Clinical Gastroenterology and Hepatology 2019;17:380–390

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review

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Description: **The purpose of this clinical practice update review is to describe key principles in the diagnosis and management of functional gastrointestinal (GI) symptoms in patients with inflammatory bowel disease (IBD).**

Methods: **The evidence and best practices summarized in this manuscript are based on relevant scientific publications, systematic reviews, and expert opinion where applicable.**

Best practice advice 1: **A stepwise approach to rule-out ongoing inflammatory activity should be followed in IBD patients with persistent GI symptoms (measurement of fecal calprotectin, endoscopy with biopsy, cross-sectional imaging).**

Best practice advice 2: **In those patients with indeterminate fecal calprotectin levels and mild symptoms, clinicians may consider serial calprotectin monitoring to facilitate anticipatory management.**

Best practice advice 3: **Anatomic abnormalities or structural complications should be considered in patients with obstructive symptoms including abdominal distention, pain, nausea and vomiting, obstipation or constipation.**

Best practice advice 4: **Alternative pathophysiologic mechanisms should be considered and evaluated (small intestinal bacterial overgrowth, bile acid diarrhea, carbohydrate intolerance, chronic pancreatitis) based on predominant symptom patterns.**

Best practice advice 5: **A low FODMAP diet may be offered for management of functional GI symptoms in IBD with careful attention to nutritional adequacy.**

Best practice advice 6: **Psychological therapies (cognitive behavioural therapy, hypnotherapy, mindfulness therapy) should be considered in IBD patients with functional symptoms.**

Best practice advice 7: **Osmotic and stimulant laxative should be offered to IBD patients with chronic constipation.**

Best practice advice 8: **Hypomotility agents or bile-acid sequestrants may be used for chronic diarrhea in quiescent IBD.**

Best practice advice 9: **Antispasmodics, neuropathic-directed agents, and anti-depressants should be used for functional pain in IBD while use of opiates should be avoided.**

Best practice advice 10: **Probiotics may be considered for treatment of functional symptoms in IBD.**

Best practice advice 11: **Pelvic floor therapy should be offered to IBD patients with evidence of an underlying defecatory disorder.**

Best practice advice 12: **Until further evidence is available, fecal microbiota transplant should not be offered for treatment of functional GI symptoms in IBD.**

Best practice advice 13: **Physical exercise should be encourage in IBD patients with functional GI symptoms.**

Best practice advice 14: **Until further evidence is available, complementary and alternative therapies should not be routinely offered for functional symptoms in IBD.**

This Clinical Practice Update was produced by the AGA Institute.

Functional bowel disorders such as irritable bowel syndrome (IBS) are usually diagnosed based on symptoms that may overlap with those associated with inflammatory bowel disease (IBD). Distinguishing symptoms of this origin from those driven by persistent pathological changes associated with IBD such as inflammation or fibrosis may be challenging. A disconnect between symptoms and degree of intestinal inflammation has been well documented in Crohn's disease (CD),[1] while imaging studies and endoscopic and histologic evaluation to assess IBD activity may not be not definitive in separating these 2 etiologies of symptoms. The evidence to guide diagnostic and therapeutic strategies is thus often limited for functional gastrointestinal (GI) symptoms in IBD patients, but may involve 1 or more approaches, taking into consideration the unique circumstances of the individual. This is critical, as overtreatment of intestinal inflammation for symptoms due to functional pathophysiology may increase the risk of significant adverse side effects while providing the patient with no symptomatic benefit. Further guidance for clinicians is needed

Abbreviations used in this paper: **BAD, bile acid diarrhea; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; FC, fecal calprotectin; FGID, functional gastrointestinal disorder; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; QOL, quality of life; SIBO, small intestinal bacterial overgrowth; UC, ulcerative colitis.**

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.08.001

in improving clinical care and outcomes for IBD patients with coexisting functional GI symptoms as there are questions surrounding this patient population including the following:

1) What steps should be taken when attempting to differentiate symptoms driven by underlying IBD from those related to functional pathophysiology?
2) What other pathophysiologic mechanisms beyond active inflammation should we consider and investigate?
3) What are they key principles in management of IBD patients with overlapping functional GI symptoms?

While a true diagnosis of IBS or other functional GI disorders using established diagnostic criteria such as the Rome IV criteria cannot be strictly applied to IBD patients, addressing functional pathophysiology is important. In the current Clinical Practice Update Expert Review we discuss evaluation and management of functional GI symptoms in patients with IBD using available evidence and expert opinion.

