Motility Evaluation in the Patient with Inflammatory Bowel Disease

Sherine M. Abdalla, MD[a], Gorav Kalra, MD[b], Baha Moshiree, MD, MS-CI[c,*]

KEYWORDS

• Functional bowel disease • Motility disorders • Gastroparesis
• Gastroesophageal reflux disease • Irritable bowel syndrome
• Dyssynergic defecation • Fecal incontinence • Small bowel bacterial overgrowth

KEY POINTS

- Patients with inflammatory bowel diseases (IBD) suffer frequently from functional bowel diseases (FBD) and motility disorders.
- Complete evaluation of ongoing symptoms not related to an inflammatory flare in patients with IBD should be prompt with consideration of these motility disorders for which diagnostic studies are now available.
- Management of FBD and motility disorders in IBD combined with continued treatment of a patient's IBD symptoms will likely lead to better clinical outcomes and improve the patient's quality of life.

INTRODUCTION

Patients with inflammatory bowel disease (IBD) have significantly higher rates of functional bowel diseases (FBD) as compared with healthy controls[1,2] and often require motility evaluation for ongoing symptoms not thought to be related to an IBD flare. In fact, 66% of patients with IBD in one study met Rome III criteria for at least one FBD and the number of FBD symptoms correlated positively with anxiety/depression scores and negatively with health-related quality-of-life scores.[1] Given the high

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[a] Department of Medicine, Jackson Memorial Hospital, University of Miami Miller School of Medicine, 1611 NW 12th Avenue, Central Building, 600D, Miami, FL 33136, USA; [b] Department of Medicine, Jackson Memorial Hospital, University of Miami Miller School of Medicine, 1120 Northwest 14th Street, CRB, 11th Floor, Miami, FL 33136, USA; [c] Department of Medicine, University of Miami Miller School of Medicine, 1120 Northwest 14th Street, CRB Suite 971, Miami, FL 33136, USA
* Corresponding author.
E-mail address: bmoshiree@med.miami.edu

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prevalence of motility disorders in patients with IBD resulting in diminished quality of life and sometimes narcotics use, it is important for physicians to recognize and treat comorbid motility disorders and FBD. The goals of this review were to summarize the most recent literature on motility disturbances in patients with IBD and to give a brief overview of the ranges of motility disturbances, from reflux disease to anorectal disorders, and discuss their diagnosis and specific management.

GASTROESOPHAGEAL REFLUX DISEASE IN INFLAMMATORY BOWEL DISEASE

Gastroesophageal reflux disease (GERD) is a widely spread condition, with a reported prevalence of up to 27.8% of the US population.[3] IBD and GERD share upper gastrointestinal (GI) symptoms, such as heartburn, chest pain, and regurgitation. In more advanced upper GI involvement in IBD, patients may even present with dysphagia, odynophagia, worsening reflux symptoms, or obstructive symptoms, such as early satiety, postprandial vomiting, and weight loss.[4] GERD is encountered more frequently in patients with IBD than in the general population. In one study of more than 450 patients with IBD, the prevalence of GERD was 62% in ulcerative colitis (UC) and 72% in Crohn's disease (CD), and having a diagnosis of GERD was associated with reduced quality of life.[2] Although the esophagus is the least common location to be affected by CD in the GI tract,[4] it is likely underdiagnosed in adults due to lack of endoscopic biopsies of the esophagus.[4] The involvement of upper GI tract in IBD is increasingly becoming recognized, however, due to the now more frequent utilization of upper GI endoscopy in the assessment of patients with IBD.

GERD can be diagnosed clinically by improvement of typical symptoms with proton pump inhibitor (PPI) therapy and/or endoscopically by an upper endoscopy with biopsies showing esophagitis, or objectively by measuring acidity and duration of acid reflux episodes using a 24-hour ambulatory esophageal pH monitoring system. The diagnosis of CD esophagitis is more challenging due to the similarity of its manifestations to those of more common entities (eg, GERD).[5]

The prevalence of esophageal CD ranges from 0.2% to 11.2% in adults and up to 43.0% in children.[6,7] The prevalence of macroscopic upper GI tract inflammation in CD on endoscopy ranges from 30% to 64% of patients with CD in pediatric literature,[8,9] whereas microscopic inflammation had been reported to be present in 70% of patients.[10,11] Consensus among gastroenterologists regarding the definition of what qualifies to be significant upper GI involvement in IBD is yet to be established.[12] Although most of the literature links upper GI tract involvement to CD, the once widespread notion that UC is never associated with upper GI tract involvement is no longer considered valid.[12] Albeit used to be considered a separate entity that may not coexist with more distal disease in the 1998 Vienna classification of IBD,[13] upper GI involvement in CD has been accepted to accompany distal disease in the 2005 Montreal classification of CD.[14]

Endoscopically, GERD esophagitis has 3 stages: active, healing, and scarring,[15,16] based on the degree of presence of redness, necrotic debris, regenerating epithelium, and epithelial staining with Lugol iodine. The endoscopic findings in CD esophagitis are similar to those of colonic disease, and usually manifest as areas of inflammation, linear ulcerations, or, in more advanced disease, mucosal nodularity, cobblestone appearance, fistulas, fibrosis, stenosis, and/or strictures.[4–6,17] Histologically, CD esophagitis shows segmental, focal inflammatory infiltration of the lamina propria, extending between the muscle fibers of the muscularis mucosa, consisting mainly of lymphocytes, and associated with edema, dilated lymphatics, and epithelioid granulomas in the lamina propria, and may be associated with focally enhanced gastritis.[17]

Granulomas are considered the histologic hallmark of CD of the esophagus, given that other causes of granulomatous inflammation of the GI are excluded and other manifestations of CD, such as colonic involvement and non-GI manifestations, are present.[17] On the other hand, GERD esophagitis has been associated with mostly nonspecific inflammatory changes,[16] including dilated intercellular spaces, intrapapillary blood vessel dilation, intraepithelial bleeding, elongated papillae, basal cell hyperplasia, acanthosis, intraepithelial eosinophils, and Langerhans cells. Granulomas should not be present in GERD-related esophagitis.

