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Bowel Disorders

Maura Corsetti,[1] Andrea Shin,[2] Brian E. Lacy,[3] Brooks D. Cash,[4] Magnus Simrén,[5] Max J. Schmulson,[6] Xiaohua Hou,[7] and Anthony Lembo[8]

[1]NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham Digestive Diseases Biomedical Research Centre, Nottingham, United Kingdom; [2]Vatche and Tamar Manoukian Division of Digestive Diseases at University of California Los Angeles, Los Angeles, California; [3]Division of Gastroenterology, Mayo Clinic, Jacksonville, Florida; [4]Functional Bowel Center, Division of Gastroenterology, Baylor Scott & White at Baylor University Medical Center, Dallas, Texas; [5]University of Gothenburg, Gothenburg, Sweden; [6]Laboratory of Neurogastroenterological Disorders, Unit of Experimental Medicine "Dr. Ruy Pérez Tamayo" (UME), Faculty of Medicine, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico; [7]Division of Gastroenterology, Union Hospital of Tongji Medical College, Huazhong University of Technology and Science, Wuhan, China; and [8]Department of Gastroenterology, Hepatology & Nutrition, Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio

Bowel disorders (BDs), previously termed functional bowel disorders, are highly prevalent disorders worldwide. These disorders affect individuals across all demographic and socioeconomic groups and have substantial economic consequences, in addition to significantly reducing quality of life. Since the Rome IV publication in 2016, research in the basic and clinical sciences has provided new insights in epidemiology, etiology, pathophysiology, diagnosis, and treatment of BDs, creating the need to revise the diagnostic framework of BDs. This article presents the updated Rome V classification of BDs in 6 distinct categories: irritable bowel syndrome, chronic constipation, functional diarrhea, functional abdominal bloating, unclassified BD, and opioid-induced constipation. Each disorder is defined, followed by sections on epidemiology, rationale for changes from prior criteria, clinical evaluation, pathophysiology, and treatment. It is in hope that the Rome V BD Committee will assist clinicians and researchers in improving diagnosis, patient care, and scientific endeavors of these common and burdensome disorders.

Keywords: Abdominal Pain; Bloating; Constipation; Diarrhea.

Bowel disorders (BDs) are a spectrum of chronic gastrointestinal (GI) disorders characterized by abdominal pain, discomfort, bloating, distension, and bowel habit abnormalities (Figure 1). According to the Rome V classification, BDs are classified into 6 categories: (1) irritable bowel syndrome (IBS); (2) chronic constipation (CC); (3) functional diarrhea (FDr); (4) functional abdominal bloating (FAB); (5) unclassified bowel disorder (U-BD); and (6) opioid-induced constipation (OIC). OIC is distinct from other BDs due to its specific pharmacological etiology but often overlaps with BDs such as IBS and functional constipation (FC). For this reason, it is included in this article.

C1. Irritable Bowel Syndrome

Definition

IBS is defined by recurrent abdominal pain and/or discomfort associated with changes in bowel habits (constipation, diarrhea, or a mix of constipation and diarrhea) with symptom onset at least 6 months before diagnosis and symptoms present during the preceding 3 months.

Epidemiology

The recent Rome Foundation Global Epidemiological Study (RFGES) found that approximately 33% of participants completing an internet survey met criteria Rome IV criteria for at least 1 BD.[1] The global prevalence of IBS was 4.3% across 24 countries surveyed online, with higher rates in Western Europe compared with Asia. The prevalence peaked at 5% among individuals aged 18 to 39 years and showed a 1.8:1.0 women-to-men ratio.[2] Subtype distribution was similar except for IBS unclassified, which had a lower prevalence. IBS significantly affects quality of life and productivity, with the greatest burden due to irritable bowel syndrome with diarrhea (IBS-D) and irritable bowel syndrome with constipation (IBS-C).[3–6]

Abbreviations used in this paper: **AE, adverse effect; BAM, bile acid malabsorption; BDs, bowel disorders; CAM, complementary and alternative medicine; CBT, cognitive behavioral therapy; CC, chronic constipation; CIC, chronic idiopathic constipation; DGBI, disorders of gut–brain interaction; FAB, functional abdominal bloating; FC, functional constipation; FDr, functional diarrhea; FMT, fecal microbial transplantation; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; Ig, immunoglobulin; OIC, opioid-induced constipation; PAMORA, peripheral acting mu-opioid receptor antagonists; PEG, polyethylene glycol; PI-IBS, postinfection irritable bowel syndrome; RCT, randomized controlled trial; RFGES, Rome Foundation Global Epidemiological Study; SBM, spontaneous bowel movement; SIBO, small intestine bacterial overgrowth; SID, sucrase-isomaltase deficiency; TCA, tricyclic antidepressant; U-BD, unclassified bowel disorder.**

Most current article

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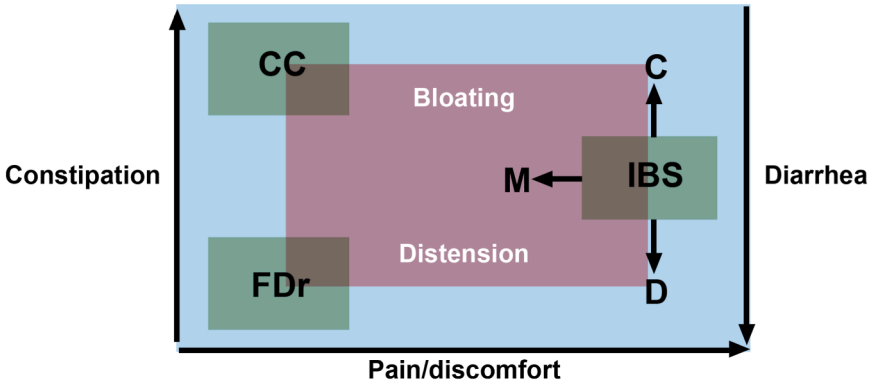

CC: Chronic constipation
FDr: Functional diarrhea
IBS-C: Irritable bowel syndrome with predominant constipation
IBS-D: Irritable bowel syndrome with predominant diarrhea
IBS-M: Irritable bowel syndrome with mixed bowel habits (D and C)

Figure 1. BDs are a spectrum of chronic GI disorders, characterized by abdominal pain/discomfort, abdominal bloating, abdominal distension, and bowel habit abnormalities.