Functional GI Symptoms in IBD: Prevalence and Consequences

The frequency of functional GI disorders in IBD varies depending on studied populations and diagnostic criteria used. For example, data from a meta-analysis indicated that the pooled prevalence for IBS in all IBD patients from 4 case-control and 9 cross-sectional studies was 39% (95% confidence interval [CI], 30%–48%), with an odds ratio compared with control subjects of 4.89 (95% CI, 3.43–6.98) and a higher frequency in patients with CD than in those with ulcerative colitis (UC) (46 vs 36%, odds ratio, 1.62; 95% CI, 1.21–2.18).[2] In the included studies, IBS was defined by diagnostic criteria (Manning, Rome I, Rome II, or Rome III) or any other validated GI symptom questionnaire and quality assessment of the 4 case control studies was low. Thus, the aforementioned numbers should be taken with caution. In addition, the presence of ongoing symptoms requires the careful exclusion of active inflammatory disease when initial evaluation suggests quiescent disease. In UC, for example, only 29% and 41% of patients who achieved a Mayo endoscopy subscore of 0 reported a normal stool frequency 8 and 52 weeks after starting therapy, respectively.[3] However, a substantial proportion of these patients had evidence of persistent histologic inflammation on biopsy despite endoscopic remission. Still, it was subsequently reported that up to 27% of UC patients with both endoscopic and histologic healing may have increased stool frequency.[4] These data highlight the challenge of defining the true prevalence of functional GI symptoms in IBD. Studies also suggest a role for mechanisms[5] not directly attributable to gut inflammation such as small intestinal bacterial overgrowth (SIBO),[6] bile acid diarrhea (BAD),[7] bowel damage from chronic inflammation, functional changes in motility or absorptive capacity; abnormalities in the enteric nervous system,[8] presence of intestinal dysbiosis,[9] or increased intestinal permeability.[10] It is interesting to note that many of these noninflammatory mechanisms, which may be a consequence of prior chronic inflammation, have also been implicated in the multifactorial pathogenesis of functional GI disorders (FGIDs) and further investigation of such mechanisms in IBD is needed.

Although the debate as to whether persistent symptoms in the presence of apparent mucosal healing are a consequence of coexisting functional disease has been described as irrelevant by some authors,[11] understanding their origin and how they can be treated is not because they consistently affect the quality of life (QOL) of patients. A longitudinal study examining the impact of persistent GI symptoms in 360 IBD patients found higher anxiety, depression, and somatization scores, and lower QOL scores in IBD patients with GI symptoms compared with those with quiescent disease but without persistent symptoms.[12] Others have shown similar findings, demonstrating anxiety and reduced vitality to be independent predictors for functional symptoms among IBD patients in remission.[13] In a study from CCFA Partners, a diagnosis of IBS in IBD was associated with higher narcotic use compared with those without an IBS diagnosis for both CD (17% vs 11%; $P < .001$) and UC or indeterminate colitis (9% vs 5%; $P < .001$). Quality of life, as measured by the Short Inflammatory Bowel Disease Questionnaire was lower in patients with a FGID diagnosis compared with those without, and was associated with anxiety, depression, fatigue, sleep disturbances, pain interference, and decreased social satisfaction.[14] Naliboff et al[15] also examined the interrelationships among GI symptoms, psychological distress, and health-related QOL in IBD, IBS, and health. In this study, psychological distress was found to be more dependent on GI symptoms in IBD compared with IBS although significant effects of psychological distress on health-related QOL between groups were similar.

Finally, an inability to reliably distinguish functional GI symptoms from IBD has obfuscated results of clinical trials in the past. It has been shown that the Crohn's Disease Activity Index, a commonly used objective endpoint criterion, may be as high in IBS as in IBD patients. The most compelling evidence regarding this confusion came from the Study of Biologic and Immunomodulator Naive Patients in CD (SONIC) trial; where there was no difference between treatment arms for patients included based on Crohn's Disease Activity Index only and no objective inflammation.[1] Since then, measurement of increased clinical and objective activity (either based on endoscopy or inflammatory biomarkers such as C-reactive protein [CRP] or calprotectin) is a prerequisite for inclusion in clinical trials. Similarly, in clinical practice, no therapeutic decision should be taken based on clinical consideration alone.

How Can We Identify Functional GI Symptoms in Patients With IBD?

Clinical Assessment

Evaluation of persistent symptoms (Figure 1) in the IBD patient should begin with a detailed symptom history including a review of bowel patterns taking into account the clinical spectrum of patient presentations as symptom severity may not always directly correlate to degree of inflammatory activity (Supplemental Figure 1). Clinicians should query patients on presence and severity of the following: associated pain, incontinence episodes, urgency, or tenesmus; alarm features (eg, weight loss, nocturnal symptoms, bleeding, high-volume or high-frequency diarrhea, fevers); recent antibiotic use; and symptom duration to identify features that may point away from a functional etiology. Presence of alarm features or acute symptom onset in patients with previously well-controlled disease should prompt the clinician to maintain a high index of suspicion for underlying inflammatory activity. Physical examination should assess for objective findings suggesting organic pathology or active IBD such as abdominal distension or masses. Careful rectal examination should inspect for perianal or anorectal disease. In those without obvious perianal pathology to explain symptoms, a digital rectal exam to palpate for mass lesions and to screen for a rectal evacuation disorder[16] should be completed.