Given the potential histology differentiation of GERD and esophagitis due to CD, endoscopy with biopsy is indicated when even mild upper GI symptoms are present in patients already diagnosed with IBD.[4] However, because CD esophagitis may go undiagnosed or misdiagnosed in a subset of patients who are asymptomatic and as the correlation of upper GI symptoms with true endoscopically and pathologically proven disease in patients with CD has not been fully established, this warrants upper GI endoscopy in all patients with established CD. This differentiation between upper GI involvement in IBD and reflux esophagitis is important, as treatment modalities used to treat each entity are different and have long-term consequences.

PPIs are frequently used to manage the symptoms of GERD and for diagnosis of reflux. PPIs, however, also have anti-inflammatory properties with improvement of IBD itself, including a decreased risk of pouchitis after ileal pouch anal anastomosis (IPAA).[18] Lack of differentiation between the 2 entities usually results in inappropriate administration of PPI therapy for symptomatic relief, which although shown to be clinically beneficial in CD esophagitis by anecdotal reports,[19] has never been proven with high-quality-level evidence-based data.[20] PPI therapy, once started, is usually continued for prolonged periods of time and this may predispose patients to the long-term side effects, most notably vitamin B12 and iron deficiency, hypomagnesemia, and increased risk of osteoporosis, pathologic fractures, chronic kidney disease, pneumonia, and enteric infections,[21,22] especially because patients with CD are also at risk of malabsorption, *Clostridium difficile* infections, and fractures.[23,24] In this context, PPIs should perhaps be even avoided in patients with IBD because they further predispose to malnutrition and bacterial overgrowth syndrome,[25,26] which results in symptoms of nausea and bloating, further exacerbating patients' symptoms.

Our Recommendations

The authors therefore recommend routine upper GI endoscopy in all patients with IBD with biopsies performed in the upper and lower esophagus and, in particular, those with established or suspected CD with upper GI symptoms. Endoscopy may conveniently be performed at the time of colonoscopy especially in those with concomitant complaints of diarrhea, and may aid in identifying sites of unsuspected CD. Moreover, routine upper GI endoscopy may be considered a comprehensive evaluation tool for determining CD extent in patients with established CD, and allows for differentiation of UC from CD in patients with predominantly colonic involvement with no small bowel or patchy colonic involvement, which are both clear signs of CD.[12] Given the risks associated with PPI use, we recommend stepping down therapy when possible, as well as increased utilization of histamine receptor antagonists (H2RAs), such as ranitidine, and calcium-containing antacids for those with infrequent symptoms, as many patients with IBD are at risk for osteoporosis. In patients with atypical or extraesophageal GERD who lack typical symptoms of pyrosis and regurgitation, we recommend pH testing to avoid giving PPIs to patients without true GERD. Patients who do not have significant acid reflux on pH testing performed while off of PPI may be classified as having functional heartburn or reflux hypersensitivity, based on the presence or

absence of symptom correlation to reflux events. Treatment of these patients is largely empiric, with trials of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or gabapentin.[27] The authors also recommend avoidance of PPI therapy in patients with IBD, given the extensive long-term side effect profile of these agents, and the likely exacerbation of symptoms in these patients (Fig. 1).

