidisciplinary team
    - For persons with pancreatic cysts, refer to centre of excellence / multidisciplinary team



## **Hamartomatous Polyposis Syndromes and the Risk of Cancer, including Colorectal Cancer (CRC): USMSTF Recommendations (2022)**

Boland CR, et al. Am J Gastroenterol 2022; 117: 846-864

### ➤ Background

- “The gastrointestinal hamartomatous polyposis syndromes are rare, autosomal dominant disorders associated with an increase risk of benign and malignant intestinal and extraintestinal tumours”.
  - These are caused by pathogenic germline alterations, and can be suspected from their clinical or pathological features
- Definition
  - “...a non-neoplastic tumour with a markedly distorted architecture composed of an abnormal mixture of cells and tissue normally present in that particular area
- The overall overdose of all hamartomatous syndromes is rare,  $\sim 1/10^5$

### ❖ Peutz-Jeghers Syndrome (PJS)

#### ➤ Genetics

- An autosomal dominant inactivating germline pathogenic variant of the STK11 serine/threonine kinase gene, which
  - Encodes the liver kinases B1 protein (LKB1)
  - Functions as a tumour suppressor gene to
  - Regulate cell growth by adenosine monophosphate (AMP) activated protein kinase
  - Negatively regulates signaling of mTOR

#### ➤ Clinical

- Missense alterations in STK11
  - Alu-mediated deletions / inversions
- Skin
  - Characteristic mucocutaneous freckles around the mouth (lips, buccal membranes)

#### ➤ Pathology

- Branching bands of smooth muscle, covered by
  - Hyperplastic glandular mucosa



➤ Diagnosis

- Diagnostic suspicion
  - Suspect PJS and perform genetic evaluation of
    - Histologically confirmed PJS polyps
      - No family history,  $\geq 2$
      - First-degree relative with PJS,  $\geq 1$
      - Characteristic mucocutaneous pigmentations
      - Family history of PJS
- Characteristic mucocutaneous pigmentation of PJS  
(Strong recommendation, low quality evidence)

➤ Risk of Cancer'

Risk of Cancer in Hamartomatous Polyposis Syndromes

| Site   | Syndrome                           | Risk, %   | Mean Age at diagnosis, yr |
|--------|------------------------------------|-----------|---------------------------|
| ○ PJS  | - Colorectal                       | 39        | 42-46                     |
|        | - Stomach                          | 29        | 30-40                     |
|        | - Small bowel                      | 23        | 37-42                     |
|        | - Breast                           | 32-54     | 37-59                     |
|        | - Ovarian (mostly SCTAT)           | 21        | 28                        |
|        | - Cervix (adenoma malignum)        | 10-23     | 34-40                     |
|        | - Uterus                           | 9         | 43                        |
|        | - Pancreas                         | 11-36     | 41-52                     |
|        | - Testicular (Sertoli cell tumour) | 9         | 6-9                       |
|        | - Lung                             | 7-17      | 47                        |
| ○ JPS  | - Colon                            | 39        | 44                        |
|        | - Stomach                          | 5-21      | 54                        |
| ○ CS   | - Breast                           | 25-85     | 38-46                     |
|        | - Thyroid                          | 3-38      | 31-38                     |
|        | - Uterus                           | 5-28      | 25                        |
|        | - Kidney (renal cell)              | 15-34     | 40                        |
|        | - Colon                            | 9-18      | 35                        |
|        | - Melanoma                         | 6         | 3                         |
| ○ HMPS | - Colon                            | Increased | -                         |

Abbreviation: SCTAT, sex cord tumours with annular tubules

Adapted from: Boland CR, et al. Am J Gastroenterol 2022; 117: 846-864 (Table 3)

- Risk of developing cancer between ages 15 to 64, 93%

| Site               | Life time risk | Mean age of diagnosis, yr |
|--------------------|----------------|---------------------------|
| - Stomach          | 29%            | 30-40                     |
| - Small intestinal | 13%            | 37-42                     |
| - Colon            | 12-39%         | 46                        |



- Risk of any cancer in PJS, 15.2; 95%CI: 2-19

| Site               | Relative Risk | 95%CI    | Cumulative Risk |
|--------------------|---------------|----------|-----------------|
| - Stomach          | 213           | 96-368   | 29%             |
| - Small intestinal | 520           | 220-1306 | 13%             |
| - Colon            | 84            | 47-87    | 39%             |
| - Esophagus        | 57            | 3-557    | 0.5%            |
| - Pancreas         | 132           | 44-261   | 36%             |
| - Ovary            | 27            | 7.3-68   | 21%             |
| - Uterus           | 16            | 2-56     | 9%              |
| - Lung             | 17            | 5-39     | 15%             |
| - Testes           | 5             | 0.1-2.5  | 9%              |
| - Breast           | 15            | 8-27     | 54%             |

- Polyposis
  - Stomach, small bowel, colon, 88% - 100%
  - Small bowel 80-90%
  - Colon, 50% - 64%

#### Recommendation

- Use a multidisciplinary approach to cancer surveillance in patients with PJS for breast, stomach, small bowel, colon, pancreas, ovaries, testes, lungs (strong recommendation, low quality evidence)
- Timing of initiation of surveillance
  - Small bowel
    - With symptoms, any age
    - With no symptoms, 8-10 yr
      - MRE/VCE; repeat q2-3yr
 (Strong recommendation, low quality of evidence)
  - Colon, stomach
    - EGD, colonoscopy, asymptomatic, 8-10 yr
    - If polyps found, repeat q2-3yr
    - If no polyps at baseline, repeat EGD/colonoscopy at 18 yr
      - If no symptoms, q3yr
      - If symptoms, EGD/colonoscopy at that time
    - Celecoxib (COX2 inhibitor), or ↓ gastric body polyps by > 50% patients with polyposis
- Removal of polyps
  - If symptomatic, or if asymptomatic ≥ 10 mm (strong recommendation, low quality evidence)



- Pancreas (ductal cancer)
  - 3<sup>rd</sup> most common malignancy
    - In 4% to 36%
      - Presentation
      - Average 41-52 yr
      - After age 24 yr in 955
    - High risk of pancreatic cancer syndromes
    - Perform MRI of pancreas, MRCP starting at 40 yr, q1-2yr (USMSTF recommend starting screening for pancreatic ductal adenocarcinoma at age 35 yr with MRI/MRCP, plus fasting blood glucose and hemoglobin A1C)

#### Recommendation

- Start MRCP / endoscopic ultrasound (EUS) at 35 yr (weak recommendation, low quality evidence)
- Gynecological Cancers
  - Lifetime Risk
 

|                    | Mean age of presentation, yr |                                     |
|--------------------|------------------------------|-------------------------------------|
| – Ovarian, 21%     | 28-35                        | ▪ Sex cord tumours, annular tubular |
| – Uterine, 9%      | 43                           | ▪ Heterogenous                      |
| – Cervical, 10-23% | 34-40                        | ▪ Rarely have lymph node metastasis |
  - A totally unreasonable knowledge for a gastroenterologist!
- Give the pathological type of cervical cancer which may be mixed (false negative) on a Pap smear in patient with PJS.
  - Adenoma malignant (poor prognosis)
- Testicles
  - Lifetime risk, 9%
  - Mean onset, 3-20 yr
  - Clinical
    - Hyperestrogenism
      - Gynecomastia
      - Virilization
      - ↑ height
  - Surveillance
    - q2yr
      - Physical exam for signs of hypoestrogenism
      - Ultrasound of testicles



- Lung
  - Lifetime risk, 7-17%
  - Cumulative risk by age 55 yr, 5% (similar to a 30 past-year of smoking who quit for 10-15 yr)
    - Recommendations
      - Stop smoking
      - Low-dose CT of lung q1yr from 55 to 74 yr
- ❖ Juvenile Polyposis Syndrome (JPS)
  - Prevalence
    - 1/10<sup>5</sup>
  - Genetics
    - Autosomal dominant
      - Inherited from a parent, 75%
        - Pathogenic variant in the BMP R1A or SMAD4 gene (60%)
        - SMAD4-allelic loss
        - Germline variant → SMAD4
        - ↓ TGF-β signalling → ↑ T cell proliferation → ↑ inflammation on stroma
      - De novo, 27%
      - Juvenile polyposis of infancy
      - SMAD4 (rather than BMPR1A) develop gastric polyps
    - Overlap with JPS and hereditary hemorrhagic telangiectasia (HHT) occurs in ~15-81% of patients with a germline SMAD4
    - Other genes may be affected
      - SMAD4, BMPR1A
      - STK11 (the PJS gene)
      - Colorectum, 98%
      - Stomach, 4%
      - Duodenum, 7%
      - Jejunum, 7%
  - Clinical
    - ↑ proinflammatory cytokines (↑↑ IL-11 ↑ TH17 activity)
    - Distinguish non-syndromic solitary juvenile polyps (JPs)
      - Cystic dilation of mucus-filled glands in an inflamed stoma
      - Aka retention/inflammatory polyps
    - Clinical criteria for diagnosis of JPS
      - ≥ 5 juvenile polyps in colorectum
      - ≥ 2 JP in any non-colorectal part of GI tract
      - ≥ 1 first degree relative with JPS, plus patient with ≥ 1JP



|              | <u>Age of diagnosis, yr</u> |
|--------------|-----------------------------|
| Stomach, 39% | 44                          |
| Colon, ~12%  | 54                          |

#### Clinical Emerald

- When to suspect JPS plus HHT
  - All the features of JPS, plus
    - Epistaxis
    - Mucocutaneous telangiectasia
    - Arteriovenous visceral malformations (AVM)
    - Digital clubbing

#### ➤ Pathology

- Multiple juvenile polyps
- Usually solitary
- Histopathology
  - Architecture
    - Cysts
  - Glands
    - Dilated
    - Filled with mucous
  - Lamina propria
    - Prominent
  - Paneth cells enmeshed within a dense infiltration of inflammatory cells

#### ➤ Risk of cancer

#### Recommendations

- Patient should have genetic evaluation for JPS if
  - $\geq 5$  JP in colorectum
  - $\geq 2$  JP in any non-GI part of GI tract
  - $\geq 1$  first degree relative with JPS, plus patient with  $\geq 1$  JP  
(Strong recommendation, low quality of evidence)
- Patient with JPS must have surveillance of stomach and colon (Strong recommendation, low quality of evidence)
- Median age of presentation, ~6 yr, multiple polyps in 39%
- Colonoscopy at initial diagnosis
  - Single polyp, 61%
  - Multiple polyps, 39%
- Cumulative risk of
  - CRC, 39%, mean age of diagnosis, 44 yr
  - Gastro cancer, 30%, median age at diagnosis, 58 yr
- Recurrence of colonic polyps after initial eradication, 45%



## ➤ Treatment

- Colonoscopy/EGD beginning at 12-15 yr, then q1-3yr
  - CRC, 39%, mean age of diagnosis, 44 yr
- If SMAD4 variant
  - Annual history/physical, CBC for anemia, rectal bleeding, beginning age 12-45 yr
- Colonic polyps
  - Endoscopic polypectomy
  - Colectomy plus ileorectal anastomosis indicated for CRC
    - Polyps not adequately managed endoscopically
    - Uncontrolled anemia from colonic bleeding
- Gastric polyps
  - SMAD4 variants
    - Asymptomatic no EGD
    - However, others recommend EGD q1yr starting at age 12-15 yr
  - Uncertain if patients with BMPR1A variants need surveillance
    - Endoscopic polypectomy
  - Partial/total gastrectomy indications
    - Gastric cancer / high grade dysplasia (HGD)
    - Inadequate endoscopic polyp removal
    - Bleeding
    - Gastric outlet obstruction
    - Protein-losing gastropathy, severe

## Recommendation

- Start EGD / colonoscopic surveillance at age 12-15 yr, or earlier if symptoms
  - Repeat procedures q1-3yr, depending upon number of polyps(Weak recommendation, low quality evidence)
- JPS plus HHT
  - Children with confirmed HHT
    - MRI of brain with/without contrast at diagnosis of JPS-HHT, repeat MRI of brain by puberty
    - Lung screening/surveillance q3-5 yr with
      - Pulse oximetry
      - Transthoracic contrast echocardiogram
  - Adulthood
    - Hemoglobin concentration at diagnosis then q1yr after age 35 yr
    - Transthoracic contrast echocardiogram of lung indicated
      - At diagnosis, then q5-60yr
      - 5 yr before planned pregnancy
      - After pregnancy





## Surveillance Guidelines in Hamartomatous Polyposis Syndromes

| Examination                        | ACG 2015              |              | Evidence Grade |
|------------------------------------|-----------------------|--------------|----------------|
|                                    | Age of initiation, yr | Interval, yr |                |
| ○ JPS                              |                       |              |                |
| – Colonoscopy                      | 12-15                 | 1-3          | Low            |
| – Upper endoscopy                  | 12-15                 | 1-3          | Low            |
| – Screen for vascular lesions      | ≤ 6 mon               | -            | -              |
| ○ PJ                               |                       |              |                |
| – Colonoscopy                      | 8, 18                 | 3            | Very low       |
| – Upper endoscopy                  | 8, 18                 | 3            | Very low       |
| – VCE                              | 8, 18                 | 3            | Low            |
| – CT or MRE of small bowel         | -                     | -            | -              |
| – MRI and/or EUS of pancreas       | 30                    | 1-2          | Low            |
| – MRI and/or mammogram             | 25                    | 1            | -              |
| – Physical examination             | Birth to teenage      | 1            | -              |
| – Pelvic examination and Pap smear | 25                    | 1            | -              |
| – Testicular examination           | Birth to teenage      | 1            | -              |
| ○ PHTS                             |                       |              |                |
| – Colonoscopy                      | 15                    | 2            | Low            |
| – Upper endoscopy                  | 15                    | 2-3          | -              |
| – Thyroid examination and US       | Adolescence           | 1            | -              |
| – MRI and/or mammogram             | 30-35                 | 1            | -              |
| – Endometrial sampling             | 30-35                 | 1            | -              |
| – Urinalysis or renal US           | 18                    | 1            | -              |
| – Skin examination                 | ~18                   | 1            | -              |

Abbreviations: ACG, American College of Gastroenterology; CT, computed tomography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography

Adapted from: Boland CR, et al. Am J Gastroenterol 2022; 117: 846-864 (Table 4)

- PTEN-Hamartoma Tumour Syndrome (PHTS)

- Definition

- Presence of

- Hamartomas of skin and GI tract (polyps in 93%, hamartomas/adenomas, affected all the GI tract)
- Mucocutaneous lesion
- Macrocephaly
- ↑ risk of benign/malignant tumours of
  - Breast, 85%
  - Thyroid, 35%
  - Endometrium, 28%
  - Kidney, 34%
  - Colon, 9%
  - Skin (melanoma), 6%



- Pathogenic variant of phosphatase and tension homolog (PTEN) gene; negative regulator of growth-promoting activity of the phosphatidylinositol 3-kinase pathway)
- Heterogeneous phenotypes: PTEN, Cowden syndrome (CS), BRRS, Lhermitte-Duclos disease (LDD), with dysplastic cerebellar gangliocytoma
- Systemic non-polyposis phenotypes of CNS, skeleton
  - Rare gain of function germline pathogenic variants in WWP1 gene, which inhibits PTEN → oligopolyposis and ↑ cancer risk (CS-like syndrome)

➤ Surveillance

|               |                      | Age of initiation, yr* | Interval, yr* |
|---------------|----------------------|------------------------|---------------|
| ○ GI          | - EGD                | 15-35                  | 2-5           |
|               | - Colonoscopy        | 15                     | 2             |
| ○ Thyroid     | - Ultrasound         | Teens                  | 1             |
| ○ Breast      | - MRI/mammogram      | 30-35                  | 1             |
| ○ Kidney      | - Urinalysis         | 18-40                  | 1             |
| ○ Endometrium | - Endometrial biopsy | 30-35                  | 1-2           |
| ○ Skin        | - Skin examination   | ~18                    | 1             |