Evaluate for Ongoing Inflammation

Objective evidence of inflammatory activity based on laboratory testing such as serum CRP and fecal

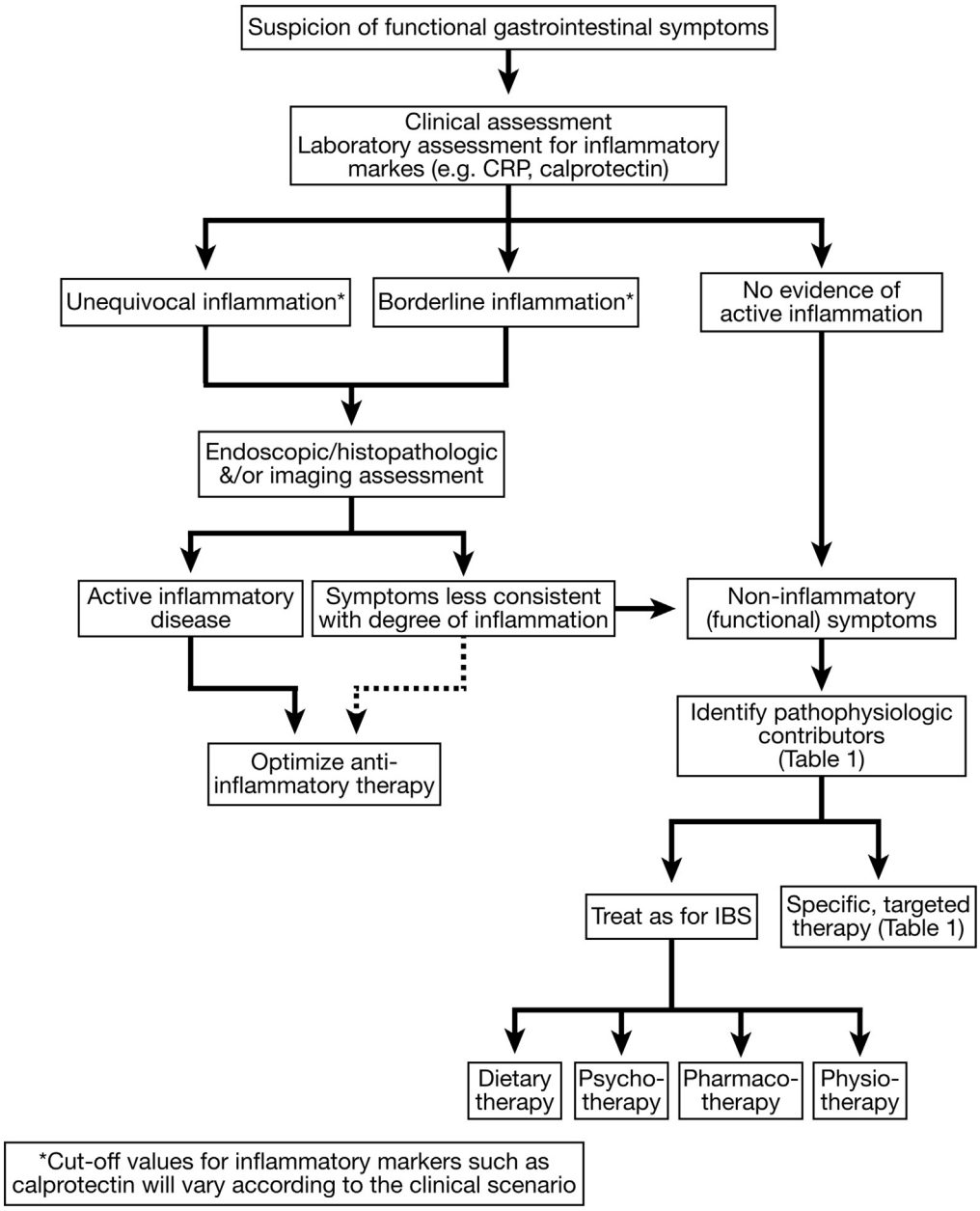

Figure 1. Diagnostic algorithm for evaluation of suspected functional gastrointestinal symptoms in patients with inflammatory bowel disease.

calprotectin (FC) should be addressed. However, the use of noninvasive biomarkers has important limitations. CRP, an acute phase reactant, has shown poor sensitivity and up to 15% of patients may fail to mount a CRP response.[17] Discerning optimal cutoffs for biomarkers remains a source of debate. In 1 retrospective review, FC levels <60 μg/g were found to be predictive of deep remission in UC patients with 86% sensitivity and 87% specificity[18] while a prior prospective study reported FC levels ≤ 40.5 μg/g to be predictive of histological remission with 41% sensitivity and 100% specificity.[19] Thresholds for fecal calprotectin in the range of 200–250 μg/g may predict endoscopic remission in both UC and CD.[20,21] Thus, while FC values <50 μg/g may be reassuring and point the clinician toward consideration of a non-IBD etiology for persisting symptoms, values between 50 and 250 μg/g may be challenging to interpret, as upper normal limits may vary and mild calprotectin elevation may be seen with nonspecific low-grade inflammation.[22] In those with mild symptoms, serial calprotectin monitoring at 3- to 6-month intervals may be appropriate to facilitate early recognition with treatment of impending disease flares.[23] If a flare is suspected, endoscopy with biopsies or dedicated imaging of the small bowel in CD patients should be considered. As previously mentioned, the potential for persistent histological or transmural inflammation even with endoscopic evidence of mucosal healing cannot go unnoticed. The role of histology and cross-sectional imaging as a therapeutic target requires further study, particularly as they may reflect inflammatory mechanisms driving refractory symptoms or leading to clinical relapse.