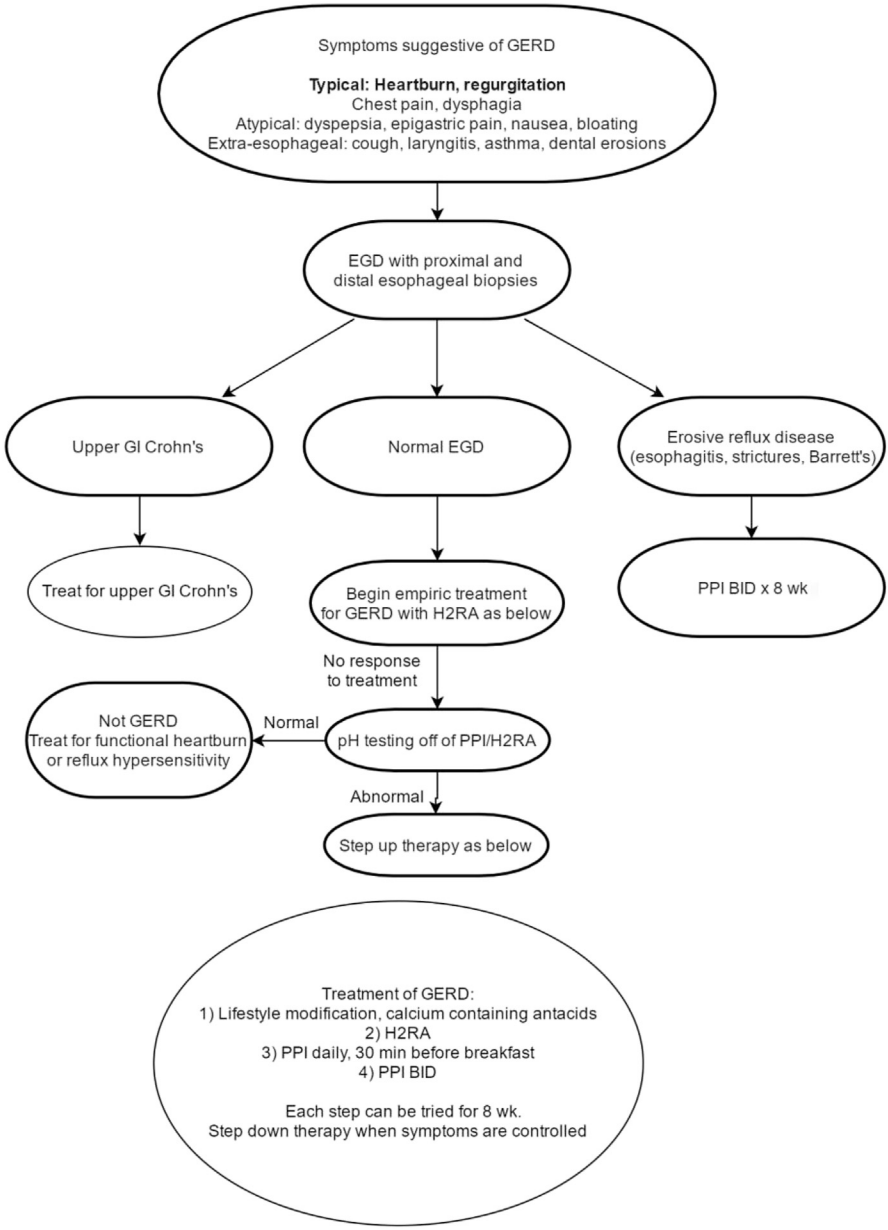

Fig. 1. Evaluation and management of suspected GERD. EGD, esophagogastroduodenoscopy.

GASTRIC DISORDERS IN INFLAMMATORY BOWEL DISEASE

Upper GI involvement occurs in approximately 34% of patients with CD, with the most common histologic correlates being gastric inflammation (84%), duodenal inflammation (28%), and gastric granulomas (23%).[28] Upper GI CD may be underdiagnosed, as a large proportion of these patients are asymptomatic.[29]

Gastroparesis

Gastroparesis (GP) is a syndrome of delayed gastric emptying in the absence of mechanical obstruction.[30] The cardinal symptoms include nausea and vomiting (N/V), early satiety, postprandial fullness, bloating, and upper abdominal pain. In severe cases, it can result in weight loss and malnutrition. The cause is most frequently idiopathic, although it can also result from diabetes, prior surgery, thyroid disease, neurologic disease, autoimmune disease, medications that retard gastric emptying, or following a viral illness.

Delayed gastric emptying (GE) appears to occur more frequently in patients with CD as compared with UC or healthy controls.[31,32] One study of children with IBD found that 33% of those with CD had had delayed GE, whereas all of the children with UC had normal GE.[31] After medical management of their CD and nutritional supplementation, significant improvements in GE were seen. Another study involving patients with IBD with moderate or no disease activity, 46% of patients with CD had prolonged GE, as compared with 20% of patients with UC.[32] In the subgroup of patients with CD, only vomiting was associated with delayed GE, whereas pain, nausea, bloating, and early satiety were not.

The mechanism for the delayed GE that occurs in some patients with IBD is unclear. In an animal model of rats with colitis induced via Trinitrobenzenesulfonic acid exposure, gastric emptying was found to be delayed, even in the absence of local gastric inflammation.[33] When these rats had their pelvic nerve sectioned, gastric emptying returned to baseline, suggesting that pelvic afferent nerve hyperactivity may contribute to delayed gastric emptying. Another study showed threefold elevations in postprandial cholecystokinin (CCK) levels in patients with CD versus controls, and postulated that excessive CCK release may contribute to delayed GE.[32] Other potential mechanisms could be loss of the interstitial cells of Cajal, which are lower in density in the small bowel tissue from patients with CD as compared with controls.[34]

Studies have also yielded conflicting results regarding the correlation between disease activity in CD and the presence of delayed GE. A study of 17 children with CD found that GE of solids was significantly slower in those who were malnourished, although liquid emptying was preserved, a phenomenon seen in patients with anorexia.[35] The delay in GE correlated with caloric intake and involvement of the duodenum (57%), but not with disease activity. Still, others have shown that disease activity may be correlated with prolonged GE.[36] Not surprisingly, patients with UC who have had previously undergone IPAA have similar solid-phase GE compared with controls,[37] but those with more than 6 bowel movements (BMs) per day have more rapid emptying of liquids as compared with those who had 6 or fewer BMs per day and those with constipation also have delayed GE.

Our Recommendations for Gastroparesis

An algorithm for the evaluation and management of suspected GP in patients with IBD is presented in **Fig. 2**. We recommend screening for delayed GE by solid-phase gastric emptying scintigraphy using the standardized method by Tougas and colleagues,[38] with a positive test having greater than 10% retention at 4 hours. Drugs that effect

