Gastroenterology 2016;150:1393–1407

Bowel Disorders

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Functional bowel disorders are highly prevalent disorders found worldwide. These disorders have the potential to affect all members of society, regardless of age, sex, race, creed, color, or socioeconomic status. Improving our understanding of functional bowel disorders (FBD) is critical, as they impose a negative economic impact to the global health care system in addition to reducing quality of life. Research in the basic and clinical sciences during the past decade has produced new information on the epidemiology, etiology, pathophysiology, diagnosis, and treatment of FBDs. These important findings created a need to revise the Rome III criteria for FBDs, last published in 2006. This article classifies the FBDs into 5 distinct categories: irritable bowel syndrome, functional constipation, functional diarrhea, functional abdominal bloating/distention, and unspecified FBD. Also included in this article is a new sixth category, opioid-induced constipation, which is distinct from the functional bowel disorders (FBDs). Each disorder will first be defined, followed by sections on epidemiology, rationale for changes from prior criteria, clinical evaluation, physiologic features, psychosocial features, and treatment. It is the hope of this committee that this new information will assist both clinicians and researchers in the decade to come.

Keywords: Abdominal Pain; Bloating; Distension; Constipation; Diarrhea; Functional Bowel Disorders; Irritable Bowel Syndrome.

Functional bowel disorders (FBD) are a spectrum of chronic gastrointestinal (GI) disorders characterized by predominant symptoms or signs of abdominal pain, bloating, distention, and/or bowel habit abnormalities (eg, constipation, diarrhea, or mixed constipation and diarrhea). The FBDs can be distinguished from other GI disorders based on chronicity (≥6 months of symptoms at the time of presentation), current activity (symptoms present within the last 3 months), frequency (symptoms present, on average, at least 1 day per week), and the absence of obvious anatomic or physiologic abnormalities identified by routine diagnostic examinations, as deemed clinically appropriate. The FBDs are classified into 5 distinct categories: irritable bowel syndrome (IBS), functional constipation (FC), functional diarrhea (FDr), functional abdominal bloating/distention, and unspecified FBD (Table 1). Also included in this article is a new sixth category, opioid-induced constipation (OIC), which is distinct from the FBDs by having a specific etiology that can produce similar symptoms as FC. Clinically, OIC can overlap with FC and so is included in this article, as clinicians may need to evaluate both concurrently and may use different treatments. This classification scheme is designed to assist both researchers and clinicians; however, it is important to acknowledge that significant overlap exists between these disorders, and these disorders should be thought of as existing on a continuum, rather than discrete disorders (Figure 1). As these disorders exist on a continuum, it may not always be possible to confidently separate them. Using evidence from the scientific literature and a consensus-based approach, the 2016 working team has revised the Rome III diagnostic criteria and updated the clinical evaluation and treatment for all FBDs.

C1. Irritable Bowel Syndrome

Definition

IBS is an FBD in which recurrent abdominal pain is associated with defecation or a change in bowel habits. Disordered bowel habits are typically present (ie, constipation, diarrhea, or a mix of constipation and diarrhea), as are symptoms of abdominal bloating/distention. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months.

Abbreviations used in this paper: **BSFS, Bristol Stool Form Scale; CBC, complete blood count; CC, chronic constipation; DD, dyssynergic defecation; FAB, functional abdominal bloating; FAD, functional abdominal distention; FBD, functional bowel disorder; FC, functional constipation; FDr, functional diarrhea; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, irritable bowel syndrome with constipation and diarrhea; IBS-U, irritable bowel syndrome unclassified; OIC, opioid-induced constipation.**

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.02.031

Table 1. Functional Gastrointestinal Disorders

C. Functional bowel disorders
- C1. Irritable bowel syndrome
- C2. Functional constipation
- C3. Functional diarrhea
- C4. Functional abdominal bloating/distension
- C5. Unspecified functional bowel disorders
- C6. Opioid-induced constipation

Epidemiology

The world-wide prevalence of IBS is 11.2% (95% confidence interval: 9.8%−12.8%) based on a meta-analysis of 80 studies involving 260,960 subjects.[1] The incidence of IBS is estimated to be 1.35%−1.5%, based on 2 separate longitudinal population studies lasting 10 and 12 years.[2,3] Prevalence rates are higher for women than for men; younger people are more likely to be affected than those older than age 50 years.[1]

C1. Diagnostic Criteria[a] for Irritable Bowel Syndrome

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Rationale for Changes From Previous Criteria

In contrast to the Rome III criteria, the term *discomfort* has been eliminated from the current definition and diagnostic criteria because not all languages have a word for "discomfort," it has different meanings in different languages, and the term is ambiguous to patients. One study of IBS patients found that patients exhibited wide variations in their understanding of this term.[4] Another study demonstrated that in 4 of 5 cases, the same individual would be diagnosed with IBS regardless of which descriptor was used.[5]

The current definition involves a change in the frequency of abdominal pain, stating that patients should have symptoms of abdominal pain at least 1 day per week during the past 3 months. This is in contrast to Rome III criteria, which defined IBS as the presence of abdominal pain (and discomfort) at least 3 days per month. The requirement for an increase in the frequency of abdominal pain is based on data from the Report on Rome Normative GI symptom survey.[6]

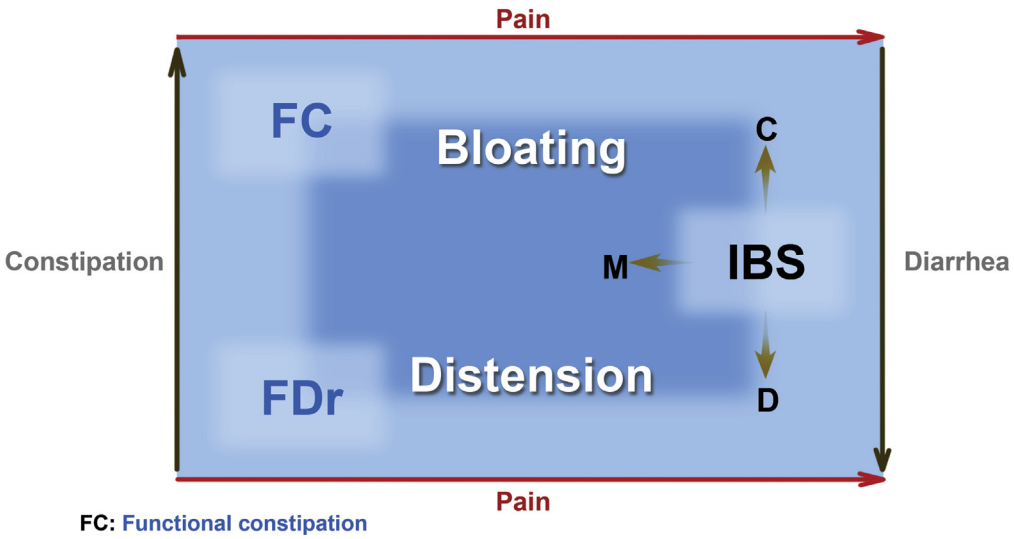

Figure 1. Conceptual framework to explain FBDs. The FBDs are classified into 5 distinct categories: IBS, FC, FDr, FAB/FAB, and unspecified FBD (U-FBD). Although often thought of as existing as completely separate and discrete disorders, it is important to acknowledge that significant overlap exists between these disorders. These disorders should be thought of as existing on a continuum, rather than as in isolation. This figure illustrates that a patient with IBS (*right*) will have symptoms of abdominal pain, in contrast to a patient with FC or FDr, who does not have abdominal pain. Bloating and distention are common symptoms frequently reported by patients with any FBD.