Anatomic Abnormalities and Other Considerations in IBD

Active small-bowel CD and complications such as stenosis and fistulas can be missed if the diagnosis is only made through ileocolonoscopy without systematic cross-sectional imaging of the small bowel.[24] Fibrostenotic disease from chronic inflammation or surgical sequelae such as ischemic strictures and adhesions leading to obstructive symptoms[25] of abdominal pain, nausea and vomiting, distention, or obstipation or constipation from fecal stasis in uninflamed colon proximal to distal colitis.[26,27] Further, although UC is traditionally thought of as a disease limited to the mucosa and superficial submucosa, mounting (and forgotten) evidence supports the existence of transmural chronic inflammation. This results in a thickening of the muscularis mucosa and increased collagen deposition compared with healthy control subjects. Accumulating data support the notion that fibrosis is a common occurrence in UC.[28] It affects the mucosa, submucosa, and in some instances, the muscularis propria and even subserosa, in particular in cases of deep ulceration. These fibrotic changes are likely to have important clinical consequences through effects on colonic motility and anorectal function, even in the absence of strictures or active mucosal disease.[29] As nicely summarized in a recent editorial, it is time in UC to look underneath the surface in developing new therapeutic interventions in IBD,[30] which may involve the future use of novel antifibrotics as explored in CD.

Investigating Pathophysiologic Mechanisms Beyond Inflammation

When objective evidence of active inflammation or IBD-specific mechanisms is insufficient to account for the nature of the persistent symptoms in IBD, alternative pathogenic mechanisms should be considered and addressed before attributing symptoms to functional GI symptoms. Several pathophysiological perturbations may contribute to GI symptoms in patients with IBD. These pathophysiologic mechanisms, may at times be uniquely associated with the IBD patient, but in many cases may overlap with pathways that have been implicated in pathophysiology of functional disorders. Subsequent testing should be guided by predominant symptom patterns.

Steatorrhea and chronic abdominal pain may occur as a consequence of PEI or chronic pancreatitis which may complicate IBD.[31] Evidence suggests an increased prevalence of PEI in IBD (odds ratio, 10.5; 95% CI, 2.5–44.8) vs. control subjects based on screening by fecal elastase, though it should be kept in mind that falsely low fecal elastase may be secondary to diarrhea[32] and the clinical significance of PEI in IBD remains undefined. BAD may not only be important in CD patients with ileal disease, but is also a common cause of functional diarrhea or diarrhea-predominant IBS.[33] Several diagnostic tests to screen for BAD are now available[33] including assessment of 48-hour fecal bile acid excretion, which has demonstrated reasonable diagnostic yield compared with ^{75}SeHCAT retention, a test that is not widely available in most countries. Serological testing of serum C4 and FGF19 may represent practical diagnostic tools for BAD, although further clinical validation is required.

Structural changes and alterations in motility or gut defenses predisposing IBD patients to SIBO may result in abdominal pain, diarrhea, bloating or other nonspecific GI symptoms. SIBO in CD is common, occurring in up to 30%.[34] It may be particularly important in those with stricturing[6] or fistulizing phenotype[35] and may be associated with hypomotility or loss of the ileocecal valve.[36] In UC, the reported prevalence of SIBO is lower and its role in producing symptoms less clear.[37] Though SIBO has traditionally been defined as positive bacterial cultures from small bowel aspirates, many experts have deemed small bowel culture to be unsatisfactory for diagnosis due to inherent limitations such as possible

contamination by oropharyngeal flora, inaccessibility of the small bowel with potential for false negatives, and the invasive and costly nature of testing.[38] Thus, recent consensus guidelines have suggested hydrogen and methane-based breath testing for SIBO using glucose or lactulose substrates until validated gold standards for testing are established. Reported sensitivity and specificity of glucose breath testing has ranged from 20% to 93% and from 30% to 86%, respectively, while sensitivity and specificity of lactulose hydrogen breath testing has ranged from 31% to 68% and from 44% to 100%, respectively.[38] Some have suggested that that lactulose breath testing be avoided due to effects on small bowel transit and concerns of its sensitivity and specificity.[39] It should, however, be noted that the effect of rapid small intestinal transit in patients with IBS has cast doubt upon some of the indices claimed to be diagnostic of SIBO, whether lactulose or glucose is used as the substrate.[40] For some patients, the suspicion of bacterial overgrowth may be high enough that empiric therapy is indicated.