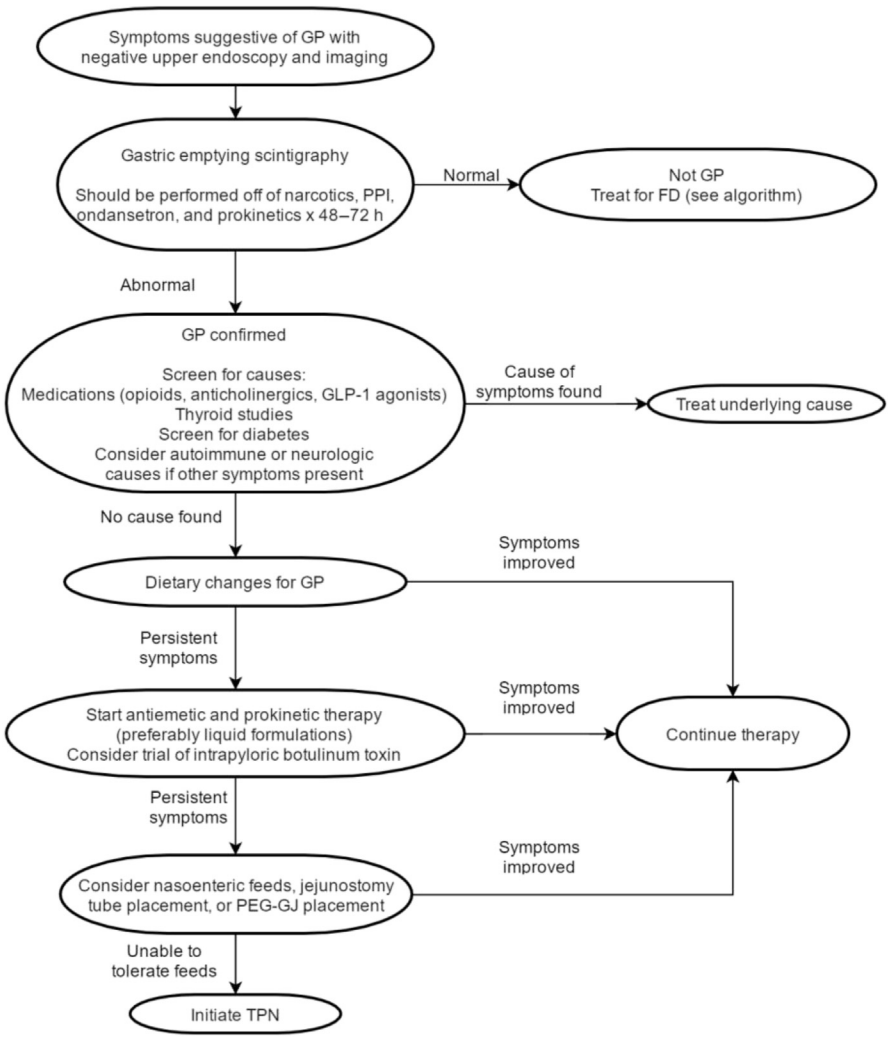

Fig. 2. Evaluation and management of suspected GP.

gastric motility, such as opioids, PPIs, ondansetron, prokinetics, anticholinergics, and glucagon-like peptide 1 (GLP-1) agonists, should be discontinued for 48 to 72 hours before testing. We recommend against the use of wireless motility capsule, as it is contraindicated in patients with CD given the risk of capsule retention in patients with possible strictures.[39] We also recommend against the use of 13-C breath testing, as its accuracy is contingent on normal small bowel absorption, which may not be the case in many patients with IBD. An upper endoscopy should be performed to exclude upper GI CD, other mucosal disease, celiac sprue, and mechanical obstruction.[30] In patients with CD, MRI enterography should be performed to exclude distal strictures resulting in recurrent partial small bowel obstruction that may mimic symptoms of GP. After GP is diagnosed, potential causes should be screened for and treated.

Initial management of gastroparesis consists of dietary modification with a low-fat, low insoluble fiber diet with small, frequent meals, and use of a liquid multivitamin.

Foods that have been found to provoke symptoms include those that are fatty, acidic, spicy, or contain significant roughage.[40] For those unable to tolerate solids, food can be blenderized or liquid nutritional supplements can be used. Antiemetics can be used to treat nausea. Although TCAs are widely used for GP, a multicenter trial of nortriptyline for idiopathic gastroparesis failed to show improvement over placebo.[41] Although macrolides are currently the most potent prokinetics available for treatment of GP,[42] their associated risk of developing *C difficile* infection with chronic use, risk of diarrhea, and potentially increased risk of sudden cardiac death limit their use in IBD.[43,44] Moreover, their long-term use is limited by the development of tachyphylaxis. As the only prokinetic approved by the Food and Drug Administration (FDA) for use in GP, metoclopramide is also to be avoided given the risk of irreversible tardive dyskinesia seen in less than 1% and inability to use the drug beyond 3 months,[45] but instead we favor the use of either domperidone, which requires an investigational new drug application through the FDA. Domperidone is a peripheral dopamine 2 (D2) receptor antagonist with effects similar to metoclopramide. It has been shown to be effective in diabetic GP,[46] although more rigorous trials are lacking. Domperidone can cause QT prolongation, and therefore electrocardiograms should be checked at baseline and while on therapy. Bethanechol is a muscarinic agonist that is inexpensive and sometimes used in the management of GP.[47] It increases lower esophageal sphincter (LES) tone and the amplitudes of gastric contractions, but does not accelerate GE.[48] Several newer prokinetics are being studied such as 5-HT_4 receptor agonists, including prucalopride and velusetrag, as well as ghrelin agonists and newer motilin agonists.[49] Relamorelin is a ghrelin agonist that has been shown to reduce vomiting frequency and accelerate gastric emptying in patients with diabetic GP.[50] When possible, liquid formulations of prokinetics should be used to facilitate absorption. **Table 1** summarizes the mechanism, dosing, and side effects of prokinetics.[30,45,47,48,51,52] We recommend against the use of gastric electrical stimulators in patients with IBD, as this has not been studied and given risk of theoretic autoimmune-type reaction to the pacer wires or infection risk in patients with IBD. In patients who are losing weight despite treatment for GP, we recommend nutritional supplementation via nasoenteric feeds, jejunostomy, or percutaneous endoscopic gastrojejunostomy (PEG-GJ) tube placement, or if these measures fail, start total parenteral nutrition.[30]

Functional Gastroduodenal Disorders

Functional gastroduodenal disorders are common in patients with IBD, with a prevalence of approximately 30%.[1] Based on the Rome IV criteria, these disorders are categorized into functional dyspepsia, belching disorders, chronic N/V disorders, and rumination syndrome.[53] Functional dyspepsia (FD) is defined as the presence of bothersome epigastric pain or burning, postprandial fullness, or early satiety, in the absence of the structural disease. Symptoms must be present for the past 3 months, with symptom onset at least 6 months before diagnosis. Patients with functional dyspepsia may be further classified as having postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), or both. Patients with PDS have bothersome postprandial fullness or early satiety occurring at least 3 days per week, whereas those with EPS have bothersome epigastric pain or burning occurring at least 1 day per week. Heartburn is not considered a dyspeptic symptom, although it often coexists with FD. Although vomiting may be present in a subset of patients, it is uncommon in FD and its presence suggests another disorder, such as gastric outlet obstruction or GP. In addition to GP and upper GI CD, the differential diagnosis of FD includes GERD, peptic ulcer disease, *Helicobacter pylori*–associated dyspepsia, eosinophilic gastroenteritis, food allergies, and many others, including medications.[54] Medications