The phrase "improvement with defecation" was modified in the current definition to "related to defecation" as a large subset of IBS patients do not have an improvement in abdominal pain with defecation, but instead report a worsening. Similarly, the word *onset* was deleted from criteria 2 and 3 of the Rome III definition, as not all IBS patients report the onset of abdominal pain directly coinciding with a change in stool frequency or form.

Clinical Evaluation

The diagnosis of IBS requires a thoughtful approach, limited diagnostic tests, and careful follow-up. The goal of diagnostic criteria is to provide a readily useable framework that can be easily applied, recognizing that no single test and no single definition are perfect.[7] Because a number of conditions have symptoms that can mimic IBS (eg, inflammatory bowel disease [IBD], celiac disease, lactose and fructose intolerance, and microscopic colitis), limited testing may be required to accurately distinguish these disorders. However, for the majority of patients, when diagnostic criteria for IBS are fulfilled and alarm features are absent, the need for diagnostic tests should be minimal.[8] Using the criteria outlined here, clinicians should make a positive diagnosis of IBS based on symptoms and limited testing; performing a battery of tests in all patients suspected of having IBS is not warranted. The diagnosis of IBS should be made based on the following 4 key features: clinical history; physical examination; minimal laboratory tests; and, when clinically indicated, a colonoscopy or other appropriate tests.

The diagnosis of IBS begins with a careful history. Abdominal pain must be present; the absence of abdominal pain precludes the diagnosis of IBS. Pain can be present anywhere throughout the abdomen, although it is more common in the lower abdomen. A history of disordered bowel habits (eg, constipation or diarrhea or both) should be identified, along with their temporal association with episodes of abdominal pain (see "Diagnostic Criteria for Irritable Bowel Syndrome Subtypes"). Unpredictable bowel pattern (≥3 different stool form types/week) reinforces the diagnosis of IBS in the diarrhea subtype (IBS-D).[9] An increasing number of consecutive days without a bowel movement is associated with the diagnosis of constipation-predominant (IBS) (IBS-C).[10] Abnormal stool frequency (>3 bowel movements/day and <3 bowel movements/week), abnormal stool form (types 1−2 or 6−7 of the Bristol scale; Figure 2), excessive straining during defecation, defecatory urgency, feelings of incomplete evacuation, and mucus with bowel movements, although common in IBS, are not specific. Abdominal bloating is present in a majority of IBS patients; abdominal distention may be reported as well, although neither is required to make the diagnosis of IBS.

Diagnostic criteria for IBS subtypes (Figure 11-11, FM 12)

Predominant bowel habits are based on stool form on days with at least one abnormal bowel movement.[a]

IBS with predominant constipation: More than one-fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and less than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7. Alternative for epidemiology or clinical practice: Patient reports that abnormal bowel movements are usually constipation (like type 1 or 2 in the picture of Bristol Stool Form Scale (BSFS), see Figure 2*A*).

IBS with predominant diarrhea (IBS-D): more than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7 and less than one-fourth (25%) of bowel movements with Bristol stool form types 1 or 2. Alternative for epidemiology or clinical practice: Patient reports that abnormal bowel movements are usually diarrhea (like type 6 or 7 in the picture of BSFS, see Figure 2*A*).

IBS with mixed bowel habits (IBS-M): more than one-fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and more than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7. Alternative for epidemiology or clinical practice: Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea, using picture of BSFS, see Figure 2*A*).

IBS unclassified (IBS-U): Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above should be categorized as having IBS unclassified.

For clinical trials, subtyping based on at least 2 weeks of daily diary data is recommended, using the "25% rule."

[a]IBS subtypes related to bowel habit abnormalities (IBS-C, IBS-D, and IBS-M) can only be confidently established when the patient is evaluated off medications used to treat bowel habit abnormalities.

Diagnostic Criteria for Irritable Bowel Syndrome Subtypes

IBS is classified into 3 main subtypes according to the predominant disorder in bowel habits: IBS-C, IBS-D, and IBS-M (Table 1). Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups should be categorized as having IBS unclassified. This group is not prevalent; difficulty in accurately classifying a patient into 1 of the 3 main subgroups might occur as a result of frequent changes in diet or medications, or inability to stop medications that affect gastrointestinal transit. Subtyping should be based on the patient's reported predominant bowel habit on days with abnormal bowel movements. The Bristol Stool Form Scale (BSFS; Figure 2) should be used to record stool consistency.[11] In order to accurately classify bowel habit

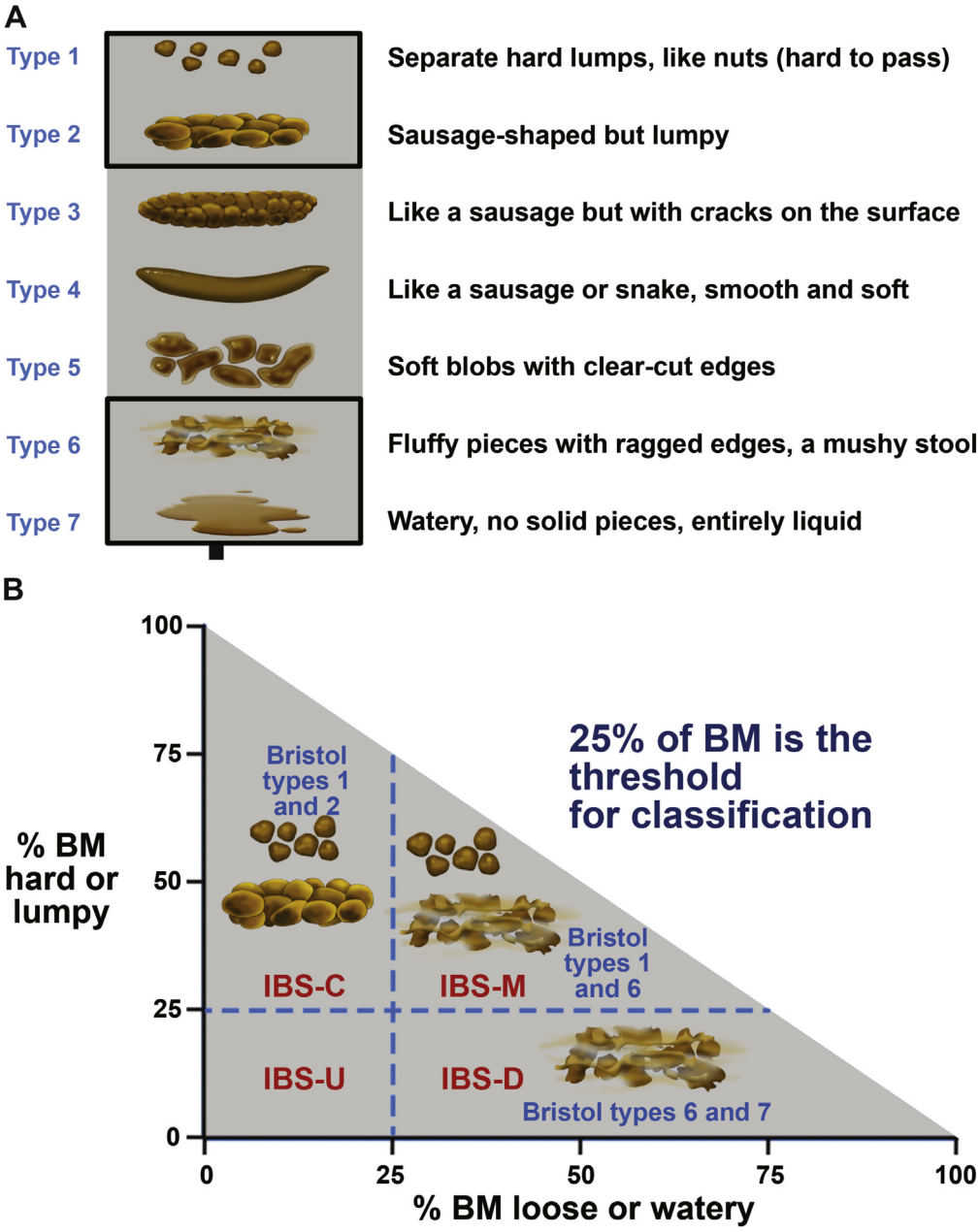

Figure 2. (*A*) The BSFS is a useful tool to evaluate bowel habit. The BSFS has been shown to be a reliable surrogate marker for colonic transit.[19] (*B*) IBS subtypes should be established according to stool consistency, using the BSFS. IBS subtyping is more accurate when patients have at least 4 days of abnormal bowel habits per month. Bowel habit subtypes should be based on BSFS for days with abnormal bowel habits.

abnormalities, patients should not be on any type of medication used to treat bowel habit abnormalities (eg, evaluation should occur off laxatives and off antidiarrheal agents). For clinical trials, the IBS subtype should be based on 14 days of daily diary reports.[12] Figure 2 illustrates a 2-dimensional display of the 4 possible IBS subtypes.