Justification for Change in Criteria

The following points highlight notable changes from Rome IV:

- Abdominal discomfort has been added to the diagnostic criteria for IBS.
- Abdominal pain or discomfort should be present at least 3 days per month on average during the preceding 3 months.
- The new specification that abdominal pain or discomfort should not be continuous has been added to differentiate IBS from centrally mediated abdominal pain syndrome.
- A supportive criterion has been added indicating that abdominal pain or discomfort should not be only related to menses has been added to differentiate IBS from menstrual-related symptoms.

C1. Diagnostic Criteria[a] for Irritable Bowel Syndrome

Recurrent, but not continuous, abdominal pain or discomfort on average at least 3 days per month in the past 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 symptom onset at least 6 months before diagnosis.

Supportive criteria: abdominal pain/discomfort should not be only related to menses.

With the implementation of Rome IV, the reported prevalence of IBS decreased significantly compared with Rome III. The RFGES found the reason for this decline was primarily due to the higher frequency threshold for pain in Rome IV (ie, at least 1 day/week) vs Rome III (ie, at least 2–3 days/month), and to a lesser extent to the removal of "discomfort."[1] In addition, several studies have reported patients with IBS who experience abdominal discomfort without pain, particularly in some countries.[7,8] To address these limitations, Rome V reintroduced "discomfort" and lowered the frequency threshold for abdominal pain or discomfort to $\geq$3 days per month.

Irritable bowel syndrome subtypes. IBS continues to be classified into 4 main subtypes based on the predominant bowel habit, as determined by the Bristol Stool Form Scale[9]: IBS with constipation (IBS-C), with diarrhea (IBS-D), with mixed bowel habit, or with unclassified bowel habit, as reported in Figure 2 and in Table 1.[10]

Clinical Evaluation

Clinicians should make a positive diagnosis of IBS based on symptoms, emphasizing that IBS is not a diagnosis of exclusion. In most patients, when IBS diagnostic criteria are fulfilled and alarm features are absent, testing should be selective and limited. The predictive value of alarm features for identifying organic disease that might explain IBS symptoms is modest. However, this limited performance may partially reflect the imprecise characterization of certain alarm features, for example, distinguishing nocturnal symptoms that awaken the patient from those that merely affect sleep quality.[10–13]

Because certain organic conditions (eg, inflammatory bowel disease [IBD], celiac disease, microscopic colitis) can mimic IBS, limited targeted testing may be appropriate. When considering such tests, clinicians should weigh the pretest probability of these conditions, guided by their prevalence in symptomatic patients. Routine follow-up visits with targeted investigations for those with persistent symptoms is cost-effective and often more reassuring

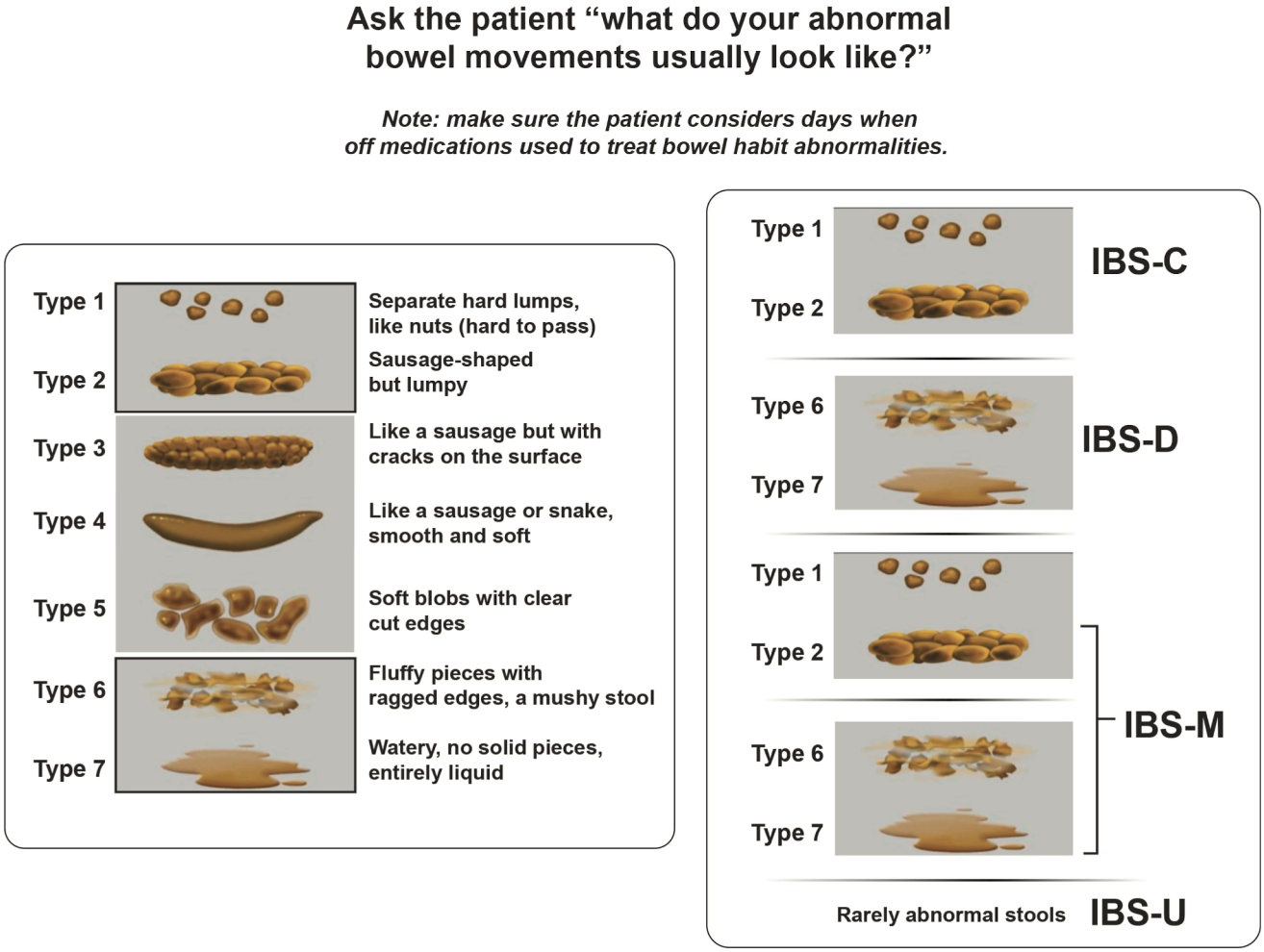

Figure 2. Guide on how to subtype patients with IBS in clinical practice according to the Bristol Stool Form Scale. IBS-M, irritable bowel syndrome with mixed bowel habit; IBS-U, irritable bowel syndrome with unspecified bowel habit.