\*these values are appropriate and reflect the recommendations of fewer guidelines

• Hereditary Mixed Polyposis Syndrome (HMPS)

- Rare, autosomal dominant due to
  - Large duplications of the promoter region or all of the GREM1 gene → ↓ bone morphogenic protein (BMP) pathway
  - May be seen in Ashkenazi Jews with Lynch syndrome
- Attenuated colonic polyposis
  - Adenomas
  - Hyperplastic
  - Juvenile
 } ▪ Mixed
- Begin screening/surveillance colonoscopy at age 20
- The PJS pathogenic variants
  - ↑ growth of normal GI (polyps)
    - GI epithelium
    - Stroma
 } ▪ Polyps

→ ↓ adenosine monophosphate-dependent activation of protein kinase → ↑ mTORC1 → polyposis



**Follow-up after Colonoscopy and Polypectomy: Update Interval for first and next (second) Surveillance Colonoscopy: a consensus update by the US Multi-society Task Force on Colorectal Cancer (USMSTF) (2020)**

Gupta S, et al. Am J Gastroenterol 2020; 115: 415-437

➤ Background

- This topic was previously reviewed and consensus guidelines were provided in 2012 (Lieberman DA, et al. Gastroenterology 2012; 143: 844-57)

Updates Since 2012 Recommendations Provided in the 2019 US Multi-Society Task Force Recommendations for Follow-up After Colonoscopy and Polypectomy based on new evidence risk of colorectal cancer outcomes

- More detailed recommendations for follow-up after removal of serrated polyps have been provided.
- 7 to 10 yr rather than 5 to 10 yr follow-up is recommended after removal of 1-2 tubular adenoma < 10 mm in size.
- Option to recommend 3-5 yr instead of 3-yr follow-up after removal of 3-4 adenomas < 10 mm in size.
- 1 yr rather than < 3 yr follow-up is recommended after removal of > 10 adenomas.
- High-quality colonoscopy is a requirement: the risk for metachronous advanced neoplasia is a surrogate for
  - The risk for incident CRC, as well as a better appreciation for
  - The risk of metachronous advanced neoplasia among individuals with baseline polyps.
- The US-MSTF CRC has also recently provided updated recommendations for
  - Personal history of CRC (Kahi, CJ, et al. Am J Gastroenterol 2016; 111; 337-346; Kahi CJ, et al. Gastrointest Endoscopy 2016; 83: 489-498, e10)
  - Endoscopic removal of colorectal lesions (Kaltenbach T, et al. Am J Gastroenterol 2020; 115: 435-64)



➤ Terminology

- There are subtle changes in the definitions of some of the terms, but even more importantly, in the recommendations the characteristics of the polyps are used whenever possible, rather than descriptive terms such as low- or high-risk lesions.

| New Terminology*           | Definition                                                                                                                                                                                                                                                           |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ○ Normal                   | ▪ A colonoscopy, where no adenoma, SSP, TSA, HP $\geq$ 10 mm, or colorectal cancer (CRC) is found                                                                                                                                                                    |
| ○ Risk                     |                                                                                                                                                                                                                                                                      |
| – Average (for CRC)        | ▪ Absence of <ul style="list-style-type: none"> <li>– Inflammatory bowel disease</li> <li>– Family history of CRC</li> <li>– Hereditary syndrome associated with increased risk</li> <li>– Serrated polyposis syndrome</li> <li>– Personal history of CRC</li> </ul> |
| – Low (adenoma)            | ▪ 1-2 non-advanced adenomas < 10 mm in size                                                                                                                                                                                                                          |
| – High (adenoma)           | ▪ 1 or more of the following findings <ul style="list-style-type: none"> <li>– Adenoma neoplasia</li> <li>– 3 or more adenomas</li> </ul>                                                                                                                            |
| ○ Advanced                 |                                                                                                                                                                                                                                                                      |
| – Adenoma                  | ▪ 1 or more of the following finds <ul style="list-style-type: none"> <li>– Adenoma <math>\geq</math> 10 mm in size</li> <li>– Adenoma with tubulovillous histology</li> <li>– Adenoma with high grade dysplasia</li> </ul>                                          |
| – Neoplasia                | ▪ 1 or more of the following findings <ul style="list-style-type: none"> <li>– Adenoma <math>\geq</math> 10 mm in size</li> <li>– Adenoma with tubulovillous histology</li> <li>– Adenoma with high grade dysplasia</li> <li>– CRC</li> </ul>                        |
| ○ Adequate                 |                                                                                                                                                                                                                                                                      |
| – Bowel preparation        | ▪ Bowel preparation adequate for visualization of polyps > 5 mm in size                                                                                                                                                                                              |
| – ADR                      | ▪ ADR $\geq$ 30% in men and $\geq$ 20% in women                                                                                                                                                                                                                      |
| – Complete examination     | ▪ Complete colonoscopy to cecum, with photo documentation of cecal landmarks, such as the appendiceal orifice, terminal ileum, or ileocecal valve                                                                                                                    |
| – High-quality examination | ▪ Examination complete to cecum <ul style="list-style-type: none"> <li>– With adequate bowel preparation</li> <li>– Performed by colonoscopist with adequate adenoma detection rate</li> <li>– Attention to complete polyp excision</li> </ul>                       |

\*specify the individual criteria being captured by the category (use 1-2 adenomas < 10 mm)

Adapted from: Gupta S, et al. Am J Gastroenterol 2020; 115: 415-434 (Table 3)



➤ Screening Colonoscopy

- Reduces risk of
  - Incident CRC on long-term follow-up (HR, 0.44; 95%CI, 0.38-0.52)
  - Fatal CRC (HR, 0.32; 95%CI, 0.24-0.45) over 300,000 person years of follow-up
- Persons who were screened and have a normal colonoscopy
  - Standardized incidence ratio (SIR) of CRC vs. standard population was
    - At 5 yr, 0.26; 95% CI: 0.19-0.32
    - At 7-10 yr, 0.60; 95%CI: 0.44-0.76
  - ↓ relative risk at 10 yr, 70% (SIR, 0.28; 95%CI, 0.24-0.33)

➤ Surveillance

- Traditional 10 yr follow-up after initial normal colonoscopy is 10 yr: ↓ incidence of
  - CRC (HR< 0.54; 95%CI: 0.31-0.94)
  - Fatal CRC (HR, 0.12; 95%CI, 0.02-0.82)
- There is no direct evidence to support the incremental effectiveness of repeat after 10 yr colonoscopy

➤ Notations

- Normal colonoscopy is associated with sustained ↓ risk for incidental fatal CRC (high quality evidence)
- Incremental effectiveness of repeat colonoscopy after baseline normal colonoscopy for further reducing CRC incidence and mortality is uncertain (insufficient evidence)
- Risk for incident and fatal CRC after baseline adenoma removal is uncertain (low quality evidence)
- Surveillance colonoscopy after baseline removal of adenoma with high-risk features (e.g., > 10 mm) may ↓ incident CRC, but it is uncertain what benefit if any this has on fatal CRC (low quality of evidence)
- It is not certain what is the impact of surveillance colonoscopy after the initial colonoscopy was low-risk (e.g., 1-2 adenomas < 10 mm) upon incident/fatal CRC (low quality of evidence)
- In patients with sessile serrated polyps on initial screening colonoscopy
  - The magnitude and significances of risk associated with SSRIs is uncertain, given limitations of available studies.”
  - The risk for incident and fatal CRC with individuals with baseline SSP is uncertain (very low quality of evidence)



## Recommendations

- Repeat CRC screening in 10 yr in patients with a normal, initial high-quality colonoscopy (Strong recommendation, high quality of evidence)
- The recommended interval for patients with adenomas, hyperplastic polyps (HPs) or sessile serrated polyps (SSPs) depends upon the finding at the initial screening colonoscopy

| Initial Findings                       | On Screening Colonoscopy | Colonoscopy (surveillance), yr | Second Surveillance Colonoscopy                     |
|----------------------------------------|--------------------------|--------------------------------|-----------------------------------------------------|
| < 10 mm                                | 1-2                      | 7-10                           | Strong recommendation, moderate quality of evidence |
|                                        | 3-4                      | 3-5                            | Weak recommendation, very low quality of evidence   |
|                                        | 5-10                     |                                | Strong recommendation, moderate quality of evidence |
| ≥ 10 mm                                |                          | 3                              | Strong recommendation, high quality of evidence     |
| Any size with tubulo-villous histology |                          | 3                              | Strong recommendation, moderate quality of evidence |
| High-grade dysplasia                   |                          | 3                              | Strong recommendation, moderate quality of evidence |
| > 10 mm                                |                          | 1                              | Weak recommendation, very low quality of evidence   |
| ≥ 20 mm, piecemeal resection           |                          | 0.5                            | Strong recommendation, moderate quality of evidence |

| Baseline                             | Finding                   | Surveillance Interval |
|--------------------------------------|---------------------------|-----------------------|
| ○ Hyperplastic polyps (HPs)          | ≤ 20 HPs, < 10 mm         | 10                    |
|                                      | Any number ≥ 10 mm        | 3-5                   |
| ○ Sessile serrated polyps (SSPs)     | < 10 mm                   | 1-2 5-10              |
|                                      |                           | 3-4 3-5               |
|                                      |                           | 5-10 3                |
|                                      |                           | 3                     |
|                                      | Any number with dysplasia | 6 mon                 |
|                                      | Any number ≥ 10 mm        | 3                     |
| ○ Traditional serrated adenoma (TSA) |                           |                       |
| ○ ≥ 20 mm, piecemeal resection       |                           | 0.5                   |

Adapted from: Gupta S, et al. Am J Gastroenterol 2020; 115: 415-434 (Table 4)



- Risk of finding a lesion on second colonoscopy (first surveillance colonoscopy)

| Screening (Initial) Colonoscopy                   | Surveillance Colonoscopy |                                                   |
|---------------------------------------------------|--------------------------|---------------------------------------------------|
|                                                   | High risk adenoma, %     | Hyperplastic polyp, sessile polyp, traditional, % |
| ○ Adenoma                                         |                          |                                                   |
| – None                                            | 4.8                      | 0.7                                               |
| – Low risk (1-2 adenoma, < 10 mm)                 | 9.7                      | 0.5                                               |
| ▪ Plus SSP (> 2 adenoma, 10 mm) high risk         | 18.4                     | 8.2                                               |
| ▪ Plus SSP                                        | 46.4                     | 3.6                                               |
| – High risk                                       |                          |                                                   |
| ▪ Sessile serrated / traditional serrated adenoma | 2.9                      | 9.6                                               |
| ▪ Serrated polyps ≥ 10 mm                         | 3.1                      | 12.3                                              |

Adapted from: Gupta S, et al. Am J Gastroenterol 2020; 115: 415-434 (Table 6)

- Risk of finding a lesion on second surveillance (colonoscopy#3: first screening, second colonoscopy after screening adenoma(s) found)

| Baseline Finding          | First surveillance                | Colonoscopy (# of Tubular adenoma) | Interval Second Surveillance (yr) |
|---------------------------|-----------------------------------|------------------------------------|-----------------------------------|
| ○ Tubular adenoma < 10 mm | None                              |                                    | 10                                |
|                           | < 10 mm                           | 1-2                                | 7-10                              |
|                           | < 10 mm                           | 3-4                                | 3-5                               |
|                           | >10 mm, or tubule-villous or HGD  |                                    | 3                                 |
| ○ Tubular adenoma ≥ 10 mm | None                              |                                    | 5                                 |
|                           | < 10 mm                           | 1-2                                | 5                                 |
|                           | < 10 mm                           | 3-4                                | 3-5                               |
|                           | ≥ 10 mm, or tubule-villous or HGD |                                    | 3                                 |

Adapted from: Gupta S, et al. Am J Gastroenterol 2020; 115: 415-434 (Table 7)

#### Recommendations

- Do **not** use “currently published: prediction models to determine intervals for surveillance (weak recommendation, very low quality of evidence)
- Manage proximal adenomas the same as distal adenomas (weak recommendation, very low quality of evidence)

For adenoma or SSP > 20 mm which have been removed by piecemeal resection, repeat colonoscopy in 6 mon (strong recommendation, moderate quality of evidence)



## Endoscopic Removal of Colorectal Lesions: Recommendations by the US Multi-society Task Force (USMSTF) in Colorectal Cancer (CRC) (2020)

Kaltenbach T, et al. Gastroenterol 2020; 158: 1095-1129

### ➤ Background

- Removal of colonic adenomatous polyps reduces mortality of CRC by 50%
- Lifetime risk of CRC ~5%
  - 90% of CRC occur > 50 yr
- Post-colonoscopy CRC
  - Missed lesions > 50%
  - Incomplete resection 20%
- Residual tissue left after polypectomy, 7% to ~25%
  - Variability likely due to variation in the technique used by endoscopist

### Recommendations

- Lesion assessment
  - Use the Paris classification to describe the surface morphology
  - To provide a common nomenclature (For the non-pedunculated adenomatous (Paris 0-II and 0-Is) lesions  $\geq 10$  mm)
  - Surface morphology should also be described as granular or granular lateral spreading lesions.
    - Use photo documentation of
      - All lesion  $\geq 10$  mm in size before removal
      - The post resection defect(Strong recommendation, low-quality evidence)
  - The endoscopist/colonoscopist should have proficiency in the use of electronic (e.g., NBI, i-scan, Fuji intelligent Chromoendoscopy), or dye (chromoendoscopy)-based image-enhanced endoscopy techniques to apply optical diagnosis classifications for colorectal lesion histology
  - Endoscopy
    - Location, size, morphology (Strong recommendation, low-quality evidence)
  - Paris classification of surface appearance Conditional recommendation, low-quality evidence)
    - 0-Is, 0-II-a/b/c (non-pedunculated adenomas)  $\geq 10$  mm
      - Describe as
        - Granular, or
        - Non-granular, lateral spreading (Conditional recommendation, low-quality evidence)
  - Photodocumentation (minimal standard)
    - All lesions  $\geq 10$  mm before resection, or after resection (Conditional recommendation, low-quality evidence)





- Physician proficiency

#### Recommendation

- Endoscopic recognition of deep submucosal lesion (Conditional recommendation, moderate quality evidence)
- Use of equipment
  - Electronic
    - Narrow band imaging (NBI)
    - Blue light imaging (BLI)
    - Fuji intelligent chromoendoscopy (FIC)
    - I-scan
- Use of dyes-based image enhanced chromoendoscopy (colorectal lesion histology) (Conditional recommendation, moderate quality evidence)

Abbreviations: APC, antigen plasma coagulation; BLI, blue left imaging; CRC, colorectal cancer; EMR, endoscopic mucosal resection; FIC, Fuji intelligent chromoendoscopy; HP, Hyperplastic polyp; LST, lateral spreading tumour; NBI, narrow band NPV, negative predictive value; PPV, positive predictive value; WLC, white light colonoscopy; yr, year

#### ➤ Paris classification

##### A minimal standard terminology of CRC lesions

- Superficial
  - Polypoid (0-I)
    - Pedunculated (0-Ip)
    - Sessile (0-Is), bulky
      - ↑ risk of submucosal invasion
  - Non-polypoid (0-II)
    - Minimal elevation (0-IIa)
      - Submucosal invasion 2%
    - Truly flat (0-IIb)
    - Minimal depression (0-IIc)
      - Uncommon (1-6% of non-polypoid lesions)
      - Submucosal invasion
 

|         |       |
|---------|-------|
| 6-10 mm | 40%   |
| > 20 mm | ~100% |
  - Excavated (0-III)
    - Ulcerated (0-III)