IBS patients frequently report that symptoms are induced or exacerbated by meals, although these symptoms are not specific enough to be included in IBS diagnostic criteria. A variety of other GI (ie, dyspepsia) and non-GI symptoms (ie, migraine headaches, fibromyalgia, interstitial cystitis, dyspareunia) are frequently present in IBS patients; the presence of these concomitant symptoms lends further support to the diagnosis.[13–16] The presence of alarm features (a positive family history of colorectal cancer, rectal bleeding in the absence of documented bleeding hemorrhoids or anal fissures, unintentional weight loss, or anemia) does not improve the performance of IBS diagnostic criteria.[17,18] However, it is reasonable to include them in a directed review, as one study showed that the absence of alarm symptoms reduced the likelihood of organic disease in subjects with IBS-D symptoms.[19] Patients should be questioned about their diet, with special attention paid to the ingestion of dairy products, wheat, caffeine, fruits, vegetables, juices, sweetened soft drinks, and chewing gum, because these can mimic or exacerbate IBS symptoms. Lastly, a brief psychosocial review should be performed.

A physical examination should be performed in every patient evaluated for IBS. This reassures the patient and helps to exclude an organic etiology. The presence of ascites,

hepatosplenomegaly, or an abdominal mass warrants further evaluation. An anorectal examination is mandatory to identify anorectal causes of bleeding, evaluate anorectal tone and squeeze pressure, and identify dyssynergic defecation.

The third step in the diagnosis of IBS is to perform limited laboratory studies, if not previously performed. A complete blood count (CBC) should be ordered, as the finding of anemia or an elevated white blood cell count warrants further investigation. A C-reactive protein or fecal calprotectin should be measured, as a systematic review and meta-analysis showed that these tests are helpful in excluding IBD in patients with symptoms suggestive of nonconstipated IBS.[20] If inflammatory markers are mildly elevated, but the probability of IBD is low, then tests should be remeasured before performing colonoscopy (if no other indication for colonoscopy exists).[21] Inflammatory markers, including fecal calprotectin, may not be useful in patients with constipation symptoms. Routine thyroid tests are not indicated in all patients, but can be checked if clinically warranted. Serologic tests for celiac disease should be performed in patients with IBS-D and IBS-M who fail empiric therapy. Upper gastrointestinal endoscopy with duodenal biopsies should be performed if serologic tests for celiac disease are positive or if clinical suspicion is high; duodenal biopsies can also be used to identify tropical sprue, which can mimic IBS symptoms.[22] Stool analysis (bacteria, parasites, and ova) may be useful if diarrhea is the main symptom, especially in developing countries where infectious diarrhea is prevalent.

A screening colonoscopy is indicated in patients 50 years and older in the absence of warning signs (45 years in African Americans), based on national recommendations. Colonoscopy is also indicated for the presence of alarm symptoms or signs, a family history of colorectal cancer and persistent diarrhea that has failed empiric therapy. Biopsies of different segments of the colon may be required in patients with chronic diarrhea to rule out microscopic colitis.[23] Bile acid malabsorption may be the cause of persistent, watery diarrhea in some patients.[24] If empiric therapy fails, scintigraphic evaluation (^{75}SeHCAT test) or postprandial serum C4 (7a-hydroxy-4-cholesten-3-one) or fibroblast growth factor 19 are diagnostic options, although none are currently widely available. Breath tests to rule out carbohydrate malabsorption may be useful in some patients with IBS symptoms and persistent diarrhea.

Physiologic Features

IBS is a multifactorial disorder with a complex pathophysiology. Factors that increase the risk of developing IBS include genetic, environmental, and psychosocial factors. Factors that trigger the onset or exacerbation of IBS symptoms include a prior gastroenteritis, food intolerances, chronic stress, diverticulitis, and surgery.[25] The resulting pathophysiologic mechanisms are variable and patient independent, and include altered GI motility, visceral hyperalgesia, increased intestinal permeability, immune activation, altered microbiota, and disturbances in brain–gut function (Figure 2).

Psychosocial Features

Psychological disturbance is associated with IBS, especially in patients who seek medical care,[26] and psychosocial factors affect outcome.[27] Regardless of care-seeking status, IBS is associated with more psychiatric distress, sleep disturbance, "affective vulnerability," and "over-adjustment to the environment."[28]

Treatment

IBS treatment begins by explaining the condition, providing reassurance as to the benign natural history, and educating the patient about the utility and safety of diagnostic tests and treatment options. Treatment should be based on symptom type and severity. In research trials, the validated IBS symptom severity scale can be used to quantify symptom severity.[29]

Although data are limited, lifestyle modifications that may improve IBS symptoms include exercise, stress reduction, and attention to impaired sleep.[30] Dietary fiber supplementation remains a cornerstone of IBS management, although its optimal use can be quite nuanced. A recent systematic review and meta-analysis identified 12 trials comparing fiber with control and found only a marginal difference in the proportion of IBS patients with persistent symptoms after any type of fiber vs the control intervention.[31] Subgroup analysis suggested that benefits for IBS symptoms were confined to soluble (psyllium/ispaghula husk) and not insoluble (bran) fiber. Certain forms of fiber, and particularly bran, can exacerbate problems of abdominal distention and flatulence.[32]

Dietary restriction of gluten may improve symptoms in some IBS patients. Two small prospective studies in IBS patients, in which celiac disease was carefully excluded, demonstrated global symptom improvement.[33,34] Dietary FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) restriction is associated with reduced fermentation and significant symptom improvement in some IBS patients.[35] In a randomized, controlled, single-blind cross-over trial, 30 IBS patients who had not previously tried dietary manipulation reported significant reduction in overall gastrointestinal symptom scores compared with those on a standard Australian diet.[36] Adding a gluten-free diet to IBS patients already on a low FODMAP diet does not offer additional benefit.[37] Another recent comparative effectiveness study concluded that a low FODMAP diet and standardized traditional teaching from a dietitian yielded similar results in IBS patients.[38]

Several peripherally acting agents are available to treat IBS-C symptoms (Table 2). A randomized controlled trial (RCT) of polyethylene glycol (PEG) vs placebo demonstrated improvements in stool frequency, stool consistency, and straining, but not abdominal pain or bloating during the 4-week study.[39] Lubiprostone is a luminally acting prostone that selectively activates type 2 chloride channels.[40,41] In 2 large, placebo-controlled, randomized studies lubiprostone (8 μg twice daily) resulted in significantly higher overall symptom response compared with placebo during 12 weeks of treatment.[42] A subsequent 52-week extension study

Table 2. Therapeutic Options for Irritable Bowel Syndrome Based on Predominant Symptom