Table 1
Mechanism, dosing, and side effects of prokinetics

		Physiologic Effect					
Drug	**Mechanism**	**Anti-emetic**	**Effect on GE**	**Visceral Sensitivity**	**Antral Motility**	**Dose**	**Side Effects**
Metoclopramide	D2 antagonist 5-HT_4 agonist	+	↑	↓	↑	5–10 mg TID-QID Liquid preferred Intranasal: 10–20 mg TID	QT prolongation, extrapyramidal side effects (tardive dyskinesia <1%) Only FDA approved medication for GP Has a black-box warning
Domperidone	D2 antagonist (peripheral)	+	↑	↓		10–20 mg TID-QID	QT prolongation, Requires IND
Erythromycin	Motilin agonist		↑			40–250 mg TID Liquid preferred	QT prolongation, risk of C diff, efficacy limited by tachyphylaxis
Azithromycin	Motilin agonist		↑			Liquid: 200–400 mg daily in 5–10 mL IV: 250–500 mg daily	QT prolongation, risk of C diff, efficacy limited by tachyphylaxis
Bethanechol	Muscarinic agonist	–	No effect		↑	10–25 mg QID	Flushing, hypotension, bladder spasms
Prucalopride	5-HT_4 agonist		↑		↑	2–4 mg daily	Diarrhea

Abbreviations: 5-HT_4, 5-hydroxytryptamine receptor 4; C diff, *Clostridium difficile*, D2, dopamine receptor 2, FDA, Food and Drug Administration; GP, gastroparesis; IND, investigational new drug application; IV, intravenous; QID, 4 times a day; TID, 3 times a day; ↓, decreases; ↑, increases; +, present; –, not present.
Data from Refs.[30,45,47,48,51,52]

that have been implicated include nonsteroidal anti-inflammatory drugs, iron, calcium channel blockers, angiotensin-converting enzyme inhibitors, steroids, and methylxanthines, which include theophylline, pentoxifylline, and caffeine.

Our Recommendations for Functional Dyspepsia

An approach to the evaluation and management of FD is presented in Fig. 3. We recommend screening for and treating comorbid psychiatric illness, as dyspepsia is frequently associated with major depression and generalized anxiety disorder.[55]

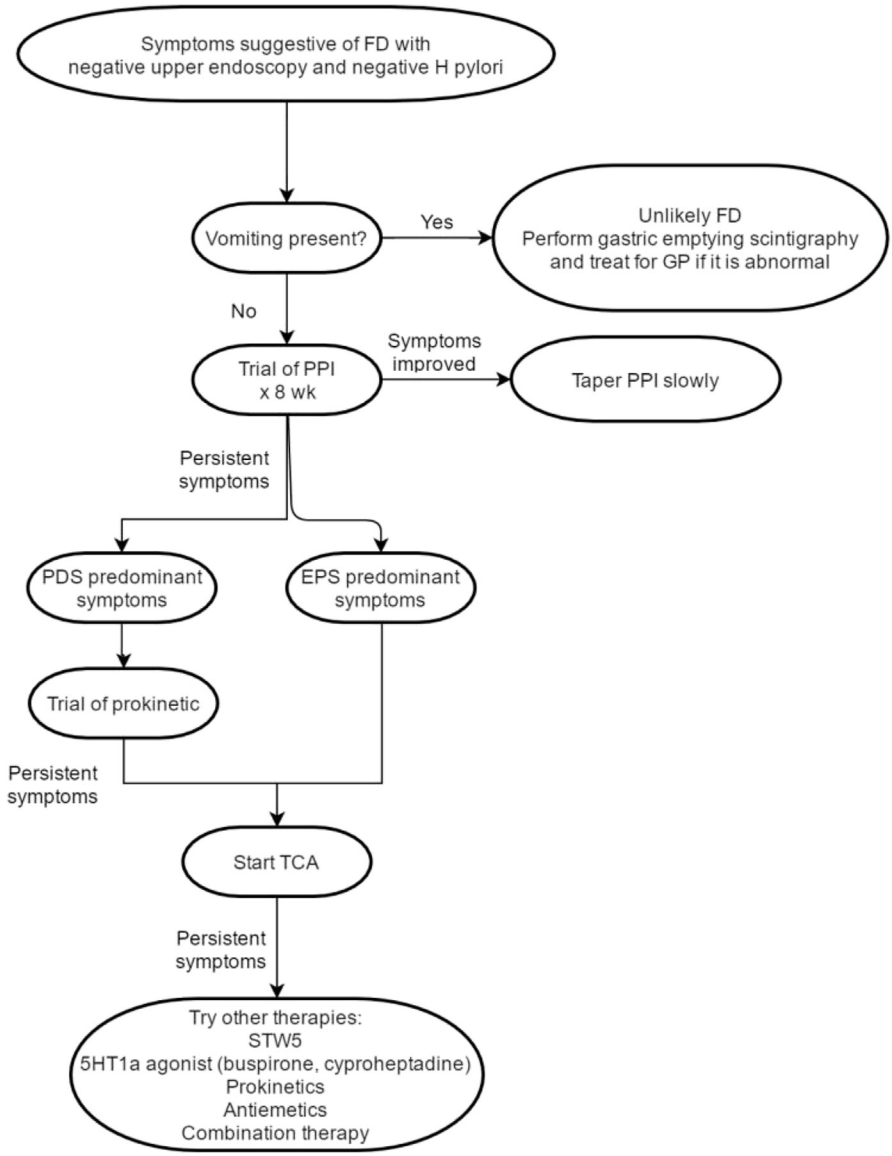

Fig. 3. Evaluation and management of FD.