- Lateral spreading tumours (LST)
  - Non-polypoid (0-II)  $\geq 10$  mm diameter
  - Subtypes
 

|                |                       |                 |           |
|----------------|-----------------------|-----------------|-----------|
| – Granular     | ▪ Homogenous (H) size | Nodular surface | LST-G-N   |
|                | ▪ Mixed               | Nodular         | LST-G-NM  |
| – Non-granular | ▪ Flat elevated       | Smooth          | LST-NG-FG |
|                |                       |                 | LST-NG-PD |
- Optical diagnosis
- NICE (narrow band imaging [NBI] international Colorectal Endoscopic)
  - Type I
    - Sessile serrated, hyperplastic
      - May have mucous cap
    - Adenoma
 

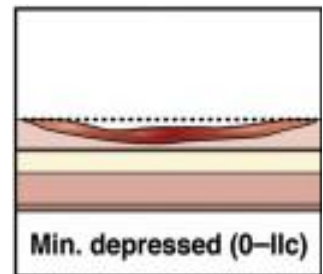
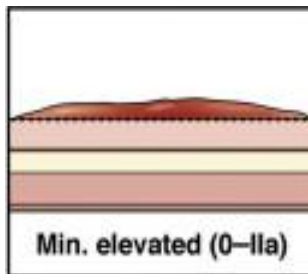
Workgroup Serrated Polyps and Polyposis (WASP) criteria for sessile serrated lesions

|           |                      |                                                                                                                                                                                  |
|-----------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ▪ Border  | Irregular/indistinct | } <ul style="list-style-type: none"> <li>– 90% accuracy</li> <li>– With change in surface pattern, or nodular component</li> <li>– Suggests dysplasia pseudodepressed</li> </ul> |
| ▪ Shape   | Irregular            |                                                                                                                                                                                  |
| ▪ Surface | Clouded              |                                                                                                                                                                                  |
| ▪ Spots   | Dark, in crypts      |                                                                                                                                                                                  |
    - Deep submucosal invasion
    - Valley sign > 90% specificity for adenoma  $\leq 5$  mm

- ❖ High-definition endoscopy (with no magnification)
  - Endoscopic changes suggestive of deep invasion

- Classification

- Paris
  - 0-IIc
  - 0-IIc plus 0-IIa

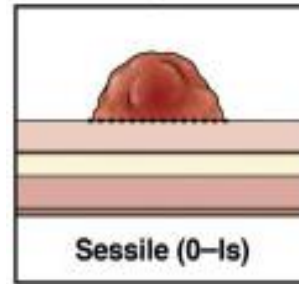


- LST
    - NG-FG
    - NG-PD
  - NICE
    - Type 3
  - Kudo
    - Pit pattern V
- } ▪ Very deep ( $> 1000 \mu\text{m}$ )

- Endoscopic appearance
  - White spots (“chicken skin”)
  - Red
  - Firm
  - Folds converge
  - Expansion



- Non-pedunculated lesion
  - Deep submucosal invasion ( $> 1000 \mu\text{m}$ )
    - $\uparrow$  risk of residual cancer in
      - Bowel wall
      - Lymph nodes
  - Superficial submucosal invasion
    - Endoscopic resection
    - Suggested by Paris 0-Is or 0-IIc



- Endoscopic management
  - HP leave
  - Rectum/sigmoid colon
  - Serrate  $> 5 \text{ mm}$  plus proximal to sigmoid
    - Biopsy
      - ↓
      - Deep mucosal invasion
      - ↓  $\rightarrow$  large sessile serrated lesions – incomplete endoscopic resection in  $\sim 50\%$
      - Surgical resection
- Expert/experienced “high confidence” endoscopist
  - Diagnosis 93% concordance of surveillance intervals
  - $> 90\%$  NPV for rectosigmoid lesions

#### ❖ Endoscopic Polyp Removal

##### Recommendations

- Diminutive ( $\leq 5 \text{ mm}$ ), and small (6-9 mm) polyps
  - Use cold snare polypectomy (Strong recommendation, high-quality evidence)
    - Do **not** use cold/hot forceps for polypectomy of lesions  $\leq 9 \text{ mm}$  (incomplete resection)
      - $\leq 2 \text{ mm}$ , use cold snare, or jumbo/large capacity forceps (Strong recommendation, moderate-quality evidence)
- Non-pedunculated (10-19 mm) polyps
  - Patients on anti-thrombotics who require endoscopic removal of lesion  $\geq 20 \text{ mm}$   
Assess possibility of stopping anti-thrombotics
  - Use cold/hot snare polypectomy +/- submucosal injection (Conditional recommendation, low-quality evidence)



- $\geq 20$  mm polyps endoscopic mucosal resection (EMR) (Strong recommendation, moderate-quality evidence)
  - The endoscopist should be experienced (Strong recommendation, low-quality evidence)
  - Use snare resection in one session, and the “...safest number of pieces (Strong recommendation, low-quality evidence)
- Submucosal recognition
  - Use a viscous solution (not saline) (Conditional recommendation, moderate-quality evidence)
  - Inject indigo carmine / methylene blue (deteriorate mucosa from muscularis propria (Conditional recommendation, moderate-quality evidence)
  - Do **not** tattoo with suspension of carbon particles (may result in submucosal fibrosis) (Strong recommendation, low-quality evidence)
- Endoscopically visible residual tissue
  - Do **not** use ablative technique ( $\uparrow$  risk of recurrence) (Strong recommendation, moderate-quality evidence)
- Bleeding intraprocedure
  - Endoscopic coagulation
    - Coagulation forceps
    - Snare tip-soft coagulation
  - Mechanical
    - Clip +/- epinephrine injection (Conditional recommendation, low-quality evidence)
- Post-EMR
  - Treat margin with adjuvant thermal ablation (Conditional recommendation, moderate-quality evidence)
  - Post-resection mucosal defect  $\rightarrow$  endoscopic clip closure (Strong recommendation, moderate-quality evidence)
  - Resection defects  $\geq 20$  cm in right-side of colon  $\rightarrow$  prophylactic closure (Conditional recommendation, moderate-quality evidence)
- Pedunculated lesions
  - For polyps  $\geq 10$  mm
    - Use hot snare polypectomy (Strong recommendation, moderate-quality evidence)
  - For polyps head  $\geq 20$  mm
    - Use prophylactic ligation of polyp stalk
      - Clips
      - Loop, detachable (Strong recommendation, moderate-quality evidence)
    - Retrieve large specimen of polyp to be better able to examine the margins of the resection (Conditional recommendation, low-quality evidence)



➤ Lesion removal

- Endoscopic
  - 30 d mortality rate (MR) 0% to 0008%
- Electric surgery
  - 30 d MR 0.7%
  - Readmission 8%
  - Repeat surgery (“redo”) 4%

• Optical Diagnosis of Colorectal Lesion, NICE Classification

|                   | Type 1                                                                                                                    | Type 2                                                                                                                       | Type 3                                                                                                           |
|-------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| ○ Colour          | <ul style="list-style-type: none"> <li>– Same or</li> <li>– Lighter than background</li> </ul>                            | <ul style="list-style-type: none"> <li>▪ Browner relative to background (verify colour arises from vessels)</li> </ul>       | <ul style="list-style-type: none"> <li>▪ Brown to dark brown</li> <li>▪ Sometimes patchy whiter areas</li> </ul> |
| ○ Vessels         | <ul style="list-style-type: none"> <li>– None, or isolated vessels may be present coursing across the lesion</li> </ul>   | <ul style="list-style-type: none"> <li>▪ Brown vessels surrounding white structures</li> </ul>                               | <ul style="list-style-type: none"> <li>▪ Area(s) of disrupted or missing vessels</li> </ul>                      |
| ○ Surface pattern | <ul style="list-style-type: none"> <li>– Dark or white spots of uniform size, or homogenous absence of pattern</li> </ul> | <ul style="list-style-type: none"> <li>▪ Oval, tubular or branched white strictures** surrounded by brown vessels</li> </ul> | <ul style="list-style-type: none"> <li>▪ Amorphous/absent surface pattern</li> </ul>                             |
| ○ Histopathology  | <ul style="list-style-type: none"> <li>– Hyperplastic and sessile serrated lesions**</li> </ul>                           | <ul style="list-style-type: none"> <li>▪ Adenoma****</li> </ul>                                                              | <ul style="list-style-type: none"> <li>– Deep submucosal invasive cancer</li> </ul>                              |

- Diagnostic criteria for colorectal lesions using NBI as recommended in NICE classification.

\*\*These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.

\*\*\*In the World Health Organization classification, sessile serrated polyp and sessile serrated adenoma are synonymous. Sessile serrated polyps often demonstrate some dark, dilated crypt orifices.

\*\*\*\*Type 2 consists of Vienna classification types 3, 4, and superficial 5 (all adenomas with either low- or high-grade dysplasia, or with superficial submucosal carcinoma).

The presence of high-grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

• Diminutive ( $\leq 5$  mm) lesions

- Almost always benign
- Cold snare technique superior to
  - Cold forceps
    - Ratio of incomplete polyp removal 20% vs. 54%,  $P < 0.0001$
    - Injury to pathological specimen 53% vs. 1.3% ( $P < 0.0001$ )



- Small (6-9 mm) lesion
  - Cold snare vs. hot snare technique
    - ↓ risk of perforation / delayed bleeding
    - ↓ coagulation syndrome
    - ↓ residual adenoma (only 0.98%)

#### ❖ Marking Polyps

##### Recommendation

- If site of polyp removal may need to be located at a later date – mark (Strong recommendation, low-quality evidence)
  - Inject marker 3-5 cm distal to lesion site
    - Record the position of the resection site relative to the marker (Conditional recommendation, very low-quality evidence), and
    - Material, volume, as well as document with photograph (Strong recommendation, low-quality evidence)
    - Using an institution-based protocol for the marking is recommended (Conditional recommendation, very low-quality evidence)
- Surveillance
  - Piecemeal EMR, lesion  $\geq 20$  mm
    - Repeat colonoscopy
      - At 6 mon, then q1yr, then q3yr (Strong recommendation, moderate-quality evidence)
    - Use enhanced imaging (electronic or dye-based methods)
    - Take targeted biopsies from site of previous resection (Conditional recommendation, moderate-quality evidence)
  - Suspected local recurrence
    - Examine entire colon as well as the post-mucosectomy scar site to exclude synchronous colorectal lesions
    - Repeat EMR plus perimeter of post-treatment site
    - Use snare or avulsion method
    - Use CO<sub>2</sub> insufflation (Strong recommendation, moderate-quality evidence)
    - Once endoscopy and biopsies of local recurrence demonstrate “clear resection” → colonoscopy q1yr, then q3yr (Conditional recommendation, low-quality evidence)
    - Use microprocessor-controlled electrosurgical units (Conditional recommendation, very low-quality evidence)
    - If initial endoscopist uncomfortable/inexperienced to remove lesion refer to patient to more experienced/trained endoscopist (Strong recommendation, low-quality evidence)
    - Fully documented procedure, including method of resection (cold/hot snare, endoscopic mucosal resection [EMR]) (Strong recommendation, low-quality evidence)



- Non-pedunculated polyp
  - Features suggestive of submucosal invasive cancer
    - Resect en bloc prior to specimen to a flat surface before sending to pathologist (easier to perform required perpendicular sectioning (Strong recommendation, low-quality evidence))
    - Expectation of pathologist
      - Measure depth of invasion, distance of cancer to vertical/lateral resection margins, lymphovascular invasion, tumour budding (Strong recommendation, moderate-quality evidence)
- Pedunculated polyp
  - Resection en bloc
  - If submucosal invasion suspected pathologist should report
    - Distance of cancer to cautery line
    - Tumour differentiation time
    - Lymphovascular invasion
 (Strong recommendation, moderate-quality evidence)
- Maintenance of competence of Colonoscopist
  - Participate in quality-assurance program
  - Use polypectomy competency assessment tools
    - Direct observation of polypectomy competency assessment tools (Conditional recommendation, low-quality evidence)
  - Repeat/record
    - Adverse events (Strong recommendation, moderate-quality evidence)
    - Refer to surgery of patients for management of benign colorectal lesions (Conditional recommendation, moderate-quality evidence)
- Endoscopic mucosal resection (EMR)
  - Non-pedunculated colorectal lesions  $\geq 20$  mm
    - Safety
      - Severe adverse events 1%
      - Local recurrence 14%
    - Inject-and-cut EMR lesions  $\geq 20$  mm
      - Piecemeal resection electrocautery
      - En bloc (1 piece) lesion  $< 20$  mm
    - Use colloidal solution
      - Not NS (0.9% NaCl)
      - $\uparrow$  rates of en bloc resection
      - $\downarrow$  rates of residual lesions



- Serrated lesions
    - Inject-and-cut EMR
      - ↓ incomplete resection
      - ↓ rates of recurrence
        - ≥ 10 mm, 26 mon ~4%
        - ≥ 20 mm, 12 mon ~8%
  - Underwater endoscopic mucosal resection
    - No need to do submucosal injection before snare resection
  - Large lesions
    - Submucosal injection
      - Saline plus dilute epinephrine, methylene blue marker → cold snare
  - Endoscopic submucosal dissection (ESD)
    - Lesions > 20 mm diameter, in which inject-and-cut EMR is difficult
      - Large depressed lesion
      - Pseudo-depressed (LST-NG) lesion
      - Fibrosis in mucosal lesion
      - Early carcinoma, local residual after endoscopic resection
      - Non-polypoid
      - Dysplasia in IBD patient
- Adverse events associated with removal of colorectal lesion
- Bleeding
    - Post-polypectomy bleeding rate 9.8/100 (95%CI, 7.7-12.1)
      - Quality target ≤ 10 / 1000 (≤ 1/100) colonoscopies
      - Prophylactic therapy not effective to ↓ risk of post-polypectomy bleeding
    - Endoscopic clipping of post-polypectomy defects in large (≥ 20 mm) non-pedunculated lesions on the proximal colon → ↓ bleeding rate from 98% to 33%; P < 0.001
  - Perforation
    - Rates
      - Overall rate, 0.08% (95%CI, 0.006% - 0.1%)
      - Lesion ≥ 20 mm, 1.5% (95%CI, 1.2% - 1.7%)
    - Timing
      - Immediate: results for muscularis propria being included in tissue grasped by snare
      - Delayed: results from deep cut or necrosis from cautery
    - Risk factors
      - Tumour
      - Cecal location
      - Male patient
      - Comorbidities e.g., renal disease
    - Tumour size ≥ 20 mm





- Use of
  - Warfarin (adj OR 2.02; 95%CI 1.10-3.10)
  - NSAIDs (adj OR 21.5; 95%CI 14.4-32.0)
  - Corticosteroids (adj OR 2.12-1.14)

Abbreviation: Adj OR, adjusted odds ratio; CI, confidence interval

- Post-polypectomy syndrome (PPS) (aka post-polypectomy coagulation syndrome, transmural burn syndrome)
  - Pathogenesis
    - Full thickness cautery injury → thermal injury of bowel wall → local inflammation of serosa → peritonitis
      - ↓ risk with carbon dioxide (CO<sub>2</sub>) rather than air insufflation
  - Endoscopic therapy
    - Useful viewing
      - Submucosal Invasive Carcinoma  
Video: <http://links.lww.com/AJG/B420>, <http://links.lww.com/AJG/B421>
      - Diminutive Polyps (≤ 5 mm)  
Video 2: <http://links.lww.com/AJG/B443>). This allows for en bloc
      - Small Polyps (6-9 mm)  
Video 3: <http://links.lww.com/AJG/B444>
      - Pedunculated Colorectal Lesion  
Video 4: <http://links.lww.com/AJG/B445>, <http://links.lww.com/AJG/B431>, <http://links.lww.com/AJG/B432>
      - Dynamic Submucosal Injection  
Video 5: <http://links.lww.com/AJG/B446>
      - Incomplete treatment of deeper layers  
Video 6: <http://links.lww.com/AJG/B422>, <http://links.lww.com/AJG/B423>
      - Cold Snare Endoscopic Mucosal Resection  
Video 7: <http://links.lww.com/AJG/B447>, <http://www.com/AJG/B448>
      - Hot Avulsion technique  
Video 8: <http://links.lww.com/AJG/B424>
      - Hot Snare Polypectomy  
Video 9: <http://links.lww.com/AJG/B425>
      - Partial or full-thickness muscularis propria resection and potential perforation  
Video 10: <http://links.lww.com/AJG/B428>
      - Endoscopic Clipping Techniques  
Video 11 and 12: <http://links.lww.com/AJG/B429>, <http://links.lww.com/AJG/B499>, <http://links.lww.com/AJG/B450>, <http://www.com/AJG/B433>