Symptom	Therapy	Dose
Diarrhea	Opioid agonists	Loperamide; 2–4 mg; when necessary Titrate up to 16 mg/d
	Diet	Low/no gluten; low FODMAP
	Bile salt sequestrants	cholestyramine (9 g bid–tid) colestipol (2 g qd–bid) colesevelam (625 mg qd–bid)
	Probiotics	Multiple products available
	Antibiotics	Rifaximin, 550 mg po tid × 14 d
	5-HT_3 antagonists	Alosetron (0.5–1 mg bid) Ondansetron (4–8 mg tid) Ramosetron 5 μg qd
	Mixed opioid agonists/antagonists	Eluxadoline, 100 mg bid
Constipation	Psyllium	up to 30 g/d in divided doses
	PEG	17–34 g/d
	Chloride channel activators	Lubiprostone, 8 μg bid
	Guanylate Cyclase C agonists	Linaclotide 290 μg qd
Abdominal pain	Smooth muscle antispasmodics	dicycylomine (10–20 mg qd–qid) Otilonium (40–80 mg bid–tid) Mebeverine (135 mg tid)
	Peppermint oil	Enteric-coated capsules, 250–750 mg, bid–tid
	Tricyclic antidepressants	Desipramine (25–100 mg qhs), amitriptyline (10–50 mg qhs)
	SSRIs	paroxetine (10–40 mg qd) sertraline (25–100 mg qd) citalopram (10–40 mg qd)
	Chloride channel activators	Lubiprostone 8 μg bid
	Guanylate cyclase C agonists	Linaclotide 290 μg qd
	5-HT_3 antagonists	Alosetron 0.5–1.0 mg bid

SSRI, selective serotonin reuptake inhibitor; qhs, at bedtime.

identified the most common adverse events as nausea and diarrhea.[43] Linaclotide is a 14-amino acid peptide that acts as a guanylate cyclase C agonist. In 2 large phase 3 trials, linaclotide was found to be more effective than placebo at improving bowel and abdominal symptoms in IBS-C patients.[44–46] A 6-month, double-blind, placebo-controlled phase 3 trial utilized a combined end point, which required improvement of ≥30% from baseline in mean daily worst abdominal pain score, as well as an increase of ≥1 complete spontaneous bowel movement from baseline for ≥6 and 12 weeks. Linaclotide proved superior to placebo in 12- and 26-week studies. Diarrhea was the most commonly reported adverse event with linaclotide. A second guanylate cyclase C agonist, plecanatide, is currently in development.[47] A small pilot study showed that supplementation of bile acids using sodium chenodeoxycholic acid may improve IBS-C symptoms in some patients.[48]

Loperamide, a synthetic peripheral μ-opioid receptor agonist that decreases colonic transit, and increases water and ion absorption, is commonly used to treat IBS-D patients. In one small placebo RCT, loperamide improved stool consistency, pain, urgency, and subjective overall response.[49] In another study, loperamide improved stool consistency, reduced bowel frequency, and reduced intensity of pain, although it increased nightly abdominal pain.[50] There is increasing evidence to support a role for bile acids in the pathophysiology of IBS-D.[24] In small pilot studies, bile acid sequestrants (eg, colesevelam and colestipol) improved stool passage and stool consistency.[51,52]

Antispasmodics are used to treat abdominal pain and spasms in all IBS subtypes. A meta-analysis involving 12 different antispasmodics found this class of drugs to be superior to placebo for the prevention of recurrent IBS symptoms.[31] A recent meta-analysis found peppermint oil, which also has antispasmodic properties, to be significantly superior to placebo for global improvement of IBS symptoms and improvement in abdominal pain. Heartburn was the most common adverse effect.[53]

Probiotics may benefit IBS patients through multiple mechanisms.[54] *Bifidobacterium infantis* 35624 led to significant improvements in abdominal pain/discomfort, bloating/distention, and/or bowel movement difficulty compared with placebo in 2 randomized, placebo-controlled trials conducted in IBS patients.[55,56] A recent meta-analysis that included 43 clinical trials using different products found probiotics to offer benefits for global IBS symptoms, pain, bloating, and flatulence.[57]

The US Food and Drug Administration approved rifaximin, a nonabsorbable antibiotic, for the treatment of IBS-D. In 2 large clinical trials, 2 weeks of treatment with rifaximin

550 mg 3 times daily in patients with nonconstipated IBS resulted in significantly more patients reporting adequate relief of global IBS symptoms and bloating during the first 4 weeks of follow-up.[58] Improvement in symptoms relative to placebo persisted for the 10-week follow-up period, even though a gradual loss of symptom response was noted. Repeat treatment with rifaximin appears to offer similar efficacy to an initial course of therapy. Patients with IBS-D who relapsed during an 18-week follow-up period were more likely to respond to retreatment with rifaximin compared with placebo.[59]

Alosetron, a highly selective 5-HT_3 antagonist, is effective at relieving pain and reducing stool frequency and rectal urgency in women with IBS-D.[31,40] Alosetron is approved with restrictions in the United States for women with severe IBS-D beginning at 0.5 mg twice daily. Uncommon adverse events include ischemic colitis and constipation, 0.95 and 0.36 cases per 1000 patient-years, respectively.[60] The 5-HT_3 antagonists ondansetron and ramosetron also appear effective in the treatment of IBS-D.[61,62]

Eluxadoline is a novel mixed μ-receptor agonist/δ-opioid receptor antagonist that has been developed as a treatment for patients with IBS-D.[63] In 2 large phase 3 trials involving >2,400 IBS-D patients, a greater percentage of eluxadoline-treated patients (75 and 100 mg oral once daily) were combined responders (both abdominal pain and diarrhea) during weeks 1−12 or 1−26 compared with patients on placebo. The most common adverse events were nausea (8%), constipation (8%), and abdominal pain (5.0%). A small number of patients experienced sphincter of Oddi dysfunction or self-limited pancreatitis. All of these patients had a history of cholecystectomy or significant ethanol consumption. Eluxadoline should be used at the lower dose and with careful monitoring in these patients.[64]

Tricyclic antidepressant agents appear effective in treating IBS symptoms.[65] In a 2-month trial of IBS-D patients, 10 mg of amitriptyline significantly improved overall IBS symptoms and reduced the frequency of loose stool and feelings of incomplete defecation, and led to a complete response (defined as loss of all symptoms).[66] A recent systematic review and meta-analysis summarized the efficacy data for selective serotonin reuptake inhibitors. Seven trials were included, demonstrating benefits of selective serotonin reuptake inhibitors over placebo for overall IBS symptoms.[65] A number of clinical characteristics, including the predominant stool complaint, the presence of insomnia, or comorbid anxiety, can influence the choice of antidepressant in an individual IBS patient. Few data are available on the use of selective norepinephrine reuptake inhibitors in IBS.

Disodium cromoglycate, a mast cell stabilizer, may improve symptoms in some IBS-D patients.[67] Two recent appropriately powered, high-quality RCTs demonstrated no significant efficacy of mesalazine vs placebo in IBS-D.[68,69] Fecal microbiota transplantation, herbal therapies, and complementary therapies are also potential treatments, however, these have not been rigorously studied. RCTs have consistently failed to show benefit of acupuncture compared with sham acupuncture.[70] The efficacy of psychological/behavioral therapies including cognitive behavioral therapy and hypnotherapy is discussed in detail in the article on psychological therapies.

Psychological and behavioral treatments relates to helping patients control and reduce pain and discomfort and are seen as ancillary to or augmenting medical treatments. Treatments include cognitive behavioral therapy, hypnosis, and various relaxation methods to reduce muscle tension and autonomic arousal believed to aggravate GI symptoms. A large number of studies in IBS confirm the values of these treatments and are discussed in detail in this issue (Biopsychosocial Aspects of Functional Gastrointestinal Disorders).