than an exclusionary diagnostic approach.[14] Notably, negative test results do not necessarily improve reassurance or quality of life, particularly in young patients with IBS.[10]

Clinical history and alarm features. Details of the key aspects to be considered in clinical history taking and physical examination are summarized in Figures 3 and 4.[10,15–18]

Role and indication for diagnostic testing. The Rome V Committee diagnostic recommendations for IBS as compared with other international guidelines are discussed as follows and summarized in Supplementary Table 1.[19–33]

Initial serologic laboratory testing and stool testing for inflammation in patients with suspected irritable bowel syndrome. A systematic review and meta-analysis found that a C-reactive protein <0.5 mg/dL was associated with a <1% probability of IBD, whereas erythrocyte sedimentation rate and fecal lactoferrin had little value in differentiating IBS from IBD.[34] Another meta-analysis reported that fecal calprotectin of ≤50 μg/g had a 99.8% negative predictive value but only a 9% positive predictive value in differentiating between IBS and IBD.[35] Because of the high negative predictive value, fecal calprotectin is widely used to exclude IBD in patients with chronic diarrhea, although it lacks specificity and may be elevated in older individuals, obesity, infection, or with proton pump inhibitors or nonsteroidal anti-inflammatory drug use.[10]

A 2017 meta-analysis of 36 studies found the prevalence of biopsy-confirmed celiac disease in IBS to be 3.3%.[36,37] Higher rates have been reported in Middle Eastern and Asian countries.[38,39] Most IBS clinical guidelines recommend serologic testing for celiac disease using immunoglobulin (Ig)A anti-tissue transglutaminase (anti-tTG) and a quantitative serum IgA level to exclude selective IgA deficiency.[37] Notably, the sensitivity of anti-tTG is reduced in patients adhering to a gluten-free diet.

Other stool laboratory testing. Stool analysis for bacteria, ova, and parasites may be appropriate in patients with diarrhea who live in or have recently traveled to areas where infectious diarrhea is common. However, in areas with a low incidence of infectious diarrhea, the diagnostic yield of stool testing is low. Most clinical guidelines do not recommend routine stool testing for bacterial or viral pathogens in patients with chronic IBS-like symptoms. Nevertheless, *Giardia lamblia,* the most common parasite

Table 1. Diagnostic Criteria for IBS Subtypes

Predominant bowel habits are based on stool form on days with at least 1 abnormal bowel movement.[a]

IBS with predominant constipation (IBS-C): >25% of bowel movements with Bristol stool types 1 or 2 and <25% of bowel movements with Bristol stool 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 the Bristol Stool Form Scale [BSFS]).*

IBS with predominant diarrhea (IBS-D): >25% of bowel movements with Bristol stool types 6 or 7 and <25% of bowel movements with Bristol stool 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).*

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

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-U. *Alternative for epidemiology or clinical practice: Patient reports that abnormal stools (both diarrhea and constipation) are rare.*

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

NOTE. To have confidence in IBS subtyping, patients should have at least 4 days of abnormal bowel habits each month. Bowel habit subtypes should be based on the BSFS for days with abnormal bowel habits. Analysis of days without a bowel movement does not increase the specificity of bowel subtyping, whereas analyzing only days with abnormal bowel movement increases it. Careful analysis of bowel diaries, using different cut points, determined that the 25% value for stool abnormalities most accurately categorized patients into subtypes and minimized the number of patients categorized as having the unclassified subtype. These recommendations are based on normative data from population studies and from clinical studies demonstrating that a large proportion of patients with IBS have some bowel movements that are within the normal range of stool consistency. Evaluation (subjective opinion and/or data from the BSFS) must be performed with the patient off of all therapies for bowel habit abnormalities (including laxatives and antidiarrheal agents). The subtype categories are considered mutually exclusive.
[a]IBS subtypes related to bowel habit abnormalities (IBS-C, IBS-D, and IBS-M) can be confidently established only when the patient is evaluated off medications used to treat bowel habit abnormalities.

causing chronic diarrhea in adults worldwide, should be considered.[40]

Fecal hemoglobin tests (fecal occult blood test [FOBT], fecal immunochemical test [FIT], multitarget stool DNA) are appropriate for colorectal cancer screening but are not recommended for differentiating IBS from structural GI disease. Similarly, routine fecal elastase testing is not recommended. Although an early study reported a higher prevalence of exocrine pancreatic insufficiency among patients with IBS,[41] a subsequent study did not confirm this association, identifying only a small number of cases, mostly in patients with a history of alcohol use.[42]

Bile acid malabsorption. Although testing for bile acid malabsorption (BAM) is not recommended in the initial IBS evaluation, it should be considered, when available, in patients with chronic diarrhea who do not respond to standard treatment. The selenium-75-tauroselcholic acid (SeHCAT) retention test is considered the gold standard test for BAM but is not available in many countries. A more accessible alternative is the serum 7α-hydroxy-4-cholesten-3-one (7C4) blood assay, which is a marker of hepatic bile acid synthesis; however, its utility in the evaluation of IBS-D has not been rigorously evaluated.

Carbohydrate maldigestion. Carbohydrate (eg, lactose, fructose, sorbitol, sucrose, starch) maldigestion can cause diarrhea, cramping, and bloating. Lactose maldigestion is most common, affecting approximately two-thirds of the global adult population, with marked ethnic and geographical variation.[43] In one study of patients with IBS, 35% had lactose maldigestion, 64% fructose maldigestion, and 25% both—rates similar to the general population.[44] Lactose hydrogen breath testing may be clinically useful in select patients, although routine testing for lactose maldigestion is not recommended as part of the initial IBS evaluation.

Sucrase-isomaltase deficiency (SID) is increasingly recognized as a potential cause of IBS-like symptoms.[45] The gold standard for diagnosing SID is quantitative disaccharidase activity assay testing of duodenal biopsies, which requires special handling and referral to a reference laboratory. The prevalence of SID in IBS remains uncertain, and the Rome V Committee does not recommend routine testing at this time.[45]

Small intestinal bacterial or intestinal methanogen overgrowth. Dysfunctional microbiota has been implicated in the pathogenesis of IBS symptoms in several studies. Small intestine bacterial overgrowth (SIBO) appears more frequently associated with IBS-D, whereas intestinal methanogen overgrowth is more often linked to IBS-C. However, guideline recommendations for dysbiosis testing are inconsistent across societies (Supplementary Table 1).[46–49] The Rome V BD Committee does not recommend routine breath testing for SIBO or dysfunctional microbiota as part of the initial diagnostic evaluation of IBS because of testing limitations and insufficient evidence supporting its diagnostic or therapeutic value.