## Post-polypectomy and Post-colorectal cancer resection surveillance: BSG, ACPGBI, BCSP, PHE and NHSE Guidelines (2020)

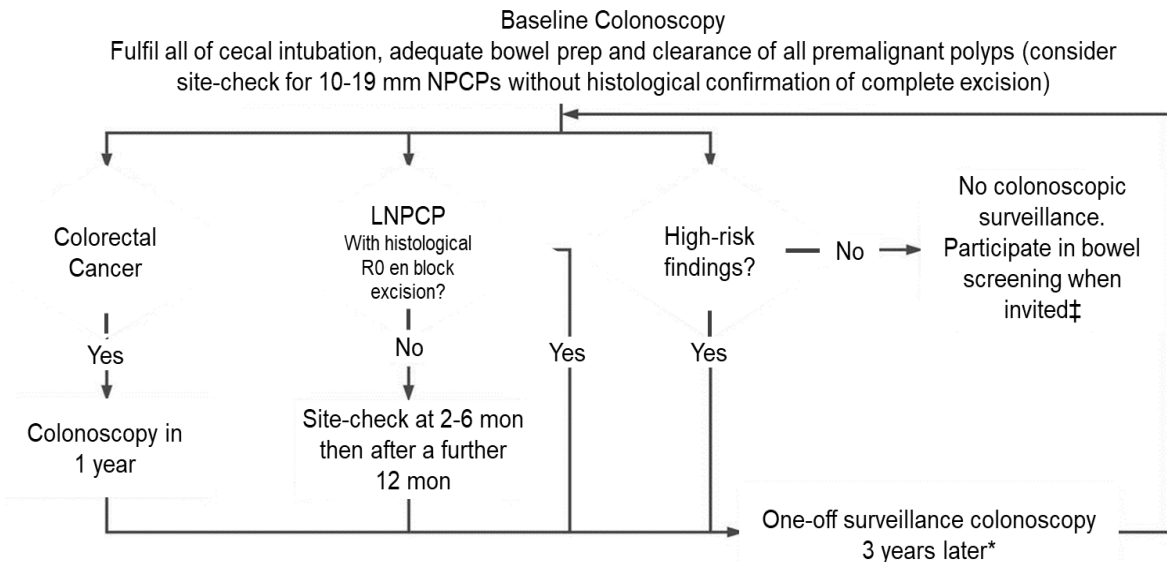
Rutter MD, et al. Gut 2020; 69: 201-223.

### ➤ Definition

- Serrated polyp
  - Hyperplastic polyps
  - Sessile serrated lesions (SSLs)
  - SSLs with dysplasia (SSLd)
  - Traditional serrated adenomas (TSA)
  - Mixed polyps
- Premalignant polyp
  - Serrated polyps (excluding diminutive (1–5 mm) rectal hyperplastic polyps)
  - Adenomatous polyps (does not include other polyps such as post-inflammatory polyps)
- Advanced serrated polyp
  - Serrated polyp
    - $\geq 10$  mm
    - Containing any grade of dysplasia.
- Advanced adenomatous polyp (advanced adenoma)
  - Adenoma  $\geq 10$  mm
  - Containing high-grade dysplasia
  - International definitions also include tubulovillous or villous histology (not part of the UK definition)
- Advanced colorectal polyp—The term includes both advanced serrated polyps and advanced adenomatous polyps.
- Advanced neoplasia
  - This term has been used historically to describe the combination of advanced adenomas and colorectal cancers.
  - The guideline development group (GDG) feels that the term is outmoded
    - It does **not** include lesions from the serrated pathway, and second
    - It combines two entities that have very different clinical significance.
  - However, as advanced neoplasia has been used extensively in the past as an outcome measure
    - The term was used as “a search term” in the evidence synthesis.



- BSG/PHE/ACPGBI Guidelines for Post-polypectomy and Post-cancer-resection Surveillance



#### Exceptions

\* In general, we recommend no surveillance if life-expectancy < 10 yr or if older than about 75 yr

‡ If patient is > 10 yr younger than lower screening age and has polyps but no high-risk findings, consider colonoscopy at 5-10 yr

#### High-risk findings

- ≥ 2 premalignant polyps including ≥ 1 advanced colorectal polyps; or
- ≥ 5 premalignant polyps

#### Definitions:

- Serrated polyps: umbrella term for hyperplastic polyps, sessile serrated lesions, traditional serrated adenomas and mixed polyps
- Premalignant polyps: serrated polyps (excluding diminutive [1-5 mm] rectal hyperplastic polyps) and adenomatous polyps
- Advanced colorectal polyps: serrated polyps ≥ 10 mm, serrated polyp with dysplasia, adenoma ≥ 10 mm, adenoma with high-grade dysplasia
- (L)NPCP: (Large; ≥ 20 mm) non-pedunculated colorectal polyp

Refer to BSG Hereditary CRC Guidelines if:

- Family history (FH) of colorectal cancer (CRC)
  - 1 first-degree relative (FDR) diagnose with CRC < 50 yr, or
  - 2 FDRs diagnosed with CRC at any age
- Personal history of CRC
  - < 50 yr
  - Any age, who also has FDR with CRC at any age



- Personal history of multiple adenomas:
  - < 60 yr with lifetime total  $\geq 10$  adenomas; or
  - $\geq 60$  yr with lifetime total  $\geq 20$  adenomas; or  $\geq 10$  + FH CRC/polypsis
- Known/suspected inherited CRC predisposes syndrome
  - Lynch syndrome or other polyposis syndrome
  - Serrated polyposis syndrome
    - $\geq 5$  serrated polyps  $\geq 5$  mm proximal to rectum, with  $\geq 2$  of  $\geq 10$  mm; or
    - $\geq 20$  serrated polyps (any size) including  $\geq 5$  proximal to rectum

Abbreviations: LNPCP, large non-pedunculated colorectal polyp; NPCPs, non-pedunculated colorectal polyps; y, years

Printed with permission: Rutter MD, et al. Gut 2020; 69: 201-223 (Figure 1)

❖ High risk criteria for future increased risk of CRC after polypectomy / CRC resection

Recommendations

- High risk for CRC
  - $\geq 2$  premalignant polyps including  $\geq 1$  advanced colorectal polyp
    - Serrated polyp of at least 10 mm in size
    - Containing ant grade of dysplasia
  - An adenoma of  $\geq 10$  mm in size, or containing high-grade dysplasia
  - $\geq 5$  premalignant polyps
- Index colonoscopy findings of adenoma with tubulovillous histology is associated with
  - $\uparrow$  risk of advanced adenomas (AA), advanced neoplasia (AN) and CRC at first surveillance

❖ Site check

- Perform “site check” colonoscopy within 2-6 mon of polypectomy/resection
  - Uncertain histological completeness of removal of non-pedunculated polyp 10-19 mm, or
  - Adenoma with high-grade dysplasia (HGD)
  - Serrated polyp, any size
- Perform subsequent colonoscopy surveillance for patients with the dose criteria based on the high-risk surveillance criteria (GRADE of evidence: low; Strength of recommendation: weak)



❖ The size of polyps

- ↑ risk of incomplete resection (colonoscopic polypectomy / en bloc resection)
  - 5-9 mm      7%
  - 10-20 mm    17%
  - Risk of incomplete resection
    - Sessile serrated polyp (SSP) adenomatous polyp
- Record polyp size as
  - En bloc “largest dimension of neoplastic tissue (adenoma or serrated) as measured by histopathological examination”
    - Endoscopic assessment of size (GRADE of evidence: Moderate; Strength of recommendation: Strong)
  - Piecemeal
  - The polyp size is used to assign surveillance intervals

❖ Testing of colonic surveillance (after colonoscopy +/- site check colonoscopy)

Recommendation

| Index Colonoscopy                                                                                                                                                                                    | Surveillance Colonoscopy                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| ○ High-risk findings                                                                                                                                                                                 |                                                                                                                      |
| – ≤ 75 yr                                                                                                                                                                                            | ▪ q3yr in persons with life expectancy > 10 yr, plus<br>(GRADE of evidence: Low; Strength of recommendation: Strong) |
| – > 75 yr                                                                                                                                                                                            | ▪ Generally, not in people older than about 75 yr<br>(GRADE of evidence: Low; Strength of recommendation: Weak)      |
| ○ No high-risk findings                                                                                                                                                                              |                                                                                                                      |
| – Do <b>not</b> do colonoscopic surveillance                                                                                                                                                         |                                                                                                                      |
| – Participate in their national bowel screening program when invited<br>(GRADE of evidence: Low; Strength of recommendation: weak)                                                                   |                                                                                                                      |
| • Clearance Colonoscopy (Site Checks) plus first surveillance                                                                                                                                        |                                                                                                                      |
| ○ Patients who have undergone a potentially curative CRC resection should have a clearance colonoscopy within a year of their diagnosis (GRADE of evidence: Low; Strength of recommendation: Strong) |                                                                                                                      |
| ○ Once a clearance colonoscopy has been performed in the postoperative period in patients who have had a CRC resection.                                                                              |                                                                                                                      |
| – The next surveillance should be performed after an interval of 3 yr.                                                                                                                               |                                                                                                                      |
| – The need for further surveillance should then be determined in accordance with the post-polypectomy high-risk criteria (GRADE of evidence: Low; Strength of recommendation: Strong)                |                                                                                                                      |



- Post-polypectomy surveillance recommendations

| Colonoscopy findings                                                           | High-risk criteria       | Low-risk (premalignant polyp(s) but no high-risk criteria)                                  | No polyps                                              |
|--------------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------|
| ○ Within national bowel screening age range or within 10 yr of lower age limit | – Colonoscopy after 3 yr | – Participate in national bowel screening when invited                                      | – Participate in national bowel screening when invited |
| ○ More than 10 yr younger than national bowel screening lower age limit        | – Colonoscopy after 3 yr | – Consider colonoscopy after 5 or 10 yr, individualized to their age and other risk factors | – Participate in national bowel screening when invited |

Printed with permission: Rutter MD, et al. Gut 2020; 69: 201-223 (Table 1)

- At least 75 yr old, or if life expectancy <10 yr
  - In general, no colonoscopic surveillance recommended
- There is ↑ risk of metachronous CRC after colonoscopy
  - This ↑ risk of metachronous CRC is associated with the presence of an initial metachronous tumour
    - The presence of synchronous CRC predisposes to ↑ risk of later metachronous CRC (RR, 13.9; 95%CI: 4.7-41.0; absolute risk of metachronous CRC is 1% in first 3 yr, then afterwards < 0.5%)
- Risk of metachronous CRC is highest in first 3 yr after diagnosis of CRC
- Suggested causes of metachronous CRC
  - CRC resection incomplete
  - Index colonoscopy missed CRC #2 (synchronous)
  - New CRC (metachronous CRC)
- Performing “clearance colonoscopy” after polypectomy/resection may detect a missed synchronous CRC.
- Post-polypectomy/resection “clearance colonoscopy” → ↑ 5 yr survival rate from 52% → 97% (P < 0.001)
  - Number of early (1 yr) clearance colonoscopies needed to
    - ↓ CRC, 143
    - ↓ CRC-related death, 926



- Low Risk Lesions
    - Low risk lesions
      - Pathologically en bloc R0 endoscopic mucosal resection (EMR)
      - LNPCP ( $\geq 20$  cm) endoscopic submucosal dissection (ESD)
      - Early polyp cancers
- } ■ Do **not** need to do site check with clearance colonoscopy
- These low-risk persons require post-polypectomy surveillance at 3 yr

## Recommendations

- Since recurrence rates are low pathologically
    - En bloc R0 endoscopic mucosal resection (EMR)
    - Endoscopic submucosal dissection (ESD) of LNPCPs
    - Early polyp cancers are low
      - No site checks are required, and
      - The patient should undergo post-polypectomy surveillance after an interval of 3 yr.
      - The need for further surveillance should then be determined in accordance with the post-polypectomy high-risk criteria
  - (GRADE of evidence: Low; Strength of recommendation: Strong)
  - Do a site check is performed 2–6 mons after piecemeal EMR or ESD of LNPCPs (at least 20 mm in size), in line with BSG/ACPGBI LNPCP guidelines.
  - Do second site check at 18 mons from the original resection is recommended to detect late recurrence.
  - Once no recurrence is confirmed, do post-polypectomy surveillance after an interval of 3 yr.
    - The need for further surveillance should then be determined in accordance with the post-polypectomy high-risk criteria (GRADE of evidence: Low; Strength of recommendation: Strong)
  - Polyp thought to have been completely resected
    - Optimal timing for site check
      - 6 mon
- Piecemeal resection
    - Proximal resection by EMR is associated with  $\uparrow$  risk of recurrence
      - 5-9% recurrence after 6-12 mon
      - Do a second site check / clearance colonoscopy at 12-18 mon, and if clear  $\rightarrow$  use standard surveillance intervals



- Consider Sydney Endoscopic Recurrence Tool (SERT)
  - Characteristics of polyps and resection method used to stratify risk of recurrence
  - Recurrence rate at 18 mon
    - Low-risk SERT, 12%
    - High-risk SERT, 36%
- } Recurrences can usually (>90%) by endoscopy
- Rates of recurrence
- EMR overall
  - En bloc 2-3%
  - Piecemeal 12-22%
- Pathological resection
- Definition
  - ≥ 50 µm clearance between dysplasia and edge of lesion
    - Without the additional site checks at 2-6 and 12-18 mon required for proximal resection, assuring the colon was comprehensively cleared of the lesions”
    - When lesion is resected en bloc and confirmed as both endoscopically and pathologically Ro
      - The risk of recurrence is sufficiently low that surveillance can be carried out at the standard surveillance interval dictated by size and number of polyps

#### Recommendations

- The need for ongoing colonoscopic surveillance should be determined by the colonoscopic findings at each surveillance procedure, using the same high-risk criteria to stratify risk (GRADE of evidence: Low; Strength of recommendation: Strong)
- In people with high-risk findings on a surveillance colonoscopy should undergo a further surveillance colonoscopy at an interval of 3 yr (with the same age-related caveats applied again) (GRADE of evidence: Low; Strength of recommendation: Strong)

#### ➤ Ongoing surveillance

#### Recommendations

- People with no high-risk findings on a surveillance colonoscopy should cease colonoscopic surveillance, but should participate in the national bowel screening programme when invited (with the same age-related caveats applied again) (GRADE of evidence: Low; Strength of recommendation: Strong)
- Surveillance colonoscopies should be performed only by
  - Colonoscopists who are either screening accredited, or
  - Whose colonoscopy performance measures (key performance indicators—KPIs) exceed the minimum standard as defined in the BSG lower GI quality standards publication
 (GRADE of evidence: Low; Strength of recommendation: Strong)





- When colonic surveillance is required after previous polypectomy, CTC is an acceptable alternative if colonoscopy is incomplete or not possible due to the patient's clinical condition (GRADE of evidence: Very low; Strength of recommendation: Strong)
- CT colonography (CTC)
  - Performance characteristics

|              | Overall pooled |             |
|--------------|----------------|-------------|
|              | Sensitivity    | Specificity |
| - 6 mm + AN  | 67%            | 92%         |
| - 10 mm + AN | 87%            | 96%         |

Abbreviations: AM, advanced neoplasia

- Post-imaging CRC (PICRC) at 34 mon follow-up, 0.61 PICRCs / 10<sup>3</sup> patient yr (4% of total cancers detected)