Breath testing following these same consensus guidelines[38] to evaluate for carbohydrate malabsorption leading to diarrhea, bloating, and flatulence may provide additional opportunities for intervention. In 1 study, lactose malabsorption was twice as frequent in UC and CD compared with in healthy control subjects and patients with FGID.[41,42] Fructose malabsorption has been shown to be more frequent in CD than in comparator groups by hydrogen breath testing unrelated to small intestinal transit, intestinal resection or SIBO.[41]

Enhanced visceral sensitivity may be considered, particularly in those with pain, although data to support this effect in IBD are conflicting. In a study comparing 19 patients with quiescent UC and 17 control subjects, van Hoboken et al[43] demonstrated increased viscerоperception by rectal barostat among UC patients in remission in addition to a weak but significant correlation between perception and the number of mucosal mast cells. However, a previous investigation of patients with UC reported rectal sensitivity to be decreased during remission and not significantly different between those with quiescent colitis and control subjects to suggest that visceral hypersensitivity was unlikely to be explained by permanent scarring or sensitization.[44]

Other special considerations may include intestinal barrier dysfunction even with endoscopic evidence of mucosal healing. Intestinal permeability as a therapeutic targets or as a marker for genetic predisposition for impaired barrier function in IBD requires further investigation.[45] In a recent study, persistent symptoms of diarrhea and abdominal pain were reported in 16.3% of IBD patients despite mucosal healing and were associated with increased intestinal permeability,[10] suggesting a role for targeting recovery of the intestinal barrier in IBD as an endpoint for control of persistent gut symptoms.

Functional GI Symptoms in IBD

If symptoms should persist despite lack of objective inflammation and appropriate management of alternative etiologies, consideration can be given for overlapping functional GI symptoms. Indeed, both FGID and IBD may share many common pathophysiologic disturbances that in some IBD patients may be a consequence of prior structural and functional bowel damage.[4] Exploration of IBS symptoms may include testing to rule out pelvic floor disorders with anorectal manometry and balloon expulsion test in those with chronic constipation, fecal incontinence, overflow diarrhea, or other defecatory disorders, as these conditions may respond to biofeedback therapy.[46] Psychiatric or psychological disturbances are associated with IBS-like symptoms in IBD while anxiety and reduced vitality have been shown to independently predict IBS-like symptoms.[13]

All aforementioned noninflammatory perturbations, together with potential investigative approaches, are outlined in the Table 1. Hence, as in patients with FGID, multiple pathogenic pathways may be relevant in patients with IBD, especially when designing a therapeutic approach.

How Can We Treat Functional GI Symptoms in Patients With IBD?

There is a paucity of randomized controlled trials or even prospective studies that have examined the impact of therapy for functional GI symptoms in patients with IBD. However, nonpharmacological therapies with efficacy in IBS and other FGID as well as pharmacological interventions are often applied in clinical practice. As mild residual inflammation and functional GI symptoms can coexist, therapy of inflammation and functional symptoms are not mutually exclusive. Therapeutic decisions for the functional symptoms are largely made on an empiric basis, being borrowed from those in patients with IBS and other FGID, and might span dietary, psychological, pharmacological, and other therapies. Attention has to be paid to pathophysiological mechanisms that might offer opportunities for specific therapies as outlined in Tables 1 and 2.

Dietary Therapy

Several dietary approaches appear to be associated with improved functional GI symptoms in IBD patients, including lactose-reduced; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP)–reduced; gluten-free; and specific-carbohydrate diets. The common denominator for improved symptoms in all of these approaches is the reduced intake of indigestible and slowly absorbed carbohydrates that may induce symptoms through luminal distension and mechanoreceptor stimulation by virtue of their osmotic effects and fermentability. This is the basis for the lactose-reduced

Table 1. Acquired Pathophysiological Mechanisms That Might Potentially Contribute to Persistent GI Symptoms in Patients With IBD and That Might Offer Opportunities For Therapy

Potential pathophysiological abnormalities	Presentation	Potential investigations	Potential therapy
Inflammation-associated abnormalities in GBA			
Anxiety and depression	Pain, IBS, fatigue	Psychological or psychiatric evaluations	Psychological therapy, antidepressant, anxiolytic
Hypervigilance, central sensitization of pain processing	Pain, IBS		Similar approaches as for IBS
Altered visceral sensory neurons (neuroinflammation) with structural, receptor and functional abnormalities; activation or sensitization of nociceptors; ↑mast cell density	Pain, IBS		
Consequences of IBD due to changes in structure or function of GI tract			
Bile acid diarrhea	Diarrhea, IBS	^{75}SeHCAT testing,[a] fecal bile acids	Bile salt sequestrant
Small intestinal bacterial overgrowth	Diarrhea, bloating, gas, pain, IBS	Breath testing, culture of small bowel aspirates	Antibiotics
Pancreatic exocrine insufficiency[31]	Pain, weight loss, bloating, diarrhea	Fecal elastase	Pancreatic enzyme replacement
Lactose or fructose malabsorption[41]	Gas, bloating, diarrhea, IBS	Breath testing	Dietary restriction
Obstipation or constipation from fecal stasis in uninflamed colon proximal to distal colitis (UC)[26,27]	Constipation	Abdominal x-ray	Laxation, prokinetic
Intestinal stenosis (CD)	Pain, obstruction	Imaging, endoscopy	Dilatation, surgery
Pelvic floor dyssynergia[46]	Pain, constipation, IBS	Rectal exam, anorectal physiological studies	Biofeedback therapy
Mechanisms not specifically associated with IBD			
Celiac disease	Diarrhea, gas, malabsorption	Celiac serology, small intestinal biopsy	Gluten-free diet

NOTE. Functional symptoms similar to irritable bowel syndrome (IBS) may be observed as a consequence of several of the aforementioned pathophysiologic abnormalities, many of which have been implicated as central and peripheral mechanisms in IBS pathogenesis. CD, Crohn's disease; GBA, gut-brain axis; GI, gastrointestinal; IBD, inflammatory bowel disease; UC, ulcerative colitis.
[a]^{75}SeHCAT testing is not widely available in most countries outside of Europe or Canada.