Gastrointestinal endoscopy. In the absence of alarm features the diagnostic yield of colonoscopy in IBS is low—particularly in IBS-C. In one study with patients with nonconstipated IBS without alarm features the diagnostic yield of a colonoscopy was only 2% (microscopic colitis was identified in 1.5%, mostly women >45 years).[50] Nevertheless, when colonoscopy is performed in patients with suspected IBS-D, clinicians should consider obtaining biopsies to rule out microscopic colitis.[14,50–55]

Defecatory disorders. Readers are referred to the section on defecatory disorders testing in the Chronic Constipation section as well as the Anorectal Disorders article for details on when and how to test these conditions.

Communicating a Positive Diagnosis and Management Plan

A diagnosis of IBS should be communicated clearly and confidently, using simple and empathetic language with an emphasis of building a strong patient-provider relationship. The article on Patient Perspective, Gender, and Age provides valuable insights into this aspect of care. Importantly, the language used by providers to explain a diagnosis of IBS is frequently more uncertain than that used for organic diseases. This uncertainty may contribute to patient skepticism and prompt requests for additional investigations.[56] Explaining IBS as a disorder of gut–brain interaction, together with a simple account of the gut–brain axis and how this is impacted by diet, stress, and cognitive, behavioral, and emotional responses to symptoms, as well as immune- and microbially mediated changes, may enhance patient understanding and acceptance of the diagnosis.[10]

Pathophysiology

IBS is a multifactorial disorder that is best conceptualized within a biopsychosocial model, with genetic, environmental, and psychosocial factors influencing susceptibility and symptom expression. Common triggers for IBS onset or flares include gastroenteritis,[57,58] dietary factors,[59] psychological factors,[60] chronic stress,[61] and surgeries.[62] More than 10% of patients develop post-infection IBS (PI-IBS) after an acute gastroenteritis[63] and recent data suggest IBS may also follow COVID-19.[64] A history of childhood or adulthood abuse increases the risk of IBS by nearly 3-fold and adult stressors can contribute to both onset and persistence.[65]

The pathophysiologic mechanisms of IBS include altered GI motility, visceral hypersensitivity, altered intestinal permeability, immune activation, altered gut microbiota, and abnormal gut–brain signaling. GI transit may be accelerated or delayed[66] and visceral hypersensitivity[67,68] can result from peripheral sensitization and/or a central amplification.[69] Autonomic nervous-system tone and hypothalamic-pituitary-adrenal axis abnormalities have been described, but their roles remain under investigation.[70] Immune activation also may contribute to IBS symptoms, supported by evidence from PI-IBS models,[57,71,72] mast cell–mediated pathways,[73] and local immune responses to food antigens.[74] Serotonin likely plays a modulatory role, with subtype-specific alterations reported, although measurement challenges remain.[75–78] Finally, abnormal intestinal permeability, particularly in IBS-D and PI-IBS, occurs in 4% to 62% of patients.[79–82]

Microbiota studies in IBS have revealed alterations in both microbial composition and metabolic function, with metagenomic and metabolomics studies suggesting IBS subtype- and symptom-specific responses.[58,83,84] Food-related symptoms may result from exaggerated sensory and motor responses, altered colonic fermentation, abnormal gas handling, or microbial instability.[85–88] Although food allergies are rare, local allergy-like intestinal reactions have been demonstrated using confocal laser endomicroscopy,[89,90] and IgG immunoreactivity to foods such as wheat and milk has been implicated.[91,92] BAM has been estimated to be present in 25% of patients with IBS-D. In addition, alterations in short-chain fatty acids, key microbial metabolites influencing motility, permeability, secretion, and immune responses, have also been proposed as contributing factors in IBS pathophysiology.[93,94]

Treatment

General aspects. Key steps of the management of BDs are outlined in Figure 5. A strong patient-provider relationship is central to effective IBS management, as it is associated with improved symptom control, greater treatment adherence, and reduced health care utilization.[16,17] Clinicians should identify each patient's most bothersome symptoms to personalize treatment goals and guide shared decision making.

Exercise, diet, and lifestyle modification. A systematic review found exercise modestly improved global IBS symptoms compared with usual care,[95] although the certainty of evidence was very low because of potential bias and the small sample size. Fiber supplementation is safe, relatively inexpensive, and potentially beneficial; a meta-analysis of 14 trials found benefit with soluble (psyllium/ispaghula husk, relative risk [RR] = 0.83; number needed to treat = 7), whereas insoluble (bran) fiber did not (RR = 0.90).[96] Among dietary interventions for IBS, a network meta-analysis found the strongest evidence for a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet.[97] The British Dietetic Association/National Institute for Health and Care Excellence diet was also more effective than a habitual diet for improving global symptoms. Emerging dietary interventions that also show promise include the Mediterranean diet, a starch-reduced and sucrose-reduced diet, a FODMAP-simple diet, and a gluten-free diet.[98]

Pharmacological treatments based on predominant bowel habit. Global guideline recommendations for IBS treatments are included in Supplementary Table 2.[10,20–33,99]

Constipation-predominant symptoms. *Laxatives.* Polyethylene glycol (PEG) (13.8–41.4 g/d) has not been extensively studied in IBS-C but is commonly recommended as initial treatment given its proven efficacy in relieving constipation. In a single 4-week randomized controlled trial (RCT) in adults with IBS-C, PEG significantly improved stool