C2. Functional Constipation

Definition

FC is a functional bowel disorder in which symptoms of difficult, infrequent, or incomplete defecation predominate. Patients with FC should not meet IBS criteria, although abdominal pain and/or bloating may be present but are not predominant symptoms. Symptom onset should occur at least 6 months before diagnosis, and symptoms should be present during the last 3 months.

Epidemiology

Few studies have evaluated the incidence and prevalence of FC. Most studies have focused on patients with chronic constipation (CC), who may or may not meet strict criteria for FC. One study reported onset rates of 40/1000 person-years when patients were resurveyed a median of 14.7 months after the initial survey.[71] Using modified Rome II criteria, a community study identified a 12-year cumulative incidence of constipation of 17.4%.[72] In adults, the mean prevalence rate of CC is approximately 14%, with rates that range from 1.9% to 40.1%.[73] Self-report rates of constipation are generally higher compared with use of Rome criteria. Risk factors for FC include female sex, reduced caloric intake, and increasing age.[74,75]

C2. Diagnostic Criteria[a] for Functional Constipation

1. Must include 2 or more of the following:[b]
   a. Straining during more than one-fourth (25%) of defecations
   b. Lumpy or hard stools (BSFS 1−2) more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
   e. Manual maneuvers to facilitate more than one fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
   f. Fewer than 3 spontaneous bowel movements per week

2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

[b]For research studies, patients meeting criteria for OIC should not be given a diagnosis of FC because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these 2 conditions might overlap.

Rationale for Changes From Previous Criteria

The following points highlight notable changes from the Rome III criteria. It is now specified that abdominal pain and/or bloating may be present but are not predominant symptoms (ie, the patient does not meet criteria for IBS). This supports the concept that FC and IBS-C are disorders that exist on a continuous spectrum.

Clinical Evaluation

FC can be diagnosed by both subjective and objective (measurable) variables. A survey study of patients with CC determined that the most frequent symptoms were straining (79%), hard stools (71%), abdominal discomfort (62%), bloating (57%), infrequent bowel movements (57%), and feelings of incomplete evacuation after a bowel movement (54%).[76] When necessary, objective tests can be performed and these measures of stool frequency, daily stool weight (<35 g/d), colonic transit, and anorectal function. Diagnostic evaluations should be performed while the patient is not taking laxatives. Mechanical obstruction, medications, and systemic illnesses can cause constipation, and these causes of secondary constipation must be excluded, especially in patients presenting with new onset constipation. Most often, however, constipation is caused by disordered function of the colon or rectum. CC can be divided into 3 broad categories: normal-transit constipation, slow-transit constipation, and defecatory or rectal evacuation disorders.

Colonic transit time can be estimated by using the BSFS (Figure 2): stool forms 1 and 2 are associated with slower transit, while stool forms 6 and 7 are associated with more rapid transit.[11] The committee recognizes that a subset of patients with symptom criteria for FC have slow colonic transit.[77] As well, some FC patients have overlapping dyssynergic defecation (DD).[31] It is the opinion of this committee that all cases of CC without evidence of structural or metabolic abnormalities to explain symptoms should be considered under the "umbrella" of FC. We acknowledge, however, that the diagnosis of slow transit constipation or a DD requires diagnostic tests (discussed later), which may modify treatment strategies.

The diagnosis of FC should be made using the following 5 key features: clinical history, physical examination, minimal laboratory tests, colonoscopy or other tests (if clinically indicated and available), and specific tests to evaluate constipation pathophysiology (if clinically indicated and available).

When taking a history, it is important to understand what the patient means when reporting constipation. A detailed history should include the duration of symptoms; frequency of bowel movements; associated symptoms, such as abdominal pain, bloating, or distention; and an assessment of stool consistency, stool size, and degree of straining during defecation. The presence of alarm features, such as unintentional weight loss (>10% in 3 months), rectal bleeding (in the absence of documented bleeding hemorrhoids or anal fissures), and a family history of colon cancer (or familial polyposis syndromes) should be elicited. A long duration of symptoms refractory to conservative measures is suggestive of an FBD. By contrast, the new onset of constipation might indicate a structural disease.[31] It is important to identify DD because it has a distinct pathophysiology and is more likely to respond to specific treatments. DD can be suspected by using specific questionnaires and by performing a thorough physical examination, although objective measures are often required (discussed later).[78,79]

A physical examination should exclude central nervous system disorders and spinal lesions. The abdomen should be examined for distention, hard stool in a palpable colon, or a mass. A careful rectal examination is essential. The perineum should be observed both at rest and after the patient strains as if to have a bowel movement. A digital rectal examination can identify a fecal impaction, anal stricture, or rectal mass. Inappropriate contraction of the puborectalis muscle and/or anal sphincter during simulated evacuation is consistent with DD.[78,79]

A CBC should be obtained if not recently performed. Thyroid-stimulating hormone and serum calcium should be performed when clinically indicated. All patients aged older than 50 years (45 years and older in African Americans) should have a screening colonoscopy based on national recommendations. The presence of alarm symptoms or a family history of colorectal cancer should prompt earlier intervention.

Testing for slow colonic transit and/or DD is neither required nor justified in all patients. Patients who do not respond to reasonable trials of empiric therapy should undergo diagnostic evaluation to identify physiological subgroups. Radiopaque markers can be used to evaluate colonic transit; this is inexpensive, simple and safe.[80,81] A radioisotope technique involves less radiation than x-ray studies and may provide more information,[82] although it is available in very few centers. Anorectal manometry and balloon expulsion testing may help identify DD.[83] Defecography may detect anatomic etiologies, such as intussusception and rectocele with stool retention, as well as inability to relax the puborectalis or decrease the anorectal angle with straining, features typical of DD.[84] Electromyography and pudendal nerve latency testing are adjunctive techniques (see section on Anorectal Disorders).

Physiologic Features

Similar to IBS, symptoms of FC arise due to a variety of pathophysiologic processes. Several studies suggest

constipation shows familial clustering.[85,86] Data supporting a direct genetic cause are sparse.[87,88] Limited data from pediatric studies raise the possibility that lifestyle factors in childhood (low fiber intake, low fluid intake, and ignoring the call to stool) may play a role in the development of constipation.[89–93] Two studies have shown that high fiber intake reduced the risk of constipation.[75,94] Regular exercise is associated with a significantly reduced risk of constipation.[75,95,96] Small RCTs have shown that there is no benefit in increasing fluid intake in those who are hydrated normally.[97]

Transit studies in constipated subjects show disparate results, with slow colonic transit in some patients but normal transit in others.[98–100] In those with delayed transit, variations exist with regard to which colonic segment is affected.[101,102] Most FC patients do not have evidence of visceral hypersensitivity when evaluated by rectal barostat testing, although some have rectal hyposensitivity.[103] Autonomic dysfunction, morphologic changes in the myenteric and submucosal plexus, and reduced neurotransmitter levels (eg, VIP, NO, 5-HT) have been demonstrated in some patients with slow transit constipation.[103–108] Confocal microscopy studies and pathology specimens from patients with slow-transit constipation undergoing colectomy have showed reduced numbers of interstitial cells of Cajal.[109–111]

Psychosocial Features

There is no specific psychological feature or personality that is associated with constipation, but constipation reporting, stool output, and gut dysmotility may be affected by personality, stress, and early toilet training.[112] Patients with severe constipation and normal intestinal transit often have increased psychological distress, and may have misperceptions about their bowel frequencies.[112,113] In addition, abnormal illness behavior is more common in patients with chronic constipation compared with nonpatients.[114] Constipation behavior can be learned in early life; deliberate suppression of defecation leads to reduced stool frequency and weight and increased transit time.[115]

Treatment

Treatment should begin by educating the patient about FC, eliminating medications (prescription, over-the-counter, complementary) that can cause or worsen constipation, asking the patient to maintain a diet that contains an adequate amount of fiber, scheduling routine bathroom time after the morning or evening meal, and elevating the feet with a foot stool or using a toilet that is lower to the ground. If symptoms persist, empiric therapy can be initiated in the absence of warning signs. If empiric therapy fails after an appropriate clinical trial (ie, 4−8 weeks), then physiological testing should be considered to identify the underlying disorder and initiate the most appropriate treatment.