diet in patients with lactose malabsorption and the low-FODMAP diet in which all short-chain carbohydrates are reduced. Indeed, in a randomized controlled feeding study in a small cohort of CD patients, typical FODMAP intake was associated with increased symptom severity.[47] Other studies have shown benefit with a reduced FODMAP diet in at least 50% of IBD patients with ongoing symptoms despite controlled inflammatory disease.[48] A blinded rechallenge study confirmed that FODMAPs are a likely dietary culprits for functional symptoms in patient with quiescent IBD.[49]

For gluten-free diet, there is currently no evidence that gluten or wheat protein is the culprit dietary component in more than a small minority of IBS patients. Observational and blinded rechallenge studies indicate that concomitant reduction in FODMAP intake is the likely mechanism, especially as fructans coexist with gluten in cereals.[50] In a recent double-blind crossover challenge among patients with self-reported nonceliac sensitivity, overall symptoms as assessed by the Gastrointestinal Symptom Rating Scale IBS version were significantly higher for those consuming fructans than those consume gluten.[51] Whether the same applies to patients with IBD has not been examined, but at least 1 in 4 patients in both UK and US surveys have found that a gluten-free diet can provide symptomatic relief, prompting 6%–8% of patients to remain gluten-free.[48] There are no completed randomized studies.

Restrictive diets are not without potential adverse effects. In conditions where undernutrition is common, such as IBD, attention to nutritional adequacy in the face of dietary restriction is essential, and dietary instruction should be delivered by a dietitian. The effects of reducing carbohydrates with prebiotic actions might have deleterious effects on the gut microbiota. However, a feeding study in which FODMAPs were strictly controlled in CD patients did not alter the relative abundance of a limited number of key bacteria with functional significance compared with microbiota associated with the patient's habitual diet.[47] More real-world data are required. Finally, while certain diets are proposed to reduce inflammation, others may potentially do the opposite. Such information needs careful study.

Psychological Therapy

Several psychological techniques, such as cognitive behavior therapy, gut-directed hypnotherapy,

Table 2. Summary of Therapies Applicable to IBS or Related Disorders and IBD

Therapy	Intervention(s)	Evidence for efficacy in IBS or related disorders	Evidence for efficacy in IBD	Overall interpretation
Diet	Low FODMAP; GFD	Evidence of benefit with ↓FODMAP intake; GFD possibly helpful in subset of IBS[69]	Evidence for benefit with ↓FODMAP in CD and IBD[49,50]; no randomized trials testing GFD in IBD	Restrictive diet potentially helpful with consideration of nutritional adequacy; further data required
Psychological therapy	Cognitive behavioral therapy, hypnotherapy, mindfulness therapy	Efficacy for abdominal symptoms, psychological distress[52]	Limited evidence supports efficacy for anxiety and depression[52]	Clinically valuable therapeutic option in IBD patients with functional symptoms
Pharmacologic treatment for constipation	PEG, stimulant laxative, secretagogue, prokinetic (eg, 5-HT_4 receptor agonists including tegaserod[a] and prucalopride[b])	PEG effective for constipation[70]; stimulants beneficial in CC[71]; secretagogues approved for IBS-C and CC; 5-HT_4 receptor agonists effective for CC[69]	Lack of clinical trial data examining specific effects of pharmacologic treatment for constipation in IBD	Osmotic and stimulant laxatives generally safe and effective for treatment of constipation in IBD: further data required on use of newer agents
Pharmacologic treatment for diarrhea	Loperamide, 5-HT_3 antagonist (alosetron[c]), bile acid sequestrant, mixed opioid agonist/antagonist (eluxadoline[d])	Net benefit with loperamide[72]; alosetron improves IBS symptoms; bile acid sequestrants improve diarrhea; eluxadoline approved for IBS-D[69]	Loperamide effective in CD[73]; bile acid sequestrants effective in CD with malabsorption[74]; no data on safety and efficacy of alosetron or eluxadoline	Hypomotility agents and bile acid sequestrants can be used for diarrhea in IBD; further study needed for newer agents
Pharmacologic treatment for pain, anxiety, depression	Antispasmodic, antidepressant (tricyclic antidepressant, SSRI)	Antispasmodics[75] and antidepressants effective in IBS[76]	Tricyclics associated with benefit in IBD[54]	Consider antispasmodics, neuropathic-directed agents, antidepressants for functional pain in IBD
Antibiotics	Rifaximin	Rifaximin approved for diarrhea-predominant IBS[62]	Rifaximin associated with negative breath test in CD[57], induction and maintenance of remission in active CD, and benefit over placebo in steroid-refractory UC[57]	Evidence for benefit; however, indication for use in IBD and mechanisms by which rifaximin exerts its benefit are unclear
Probiotics	Multiple agents	Variable success	Efficacy for functional symptoms in IBD has not been evaluated	Further data supporting use of probiotics for functional symptoms in IBD needed; however, risk of harm is low
Pelvic floor therapy	Biofeedback for dyssynergic defecation	Beneficial for treatment of constipation with dyssynergia	Benefit with biofeedback in 30% IBD patients in remission with defecatory disorders[46]	Potential for benefit; however, formal study is needed
Physical exercise	Exercise	Exercise improves GI symptoms[67]	Exercise beneficial in quiescent or mild IBD[65] and associated with ↓risk of active disease[66]	Likely beneficial with low risk of harm. No formal evaluation for functional symptoms in IBD reported
CAM	Herbal therapy, dietary supplements, acupuncture, moxibustion, yoga	CAM such as herbal therapies and acupuncture potentially beneficial, but rigorous clinical trials lacking[69]	Marijuana may reduce symptoms, but does not clearly alter disease course; Curcumin associated with induction and maintenance of remission in UC; Higher remission rates with aloe vera in UC; Acupuncture and moxibustion superior to oral sulfasalazine in IBD[65]	Further research needed to validate CAM for functional symptoms in IBD