Moreover, patients with IBD have higher rates of depression than the general population.[56] Initial management of FD includes testing and treating for *H pylori* as well as a trial of PPI. In patients who respond to a trial of PPI, we recommend step-down therapy to H2RAs, given the risks of PPI use in patients with IBD. For patients who meet criteria for PDS, a trial of a prokinetic should be considered. TCAs, such as amitriptyline, have been shown to be effective in FD, whereas SSRIs have not been effective.[57] STW 5 is a preparation of 9 herbs that has been shown to be safe and effective for the treatment of FD.[58] A trial of cyproheptadine can be considered, as it has been shown to reduce dyspeptic symptoms in children.[59] Buspirone, a 5-HT_{1A} agonist, causes fundic relaxation and has been shown to be effective in a small trial.[60]

PRESENCE OF IRRITABLE BOWEL SYNDROME IN INFLAMMATORY BOWEL DISEASE

Patients with IBD often present with multiple GI symptoms, such as mild to moderate diffuse or localized abdominal pain and diarrhea with increased fecal frequency and urgency, as seen in patients with FBD called irritable bowel syndrome with diarrhea (IBS-D). IBS-D is now better defined by the new Rome IV criteria as a bowel disorder with the omission of the word "functional," given the complex mechanisms involved in its pathogenesis combining genetic, environmental, psychological, and immunologic mechanisms, which then result in altered GI motility, visceral hypersensitivity with disturbances in brain-gut interactions, intestinal dysbiosis, and immune activation similar to IBD.[61] In fact, a significant portion of patients with IBD, a third of patients with UC, and half of patients with CD, continue to have abdominal pain while in remission confirmed by the lack of any inflammatory markers or signs of active disease, and this finding impacts the quality of life of patients with even quiescent IBD.[62,63] This ambiguity in the immediate cause of ongoing abdominal complaints, whether caused by inflammation or visceral hypersensitivity, poses a challenge to treating physicians, as the patients' symptoms may not necessarily be due to active CD but rather due to IBS. Interestingly, Keohane and colleagues,[64] found that almost 60% of a subgroup of patients with CD in clinical remission and with a low C-reactive protein (CRP) meet the ROME II criteria for IBS. This finding is similar to the visceral hypersensitivity seen in patients with IBS, especially in the postinfectious subtype, in which an inflammatory trigger leads to a both peripheral and central sensitization manifesting as the symptoms of diarrhea and abdominal pain IBS.[65] Given the prevalence of IBS as high as 10% to 15% of the general US population, then if by chance alone, there is a high probability that some patients with IBD will also have IBS.[66] Moreover, many patients who are diagnosed with IBD, may have been initially misdiagnosed as IBS several years prior due to the overlap in symptomatology or as a prodromal period in CD.[67] Oftentimes, aggressive treatment of the underlying inflammation suspected in patients with IBD despite lack of serologic, endoscopic or imaging diagnosis, is a mainstay of management. Many scientists propose that IBS-D maybe an "incomplete" CD.[68] Although, some clinicians may choose to treat the overlapping symptoms of IBD and IBS empirically, the response to treatment may not necessarily be indicative of active disease but based on a recent meta-analysis, may be secondary to a placebo effect, which can be as high as 33% in IBS trials (155 trials), 35% in UC trials (82 trials), and 25% in CD.[69,70]

Diagnosis and Differentiation from Inflammatory Bowel Disease and Small Intestinal Bacterial Overgrowth

Treatment of quiescent IBD by increasing the dose of immunosuppressive agents will likely increase the risk for side effects, including malignancy, infections, and

malabsorption. Therefore, how do we identify those patients who present with symptoms due to an FBD versus those with active inflammation or long-term consequences of their IBD? A few recent developments in new biomarkers for the treatment of patients with IBS-D have enhanced our ability to differentiate IBS from non-IBS, IBD. This development of validated biomarkers that can help identify and separate those patients with FBD from those with active inflammation is at its preliminary stages but would be invaluable for clinical care, as it is incorporated into the new ROME IV criteria.[61] Some of these are existing biomarkers, CRP level in serum and fecal calprotectin, which are associated with objective mucosal inflammation in patients with IBD and may have high sensitivity and specificity as a screening tool for IBD in adults and children.[71] These tests could even differentiate IBS-D from microscopic colitis, thus avoiding need for endoscopy in a subset of patients.[72] Other newly developed markers are antibodies against cytolethal distending toxin B, which is produced by all gram-negative bacteria with subsequent development of other antibodies, through a molecular mimicry, to vinculin.[73] Vinculin is a cytoskeletal protein that binds adhesion molecules to actin, thereby supporting the intestinal barrier against injury. High levels of both antibodies have been detected in patients with IBS-D subtype but not in IBD, with a specificity of 92% and a sensitivity of 44%. Although the test does not differentiate celiac disease from IBS, it may be a reliable test for "ruling in" IBS, therefore minimizing use of invasive testing as would be necessary for ruling out IBD. Correct identification of IBS would have huge implications for the treatment and identification of quiescent CD, which would mimic IBS.

Another possibly distinct (but not mutually exclusive) entity coexisting with IBD and IBS may be small intestinal bacterial overgrowth (SIBO) defined as clinical or laboratory evidence of malabsorption due to an increased population of small bowel bacteria. The clinical presentation of a patient with SIBO can be similar to IBS, IBD, celiac disease, carbohydrate malabsorption, and even partial mechanical obstruction. These symptoms include abdominal fullness, bloating, upper periumbilical or epigastric abdominal pain, diarrhea, weight loss, and/or nausea with vomiting and weight loss.[74] The presence of bacteria in the small bowel results in intestinal fermentation with production of gases, production of metabolites in addition to degradation of carbohydrates, production of short-chain fatty acids altering motility and leading to symptoms in IBS (4%–54%), and possibly UC (15%) and CD (28%).[75–77] These rates depend on the method of diagnosis used: breath testing or duodenal/jejunal aspirates and cultures. IBD itself is a risk factor for having a positive = jejunal aspirate. This "gold standard" is both invasive and costly with limitations depending on type of method for cultures obtained.[78] Hydrogen breath testing by both lactulose and glucose breath testing methods is an alternative to obtaining aspirates in patients with suspected SIBO and rely on high levels of methane and hydrogen. However, both lactulose (an osmotic laxative) and glucose have been shown to accelerate intestinal transit and especially in patients with diarrhea (IBD or IBS) could result in false-positive findings due to rapid arrival of substrate to the right colon.[79] We do not advocate breath testing in patients with symptoms of diarrhea and known IBD. A recent North American Consensus Meeting has made an effort to standardize testing for SIBO, noting jejunal cultures of $\geq 10^3$ coliforms/mL colonic bacteria and not $\geq 10^5$ as the new standard SIBO definition with further standardizing of breath testing.[80]