Empiric therapy should begin with a fiber supplement (Table 3).[116] Insoluble, nonfermentable fiber accelerates transit by increasing stool biomass leading to direct stimulation of secretion and motility. Soluble, more fermentable forms of fiber may accelerate transit via hydrophilic properties and the osmotic effects of fermentation byproducts. Total fiber intake of 20−30 g/d is recommended, although dose-dependent bloating, distention, and flatulence can affect tolerability and compliance. Constipated patients with severely delayed colon transit and/or obstructed defection are less likely to improve with fiber.[31,77]

Table 3. Therapeutic Options for Functional Constipation

Drug	Dose
Psyllium	Up to 30 mg/d in divided doses
PEG	17−34 g/d
Chloride channel activators	Lubiprostone, 24 μg bid
Guanylate cyclase C agonists	Linaclotide 145 μg qd
Prucalopride	2−4 mg/d

Prospective RCTs dictating the choice of therapy after a patient fails fiber therapy are not available. However, osmotic agents are often used next, given their safety, cost, and efficacy.[31,73,117,118] Osmotic laxatives (eg, lactulose, lactitol, mannitol, and sorbitol) are not absorbed by the small intestine; ingestion causes net water and electrolyte secretion, resulting in reduced stool viscosity and increased fecal biomass with secondary effects on peristalsis.[113–115] Side effects include dose-dependent abdominal cramping and bloating.[115] PEG, another osmotic agent, has been evaluated in high-quality RCTs of up to 6 months.[116] PEG is superior to placebo and lactulose in adults and children.[119–123] Adverse effects of PEG include distention and diarrhea. Saline laxatives, including magnesium citrate, magnesium sulfate, and sodium and disodium phosphate, induce movement of water into the small intestine and colon. RCTs evaluating the efficacy of these agents have not been performed; they should be used cautiously in the elderly and avoided in those with renal impairment.[124]

Stimulant laxatives (diphenylmethane derivatives, eg, bisacodyl, sodium picosulfate, and conjugated anthraquinone derivatives, eg, cascara sagrada, aloe, and senna) decrease water absorption and stimulate intestinal motility and prostaglandin release.[125–127] RCTs have demonstrated clinical benefits for stool frequency and other constipation-associated symptoms with bisacodyl and sodium picosulfate in patients with CC.[128,129] The most common side effects are abdominal pain and diarrhea.[128,129]

Two pro-secretory agents (secretagogues) improve symptoms of CC. In 4 week, RCTs of patients with CC, lubiprostone (24 μg twice daily with food) proved superior to placebo at increasing stool frequency, improving stool consistency and reducing straining and overall constipation symptoms.[130–132] Nausea and diarrhea were the most common adverse events. In 12-week RCTs, linaclotide (145 μg once daily) was more effective than placebo at increasing stool frequency, improving stool consistency, straining, and overall constipation symptoms.[133] The most common treatment-associated side effect was diarrhea. Plecanatide, another guanylate cyclase C agonist, at 3 mg once daily, may also be effective for FC.[134]

Elobixibat is a nonabsorbed, small molecule that inhibits ileal bile acid transporters. Still under development at this time, elobixibat improves stool frequency and other constipation associated symptoms in patients with CC. The most commonly reported adverse events have been dose-dependent abdominal pain and diarrhea.[135–137]

5-HT_4 receptor agonists stimulate peristalsis and accelerate gastrointestinal transit.[138–140] Tegaserod, a highly selective, partial 5-HT_4 receptor agonist, was found superior to placebo at improving stool frequency and other constipation associated symptoms.[141,142] Tegaserod was withdrawn from the United States and most other markets in 2007 due to concerns involving possible cardiovascular adverse events. Prucalopride is a dihydrobenzofurancarboxamide derivative with greater selectivity for the 5-HT_4 receptor compared with other 5-HT_4 agonists. RCTs have reported that prucalopride (1−4 mg daily) improves CC symptoms, including stool frequency, stool consistency, and straining. The most common adverse events of headaches, nausea, and diarrhea tended to occur within 24 hours of initiating treatment and were often transient.[143,144]

Prunes (50 g or roughly 6 prunes twice daily)[145] and hemp seed extract (7.5 g twice daily) improved stool frequency and constipation severity during separate 8-week trials.[146] A systematic review that included the results of 5 RCTs concluded that probiotics may increase stool frequency and improve stool consistency in patients with CC—organisms studied included *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *Escherichia coli* Nissle 1917.[147]

C3. Functional Diarrhea

Definition

Functional diarrhea (FDr) is an FBD characterized by recurrent passage of loose or watery stools. Patients with FDr should not meet criteria for IBS although abdominal pain and/or bloating may be present, but are not predominant symptoms. Recurrent passage of loose or watery stool onset should have occurred at least 6 months before diagnosis and symptoms should be present during the last 3 months.

Epidemiology

The incidence and prevalence of FDr have not been well investigated. Using a matched, case−control approach, the incidence of FDr was estimated at 5 per 100,000 patient-years, and a preceding infectious gastroenteritis was a significant risk factor.[148] Reported prevalence rates for FDr range from 1.5% to 17%.[149–153]

C3. Diagnostic Criterion[a] for Functional Diarrhea

Loose or watery stools, without predominant abdominal pain or bothersome bloating, occurring in >25% of stools.[b]

[a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

[b]Patients meeting criteria for diarrhea-predominant IBS should be excluded

Rationale for Changes From Previous Criteria

Changes from Rome III criteria include removing the term *mushy,* as this was felt to be redundant, and specifying that abdominal pain and/or bloating may be present but are not predominant symptoms (ie, patients do not meet criteria for IBS). In addition, 75% of stools being loose has been changed to >25% based on data from the Rome Normative GI symptom survey.[6]

Clinical Evaluation

The diagnosis of FDr should be made based on 3 key features: clinical history; physical examination; and limited diagnostic tests. The evaluation should start with a careful history. Diarrhea should be defined by stool form, not frequency, as stool consistency correlates well with colon transit.[11] IBS should be excluded (see section on IBS). A stool diary incorporating the BSFS (Figure 2) helps to verify stool consistency and excludes pseudodiarrhea.[154] A dietary history should be taken to exclude lactose and fructose malabsorption, and the ingestion of excess amounts of fiber or poorly absorbed carbohydrates. Alarm features, such as unintentional weight loss, diarrhea awakening the patient, recent antibiotic use, hematochezia (in the absence of documented bleeding hemorrhoids or anal fissures), high-volume diarrhea (>250 mL/d), very frequent bowel movements (>6−10 per day), evidence of malnutrition, or a family history of colorectal neoplasia, celiac disease, or inflammatory bowel disease, should prompt further investigation.[155,156]

The physical examination of a patient with FDr should be normal. A careful anorectal examination should be performed to assess anal sphincter tone (especially important in patients with incontinence), and to identify a mass, fissure, or hemorrhoidal disease (especially important in a patient with hematochezia).