NOTE. CAM, complementary alternative medicine; CC, chronic constipation; CD, Crohn's disease; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GFD, gluten-free diet; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; PEG, polyethylene glycol; SSRI, selective serotonin reuptake inhibitor; UC, ulcerative colitis.

[a]Tegaserod taken off market due to concern for possible cardiovascular events.

[b]Prucalopride is not available in the United States.

[c]Alosetron approved with restrictions for women with severe diarrhea-predominant IBS in United States.

[d]Eluxadoline associated with increased risk of pancreatitis and should be used with careful monitoring following Food and Drug Administration prescribing information.

mindfulness therapy, and psychodynamic psychotherapy have strong evidence of efficacy for abdominal symptoms in patients with IBS.[52] The evidence base for benefits of such techniques in patients with IBD is less compelling and most studies have addressed coping skills, anxiety, and depression rather than abdominal symptoms or inflammatory activity,[52] although novel approaches with incorporation of positive psychogastroenterology has shown promise.[53] The high prevalence of psychological comorbidities in patients with IBD gives greater impetus to try psychological strategies in patients with functional GI symptoms and IBD, particularly in light of existing data to suggest that GI symptoms may be more directly linked to psychological distress affecting health-related QOL in IBD than in IBS alone.[15]

Pharmacological Therapy

Few high-quality studies have directed attention toward the use of pharmacotherapy in relieving functional GI symptoms in patients with IBD, yet pharmacotherapy is commonly applied. Therapies are generally directed toward relief of specific symptoms: laxatives or prokinetic agents are applied in chronic constipation, particularly in association with distal UC; hypomotility agents or antidiarrheals such as loperamide, bile acid sequestrants for presumed BAD, and pancreatic enzyme replacement therapy for presumed PEI may be used for chronic diarrhea; antispasmodics or neuropathic-directed analgesia may be used for chronic pain; and antidepressant and anxiolytic medication may be used for abdominal symptoms as well as for anxiety or depression. One retrospective cohort study in 81 IBD patients with functional GI symptoms demonstrated that tricyclic antidepressants lead to a clinically relevant benefit for symptoms.[54] The use of opiates should be avoided for management of chronic abdominal pain in general, and particularly in patients with IBS symptoms after remission of acute inflammation. Widespread use of opiates in clinical practice for noncancer pain has been tied to increasing risk of overdose and may contribute to opioid-induced GI side effects.[55] The study of novel agents for the treatment of visceral pain such as APB371, a cannabinoid receptor type 2 agonist is currently underway in phase 2 clinical trials in CD.[56] The application of other newer IBS-related therapies in patients with IBD has yet to be reported.

Manipulating the Gut Microbiota

Antibiotics such as rifaximin are often applied for presumed SIBO, but formal evaluation for this indication in IBD remains limited to a small randomized study of 14 CD patients with inactive ileal disease and breath test–diagnosed overgrowth SIBO. In this study, all 7 patients randomized to rifaximin had a negative follow-up breath test, while only 2 of 7 randomized to placebo achieved this response.[57] In IBD patients with active luminal disease, there has been evidence suggesting rifaximin to be effective in inducing[58,59] and maintaining[60] remission in CD while limited older data in steroid-refractory UC has demonstrated benefit over placebo.[61] Rifaximin has demonstrated efficacy in relieving IBS symptoms of bloating, abdominal pain, and loose or watery stools among patients with nonconstipation predominant IBS in multiple controlled clinical trials, and is approved for the treatment of diarrhea-predominant IBS.[62] A recent study showed modest changes in microbial richness with rifaximin treatment in IBS. However, the exact mechanism by which rifaximin exerts its beneficial effects—whether by changing gut microbiota in general or by reducing SIBO—remain uncertain.[63] Moreover, in a recent cross-sectional analysis, no association was observed between IBS symptoms and microbiome alterations among patients with IBD although effects of confounding could not be excluded.[64] Probiotics have been widely studied for functional GI symptoms with variable success, though the increments of benefit are often small. Efficacy for such symptoms in patients with IBD has not been evaluated. Fecal microbiota transplantation has been directed toward mucosal inflammation rather than functional symptoms.