#### Recommendation

- If colonic surveillance is required after curative-intent resection of CRC, only use CTC for individuals in whom colonoscopy is contraindicated or not possible due to the patient's clinical condition (GRADE of evidence: Moderate; Strength of recommendation: Strong)
- Anastomotic recurrence, metachronous cancers
  - CRC
    - Sensitivity, 95%
    - Specificity, 100%
- Comparison of CTC vs. colonoscopy

| Polyps           | Sensitivity | Specificity |
|------------------|-------------|-------------|
| - ≥ 6 mm polyps  | 44%         | 92%         |
| - ≥ 10 mm polyps | 77%         | 96%         |

- Radiation risk of CRC
  - Average effective radiation dose indication < 3mSv
  - Average annual background radiation exposure per yr < 5 mSv
  - Risk of radiation-induced cancer decreases with age

#### Recommendation

- When post-polypectomy surveillance is indicated, the radiation risk of CTC is likely to be outweighed by its potential benefits (GRADE of evidence: High; Strength of recommendation: Strong)



- FIT testing for surveillance
  - 3-FIT tests used for surveillance, sensitivity
    - For CRC, 72%
    - For advanced adenomas (AA), 57%
- Do **not** use of fecal immunochemical testing (FIT) for surveillance after resection of premalignant colorectal polyps, as there is insufficient evidence (GRADE of evidence: Low; Strength of recommendation: Strong)
- Capsule colonoscopy (CC)
  - Adequate assessment by CC in only 43%

## Recommendation

- Do **not** use colon capsule (CC) for surveillance after resection of premalignant colorectal polyps, as there is insufficient evidence (GRADE of evidence: Very low; Strength of recommendation: Strong)
- Findings at index colonoscopy and risk of findings (AA, advanced neoplasia [AN], CRC) at first surveillance colonoscopy
  - Adenoma with tubulovillous histology
    - ↑ risk of AA, AN, CRC at first surveillance colonoscopy
  - Components on index colonoscopy
    - Tubulous
      - ↑ risk of AA
      - 18% (OR, 1.93; 95%CI: 1.59-2.34)
    - Villous
      - 25% (OR, 3.03; 95%CI: 2.33-3.95)
- Adenomas with high-grade dysplasia at index colonoscopy are associated with ↑ risk of AA, AN and CRC at first surveillance (GRADE of evidence: Moderate)
  - Adenoma size
 

|                                             |   |                                                                                                |                                                                                                   |
|---------------------------------------------|---|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Evidence that adenoma<br>≥ 20 mm<br>≥ 10 mm | } | ▪ At index colonoscopy associated with ↑ risk of AA, AN, CRC at first surveillance colonoscopy | → Consistent AA (GRADE of evidence: Moderate)<br><br>→ Inconsistent (GRADE of evidence: Moderate) |
|---------------------------------------------|---|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
- Adenoma number
- Inconsistent evidence for index colonoscopy predicting that the first surveillance colonoscopy will show ↑ risk of AA, AN, or CRC.
- Older age (GRADE of evidence: Moderate)
- Inadequate bowel preparation (GRADE of evidence: Low)
- Incomplete index colonoscopy (GRADE of evidence: Low)
- Advance serrated polyps (do surveillance as per AAs) (GRADE of evidence: Low)
- Adenomatous polyps plus serrated polyps have additive risk (GRADE of evidence: Low)
- Inconsistent evidence for index colonoscopy predicting that the first surveillance colonoscopy will show ↑ risk of AA, AN, or CRC.



- Adenomas plus
  - HGD (GRADE of evidence: Moderate)
  - $\geq 10$  mm (GRADE of evidence: Moderate)
  - Proximal (GRADE of evidence: Low)
  - Sessile/flat (GRADE of evidence: Low)
  - Multiple polyps predicting CRC inconsistent, evidence for an association with an  $\uparrow$  risk of CRC at first surveillance (GRADE of evidence: Moderate)
  - Family history of CRC (which falls short of warranting family history surveillance in its own right) is not associated with an  $\uparrow$  risk of AA, AN or CRC at first surveillance (GRADE of evidence: Moderate)
  - Smoking (GRADE of evidence: Low)
- $\downarrow$  risk
  - Younger age at index colonoscopy predicts  $\downarrow$  risk of AA, AP, CRC incidence / mortality on first surveillance colonoscopy (GRADE of evidence: Moderate)
- Serrated polyps  $< 10$  mm (except for rectal hyperplastic polyps) should be followed by surveillance of adenomas  $> 10$  mm, because they are both of  $\uparrow$  risk for CRC (GRADE of evidence: Low)
- Surveillance interval does not  $\downarrow$  CRC incidence/mortality if  $< 3$  yr (GRADE of evidence: Low)
- Insufficient evidence
  - To determine
    - If surveillance interval of 3 yr is better than a longer interval to  $\downarrow$  CRC incidence/mortality (GRADE of evidence: Low)
    - Who benefits most from a second surveillance colonoscopy (GRADE of evidence: Low)
    - What is optimal interval between first and second surveillance colonoscopy (GRADE of evidence: Low)
    - At what age of life expectancy surveillance colonoscopy "...can be stopped without  $\uparrow$  risk of future CRC (GRADE of evidence: Very low)
- Risk of colonoscopy
  - $\uparrow$  risk of colonoscopy with  $\uparrow$  age, comorbidities
  - Perforation risk, overall  $\sim 0.04\%$  (40/10<sup>5</sup>)
    - Post-polypectomy bleeding (PPB), 0.08% to 0.1%
    - Adverse GI event
      - Risk per 1000
      - Adjusted predicts risk age 80-87 yr vs. 66 to 69 yr, 8.8: 95%CI: 6.9 to 10.7, vs 5.0; 95%CI: 3.8-6.2
      - 30 d risk of adverse event, age 70-74 yr, 5.6/1000 (95%CI: 4.9-6.8) vs. age 75-79 yr, 10.3/1000 (95%CI: 8.6-11.1)
      - $\uparrow$  risk of post-polypectomy hospitalization (aOR, 1.28; 95%CI: 1.07-1.53; p=0.006)



## Hereditary cancer/polypsis risk

- Management of patients with a higher-than-average risk of CRC due to
  - Hereditary CRC syndromes
  - Serrated polyposis syndrome and
  - Other high familial CRC risks are covered in separate guidelines.
- A family history of colorectal cancer:
  - A family history of one first degree relative diagnosed with CRC < 50 yr, or
  - Two affected first-degree relatives diagnosed with CRC at any age.
- A patient with personal history of CRC diagnosed < age 50 yr (early onset CRC).
- A patient with a personal history of CRC diagnosed at any age, who also has a first degree relative diagnosed with CRC at any age.
- Patients with multiple polyps
  - Patients under 60 yr of age with  $\geq 10$  adenomas
  - Patients from 60 yr of age with
    - $\geq 20$  adenomas or  $\geq 10$  adenomas plus a family history of CRC/polypsis
- Patients with known or suspected inherited CRC predisposition syndromes including:
  - Lynch syndrome
  - Polyposis syndromes including
    - Serrated polyposis syndrome (SPS) and
    - Familial polyposis
- The diagnostic criteria for SPS have been redefined in a 2019 update by the World Health Organization:
  - $\geq 5$  serrated polyps proximal to the rectum all being  $\geq 5$  mm in size, with two or more  $\geq 10$  mm in size; or
  - $\geq 20$  serrated polyps of any size distributed throughout the large bowel, plus  $\geq 5$  serrated polyps proximal to the rectum included in the final polyp count.
    - The polyp count is cumulative over multiple colonoscopies.



## COLORECTAL CANCER (CRC)

### Colorectal Cancer Screen: ACG Guidelines (2021)

Shaukat A, et al. Am J Gastroenterol 2021; 116: 458-79

#### Recommendations

- Screening for CRC in average-risk individuals
    - Between ages 50 and 75 yr to ↓ incidence of advanced adenoma, CRC, and mortality from CRC (recommendation) (Strong recommendation; moderate-quality evidence)
    - Between ages 45 and 49 yr to ↓ incidence of advanced adenoma (AA), colorectal cancer (CRC), and mortality from CRC (Conditional recommendation; very low-quality evidence)
  - The decision to continue screening beyond age 75 yr should be individualized (Conditional recommendation; very low-quality evidence).
  - Use colonoscopy and fecal immune testing (FIT) as the primary screening modalities for CRC screening (Strong recommendation; low-quality evidence).
  - For individuals unable or unwilling to undergo colonoscopy or FIT, consider flexible sigmoidoscopy, multitarget stool DNA (mt-sDNA) test, CT colonography or colon capsule endoscopy (Conditional recommendation; very low-quality evidence).
- Screening tests
- One-Step: Colonoscopy
    - Overall CRC incidence
      - ↓ 69% (95% CI: 13-78%)
    - Mortality
      - ↓ 68% (95% CI: 57% - 77%)
      - Similar benefits reported in other studies e.g.,
        - Nurses Health Study and Health
        - Professionals Fellowship Study
        - US Veterans Kaiser Permanente study
  - Two-step: Stool tests (positive stool test → colonoscopy)

|            | ↓ mortality | Follow-up, yr |
|------------|-------------|---------------|
| – Biennial | 18%         | 30            |
| – Annual   | 20%         | 18            |
|            | 33%         | 20            |



- Fecal Immune test (FIT)

| Quantitative cut-off,             | µg/g stool hemoglobin | Sensitivity | Specificity |
|-----------------------------------|-----------------------|-------------|-------------|
| - CRC                             | 20                    | 79%         | 71%         |
| - Advanced adenomas (AA)          | 10                    | 91%         | 90%         |
| - Sessile serrated lesions (SSL)  |                       | 6-56%       |             |
|                                   |                       | 5-16%       |             |
| - Overall CRC detection rate, 80% |                       |             |             |

#### Practice Alert

- A positive FIT test requires a follow-up screening colonoscopy
  - Undertake quality assurance program to ensure that best practise (high quality) colonoscopy is performed.

- Multitarget stool DNA (mt-sDNA)

#### - Targets

- Hemoglobin FIT
- 3 kRAS Mutant
- BMPs Methylated
- NDRE4 Methylated

#### - Diagnostic accuracy: mt-sDNA vs. FIT

- CRC 92% vs. 74%
  - AA 42% vs. 24%
  - SSL ≥ 10 mm 42% vs. 5%
- } 87% vs. 95%

- There is ↓ specificity of mt-sDNA with ↑ age of patient

#### - Interval retesting

- Asymptomatic patient, mt-sDNA+, normal high-quality colonoscopy → **no** additional testing, unless indicated by other symptoms or laboratory testing
- sDNA+ → repeat mt-sDNA (or other screening test) in 3 yr

- Performance characteristics for stool and blood tests for CRC

|            | Sensitivity | Specificity |
|------------|-------------|-------------|
| - FIT      | 79%         | 94%         |
| - mt-sDNA  | 92%         | 87%         |
| - Septin 9 | 48%         | 91%         |



- Flexible Sigmoidoscopy (FS)
  - If adenomas found on FS → colonoscopy

|                 |                                                                                                        | ↓ CRC incidence | ↓ CRC mortality |
|-----------------|--------------------------------------------------------------------------------------------------------|-----------------|-----------------|
| - Men and women | 55 to 64 yr                                                                                            | 18-23%          | 22-31%          |
|                 | 55 yo 74 yr                                                                                            | 21%             | 26%             |
| - Women         |                                                                                                        |                 |                 |
|                 | Pooled trials show that in women ≥ 60 yr, flexible sigmoidoscopy does not ↓ CRC incidence or mortality |                 |                 |

❖ Other testing

• Diagnostic Imaging (CTC, CC)

- For persons who
    - Refuse colonoscopy or FIT, or
    - Are not candidates for colonoscopy
- } Consider T colography (CTC), or capsule colonoscopy (CC)

|       | Size    | Sensitivity | Specificity |
|-------|---------|-------------|-------------|
| ○ CTC | ≥ 6 mm  | 68-98%      | 80-93%      |
|       | ≥ 10 mm | 67-94%      | 86-98%      |

MCQ Gems

- CTC is similar in performance characteristics for polyps > 10 mm, but is less effective for detection of polyps < 5 mm
- CTC does not require sedation, and has almost no risk of perforation.
  - CTC does require a bowel preparation for cleansing

• Capsule colonoscopy (CC)

- Only 79% of CC's completed

| Sizes   | Sensitivity | Specificity |
|---------|-------------|-------------|
| ≥ 6 mm  | 81%         | 93%         |
| ≥ 10 mm | 80%         | 97%         |

- Comparison of CTC vs CC
  - ≥ 6 mm      32% vs. 84%
  - ≥ 10 mm    53% vs. 84%



- Blood test: Septin 9

|                                                                                                            | Sensitivity | Specificity |
|------------------------------------------------------------------------------------------------------------|-------------|-------------|
| ○ Pooled tests                                                                                             | 62%         | 88%         |
| ○ Enhanced assay                                                                                           | 90%         | 88%         |
| ○ Do <b>not</b> use Septin 9 for CRC screening (Conditional recommendation, very low-quality of evidence). |             |             |

➤ Consideration of Changing Age of Screening/Surveillance

- Screening Average Risk Persons earlier, age 45 yr

- Recommended age of initiated CRC screening in average age persons
  - Age 50 yr
    - MSTF (US Multi-specialty task force)
    - USPSTF (US Preventive Services Task Force)
  - Age 45 yr
    - ACS (American Cancer Society)

“These qualified recommendations were based on predictive modeling analysis and age-cohort epidemiology evidence”

CRC Screening

- Age in perspective: why to initiate CRC screening at 45 yr
  - Moving the age of initiating CRC screening in average risk patients from age 50 to age 45 yr old → 25 more life-years gained per 1000 intervals (700 days per person)

- Senior Citizens

- Considerations
  - ↑ life expectancy
    - ↑ comorbidities
    - ↑ CRC
  - The benefits of polypectomy are delayed for ~ 7-10 yr (time for adenoma → CRC development to occur)
  - ↑ complications of colonoscopy ↑ with age
  - “The value of screening declines as the risk of dying from other causes increases”
  - Suggestion
    - “The decision to continue or discontinue screening in the elderly should not be solely based on chronological age”
  - Guideline author’s opinion
    - “In adults age 86 yr and above, screening is **not** recommended because of competing causes of mortality”
    - However, it is acknowledged that there is room for discussion: “... to participate in shared discussion making for screening individuals older than 75 yr”





This author suggests

- At any age of the patient, discuss the risk vs. benefits of CRC screening
  - Recognize that it is the patient's physiological and chronological age which predicts their likely benefits of continuing CRC surveillance.
- If patient is healthy enough to undergo surgical treatment
  - If no CRC is found on FIT or colonoscopy, and patient does not have serious comorbidities, and wishes to continue screening, then by all means have this discussion.

- Genetic Background

- Persons who are African American have
  - ↑ incidence of CRC (males, 24% ↑; females, 19% ↑)
  - ↑ sex and stage-adjusted mortality from CRC; men, ↑ 47%; women, 34%)

A Moment to Reflect

- Health systems with equal access to the screening-diagnosis-treatment care paradigm, do not show such disparities (between races, with regards to early onset CRC)
- “..modelling studies show similar benefit of CRC screening in African American and in “whites” starting at the age of 45 yr
  - In Canada, it is uncertain if CRC screening should begin earlier in our Indigenous or African ancestry persons.