A CBC and C-reactive protein should be checked in all patients with chronic diarrhea. A thyroid profile can be performed if there is clinical suspicion of hyperthyroidism. Serologic tests for celiac disease should be checked in those that fail empiric therapy (and consider esophagogastroduodenoscopy with duodenal biopsies if antibody tests are positive or if clinical suspicion is high). Stool analysis (bacteria, parasites, and ova) should be performed in endemic areas, and fecal calprotectin should be checked if clinical suspicion for an inflammatory process is high. Giardiasis and tropical sprue should be excluded in the appropriate clinical setting.

For patients with persistent symptoms, stool specimens can be analyzed for fecal elastase-1 and fat to identify a malabsorptive process; a negative test should minimize the need for further diagnostic studies.[157] Colonoscopy should be considered in those who have failed empiric therapy, in those with alarm symptoms, and in all patients older than age 50 years for screening purposes (older than age 45 years in African Americans) based on national recommendations. When performed, random biopsies should be obtained from both the right and left colon to rule out microscopic colitis. Bile acid malabsorption, which is an

often overlooked diagnosis in patients with longstanding diarrhea, can be identified, when available, by using ^{75}SeHCAT.[158] Breath tests can identify carbohydrate malabsorption, but if not available, then dietary exclusion of the suspected carbohydrate (eg, 3–4 weeks) is recommended.

Physiologic Features

Similar to other FBDs, no single pathophysiological abnormality can explain the cause of FDr in every patient. Rather, a number of diverse mechanisms seem to contribute to symptom generation, including altered GI motility, brain–gut disturbances, genetic and environmental factors, prior infections, and psychosocial factors.[159] Genetic studies in FDr patients have not been performed. One study reported that fasting and postprandial colonic propagating contractions are increased in FDr, while a small pilot study showed normal left colonic tone during fasting and a reduced duration of increased tone postprandially.[160,161] Similar to IBS, a prior infection can lead to post-infectious FDr.[162,163]

Psychosocial Features

There are few data on psychological features in FDr patients. While anxiety often accompanies IBS, few data apply specifically to FDr. Acute stress accelerates colonic transit in humans and animals,[164] but the relevance of this finding to chronic stress, and to FDr patients, is uncertain.

Treatment

Few studies have evaluated specific treatments for FDr patients. Data from studies in patients with other conditions like IBS-D tend to be extrapolated to the treatment of patients with FDr. Dietary interventions and fiber supplementation have not been evaluated. Loperamide, a μ-opioid agonist, improves stool frequency and consistency, as well as urgency and incontinence, in patients with FDr and IBS-D.[49,50,165] Cholestyramine (4 g twice daily) is effective and safe for short-term treatment of patients with FDr presumably secondary to bile acid malabsorption.[166] Probiotics, antibiotics, and 5-HT_3 antagonists may all improve diarrhea symptoms but have not been tested specifically in FDr patients.

C4. Functional Abdominal Bloating/Distension

Definition

Functional abdominal bloating (FAB)/distention (FAD) is characterized by symptoms (subjective) of recurrent abdominal fullness, pressure, or a sensation of trapped gas (FAB), and/or measurable (objective) increase in abdominal girth (FAD). Patients should not meet criteria for other FBDs, although mild abdominal pain and/or minor bowel movement abnormalities may coexist. Symptom onset should be at least 6 months before diagnosis and the predominant symptom (bloating or distention) should be present during the last 3 months.

FAB and FAD should be classified as a single entity (functional abdominal bloating/distention) although they encompass 2 different symptoms/signs. These conditions may exist independently, although they frequently coincide in the same individual. The distinct nature of these disorders is demonstrated by research showing that only 50%–60% of patients with bloating have abdominal distention and the correlation between abdominal bloating and an increase in abdominal girth is poor.[167,168] Further research may allow FAB and FAD to be considered separate entities.

Epidemiology

The incidence of functional bloating has not been evaluated in large prospective studies. The prevalence of bloating is better described. A large (n = 2510) telephone survey of US adults reported that 15.9% had symptoms of bloating or distention in the month before the interview.[169] Women were more likely to report bloating than men (19.2% vs 10.5%) to rate their bloating as severe (23.8% vs 13%). Two other large prospective studies of US adults identified similar prevalence rates of bloating (21% and 19%).[170,171] Patients with FGIDs are more likely to report co-existing symptoms of bloating, especially those with IBS-C and FC.[172–177]

Rationale for Changes From Previous Criteria

The current definition includes the addition of the phrase "abdominal fullness, pressure or a sensation of trapped gas" to reflect commonly reported symptoms. FAD has been added as a separate diagnosis. This addition helps distinguish subjective sensations of bloating from the objective finding of an increase in abdominal girth seen in patients with FAD. The change in definition also reflects the use of new technologies (eg, abdominal plethysmography) and a new understanding of the pathophysiology of distention. FAD is typically seen in conjunction with FAB, although it can occur independently. A further change from the Rome III criteria is the acknowledgment that FAB/FAD patients may also report symptoms of mild abdominal pain and/or minor bowel movement abnormalities.

C4. Diagnostic Criteria[a] for Functional Abdominal Bloating/Distension

Must include both of the following:

1. Recurrent bloating and/or distention occurring, on average, at least 1 day per week; abdominal bloating and/or distention predominates over other symptoms.[b]
2. There are insufficient criteria for a diagnosis of irritable bowel syndrome, functional constipation, functional diarrhea, or postprandial distress syndrome.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

[b]Mild pain related to bloating may be present as well as minor bowel movement abnormalities.

Clinical Evaluation

FAB/FAD should be diagnosed based on the following 3 key features: clinical history, physical examination, and limited diagnostic studies.

The evaluation of a patient with abdominal bloating and/or distention should begin with a careful history, which includes the onset of symptoms, the relationship to diet (eg, wheat, dairy, fructose, fiber, nonabsorbable sugars) and bowel habits, and the presence of symptoms suggestive of other FGIDs. Alarm features, such as anemia and unintentional weight loss, should be assessed, as these symptoms may be evidence of a malabsorptive process. Patients with FAB/FAD typically report a worsening of symptoms as the day progresses, particularly after meals, but alleviation of symptoms overnight.[178,179] Diurnal worsening of bloating is frequently accompanied by increased girth.[180]

During the physical examination, bloating (subjective) and distention (objective) should be differentiated and explained to the patient. The term *abdominal distention* should be reserved for patients who show a visible increase in abdominal girth. Evidence of a partial bowel obstruction or organomegaly warrants further evaluation. A pelvic examination should be performed when appropriate.

Validated guidelines for the evaluation of bloating do not exist. Many clinicians favor empiric therapy in the absence of warning signs. Alternatively, limited testing may be useful. An abdominal x-ray can evaluate for possible obstruction. A CBC should be performed if there are warning signs of anemia. Serologic tests can be used to identify celiac disease. If the clinical suspicion for celiac disease is high, or if serological test are positive, an upper endoscopy with duodenal biopsies should be performed. Small intestinal bacterial overgrowth can be evaluated by culturing the jejunal aspirate or by performing a breath test, preferably with glucose.[181]

Physiologic Features

The pathophysiology of bloating remains incompletely understood, in part, because the etiopathophysiology varies from patient to patient. Potential causes include visceral hypersensitivity, abnormal intestinal gas transit, impaired evacuation of rectal gas, colonic fermentation, small intestine bacterial overgrowth, and gut microbiota alterations.[75]

The pathophysiology of abdominal distention is better understood due to innovations in technology, including abdominal inductance plethysmography, a novel technique that can measure abdominal distention. An abnormal viscerosomatic reflex involving the diaphragm and the abdominal wall muscles seems to be responsible for the symptom of distention in many FGID patients.[182] The precise etiology of this reflex is unknown; one study of IBS patients identified a relationship with rectal hyposensitivity.[183] Slow intestinal transit may contribute to distention in some patients.[184]

Psychosocial Features

Questionnaire studies evaluating the psychosocial features of patients with functional abdominal bloating/distention have not been published.