Pelvic Floor Therapy

The application of pelvic floor therapy targeting dyssynergic defecation has shown gratifying benefit in many patients with IBS and constipation. In a study of 30 patients with IBD in remission and defecatory disorders, 30% had clinically relevant benefit from biofeedback therapy[46] The potential for such an approach in those with functional symptoms requires greater exploration.

Complementary and Alternative Medicine

The application of complementary and alternative medicine and functional foods to patients with in IBD has been recently reviewed,[65] but studies have not been directed specifically at functional GI symptoms. For example, marijuana may reduce symptoms in IBD, but does not clearly alter disease course based on objective assessment of disease activity. Curcumin has been associated with induction and maintenance of remission in UC, although studies may have been inadequately blinded. Higher remission rates were also reported in 1 study with aloe vera in UC. Acupuncture and moxibustion were found to be superior to oral sulfasalazine in IBD. However, studies have generally been of low quality.[65]

Physical Exercise

Programs involving moderate exercise have in general, been shown to improve well-being and to be safe in patients with quiescent or mildly active IBD without

detectable benefit to inflammatory activity.[65] In a study using the CCFA Partners cohort, higher exercise levels were also found to be associated with decreased risk of active disease among CD patients in remission.[66] In IBS, physical activity has been shown to improve GI symptoms in a randomized clinical trial.[67] Whether exercise would be of benefit in patients with IBD and concomitant functional GI symptoms is untested.

Future Directions

While there appears to be increased recognition by clinicians that GI symptoms not fully derived from IBD commonly complicate the clinical picture in patients with IBD, better diagnostic evaluation is needed to further define the contribution of each to a patient's symptoms. This may be assisted by identifying novel biomarkers for FGID and IBD incorporating approaches based on genetic, metabolomic, proteomic, and microbial pathways. Another important area of focus should include integration of bidirectional brain-gut pathways and studies on the role of stress or psychological health, which may have important implications for clinical presentation and noninflammatory symptom management in patients with IBD.[68] In the future, therapeutic approaches that are not empiric, but based on the results of well-designed randomized controlled trials will greatly enhance the clinician's ability to more effectively apply a personalized management plan for functional symptoms as well as therapy of the inflammation itself.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.08.001.

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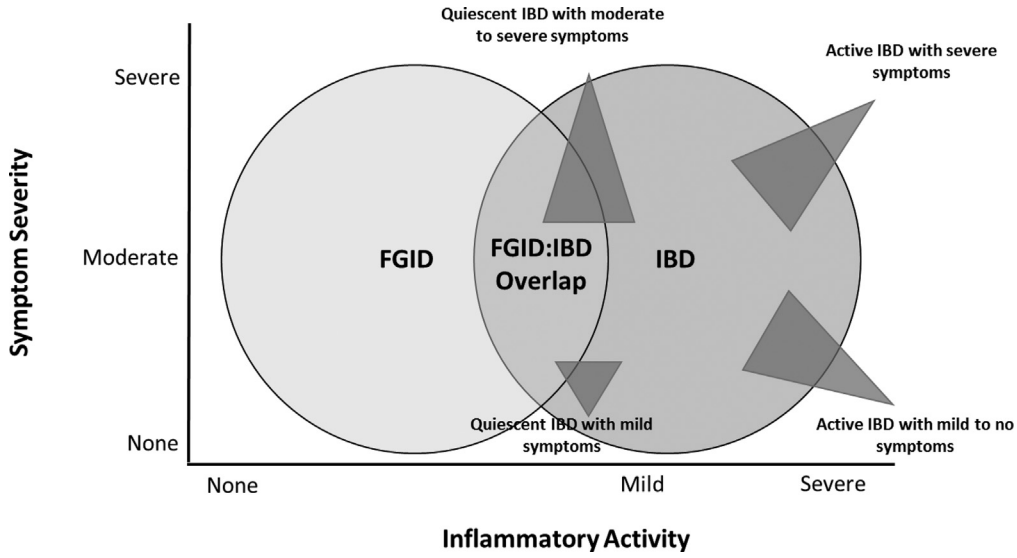
Conflicts of interest
These authors disclose the following: Jean-Frederic Colombel has served as consultant, advisory board member, speaker or speaker's bureau for AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen and Janssen, Lilly, Medimmune, Merck & Co, Pfizer, PPM Services, Protagonist, Second Genome, Seres, Shire, Takeda, Theradiag, Theravance Biopharma. He has received research grants from: AbbVie, Takeda, Janssen and Janssen. He owns stock options in Intestinal Biotech Development, Genfit. Peter R. Gibson has served as consultant or advisory board member for Ferring, Janssen, Merck, Danone, Allergan, Celgene and Takeda. He has received research grants for investigator-driven studies from AbbVie, Danone and A2 Milk Company. His Department financially benefits from the sales of a digital application and booklets on the low-FODMAP diet. He has published an educational/recipe book on the low-FODMAP diet. Andrea Shin discloses no conflicts.

Funding
Andrea Shin is supported, in part, by grants KL2TR001106, and UL1TR001108 (A. Shekhar, PI) from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award.



Supplementary Figure 1. Clinical spectrum of active inflammation and persistent gastrointestinal symptoms in patients with inflammatory bowel disease.