Our Recommendations

Given the complexity and overlap of IBS, IBD, and SIBO, we first advocate dietary measures with 2 diets found to be most effective in patients with IBD and IBS: Low FODMAP diet and less consistently, a gluten-free diet[81] (**Fig. 4**). Two probiotics

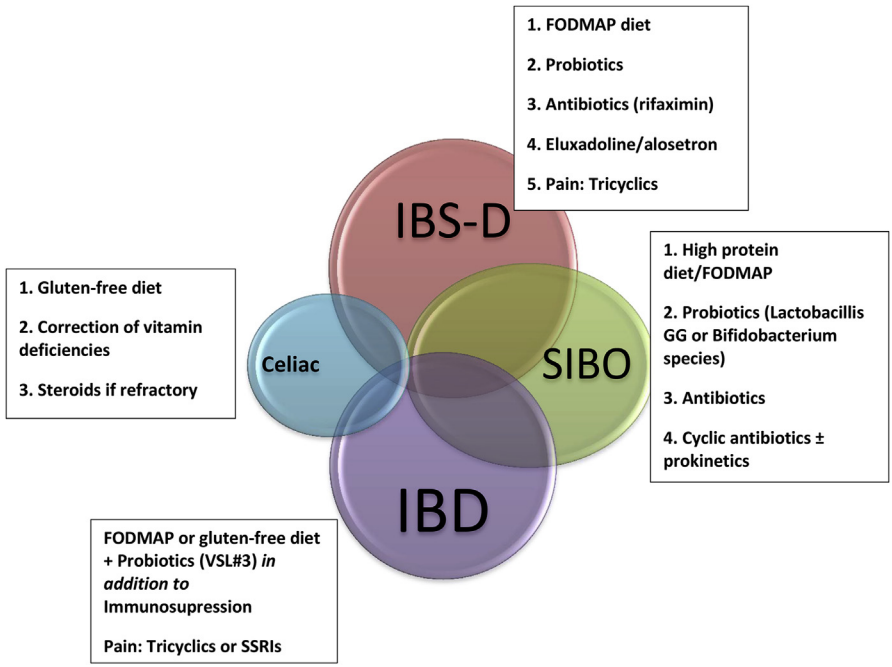

Fig. 4. Management of overlapping diseases.

most studied in patients with IBD and IBS, *Bifidobacterium infantis* and the combination probiotic VSL#3, are advocated as first-line treatments; however, one should note that probiotics treat only pain and bloating but not fecal urgency or frequency.[82] These therapies may be followed by treatments for concomitant IBS-D targeting serotonin (alosetron), opiate agonists (eluxadoline), and nonsystemically absorbed antibiotics (rifaximin), which are now the 3 FDA-approved treatments for IBS-D. Incorporating use of antidepressants, such as the TCAs especially in patients with IBD with frequent comorbidities, such as anxiety and depression, also may be helpful to treat the visceral hypersensitivity, and as tricyclics are less likely to cause more diarrhea.[56] In patients found to have significant weight loss with suspected small bowel dysmotility causing SIBO, or in those with normal transit and imaging excluding a stricture as the cause of continued symptoms, empiric treatment of SIBO with a nonsystemic antibiotic such as rifaximin versus other antibiotics should be started, although trials of rifaximin in exclusively patients with SIBO do not exist in well-designed studies.[83] If the patient continues to decline, however, without evidence of an inflammatory cause, jejunal aspirates should be done with cultures added for possible fungal overgrowth. Checking for micronutrient deficiencies is also important, as patients with SIBO often have high or normal folate and vitamin K levels, as they are produced by bacteria.

EVALUATION OF ANORECTAL DISEASES IN INFLAMMATORY BOWEL DISEASE

The anorectum is commonly involved in patients with UC (100%) and CD (15%–80%), where inflammation, fistulous disease, or surgery in the anorectal area leads to fibrosis, rectal hypersensitivity, and a noncompliant rectum.[84] Although advances in the treatment of IBD with use of biologic agents, and surgical reconstructive techniques, such as IPAA have modified the treatment of fistulas and other anorectal

diseases in patients with IBD, still, fecal incontinence, defecatory dysfunction such as puborectalis muscle dysfunction, and pelvic pain occur commonly in IBD and greatly impact a patient's quality of life.[85,86]

Fecal Incontinence in Inflammatory Bowel Disease

Fecal incontinence is one of the main anorectal complaints of patients with IBD and is reported in up to 25%, higher than the average population.[87] Besides diarrhea itself, which may be multifactorial and due to ongoing inflammation, pouchitis, bile acid malabsorption, concomitant FBD, lactose intolerance, and SIBO, sphincter damage due to presence of fistula and anal fibrosis can also contribute. Earlier reports based on anorectal manometry testing have found patients with UC and active disease have increased rectal hypersensitivity and contractility whereas rectal compliance is impaired in those with both quiescent and active UC suggesting chronic changes of rectal wall with fibrosis may be responsible.[88] Patients with active disease and anorectal manometry showing lower rectal compliance have a higher risk of incontinence, similar to those with higher fatigue of sphincter muscles with or without sphincter defects seen on ultrasonography.[89]