Treatment

Few therapeutic trials have been conducted in patients with FAB/FAD. Most studies have evaluated abdominal bloating in patients with other FGIDs (Tables 2 and 3). Simethicone, an anti-foaming agent, was reported to improve the frequency and severity of gas, distention, and bloating in one small old study of patients with upper gastrointestinal symptoms.[185] α-Galactosidase improved symptoms of gas and bloating in healthy volunteers fed a high-fat meal.[186] In 2 separate 4-week trials, peppermint oil resulted in a significant decrease in abdominal distention compared with placebo.[187,188] Lubiprostone improved symptoms of bloating in 2 phase 2 studies in IBS-C patients (8 μg twice daily) compared with placebo.[42] Similarly, linaclotide also improved bloating symptoms in the phase 3 studies for chronic idiopathic constipation[133] and IBS-C.[44–46] In CC patients with predominant symptoms of bloating, linaclotide showed a significant improvement in bloating symptoms.[189] Desipramine, in conjunction with cognitive behavioral therapy, resulted in an improvement in bloating, although the effects of desipramine alone remain unclear.[190] A small, crossover-trial with citalopram showed an improvement in the number of days without bloating at 3 and 6 weeks.[191] In a study of 28 patients with abdominal bloating, intravenous neostigmine caused immediate clearance of infused jejunal gas compared with placebo.[192] However, in patients with IBS and bloating, pyridostigmine provided only minimal improvement in bloating.[193]

C5. Unspecified Bowel Disorders

Definition

In some cases, a patient may not fulfill diagnostic criteria for any of the 4 specific FBDs categories, in which case the patient should be considered to have an unspecified FBD.

C5. Diagnostic Criterion[a] for Unspecified Functional Bowel Disorder

Bowel symptoms not attributable to an organic etiology that do not meet criteria for IBS or functional constipation, diarrhea, or abdominal bloating/distention disorders.

[a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

C6. Opioid-Induced Constipation

Opioid-induced bowel disorders refers to a spectrum of disorders that develop secondary to the actions of opioids on the GI tract and the central nervous system. As opiate use has increased, so has the recognition that these agents have a number of adverse effects on the GI tract. It is the opinion of this committee that opioid-induced effects on the GI tract should not be considered a distinct FGID, but rather should be categorized as an opioid-induced adverse effect. There is, however, frequently overlap between these disorders. For example, FC may overlap with, or exacerbate, OIC (and vice

versa). For that reason, it is important to recognize one of the most common opioid-induced bowel disorders, OIC, which is the focus of this section.

Definition

OIC can be defined as a change, when initiating opioid therapy, from baseline bowel habits and defecation patterns, that is characterized by any of the following: reduced bowel frequency; development or worsening of straining; a sense of incomplete evacuation; or a patient's perception of distress related to bowel habits.[194] The occasional patient may also develop fecal impaction with overflow incontinence, while others may report symptoms compatible with overlapping opioid-induced bowel disorders (eg, reflux, nausea, bloating).

C6. Diagnostic Criteria for Opioid-Induced Constipation

1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:
   a. Straining during more than one-fourth (25%) of defecations
   b. Lumpy or hard stools (BSFS 1−2) more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
   e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
   f. Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives

Epidemiology

The prevalence of OIC is 41% in patients with chronic noncancer pain taking opioids, based on a systematic review of 8 placebo-controlled studies.[195] In a study of cancer patients taking opioids for pain, the incidence of constipation was approximately 94%.[196]

Clinical Evaluation

The diagnosis of OIC should be made based on the following 3 key features: clinical history, physical examination, and limited diagnostic tests. The first step in the diagnosis of OIC is to ascertain the relationship of constipation symptoms with the use of opioids to determine whether a temporal relationship exists (see diagnostic criteria). If a temporal relationship exists, then the clinician should identify the type, severity, and frequency of constipation symptoms (eg, reduced stool frequency, straining, sense of incomplete evacuation, hard stools). The presence of alarm features, such as unintentional weight loss (>10% in 3 months), rectal bleeding (in the absence of documented bleeding hemorrhoids or anal fissures), and a family history of colon cancer (or familial polyposis syndromes) should be elicited. A physical examination should be performed to determine whether an organic problem exists to account for symptoms; a careful anorectal examination can identify structural issues and DD. Few data are available regarding the clinical utility of tests in patients with suspected OIC. If clinically indicated, simple laboratory tests (eg, CBC, complete metabolic profile, serum calcium and thyroid-stimulating hormone) are reasonable, while an abdominal x-ray (kidney, ureter, and bladder) can identify fecal impaction and the level of stool burden. Patients aged older than 50 years (45 years and older in African Americans) should have a screening colonoscopy based on national recommendations, as should patients with warning signs (eg, anemia, hematochezia not thought due to hemorrhoidal bleeding or fissures, and a family history of colorectal cancer).

Physiologic Features

The 3 classes of opioid receptors in the GI tract (μ, κ, and δ) are all G-protein−coupled receptors that reduce acetylcholine release.[197] OIC develops when GI tract opioid receptors are activated by oral opioids leading to a decrease in propulsive activity; an increase in nonpropulsive contractions; a decrease in pancreatic, biliary, and gastric secretions; and an increase in anal tone. These physiologic changes may lead to the symptoms of constipation described previously.

Psychosocial Features

Although not as extensively studied as IBS or functional constipation, patients with OIC report a significant reduction in quality of life.[198,199] One-third of patients treated with opioids missed or decreased the dose of prescribed opioids due to GI side effects; this can further reduce quality of life.[198]

Treatment

The initial treatment of OIC is similar in many ways to the treatment of FC. Laxatives are recommended for both the prophylaxis and management of OIC in patients with cancer by the European Association for Palliative Care.[200] Lubiprostone, a chloride channel activator, is FDA approved for the treatment of OIC in adults with noncancer pain.[201]

Additional treatment options for patients with OIC involve the use of opioid receptor antagonists that block opioid actions either centrally or peripherally, thereby minimizing or preventing the negative effects of opioids on intestinal secretion and colonic propulsion.[202] Naloxone and nalbuphine are 2 medications classified as centrally active agents. Because these agents cross the blood−brain barrier, they may precipitate opioid withdrawal symptoms.[203,204] A combination product of an opioid antagonist (naloxone) and

an opioid agonist (oxycodone) is available in Europe and has received approval for patients with severe pain.

Peripherally acting μ-opioid receptor antagonists block opioid receptors in the GI, but not central, receptors and thus do not lead to symptoms of withdrawal. Three agents are now available. Subcutaneous methylnaltrexone is approved for OIC in patients with chronic noncancer pain and for patients with advanced illness receiving palliative care who have had an inadequate response to laxative therapy.[205,206] The European Association for Palliative Care guidelines recommend subcutaneous methylnaltrexone as a second-line treatment option for OIC in patients with chronic cancer pain when traditional laxatives are not effective.[200] Alvimopan, available in the United States but not in Europe, is a peripherally acting μ-opioid receptor antagonist indicated only for preventing or shortening the course of postoperative ileus after bowel resection and is therefore available for hospital use only.[207] It is not currently approved for use in OIC in either Europe or the United States. Naloxegol, an oral PEGylated derivative of naloxone, was approved by the FDA for the treatment of OIC in adult patients with noncancer pain in September 2014.[208] Naloxegol was approved by the European Medicines Agency for the treatment of OIC, but without the limitation of restricting use to noncancer pain patients. Another peripherally acting μ-opioid receptor antagonist, Naldemedine, has successfully completed early clinical trials at the time of this publication.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.02.031.

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Conflicts of interest
The authors disclose no conflicts.

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