- Miss Rates

- While colonoscopy remains the “gold standard” for CRC screening
  - Colonoscopy is not perfect, and the risk of a missed cancer is ~ 5-10%.
  - These “interval” / post-colonoscopy colorectal cancer (PCCRC) are defined as
    - “CRC diagnosed after a colonoscopy which did not detect cancer”
    - The rate of PCCRC is predicted to be 1 per 3,174 colonoscopies (95% CI 1/2710 to 1/3875 colonoscopies)
    - The author recommends that every physician who is performing screening colonoscopy must maintain their personal record of guideline-based outcomes, such as adenoma detection rate (ADR).
- Quality improvement programs are targeted to ↓ risk of PCCRC



- ❖ Interval of Repeat Screening (“screening intervals”)
  - There are no RCTs comparing various screening intervals
  - Suggested intervals that should be followed for screening modalities:
    - FIT, q1yr
    - Colonoscopy, q10yr after normal initial high quality screening colonoscopy
 (Strong recommendation; low-quality evidence)
  - Note that the data for the benefit of FIT testing gives approximately similar benefits for testing q1yr vs. q2yr but nonetheless some guidelines still recommend FIT testing q1yr.
  - For other screening modalities:
    - Multitarget stool DNA test, q3yr
    - Flexible sigmoidoscopy, q5–10 yr
    - CTC, q5yr
    - CC, q5yr
 (Conditional recommendation; very low-quality evidence)

- Family History

#### Recommendations

- First Degree Relatives (FDR)
  - Do CRC screening colonoscopy at age 40, or 10 yr before the youngest affected relative (whichever is earlier) for individuals with CRC or advanced polyp in 1 first-degree relative (FDR) at age <60 yr, or CRC, or advanced polyp if ≥2 FDR at any age.
  - Do interval colonoscopy every 5 yr.
 (Conditional recommendation; very low-quality evidence)
- Perform genetic evaluation when there is higher familial CRC burden (higher number and/or younger age of affected relatives) (Conditional recommendation; very low-quality evidence)
- Start CRC screening at age 40 or 10 yr before the youngest affected relative, and then resuming average-risk screening recommendations for individuals with CRC or advanced polyp in 1 FDR at age ≥60 yr (Conditional recommendation; very low-quality evidence)
- In individuals with 1 second-degree relative (SDR) with CRC or advanced polyp
  - Follow average-risk CRC screening recommendations (Conditional recommendation; low-quality evidence).
- Endoscopists performing screening colonoscopy should measure their individual cecal intubation rates (CIRs), adenoma detection rates (ADRs), and withdrawal times (WTs) (Strong recommendation, moderate-quality evidence for ADR, low-quality of evidence for WT, and CIR).
- Colonoscopists with ADRs below the recommended minimum thresholds (~25%) (men, 30%; women, 20%) should undertake remedial training (Conditional recommendation, very low-quality evidence).



- Colonoscopists should spend at least 6 min inspecting the colonic mucosa during withdrawal (Strong recommendation, low-quality evidence).
- Colonoscopists should achieve CIRs of at least 95% in screening subjects (Strong recommendation, low-quality evidence).
- Chemoprevention
  - Diet modification
  - Low-dose aspirin
  - Statins (controversial)

#### Recommendations

- Use low-dose aspirin in
  - Persons between the ages of 50–69 yr with a cardiovascular disease risk of  $\geq 10\%$  over the next 10 yr
  - Persons who are not at  $\uparrow$  risk for bleeding, and who are willing to take aspirin for at least 10 yr to  $\downarrow$  risk of CRC.
 (Conditional recommendation; low-quality evidence)
- Do **not** use aspirin as a substitute for CRC screening (Strong recommendation, low-quality evidence).
- Organize CRC screening programs to  $\uparrow$  adherence compared with opportunistic screening (Strong recommendation; low-quality evidence)
- Use the following strategies to improve adherence to screening:
  - Patient navigation
  - Patient reminders
  - Clinician interventions
  - Provider recommendations, and
  - Clinical decision support tools
 (Conditional recommendation; very low-quality evidence)

Abbreviations: AA, advanced adenoma; AJCC, American Joint Committee on Cancer; CC, colonic capsule; CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; CTC, CT colography; EMR, endoscopic mucosal resection; FIT, fecal immune test; FOBT, guaiac fecal occult blood; GRADE, Grading of Recommendations Assessment, Development and Evaluation; JNET, Japanese Narrow Band Imaging Expert Team; LNM, lymph node metastasis; LST-G, laterally spreading tumor, granular type; LST-NG, laterally spreading tumor, non-granular type; mt-sDNA, multitarget stool DNA; NBI, narrow band imaging; NICE, Narrow Band Imaging International Colorectal Endoscopic; OR, Odds ratio; PCCRC, post-colonoscopy colorectal cancer; RR, relative risk; USMTF, US Multi-society Task Force on Colorectal Cancer; yr, year



## Fecal Immunochemical Testing (FIT) to Screen for Colorectal Neoplasia: USMSTF/ASGE Recommendations (2017)

Robertson DJ, et al. Gastrointestinal Endoscopy 2017; 85: 2-21.

- Performance of FIT test
  - When FIT test is positive in the context of CRC screening
    - FIT and Gualic Fecal Occult Blood Test (gFOBT) have similar specificity, but FIT > gFOBT sensitivity
    - FIT single-sample has greater patient adherence than gFOBT 3 cards / 6 stool samples
    - There is no special diet that needs to be taken before FIT
    - FIT done on “...spontaneous passed stool specimens” (not on stool from digital rectal examination [DRE])
  - Use FIT test rather than gFOBT
- When FIT test is positive → perform colonoscopy (do not repeat FIT)
  - Adenoma detection rate (ADR) on colonoscopy after positive FIT
    - Men, 45%
    - Women, 35%
  - If colonoscopy is negative after positive FIT
    - Do **not** do EGD
    - If colonoscopy is negative sometime in the past, but FIT test is positive now
      - Repeat colonoscopy
- Quality measures
  - Quality metres for FIT
    - FIT completion rate to those offered testing,  $\geq 60\%$
    - Proportion returning FIT that cannot be processed by the laboratory,  $< 5\%$
    - Colonoscopy completion rate for those with a positive FIT,  $\geq 80\%$
  - Fecal immunochemical tests (FITs) are used in some provinces / countries to screen for colorectal cancer (CRC), but also to be the gate keeper for approval of screening colonoscopy to detect advanced adenomatous colonic polyps / CRC.
  - The performance characteristics for FIT for CRC are only modest

|             | Performance characteristics for CRC |             |
|-------------|-------------------------------------|-------------|
|             | Sensitivity                         | Specificity |
|             | Mean (95% confidence interval)      |             |
| – Overall   | 71% to 91%                          | 90% to 95%  |
| – T1        | 40% (21% to 64%)                    |             |
| – T3        | 83% (68% to 91%)                    |             |
| – CRC       |                                     |             |
| ▪ Stage I   | 73% (65% to 79%)                    |             |
| ▪ Stage II  | 80% (74% to 84%)                    |             |
| ▪ Stage III | 82% (77% to 87%)                    |             |
| ▪ Stage IV  | 79% (70% to 86%)                    |             |



- The multitarget stool DNA (mt-sDNA) test for screening for CRC involves a combination of "...methylated BMP3 and NDRG4 mutant KRAS and B-actin, and measures hemoglobin through immunochemical testing"
  - A positive test has a positive predictive value (PPV) of 67%, with higher PPV (73%) for persons who have not had a previous colonoscopy (Eckmann JD, et al. Am J Gastroenterol 2020; 115: 608-615)

## Recommendations

- Perform repeated 1 sample FIT testing every year (Recommendation, low quality evidence)
  - FIT testing superior to 3-card FOBT (Strong recommendation; high quality evidence)
  - No need to change diet / medications for FIT
  - Do **not** use DRE-obtained stool (use "spontaneously passed stool for testing) (Weak recommendation; very low-quality evidence)
- When FIT test positive
  - Perform colonoscopy (Strong recommendation, moderate quality of evidence)
  - Especially any of the following apply clinical context (e.g., other worrisome, signs, symptoms, or laboratory values)
    - Patient factors
      - Risk factors for advanced neoplasia)
      - Patient preference
      - Prior colonoscopy examination quality (e.g., poor bowel preparation, endoscopists' poor adenoma detection rate) (Weak recommendation. Low quality evidence)
  - Use threshold for cut-off for positive test, hemoglobin  $\leq 20$   $\mu\text{g/g}$  (Weak recommendation; low quality of evidence)
  - Otherwise, so not search for GI causes of iron deficiency or for cases of symptoms / signs of upper GI pathology (Weak recommendation; very low-quality evidence)
- FIT positive, recent colonoscopy negative, consider repeat colonoscopy
- Follow manufacturer's recommendation re storage and transport of FIT test (Weak recommendation; low quality evidence)

Abbreviations: CRC, colorectal cancer; DRG, digital adenoma detection rate; EGD, esophagogastroduodenoscopy; FIT, fecal immune testing gFOBt, guaiac fecal occult blood test; USMSTF, Multi-Society Task Force



## Screening for Colorectal Cancer (CRC) US Preventive Services Task Force (USPSTF) Recommendation Statement (2016)

US Preventive Services Task Force. JAMA. 2016;315(23):2564-2575.

### ➤ Demography

- CRC is the second commonest cause of cancer death in the United States.
  - In 2016, an estimated 134 000 persons were diagnosed with the disease
    - About 49 000 died from it.
  - CRC is most frequently diagnosed among adults aged 65 to 74 yr
    - The median age at death from colorectal cancer is 73 yr.
- The USPSTF recommends screening for CRC starting at age 50 yr, and continuing until age 75 yr (A recommendation).
  - The net benefit of screening for CRC in adults aged 76 to 85 yr who have been previously screened is small
  - Adults who have never been screened for CRC are more likely to benefit.
- The decision to screen for CRC in adults aged 76 to 85 yr should be an individual one, taking into account the patient's overall health and prior screening history (C recommendation).
- Screening would be most appropriate among adults who
  - Are healthy enough to undergo treatment if CRC is detected, and
  - Do **not** have comorbid conditions that would significantly limit their life expectancy.
- The USPSTF
  - No head-to-head studies demonstrate that any of the screening strategies it considered are more effective than others, although the tests have varying levels of evidence supporting their effectiveness.
  - No review/consideration of evidence on the effectiveness of any particular surveillance regimen after diagnosis and removal of adenomatous polyps or CRC.
- A positive family history (excluding known inherited familial syndromes) is linked to ~20% of cases of CRC.
  - ~ 3-10% of the population has a first-degree relative with CRC
    - The USPSTF did not specifically review the evidence on screening in populations at ↑ risk.
  - Other professional organizations recommend that patients with a family history of colorectal cancer (a first-degree relative with early-onset CRC, or multiple first-degree relatives with the disease) be screened more frequently, starting at a younger age and with colonoscopy rather than fecal immune testing (FIT).



- Recommendations of others associations:
    - AGA: Every 10 yr as the single preferred screening strategy, beginning age 45 yr
    - ACP: Do **not** screen average-risk adults younger than 45 yr, older than 75 yr, or with an estimated life expectancy of < 10 yr.
  - Canadian Task Force on Preventive Health Care recommended that adults aged 50 to 59 yr (weak recommendation) and 60 to 74 yr (strong recommendation) be screened for colorectal cancer with
    - gFOBT or FIT every 2 yr or
    - Flexible sigmoidoscopy every 10 yr
  - It recommended
    - Against screening in adults  $\geq 75$  yr (weak recommendation), and
    - In favour of using colonoscopy as a primary screening test (weak recommendation)
- Characteristics of CRC Screening Strategies

| Screening Method                                                                                                                                                                                | Evidence of Efficacy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Other Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Stool-based tests               <ul style="list-style-type: none"> <li>○ gFOBT, q1yr</li> <li>○ FIT</li> <li>○ FIT-DNA; q1-3 yr</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>– RCTs with mortality end points:               <ul style="list-style-type: none"> <li>▪ High-sensitivity versions (e.g., Hemoccult SENSА) have superior test performance characteristics than older tests (e.g., Hemoccult II)</li> </ul> </li> <li>– Test characteristic studies:               <ul style="list-style-type: none"> <li>▪ <math>\uparrow</math> accuracy compared with gFOBT</li> <li>▪ Can be done with a single specimen</li> </ul> </li> <li>– Test characteristic studies;               <ul style="list-style-type: none"> <li>▪ Specificity &lt; FIT (<math>\uparrow</math> false-positive results, <math>\uparrow</math> diagnostic colonoscopies, and <math>\uparrow</math> adverse events per screening test</li> <li>▪ <math>\uparrow</math> sensitivity compared with FIT per single screening test</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>– Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test to perform at home)</li> <li>– Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)</li> <li>– There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test</li> </ul> |



| Screening Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Evidence of Efficacy | Other Considerations |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|----------------------|
| <ul style="list-style-type: none"> <li>Direct Visualization tests <ul style="list-style-type: none"> <li>Colonoscopy; q10yr <ul style="list-style-type: none"> <li>Prospective cohort study with mortality end point</li> <li>Requires less frequent screening</li> <li>Screening and diagnostic follow-up positive findings can be performed during the same examination</li> </ul> </li> <li>CT colonoscopy; q5yr <ul style="list-style-type: none"> <li>Test characteristic studies</li> <li>There is sufficient evidence about the potential harms of associated extracolonic findings, which are common</li> </ul> </li> <li>Flexible sigmoidoscopy, q5yr <ul style="list-style-type: none"> <li>RCTs with mortality end points: <ul style="list-style-type: none"> <li>Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies</li> </ul> </li> <li>Test availability has declined in the United States</li> </ul> </li> <li>Flexible sigmoidoscopy with FIT, q1yr <ul style="list-style-type: none"> <li>RCT with mortality end point (subgroup analysis)</li> <li>Test availability has declined in the United States</li> <li>Potentially attractive option for patients who want endoscopic screening but want to limit exposure</li> </ul> </li> </ul> </li> </ul> |                      |                      |

Printed with permission: US Preventive Services Task Force. JAMA. 2016;315(23):2564-2575 (Table 1)





- Screening for Colorectal Cancer: Clinical Summary

- Population
  - Adults aged 50 to 75 yr
  - Adults aged 76 to 85 yr
- Recommendation
  - Screen for colorectal cancer starting at age 50 yr (Grade: A)
  - The decision to screen for colorectal cancer is an individual one (Grade: C)
- Risk assessment
  - For the vast majority of adults, the most important risk factor for colorectal cancer is older age
  - Other associated risk factors include family history of colorectal cancer, male, sex, and black race.
- Screening tests
  - There are numerous screening tests to detect early-stage colorectal cancer, including stool-based tests (gFOBT, FIT, and FIT-DNA), direct visualization tests (flexible sigmoidoscopy, alone or combined with FIT; colonoscopy; and CT colonography), and serology tests (SEPT9 DNA test)
  - The USPSTF found no head-to-head studies demonstrating that any of these screening strategies are more effective than others, although they have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations
- Starting and Stopping Ages
  - The USPSTF concluded that the evidence best supports a starting age of 50 yr for the general population.
    - The age at which the balance of benefits and harms of colorectal cancer screening becomes less favourable varies based on a patient's life expectancy, health status, comorbid condition, and prior screening status.
  - The USPSTF does **not** recommend routine screening for colorectal cancer in adults 86 yr and older
- Treatment and interventions
  - Treatment of early-stage colorectal cancer generally consists of local excision or simple polypectomy for tumours limited to the colonic mucosa or surgical resection (via laparoscopy or open approach) with anastomosis for larger, localized lesions.



- Balance of benefits and harms
  - The USPSTF concludes with high certainty that the net benefit of screening for colorectal cancer is substantial.
  - The USPSTF concludes with moderate certainty that the net benefit of screening for colorectal cancer in adults aged 76 to 85 yr who have been previously screened in small.
  - Adults who have never been screened are more likely to benefit.
  - Screening is most appropriate for those healthy enough to undergo treatment and those without comorbid conditions that significantly limit their life expectancy
- Other relevant USPSTF recommendations
  - The USPSTF has made a recommendation on aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in average-risk adults.
    - This recommendation is available on the USPSTF website (<http://www.uspreventiveservicestaskforce.org>).

Printed with permission: US Preventive Services Task Force. JAMA. 2016;315(23):2564-2575 (Table 2)

Abbreviations: ACP, American College of Physicians; AGA, American Gastrointestinal Association; FIT, fecal immune testing; gFOBT, guaiac-based fecal occult blood test; RCT, randomized controlled trial; USPSTF, US Preventive Services Test Force



## Colorectal Cancer Screening: United States Multi-Society Task Force (USMSTF) (2017)

Rex DR, et al. Am J Gastroenterol 2017;112(7):1016-1030.