In patients with UC status-post IPAA, fecal incontinence and functional outcomes are not different according to a meta-analysis of 53 studies with a durability of 90% if done in the experienced setting.[90] Furthermore, fecal incontinence is not seen more frequently in patients with IPAA with a hand sewn versus stapled anastomoses.[90,91] In patients with suspected sphincter damage either due to obstetric surgery or other structural defects found by manometry or ultrasonography of anorectum, a modified IPAA has been suggested by some can be done to improve risk of incontinence.[92] Therefore, diagnostic testing preoperatively with anorectal manometry can be useful in ruling out sphincter defects before IPAA, especially if sphincter defects are suspected[93] (**Fig. 5**). Few long-term follow-ups of patients with IBD and fecal

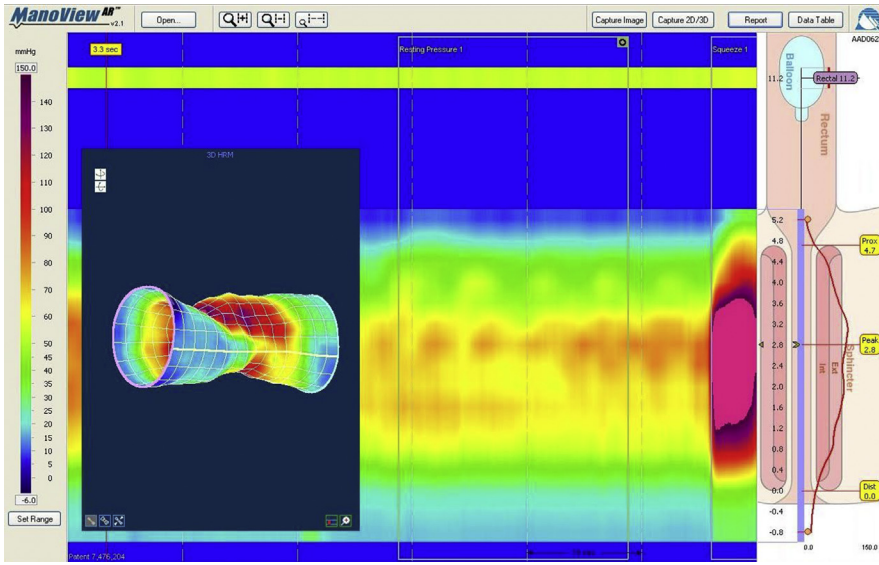

Fig. 5. Anorectal manometry image showing internal sphincter weakness with slight anterior and posterior defect on 3-dimensional imaging in a patient with CD with severe perianal disease status-post ileostomy. Manometry was done for symptoms of fecal incontinence and before ileostomy takedown.

incontinence have been performed, with one study showing that after 14 years, 54% of patients with IBD with perianal lesions continue to have mild complaints.[94] Most of these patients, 39%, had prior history of fistulous disease at baseline. Depression and even suicidal symptoms are higher in patients with CD and perianal disease, therefore many advocate use of a validated fecal continence questionnaire in patients with IBD (ICIQ-IBD).[95,96]

Our Recommendations

Several therapies are available for treatment of fecal incontinence, including biofeedback therapy, fiber supplementation for bulking, and loperamide. Other minimally invasive techniques for treatment of fecal incontinence have been studied in IBD in small case series including sacral nerve stimulation, posterior tibial nerve stimulation, or bulking agents, showing some efficacy in a subset of patients with IPAA.[97,98]

Pelvic Floor Disorders in Inflammatory Bowel Disease

Pelvic floor disorders, such as dyssynergia, causing an obstructive defecation and subsequent fecal impaction with overflow diarrhea are also common among patients with IBD, although the true prevalence of these disorders is unknown.[99] One study of a group of patients with IBD with quiescent disease (23 CD, 6 UC) found defecatory disorders by manometry testing to be 67%, 10%, and 6%, respectively, in those with constipation, stool frequency, and incontinence with and without rectal pain. All but one met criteria for dyssynergia with inability to expel the balloon during defecation and with anismus during push maneuvers. Abdominal radiograph showed that most patients in this study with complaints of frequent stooling had overflow diarrhea due to constipation. The authors stress the importance of a good physical examination, including a rectal examination, in the evaluation of patients with all anorectal diseases to rule out anorectal cancers found more frequently in patients with IBD, ruling out prolapse of rectum or pouch, and other structural or functional anorectal diseases.

Our Recommendations

Treatment of patients with these disorders, however, should begin with conservative therapy of increase of fiber and fluid intake and osmotic laxatives as tolerated. If symptoms persist, physiologic testing with anorectal manometry and balloon expulsion to evaluate for pelvic floor disorders should be performed. Biofeedback therapy should be initiated in most cases perhaps even before use of laxatives, as it is longer lasting and may completely resolve the defecatory symptoms.[100] Transit studies are rarely indicated for patients with CD or UC to evaluate for slow-transit constipation, and although Sitzmarker studies can be performed, the wireless motility capsule is contraindicated in patients with CD due to risk of capsule retention, although this may be a better tool for evaluation of whole gut motility. Use of MRI defecography is yet to be determined but may help with evaluation of rectal volume and dispensability as well as rule out fistulous disease or structural defects. In patients with pelvic pain, a multidisciplinary management team may be necessary to avoid unnecessary laparotomy for adhesions in patients already at high risk of wound healing and infection. Rehabilitation therapy with specialists trained in pelvic pain with avoidance of narcotic use will greatly impact patient care and lead to an improved quality of life for these patients.

SUMMARY

Patients with IBD have overlapping symptoms with both motility and functional bowel diseases. In patients with quiescent disease or continued symptoms despite dose

escalation, diagnostic testing and a thorough evaluation for other concomitant gastrointestinal disorders should be performed to further improve management of these patients with chronic illnesses and to minimize the risk of further unnecessary immunosuppression or that of empiric treatments that may predispose patients to infections or further malnutrition.

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