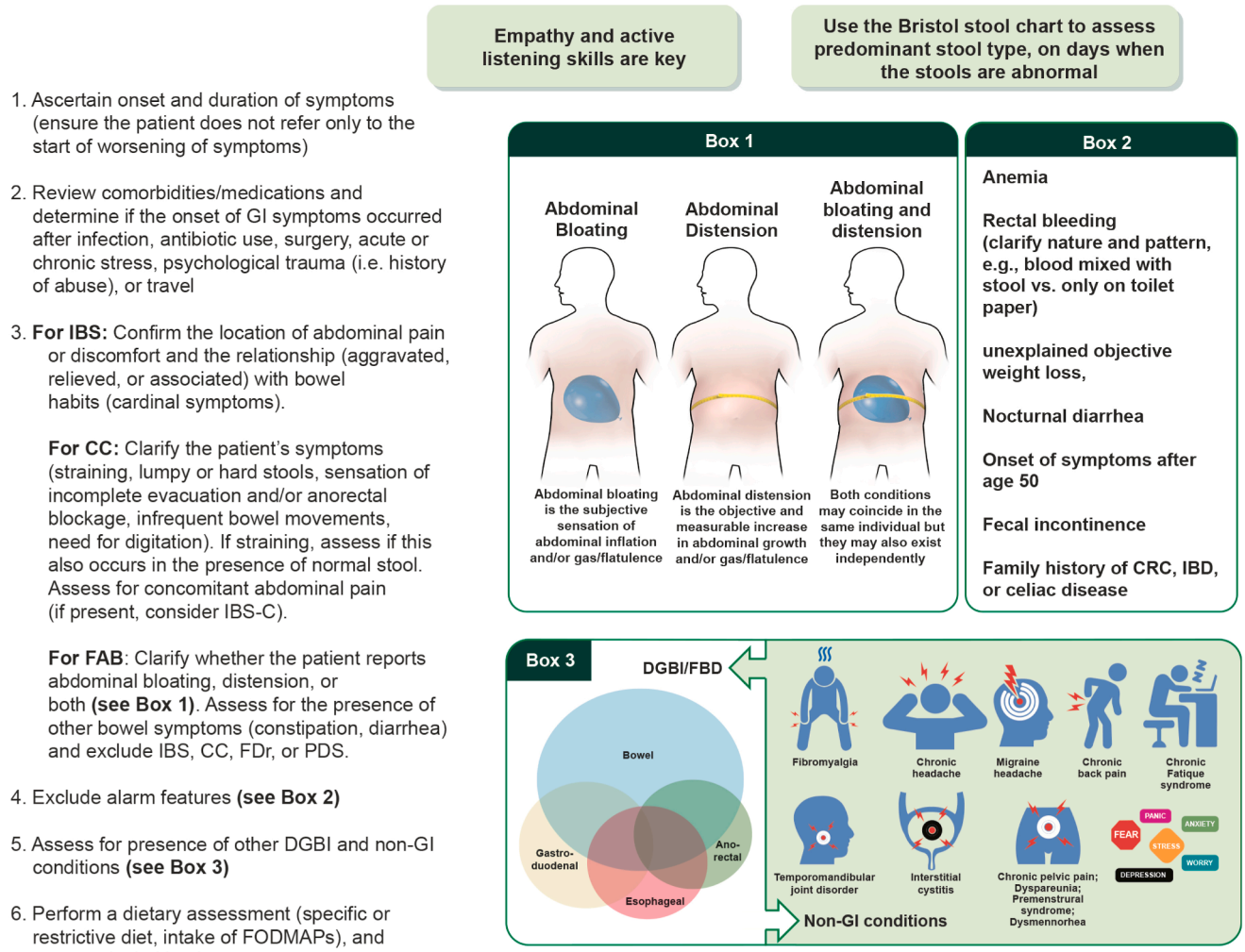

Figure 3. BDs focused on clinical history taking. CRC, colorectal cancer; FBD, functional bowel disorder; PDS, postprandial distress syndrome.

frequency, stool consistency, and straining, but did not improve abdominal pain or bloating.[100]

Secretagogues. Current pharmacologic therapies for IBS-C include secretagogues and ion transport inhibitors, which enhance intestinal fluid secretion through distinct mechanisms. Lubiprostone activates type-2 chloride channels, whereas linaclotide and plecanatide activate guanylate cyclase C receptors, resulting in an increase in chloride secretion into the GI lumen.

In phase 3 trials, lubiprostone (8 μg twice daily, 12-week trials) produced higher overall response rates (moderate or significant relief of IBS $\geq$2 of the first 4 weeks and $\geq$6 of the total 12-week treatment period) than placebo (17.9% vs 10.1%), with nausea (8% vs 4% placebo) and diarrhea (6% vs 4% placebo) as the most common adverse events (AEs).[101] Linaclotide (290 μg once daily, 12- and 26-week trials) significantly increased the proportion of patients reporting "considerable" or "complete" relief of their IBS-C symptoms for at least 6 of the first 12 weeks than patients receiving placebo. Benefits for stool frequency occur relatively rapidly, whereas the maximal benefits for abdominal pain or bloating occur at 6 to 8 weeks. Diarrhea was the most frequent AE (18%–20% vs 2% placebo).[102,103] In the phase 3 trials, plecanatide (3 mg once daily, 12-week trials) significantly improved the composite endpoint ($\geq$30% improvement in abdominal pain and an increase $\geq$1 complete spontaneous bowel movements (SBMs) per week from baseline) vs placebo (27.4% vs 16.9%).[104] Like linaclotide, stool frequency tends to occur sooner than benefits for abdominal pain or bloating. Diarrhea occurred in 4% to 5% vs 1% with placebo.

Sodium/hydrogen exchanger isoform 3 inhibitor. In contrast to secretagogues, tenapanor decreases the absorption of sodium by inhibiting the intestinal sodium/hydrogen exchanger isoform 3. Tenapanor (50 mg twice daily, 12- and 26-week trials) significantly improved the composite endpoint compared with placebo (27.0% vs 18.7%; 36.5% vs 23.7%, respectively) with diarrhea as the most common AE (16% vs 3.7%).[104]

Prokinetic agents (5-HT$_4$ receptor agonists). Tegaserod improved IBS-C symptoms in phase 3 trials;

1. Examine abdomen to evaluate for tenderness, distension, or masses and differentiate distention from ascites and adiposity.

2. Perform digital rectal examination to
   (a) Identify anorectal causes of bleeding (mainly hemorrhoids and fissures)
   (b) Evaluate perianal appearance, sensation, anal reflexes, anal sphincter tone, and contraction patterns of the puborectalis and/or anal sphincter
   (c) Observe for abnormal abdominal wall contraction during simulated evacuation in patients with constipation, which may indicate dyssynergic defecation or pelvic floor dysfunction.