### ➤ Objective

- ↓ risk of CRC by finding following or removing premalignant colonic polyps

### Recommendations

- Average risk, age  $\geq 50$  yr (strong recommendation; moderate-quality evidence), but age 45 for “African American” (weak recommendation, very low-quality evidence).
  - Note that persons with symptoms e.g., bleeding, iron deficiency, have a need for investigation for “case finding”, not for screening (Strong recommendation, moderate-quality evidence)
- Consider stopping screening
  - Negative previous screening (especially by colonoscopy)
    - Age 75 yr, or
    - When life expectancy  $< 10$  yr (Weak recommendation, low quality evidence)
    - No previous screening: consider starting screening up to age 85 (depending on comorbidities) (Weak recommendation, low-quality evidence).

### ➤ Surveillance recommendations

- FIT q1yr; colonoscopy q10yr (if screening colonoscopy normal); CT colonoscopy q5yr, FIT-fecal DNA, q3yr
  - May also consider flexible sigmoidoscopy, capsule colonoscopy
  - Maintain quality assurance program for FIT, colonoscopy
  - Suggestive: colonoscopy, or FIT-positive → colonoscopy

### ❖ Multi-Society Task Force ranking of current colorectal cancer screening tests

- Tier 1
  - Colonoscopy q10yr
  - Annual fecal immunochemical test (FIT), q1yr
- Tier 2
  - CT colonography q5yr
  - FIT/fecal DNA, q3yr
  - Flexible sigmoidoscopy q10yr (or q5yr)
- Tier 3
  - Capsule colonoscopy, q5yr
- Septin 9 **not** currently recommended Available tests



- Screening average-risk persons begins age 50 yr with
    - Colonoscopy q10yr, or
    - Annual FIT as first-tier options for screening the average-risk persons
    - FIT, q1yr, or
    - Colonoscopy q10yr (Strong recommendation; moderate quality evidence)
  - Measure quality of testing
    - FIT (Strong recommendation, low-quality evidence)
    - Colonoscopy (Strong recommendation, high-quality evidence)
- ↓
- Patient refusal
- ↓
- Perform
- CT colonoscopy q5yr, or
  - FIT – fecal DNA q3yr, or
  - Flexible sigmoidoscopy q3yr (Strong recommendation, high-quality evidence) in patient)
- ↓
- Patient refusal
- ↓
- Do **not** do
- Capsule colonoscopy (Weak recommendation, low-quality evidence)
  - Septin 9 testing (Weak recommendation, low-quality evidence)

#### ➤ Family History

- No longer average risk screening
  - First/second degree relative, CRC, or documented advanced adenoma (AA)
    - 10 yr younger than the age at which the youngest first-degree relative may be diagnosed, or age 40 yr, whichever is earlier
    - Start, interval q5yr
- First degree relative's age < 60 yr
  - These ages of initiation may need to be altered, since recent guidelines suggest age 45 yr to initiate average risk persons.
- ≥ 1 first-degree relative ≥ 60 yr with a documented “advanced-serrated lesion (weak recommendation, very low-quality evidence)
  - SSP/TSA ≥ 10 mm
  - SSP with dyspepsia

} As above for advanced adenoma (AA) (weak recommendation, very-low quality evidence)
- If patient declines colonoscopy, substitute FIT q1yr (Strong recommendation, moderate quality evidence)

Abbreviations: CRC, colorectal cancer; SSP, sessile serrated polyp; TSA, traditional serrated adenoma; USMSTF, US Multi-Society Task Force; yr, year



## Screening for CRC in Persons who have First or Second Family Member with CRC or Advanced Adenoma: CAG and AGA Clinical Practice Guideline (2018)

Leddin D, Lieberman DA, et al. Gastroenterology 2018; 155: 1325-1347

### ➤ Demography

| Family History                    | Relative | Screening           | Onset                 | Interval |
|-----------------------------------|----------|---------------------|-----------------------|----------|
| Colorectal Cancer (CRC)           | ≥ 1 FDR  | Colonoscopy, or FIT | Age 40-50 yr,         | q5-10 yr |
| Documented Advanced Adenoma (DAA) |          | or FIT              | or 10yr               | q1-2 yr  |
| CP                                | ≥ 2 FDRs | Colonoscopy, or FIT | Age 40-50 yr, or 10yr | q5yr -   |
|                                   | ≥ 1 SDRs | Colonoscopy, or FIT | Age 50 yr             | ARG      |
| Advanced Adenoma (AA)             | ≥ 1 FDR  | Colonoscopy or FIT  | Age 50                | ARG      |

- Prevalence of a person who has first-degree relatives (FDRs) with CRC
  - ≥ 1, 3% to 10%
- Persons in a population-based screening program only ~55%
- ↑ risk of CRC
  - Personal history of IBD
    - Hereditary syndrome ~5% of CRC population
    - Non-hereditary syndromes, but family history (FH) (presumed mutations and defects in uncertain genes)
  - Family history of CRC
- Lynch syndrome (hereditary non-polyposis colon cancer, [HNPCC])
- Familial adenomatous polyposis (FAP)
  - Attenuated familial adenomatous (AFAP)
  - MUTYH-associated polyposis (MAP)
- Peutz-Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- Cowden syndrome (CS)
- Serrated [hyperplastic] polyposis syndrome (SPS)



Abbreviations: AA, advanced adenoma; AFAP, attenuated familial adenomatous; ARG, age-related guidelines; CS, Cowden syndrome; DAA, documented advanced adenoma; FAP, familial adenomatous polyposis; FDR, first-degree relatives; FH, family history; FIT, fecal immune testing; HNPCC, hereditary non-polyposis colon cancer; JPS, Juvenile polyposis syndrome; MAP, MUTYH-associated polyposis; PJS, Peutz-Jeghers syndrome; SDR, second degree relatives; SPS, Serrated [hyperplastic] polyposis syndrome

- Please see recent related guidelines
  - Gupta S, et al. J Natl Compr Canc Netw 2017;15(12):1465–1475.
  - Also please see table below for recommendations as to which persons with a family history of CRC / associated cancers) should be referred to a clinical geneticist.

## Recommendations

- 1 or more FDR with a history of CRC
  - Screening for CRC  
GRADE: Strong recommendation, moderate-quality evidence.  
Vote: strongly agree, 100%
- 1 FDR with history of CRC
  - Colonoscopy as the preferred screening test (vs. no screening or all other screening modalities)  
GRADE: Conditional recommendation, very-low-quality evidence  
Vote: strongly agree, 88%; agree, 13%
  - FIT as second-line screening option  
GRADE: Conditional recommendation, moderate-quality evidence  
Vote: strongly agree, 50%; agree, 38%; uncertain, 13%
  - For screening colonoscopy
    - Commence CRC screening at age 40-50 yr or 10 yr younger than the age of diagnosis of the FDR, whichever is earlier  
GRADE: Conditional recommendation, very-low-quality evidence  
Vote: strongly agree, 50%; agree, 50%
    - 5-10 yr as screening intervals  
GRADE: Conditional recommendation, very-low-quality evidence.  
Vote: strongly agree, 25%; agree, 63%; uncertain, 13%
  - For screening FIT
    - Commence CRC screening at age 40-50 yr or 10 yr younger than the age of diagnosis of the FDR, whichever is earlier  
GRADE: Conditional recommendation, very-low-quality evidence  
Vote: strongly agree, 25%; agree, 75%
    - Use 1-2 yr as screening intervals  
GRADE: Conditional recommendation, very-low-quality evidence.  
Vote: strongly agree, 38%; agree, 63% or more FDRs with CRC



- 2 or more FDR with history of CRC
  - Use colonoscopy as the preferred screening test over no screening or all other screening modalities  
GRADE: Strong recommendation, very-low-quality evidence.  
Vote: strongly agree, 63%; agree, 38%
  - Commence CRC screening at age 40 yr or 10 yr younger than the age of diagnosis of the earliest diagnosis FDR, whichever is earlier  
GRADE: Conditional recommendation, very-low-quality evidence.  
Vote: strongly agree, 63%; agree, 38%
  - Use 5 yr as screening intervals  
GRADE: Conditional recommendation, very-low-quality evidence  
Vote: strongly agree, 38%; agree, 63% 1 or more SDR with CRC
- 1 or more SDRs with history of CRC
  - Screening (vs. no screening)  
GRADE: Strong recommendation, moderate-quality evidence  
Vote: strongly agree, 88%; agree, 13%
  - Commence CRC screening at age 50 yr  
GRADE: Conditional recommendation, low-quality evidence  
Vote: strongly agree, 50%; agree, 50%
  - Screening tests and intervals in accordance with average-risk guidelines  
GRADE: Conditional recommendation, very low-quality evidence.  
Vote: strongly agree, 38%; agree, 63% 1 or more FDR with advanced adenoma
- 1 or more FDR with history of a documented advanced adenoma
  - Screen (vs. no screening)  
GRADE: Strong recommendation, moderate-quality evidence  
Vote: strongly agree, 63%; agree, 38% No recommendation.
  - Colonoscopy or FIT over no screening or all other screening modalities  
GRADE: Conditional recommendation, very-low-quality evidence  
Vote: strongly agree, 63%; agree, 38%
  - Undergoing screening with
    - Colonoscopy or FIT, commence CRC screening at age 40-50 yr or 10 yr younger than the age of diagnosis of the FDR, whichever is earlier  
GRADE: Conditional recommendation, very-low-quality evidence  
Vote: strongly agree, 38%; agree, 38%; uncertain, 25%
    - Colonoscopy, 5–10 yr as screening intervals  
GRADE: Conditional recommendation, very low-quality evidence  
Vote: strongly agree, 13%; agree, 75%; uncertain, 13%



- 1 or more FDR with history of non-advanced adenoma or polyp of unknown histology
  - Screening in accordance with average-risk guidelines
 GRADE: Conditional recommendation, low-quality evidence  
 Vote: strongly agree, 63%; agree, 38%

- Multiple parallel systematic review streams, informed by 10 literature searches, assembled evidence on 5 principal questions around the effect of an FH of CRC or adenomas on the risk of CRC, the age to initiate screening, and the optimal tests and testing intervals. The GRADE (Grading of Recommendation Assessment, Development and Evaluation) approach was used to develop the recommendations.
- Persons > 50 yr:      M ~ 30%      }      ▪ Prevalence of advanced adenoma is ~7%  
                                          risk of adenoma      F ~20%      }      ▪ Thus ~25% of persons with adenomas have AAs

## Criteria

- Diagnosis of CRC and >10 colorectal adenomas
- Personal history of ≥20 adenomas
- Desmoid tumor, multifocal or bilateral CHRPE
- Meeting the revised Bethesda Guidelines
- A family history that meets Amsterdam Criteria
- Colorectal (or endometrial) cancer with microsatellite instability or immunohistochemistry consistent with Lynch syndrome
- Multiple gastrointestinal hamartomatous polyps or serrated polyposis syndrome
- A family with a known hereditary syndrome associated with CRC +/- a known mutation
- Papillary thyroid cancer that is the cribriform-morular variant, or hepatoblastoma





- Suspected
  - FAP
  - Lynch syndrome
  - PJS, JS, SPS
  - Hereditary syndrome
- Eyes
  - Congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Thyroid
- Risk of CRC in person with
  - Adenoma
    - ↑ 35% (RR, 1.35; 95%CI, 1.25 to 1.46)
  - Advanced adenoma
    - ↑ 70% (RR, 1.68; 95% CI, 1.29 to 2.18)
- Advanced adenoma (AA) → ↑ risk of developing AA
  - Siblings of persons with any adenoma
    - ≥ 1 advanced adenoma
      - 6x ↑ risk of having AA (OR, 6.05; 95%CI, 2.74 to 13.36)
      - 3x ↑ risk of having any adenoma (OR, 3.29; 95%CI, 2.16 to 5.03)
  - ↑ risk of CRC was ↑ age of persons who are at average or ↑ risk
    - The cumulative incidence curves are parallel: risk of CRC
      - With FH, 40 yr
      - No FH, 50 yr
  - "Initiating screening at age 40 yr (OR 10 yr younger than the age of diagnosis of the FDR) among individuals with an FH of CRC has been associated with the low CRC rate of only 3%
- Summary of Recommendations for Screening for Colorectal Cancer in Individuals With a Family History According to Decreasing Level of Elevated Risk of Colorectal Cancer<sup>a</sup>
  - ≥ 1 SDR with CRC, or ≥ 1 SDR with non-DA
    - Guidelines for average risk persons
  - ≥ 1 FDR with DAA/CRC
    - Colonoscopy/FIT
      - Begin at 40-50 yr, or 10 yr younger than age of affected FDR
      - Repeat colonoscopy q5-10 yr, or repeat FIT q1yr
  - ≥ FDR with CRC
    - Colonoscopy
      - Begin at 40-50 yr, or 10 yr younger than age of earliest CRC in affected FDR
      - Repeat colonoscopy q5yr



- Benefit
  - Screening flexible sigmoidoscopy →
    - ↓ incidence of CRC (RR, 0.78; 95%CI, 0.74 to 0.80)
    - ↓ all cause mortality (RR, 0.97; 95%CI, 0.96 to 0.99)
    - ↓ CRC mortality (RR, 0.72; 95%CI, 0.65 to 0.80)
  - Screening colonoscopy →
    - ↓ incidence of CRC (RR, 0.31; 95%CI, 0.12 to 0.77)
    - ↓ mortality of CRC (RR, 0.32; 95%CI, 0.23 to 0.43)
      - There is no difference of screening program participation rates between colonoscopy and guaiac fecal occult blood test (gFOBT)
  - gFOBT →
    - ↓ incidence of CRC (RR, 0.96; 95%CI, 0.90 to 1.02)
    - All cause mortality (most statistically significant; RR, 1.00; 95%CI, 0.99 to 1.10)
    - CRC mortality (RR, 0.87; 95%CI, 0.82 to 0.92)
  - Fecal immunochemical test (FIT) vs. gFOBT →
    - ↑ neoplasia detection rate (RR, 2.15; 95% CI, 1.58 to 2.94)
    - ↑ uptake rate (RR, 1.16; 95%CI, 1.05 to 1.28)
    - Performance characteristics of FIT in person with FH of CRC
      - To detect CRC
        - Sensitivity 86% (95%CI, 31% to 99%)
        - Specificity 91% (95%CI, 89% to 93%)
      - To detect other CRC or AA
        - Sensitivity 46% (95%CI, 37% to 56%)
        - Specificity 93% (95%CI, 90% to 95%)



## BOWEL CLEANSING FOR COLONOSCOPY

### Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US Multi-Society Task Force (USMSTF) on Colorectal Cancer

Johnson DA, et al. Am J Gastroenterol 2014; 109: 1528-45

#### ➤ Education and facilities

##### Recommendations

- Provide oral and written patient education instructions. "...for all components of the colonoscopy preparation and emphasize the importance of compliance (Strong recommendation, moderate quality evidence)
- Ensure patient has "appropriate support and process measures...to achieve adequate colonoscopy preparation" (Strong recommendation, low-quality evidence)
- Bowel cleansing diet
  - Use low residue or full fluids until the evening of the day before colonoscopy (Weak recommendation, moderate-quality evidence)
  - Split dose regimen
    - First dose, evening before colonoscopy (Strong recommendation, high-quality of evidence)
    - Second dose, begin 4 to 6 h before the time of colonoscopy, with completion of the last dose  $\geq 2$  h before the time of the colonoscopy (strong recommendation, moderate quality evidence)
  - Advantage of split dosing:  $\uparrow$  patient
    - Acceptance and willingness to have a second colonoscopy (Strong recommendation, high quality evidence)
  - Specific patient populations
    - Children/adolescents, seniors
      - Sodium phosphate (NaP)
      - Do **not** use NaP in persons with IBD (Weak recommendation, low quality evidence)
    - Pregnancy
    - Bariatric surgery
      - Low-volume preparations, or
      - High-volume preparations given over a larger interval (Weak recommendation, very low quality)
  - Persons at  $\uparrow$  risk for poor bowel preparation
    - History of
      - Constipation
      - Previous persons inadequate bowel preparation
      - Colonic resection
    - Constipating medication
    - Diabetes mellitus
    - Spinal cord injury (Weak recommendation, low quality evidence)
  - Same day regimen
    - Alternative [not as adequate] as split dose
    - Especially suitable for afternoon colonoscopy
    - **No** suitable for constipation patient (Strong recommendation, high quality evidence)

Give additional  
purgatives



- Preparations
  - Consider patient factors when selecting colonoscopy preparation (age, comorbidities, prior colonoscopy preparations (Strong recommendation, moderate quality evidence)
  - In healthy non-constipated individuals, 4 L PEG-ELS formulation produces a bowel cleansing quality that is **not** superior to a lower-volume PEG formulation (Strong recommendation, high quality evidence)
  - OTC preparations, or by prescription 4 L PEG-ELS with bisacodyl (2 L at each setting)
  - Do **not** use magnesium-based preparation for persons with chronic renal disease (Weak recommendation, very low-quality evidence)
  - For most patients, the routine use of adjunctive agents for bowel cleansing before colonoscopy is **not** recommended (Weak recommendation, moderate quality evidence) (please see special considerations, next page)
- Salvage options
  - Use large volume enemas (Weak recommendation, very low-quality evidence)
  - Through the colonoscopy enemas (particularly for patients receiving propofol sedation)
  - Awakening patient from sleep to continue with cathartic intake and reattempting colonoscopy the same or next day (Weak recommendation, low-quality evidence)
- Colonoscopy after inadequate bowel preparation
  - Beyond rectosigmoid, inadequate to see polyp < 5 mm
    - Recleansing and repeating colonoscopy the same day, or
    - Reschedule for another time, using an aggressive preparation regime (Strong recommendation, low quality evidence)
      - Preparation inadequate, beyond the cecum
    - Repeat colonoscopy with a more aggressive preparation regime within 1 yr
    - Advanced neoplasia seen
      - Repeat colonoscopy in < 1 yr (Strong recommendation, low quality evidence)

Abbreviations: h, hour; L, litre; OTC, over the counter; PEG-ELS, polyethylene glycol – electrolyte lavage solution; USMSTF, US Multi-society Task Force

- Quality evaluation
  - Definition of adequate cleansing
    - “Cleansing that allows a recommendation of a screening or surveillance interval appropriated to the findings to the findings of the examination” (colonoscopy)
  - Target
    - Such patient should achieve “adequate cleansing” in ≥ 85% of their examinations (Strong recommendation, low quality evidence)
  - Assess quality of bowel preparation “after all appropriate efforts to clear residual debris (Strong recommendation, low-residual evidence)
  - Use an accepted bowel preparation scale (Johnson DA, et al. Am J Gastroenterol 2014; 109: 1528-45), such as
    - Aronchick Bowel Preparation Scale
    - Boston Bowel Preparation Scale



## ACUTE LOWER GI BLEEDING (LGIB)

### Diagnosis and management of acute lower gastrointestinal bleeding: BSG Guidelines (2018)

Oakland K, et al. Gut 2019; 68: 776-789

#### ➤ Demography

- Incidence (United Kingdom)
  - 33 to 87 / 10<sup>5</sup>
- Mortality rate (MR)
  - Development of LGIB
    - In hospital, 18%
    - Out of hospital, 3.4%
    - Transfusion requirements ≥ 4 units of packed red blood cells (PRBCs)
  - ↑ with age / number of comorbidities

#### ➤ Causes

- Diverticulosis – Severe bleeding in ~60%
- Angiodysplasia – Commonest in cecum
- Proctopathy – Colitis, colorectal cancer/polyps (including post-polypectomy bleeding), radiation damage
- Idiopathic (~25%)
- Classification of severity

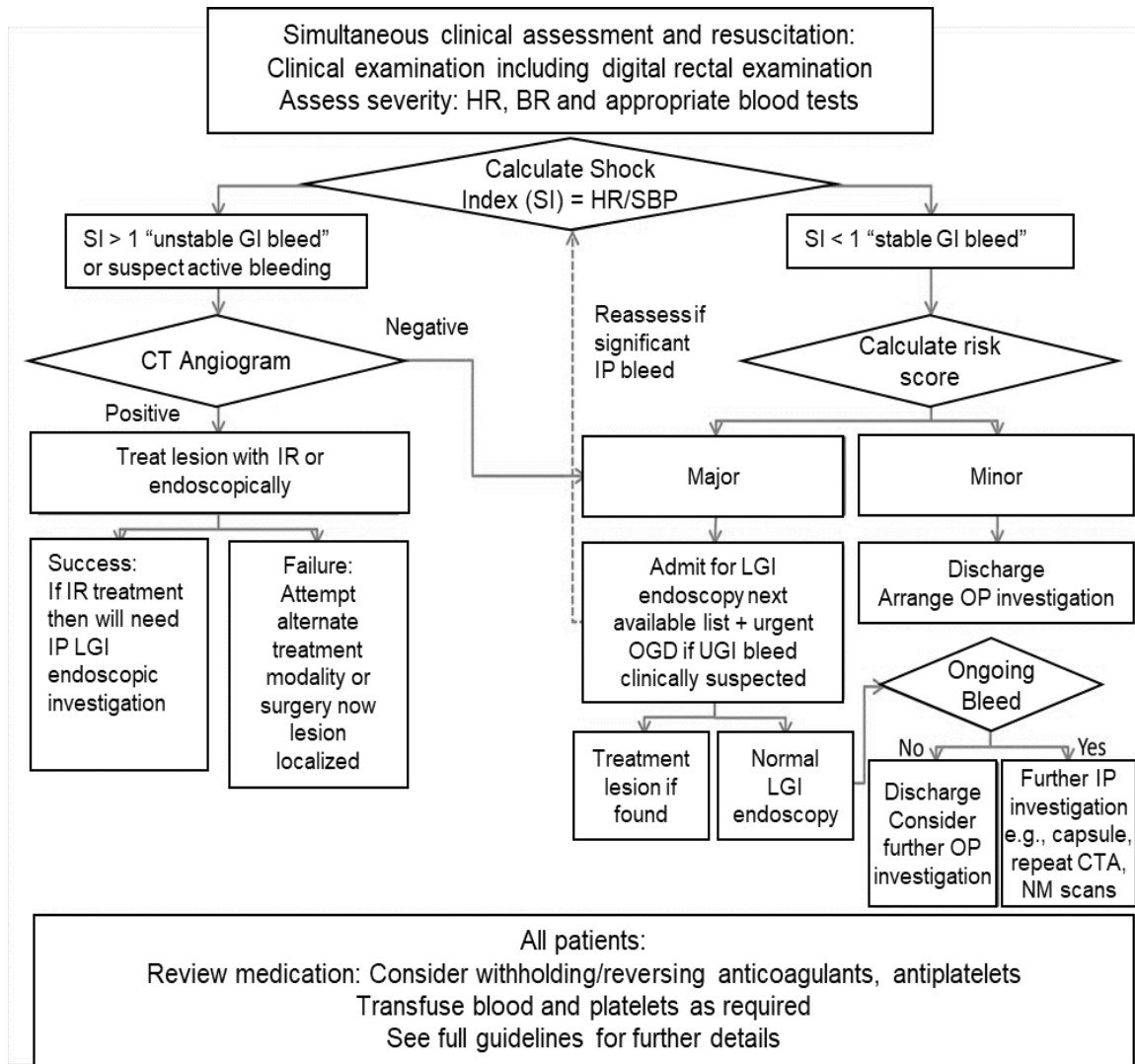
|          | Shock Index | (HR/SBP) | } Oakland risk<br>assessment score |
|----------|-------------|----------|------------------------------------|
| Stable   | <1          | Major    |                                    |
| Unstable | >1          | Minor    |                                    |

Weak recommendations, moderate quality evidence

- Some of the individual components (self-terminating)
  - Oakland score (OS)
    - ≤ 8
      - Minor bleed, patient has 95% chance of safe discharge, low risk of adverse outcomes; rebleeding, need for PRBC transfusion; not sensitive to predict mortality
    - > 8
      - Major bleed, patient requires hospitalization



- Management algorithm for patients presenting with acute lower gastrointestinal bleeding.



Shock index (SI) is calculated by dividing the heart rate (HR) by the systolic blood pressure (SBP).

Abbreviations: IP, inpatient; IR, interventional radiology; EGD, esophagogastro-duodenoscopy; OP, outpatient; UGI, upper gastrointestinal

Printed with permission: Oakland K, et al. Gut 2019; 68: 776-789 (Figure 1)



- Shock index > 1 predicts that angiography will show extravasation of blood

Variables comprising the Oakland score Predictor Score component value Age

| Predictor                 |            | Score Component Value |
|---------------------------|------------|-----------------------|
| ○ Age                     | - < 40     | 0                     |
|                           | - 40-69    | 1                     |
|                           | - ≥ 70     | 2                     |
| ○ Gender                  | - Female   | 0                     |
|                           | - Male     | 1                     |
| ○ Previous LGIB admission | - No       | 0                     |
|                           | - Yes      | 1                     |
| ○ DRE findings            | - No blood | 0                     |
|                           | - Blood    | 1                     |
| ○ Heart Rate              | - <70      | 0                     |
|                           | - 70-89    | 1                     |
|                           | - 90-109   | 2                     |
|                           | - ≥110     | 3                     |
| ○ Systolic blood pressure | - <90      | 5                     |
|                           | - 90-119   | 4                     |
|                           | - 120-129  | 3                     |
|                           | - 130-159  | 2                     |
|                           | - ≥160     | 0                     |
| ○ Hemoglobin (g/L)        | - <70      | 22                    |
|                           | - 70-89    | 17                    |
|                           | - 90-109   | 13                    |
|                           | - 110-129  | 8                     |
|                           | - 130-159  | 4                     |
|                           | - ≥160     | 0                     |

Patients scoring ≤8, with no other indications for hospital admission are suitable for immediate discharge from Accident and Emergency and outpatient investigation.

Abbreviations: DRE, digital rectal examination; LGIB, lower gastrointestinal bleeding.

Printed with permission: Oakland K, et al. Gut 2019; 68: 776-789 (Table 1)



## Recommendation

### ➤ Diagnosis

- Minor, OS  $\leq 8$ 
  - No comorbidity / other indication for hospitalization
  - Discharge home. With early (within 2 wk) outpatient/clinic follow-up (Strong recommendation, moderate quality evidence)
- Major, OS  $> 8$ 
  - Hospitalizations
  - Colonoscopy (next available list" (Strong recommendation, moderate quality evidence)
  - Diagnostic yield, 42-90%
  - Diagnostic yield
    - Colonoscopy, 72%
    - Sigmoidoscopy, 77%
    - No different diagnostic outcome with colonoscopy vs. CT angiography
    - Suggestion: CTA if patient is unstable
- Colonoscopy for stable patient
  - Timing
    - Colonoscopy in  $< 24$  h of admission results in
      - $\downarrow$  PRBC transfusion stay
      - $\downarrow$  length of hospital
      - $\uparrow$  therapeutic yield
      - No difference in mortality
    - Use regular bowel preparation when patient is stable
- CTA for unstable patient

## Recommendation

- Unstable shock index  $> 1$  (heart rate [HR] / systolic blood pressure [SBP]) after initial resuscitation +/- active bleeding stopped
  - Perform CTA (Strong recommendation, low quality evidence)
  - In unstable patient, perform CTA within 60 min (Strong recommendation, low quality evidence)
- Performance characteristics of OTA
  - Sensitivity, 79-95%
  - Specificity, 95-100%
  - Optimal to detect bleeding of  $\sim 0.3$ -1.0 mL/min, i.e, hemodynamic instability, active LGIB with shock index  $\geq 1$





### Clinical Tips

- The incidence of LGIB from hemorrhoids is sufficiently high (~27%) that especially in patients with fresh red blood per rectum, anorectal inspection and anoscopy should be considered.
- If CTA/anoscopy non-contributing
  - colonoscopy
  - esophagogastroduodenoscopy (EGD) to exclude 10% chance of upper GO bleeding source.

- Consider performing a nuclear medicine scan or video capsule endoscopy (VCE) if CTA, colonoscopy/EGD are negative, especially if bleeding is intermittent/slow
  - Sensitivity
    - Nuclear medicine, 60-93%
    - VCE, 50-72% (when performed within 48 h)

### ➤ Treatment

- Endoscopic hemostatic therapy (EHT)
  - Injection (epinephrine)
    - 4-quadrant injection, 1:10,000 epinephrine, among the vessel
  - Clipping
    - ↑ risk of perforation when performed above rectum
  - Thermal coagulation
    - Bipolar
    - Argon plasma coagulation (APC)
  - Ligation band loops
  - Hemostatic powder
- EGD
  - As above, except glue injection for gastric varices, and medical therapy with PPIs, octreotide, midodrine, and ceftriaxone
- Embolization
  - When extravasation of blood seen on a CTA → platinum coils, N-butyl cyanoacrylate, polyvinyl alcohol particles
  - Outcomes
    - Nuclear medicine, 60-93%
    - Bowel ischemia, 7-24%
    - Rebleeding
      - Early, 10-50%
      - Late, 25% at 2 yr

▪ Perform 2 modalities of EHT for greater success



- When LGIB with no diagnosis or malignancy, embolization may be done empirically
  - Success rates
    - Acute LGIB, 98%
    - Non-acute, 68%
  - Mortality rate (embolization)
    - Empirical, 31%
    - Targeted, 9%

## Recommendation

- Perform emergency laparotomy (usually for emergency subtotal colectomy) only when OTA/endoscopy (including “on-table endoscopy”) fails to localize bleeding (“...except under exceptional circumstances”) (Strong recommendation, low quality evidence)

## • Transfusions

### Recommendations

- When in need of blood transfusions
  - Stable patients
    - Target initiation of transfusion when hemoglobin concentration (Hg)
  - Stable patients with cardiovascular disease (including acute coronary syndrome) peripheral vascular disease, stroke, target initiation at 80 g/L, and concentration of Hg additional/maintained of 80-100 g/L (Strong recommendation, low quality evidence)
  - Benefit of restrictive transfusion (including from esophageal varices)
    - ↓ rebleeding
    - ↓ mortality
- The need for transfusion of fresh frozen plasma is uncommon.

## ❖ Management of Anticoagulant and Antiplatelet Drugs

### • Warfarin

- All patients
  - Stop warfarin at presentation with bleeding (weak recommendation, low quality evidence)
- Unstable patient
  - Reverse anticoagulation effect of warfarin (↑ INR) with platelet complex concentrate (PCC) and vitamin K (strong recommendation, moderate quality evidence)
- High thrombotic risk patient
  - Mitral valve
    - Stenosis
    - Mitral valve
  - Prosthetic valve plus atrial fibrillation
  - Venous thrombosis within 3 mon

- Bridge warfarin / DOAC with low molecular weight heparin (LMWH) at 48 h after LGIB/UGIB

(Strong recommendation, low quality evidence)



- Aspirin (ASA)
  - Primary prophylaxis for cardiovascular (CV) events
    - Stop permanently (weak recommendation, low quality evidence)
  - Secondary prophylaxis
    - Usually continues ASA
    - If ASA stopped, restart after bleeding stops
- Dual Antiplatelet Therapy (DAPT): ASA plus P2Y<sub>12</sub> Receptor Antagonist (PRA)
  - Patient with coronary stent
    - Usually continue DAPT (ASA + PRA)
  - Unstable bleeding
    - Continue ASA
    - Stop PRA, restart within 5 d

(Strong recommendation, moderate quality of evidence)
- Antifibrinolytic Drugs
  - Not recommended to use tranexamic acid





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