3. Blood tests:
   (a) All patients: CBC to exclude anemia, CRP, celiac serology
   (b) Selective: CMP, TSH
   (c) Do not routinely check: ESR, anti-vinculin/CdtB, malabsorption tests

4. Stool tests:
   (a) All patients: none
   (b) Selective: Giardia lamblia antigen, enteric pathogens, calprotectin **(see Box 1 for cutoff values)**, lactoferrin, enteric pathogens, C. *difficile*
   (c) Do not routinely check elastase, fecal fat, occult blood, O&P, culture, microbiota assays

5. Colonoscopy **(see Box 2)**

6. Consider BAM **(see Box 3)**

7. Consider anorectal physiology testing **(see Box 4)**

Box 1

Fecal calprotectin <100: normal
Fecal calprotectin >100 but <250: indeterminate, repeat off non-steroidal anti-inflammatory drugs
Fecal calprotectin ≥250: abnormal

Box 2

Colonoscopy: consider if fecal calprotectin abnormal or suspected microscopic colitis (female, age ≥50 years, co-existing autoimmune disease, nocturnal or severe watery diarrhea, duration of diarrhea <12 months, weight loss, or use of potential precipitating drugs [i.e. non-steroidal anti-inflammatory drugs or proton pump inhibitors])

Box 3

BAM: Consider in cases of chronic diarrhea not responding to treatment, with atypical presentation (e.g., nocturnal diarrhea), and/or in presence of obesity or previous cholecystectomy.

Box 4

Anorectal physiology testing: consider in presence of CC or FAB not responsive to treatments, symptoms and/or DRE suggestive of defecatory disorders, and/or fecal incontinence.

Figure 4. Stepwise approach for the initial diagnostic evaluation of BDs. BAM, bile acid malabsorption; CBC, complete blood count; CdtB, cytolethal distending toxin B; CMP, complete metabolic profile; CRP, C-reactive protein; DRE, digital rectal examination; ESR, erythrocyte sedimentation rate; O&P, ova and parasites; TSH, thyroid-stimulating hormone.

however, it is no longer available for commercial reasons. Only a limited number of phase 2 trials have been conducted with mosapride and prucalopride has not been widely evaluated in patients with IBS-C.

Diarrhea-predominant symptoms. *Bile acid sequestrants.* Two small open-label studies have shown that colestipol and colesevelam may improve bowel symptoms in patients with IBS-D, although no comparators

Figure 5. Stepwise treatment approach in BDs.

were provided and no head-to-head comparison data are available.[105,106]

Opioid agonists/antagonists. Loperamide is a synthetic peripheral mu-opioid receptor agonist that decreases colonic transit and increases water and ion absorption. Some clinical guidelines recommend loperamide as initial treatment for IBS-D, particularly for control of stool frequency and urgency.[107,108]

Eluxadoline is a mixed μ and κ opioid receptor agonist and a δ opioid receptor antagonist. In phase 3 trials, patients with IBS-D receiving eluxadoline (75 or 100 mg twice daily) for either 26 or 52 weeks were more likely to meet the primary composite endpoint than patients randomized to placebo (23.9% and 25.1% vs 17.1%, respectively, for the 26-week study; 28.9% and 29.6% vs 16.2%, respectively, for the 52-week study). The most common AEs reported with eluxadoline (combined doses) vs placebo were nausea (7.7% vs 5.1%), constipation (8.0% vs 2.5%), and abdominal pain (6.5% vs 4.1%).[109] Due to serious AEs, eluxadoline should not be prescribed for patients with a history of pancreatitis, sphincter of Oddi dysfunction, alcohol abuse, or prior cholecystectomy and in severe hepatic impairment.

Pain-predominant symptoms. *Antispasmodics and peppermint oil.* Antispasmodic agents reduce smooth intestinal muscle contractility through direct myorelaxant effects or antimuscarinic or anticholinergic activity. Peppermint oil acts primarily via calcium channel blockade, producing direct smooth muscle relaxation. A meta-analysis of 22 randomized, placebo-controlled trials found that, among the various antispasmodics studied, otilonium, hyoscine, and peppermint oil showed the most consistent efficacy.[110] Other meta-analyses have reported a number needed to treat between 3 and 4 for peppermint oil compared with placebo. In addition, antispasmodic combinations, like alverine citrate and pinaverium bromide combined with simethicone, have shown to improve abdominal pain and bloating in controlled studies.[111]

Common side effects with traditional antispasmodics include dry mouth, constipation, urinary retention, and visual disturbances. Peppermint oil is generally well tolerated, although AEs including heartburn may occur.[111]

Central neuromodulators. Among the central neuromodulators used to treat IBS, such as tricyclic antidepressants (TCAs) (eg, amitriptyline, desipramine), selective serotonin reuptake inhibitors, and atypical agents (eg, mirtazapine), TCAs are the best studied. A meta-analysis of 12 RCTs involving 787 patients with IBS using 6 different types of TCAs and a recent large study in primary care found TCAs were more likely to improve global IBS symptoms than placebo. In the ATLANTIS RCT, low-dose amitriptyline (10–30 mg nightly) significantly improved global IBS symptom severity and patient-reported relief compared with placebo over 6 months, with dry mouth and drowsiness as the most common AEs.[112] Tertiary amines (imipramine and amitriptyline) are more likely to cause side effects than secondary amines (desipramine, nortriptyline) because of their greater antihistaminic and anticholinergic effects. Selective serotonin reuptake inhibitors have not been shown to have benefits on abdominal pain; however, they may be clinically useful for patients with coexisting anxiety, depression, or other forms of psychological distress.

5-HT_3 antagonists. 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. Alosetron is approved by the Food and Drug Administration for the treatment of women with IBS, at a starting dose of 0.5 mg twice daily. Other $5HT_3$ receptor antagonists such as ramosetron and ondansetron are also effective at alleviating symptoms of IBS-D, although ondansetron does not improve abdominal pain. A meta-analysis of 4 RCTs found that patients treated with ondansetron were more likely to have an improvement in overall IBS-D symptoms than those treated with placebo.[113]

Microbiome and immune modulators. *Probiotics.* A meta-analysis and systematic review of 82 trials involving 10,332 subjects found moderate certainty that probiotics containing *Escherichia* strains improved global IBS symptoms, whereas evidence for *Lactobacillus* strains was of low certainty.[114] There was also low certainty of evidence for improvement in abdominal pain with *Saccharomyces cerevisae I-3856* and *Bifidobacterium* strains, and very low certainty of evidence for bloating with combination probiotics and *Bacillus* strains. The risk of AEs was similar between probiotics and placebo.

Rifaximin. In phase 3 trials, rifaximin (550 mg 3 times a day for 14 days), a minimally absorbed antibiotic, resulted in significantly more patients reporting adequate relief of global IBS-D symptoms (40.8% vs 31.2%) and bloating (39.5% vs 28.7%) than placebo.[115] Improvement in symptoms persisted for the 10-week follow-up period. A subsequent trial found that up to 2 retreatments with rifaximin were superior to placebo in improving IBS-D symptoms.[116] A meta-analysis of 6 RCTs confirmed rifaximin's efficacy, showing greater overall IBS symptom relief than placebo (RR = 1.22). AEs with rifaximin were like placebo.[117]

Fecal microbial transplantation. A meta-analysis of 8 clinical trials involving 4484 subjects did not find a significant improvement in global symptoms in IBS at 12 weeks in comparison with placebo.[118] In subgroup analysis, fecal microbial transplantation (FMT) administered via colonoscopy or gastroscope was superior to placebo, whereas capsules were not. The quality evidence to support recommending FMT in IBS was very low. Current guidelines recommend against the use of FMT in IBS outside of a clinical trial.

Mast cell stabilizers and H1-receptor antagonists. Small studies of patients with IBS-D have reported improvement in symptoms of IBS and diarrhea with the mast cell stabilizer disodium cromoglycate and the H1-receptor antagonist ebastine.[119] Further prospective multicenter studies are needed to confirm these preliminary results.[119]

5-Aminosalicylic acid. A meta-analysis of 8 RCTs found mesalamine to be more efficacious than placebo for global IBS symptoms (RR of not improving 0.86) but not for abdominal pain or bowel habits. Overall quality of evidence

was low and therefore further trials are needed to define its role in IBS.[120]

Complementary and alternative medicine. A systematic review and meta-analysis of complementary and alternative medicine (CAM) clinical trials in patients with IBS found that several interventions, including herbal therapy, dietary supplements, and mind-body therapy, were associated with improved overall response compared with placebo, although the certainty of estimates was low.[121] In contrast, body-based and energy healing therapies showed no significant benefit over placebo/sham. Overall, the quality of evidence across CAM therapies was low, highlighting the need for more rigorous high-quality RCTs.

Brain–gut behavior therapies. Brain–gut behavior therapies, also called brain–gut psychotherapy, encompasses interventions such as cognitive behavioral therapy (CBT), gut-directed hypnotherapy, mindfulness, and exposure therapy, among others.[122] A systematic review and meta-analysis found self-administered or minimal contact CBT, face-to-face CBT, and gut-directed hypnotherapy had the most evidence for efficacy. All studies were at high risk of bias.[123] Digital therapeutics (apps) offer an accessible and affordable alternative for patients seeking psychological interventions for IBS. However, given the rapidly changing landscape for digital apps, clinicians should evaluate each patient's needs, mental health status, and potential risks before recommending them.

Multidisciplinary approach. A multidisciplinary approach that integrates psychological, behavioral, and dietary therapies has been recommended for selected patients with IBS. In an open-label, single-center study, patients receiving multidisciplinary care were more likely to report improvement in IBS symptoms compared with those receiving standard care.[124]

C2. Chronic Constipation

Definition

CC, previously called functional constipation (FC), is a bowel disorder characterized by difficult, infrequent, or incomplete defecation. The change in nomenclature reflects the overall trend in Rome terminology away from the term "functional." The Rome BD Committee chose CC, rather than chronic idiopathic constipation (CIC), to emphasize that CC is rarely secondary to organic etiologies. In general, CC, FC, and CIC can be considered interchangeable terms. CC is used in this section unless, for historical reasons, the terms FC or CIC were used in a prior study. Patients with CC should not meet diagnostic criteria for IBS and symptom onset should occur at least 6 months before diagnosis, with symptoms present during the preceding 3 months. Conceptually, the main distinction between CC and IBS-C is the absence or presence of predominant abdominal pain or discomfort. However, this distinction is not always clear because some abdominal pain or discomfort may occur in many patients with constipation. However, in CC these symptoms are not the predominant clinical feature.[125]

A subgroup of individuals experiences recurrent but intermittent constipation that does not meet the definition of CC. This disorder, termed occasional constipation, has been defined by the Rome Foundation Working Team as "the presence of at least 1 functional constipation symptom, in the absence of alarm signs or symptoms, occurring at irregular and infrequent intervals, which is bothersome enough to induce a patient to seek management."[126]

Epidemiology

Constipation prevalence varies depending on definitions and self-reporting. A meta-analysis (1990–2020) reported rates ranging from 10.1% to 15.3% using Rome I–IV criteria. In the RFGES internet survey, the pooled FC prevalence was 11.7%, ranging from 7.7% in Australia to 16.6% in Japan, and was higher than IBS prevalence.[1,127,128] Most cases of constipation resolve over time, although 21% have intermittent symptoms and 1 study found only one-third of FC cases remain stable after 12 months.[129] CC affects mental health more than physical health-related quality of life (HRQoL) and contributes to higher health care costs and significant reduction in work productivity.[130–136]

C2. Diagnostic Criteria[a] for Chronic Constipation

Must include:

1. Two or more of the following:
   a. Straining during more than one-fourth (25%) of defecations
   b. Lumpy or hard stools (Bristol Stool Form Scale 1–2) in more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation in more than one-fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage in more than one-fourth (25%) of defecations
   e. Manual maneuvers used to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
   f. Fewer than 3 SBMs per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for IBS

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

Clinical Evaluation

Details of the key aspects to be considered during the clinical history and physical examination, including digital rectal examination, are summarized in Figures 3 and 4.[137,138]

Role and indication for diagnostic testing. A positive diagnosis of CC can be made in most patients based on typical clinical symptoms and the absence of alarm features without the need for extensive diagnostic testing. A summary of Rome V and current societal clinical practice guidelines is summarized in Supplementary Table 3.[33,139–147]

Initial serologic laboratory tests. A complete blood count should be reviewed to exclude anemia, an alarm feature. Thyroid-stimulating hormone and serum calcium testing should be performed when clinically indicated (eg, suspected hypothyroidism or diseases inducing hypercalcemia).

Stool laboratory testing, breath testing, and gastrointestinal endoscopy. Recommendations regarding these tests are like those outlined in the IBS section and also apply equally to the diagnostic approach to CC.

Imaging. Imaging studies (barium enema, ultrasound, computerized tomography, magnetic resonance, etc) have minimal diagnostic value for CC in the absence of alarm features or relevant comorbidities and are not generally recommended.

Defecatory disorders testing. Tests to identify patients with defecation disorders are reviewed in detail in the Anorectal Disorders article. The Rome V BD Committee recommends performing anorectal function tests for patients who do not respond to therapeutic interventions, rather than during the initial evaluation. However, testing may be warranted earlier if there is strong suspicion of a defecatory disorder, such as findings on digital rectal examination.

Measurement of colon transit. After excluding defecatory disorders, colonic transit testing using radiopaque markers, scintigraphy, or wireless motility capsule may be considered in patients with persistent symptoms despite medical therapy. Delayed colonic transit suggests a motility disorder, although this finding does reliably predict treatment response. If surgical intervention for refractory constipation is under consideration, upper gut transit evaluation should be performed to exclude a diffuse GI motility disorder, which could influence surgical decision making.

Colonic manometry. Colonic manometry is not widely available outside of academic centers and the clinical relevance of colonic manometry results on the clinical management of CC remains uncertain.

Pathophysiology

Pathophysiologic mechanisms of CC overlap significantly with IBS-C.[124,148] Major risk factors for CC include female sex, increasing age, lower socioeconomic status, physical activity, surgeries, medical conditions, and medications.[149] Constipation frequently clusters within families, but genetic contributions are likely modest or influenced by epigenetics, gene expression, and environmental features.[150] Diet and lifestyle may influence risk, but data are mixed.[151,152] One study reported reduced constipation risk with "high fiber" intake,[151] whereas others found no clear dose-response relationship. Regular exercise is associated with a reduced risk of constipation. Evidence for the link between fluid intake and constipation is inconsistent.[152]

Most patients with CC have normal transit constipation, whereas a small proportion demonstrate slow transit constipation.[140,153] Defecatory disorders are the second most common type of CC and may co-occur with slow transit constipation.[140] Fecal microbiota composition has been linked to colonic transit.[153] Slow transit may result from motor disturbances such as reduced high-amplitude propagated contractions, diminished postprandial colonic tone or compliance, and impaired GI physiologic responses. Advanced mapping and high-resolution techniques have shown regional abnormalities in colonic propagating pressure waves and decreased pan-colonic pressurizations in refractory constipation.[140] Differences in transit, motor function, sensitivity, colonic volume, and luminal content distribution may help distinguish constipation subtypes (eg, IBS-C vs CC).[154] Available evidence suggests that patients with CC generally do not have rectal hypersensitivity, and some may even be hyposensitive.[155] Histopathologic studies have identified abnormalities in the myenteric and submucosal plexus,[156] altered numbers of excitatory/inhibitory myenteric plexus neurons, and changes in neurotransmitters such as substance P,[157] vasoactive intestinal polypeptide, and nitric oxide.[158,159] Reductions in colonic enteroglucagon- and serotonin-containing endocrine cells and abnormalities in interstitial cells of Cajal also have been described.[160,161] Serotonin dysregulation, including microbially mediated serotonin transporter (SERT) expression and 5-HT levels, may further affect rectal sensation and evacuation dynamics.[150]

Although no specific psychological profile defines CC, personality, stress, and late toilet training may influence symptoms. Patients with severe constipation and normal intestinal transit often have increased psychological distress or misperceive bowel frequency. Constipation also has been associated with anxiety, depression, insomnia, poor self-rated health, and early-life adversity.[162]

Treatment

Lifestyle modifications. Increasing physical activity, scheduling a regular bathroom routine, and using a footstool to elevate the feet during defecation may improve constipation symptoms in some patients, although supporting evidence remains limited.[139]

The Rome V BD Committee recommendations for CC are compared with other international guidelines and are summarized in the Supplementary Table 4.[33,139–146]

Peripherally acting agents. *Fiber supplementation and bulk laxatives.* Many patients with constipation benefit from fiber supplementation. In general, a total fiber intake of 20 to 30 g/d is recommended, using either soluble or insoluble, nonfermentable fiber. Psyllium is the best studied fiber, showing improvement in stool frequency compared with control at mean effective doses ranging

from 7 to 20 g/d.[163] Kiwi and prunes have also recently been shown in small RCTs to benefit some patients.

Osmotic laxatives. Lactulose at dosages of 15 to 30 mL (once or twice daily) can improve CC symptoms but is frequently associated with abdominal cramping and bloating. Magnesium products are generally safe and effective but may lead to electrolyte imbalances at high doses in older individuals or those with renal impairment. PEG is the most extensively studied osmotic laxative and has been shown to improve symptoms of CC in high-quality RCTs lasting up to 6 months.[164]

Stimulant laxatives. RCTs using bisacodyl and sodium picosulphate have demonstrated improvement in stool frequency in patients with CC during 4-week trials.[165,166] There is no evidence that stimulant laxatives are habit forming or cause structural or functional damage to the colon.

Secretagogues. In 4-week phase 3 trials, lubiprostone (24 μg twice daily) increased the number of SBMs in patients with CIC compared with placebo.[167,168] The most common AEs reported were nausea (31.7% vs 3.3% placebo) and diarrhea (11.7% vs 5.7% placebo). In a study conducted in Japan, lubiprostone significantly increased SBMs by week 1 and this improvement was maintained through 12 weeks of treatment.

In two 12-week, phase 3 trials, linaclotide 145 and 290 μg once daily, were more effective than placebo at increasing stool frequency, improving stool consistency, straining, and overall constipation symptoms in patients with CIC.[169] The most common treatment associated side effects was diarrhea (16% vs 5% placebo). In a Japanese phase 3 trial, linaclotide 0.5 mg once daily significantly increased SBM compared with placebo and complete SBM responders.

In 2 phase 3 trials, plecanatide 3 mg once daily significantly improved stool frequency compared with baseline. Diarrhea was reported in 5.1% vs 1.3% placebo.[167]

Bile acid transport modulation. Elobixibat inhibits ileal bile acid transporters thereby increasing proximal colon bile acids, modulating colonic secretion and motility. In a phase 2B RCT, elobixibat (10 and 15 mg) improved stool frequency more than placebo. Similar benefits were noted in a short (2-week) phase 3 study conducted in Japan.[170] The most common AE was diarrhea (13% vs 0% placebo). Elobixibat is approved for the treatment of CC in Japan.

Systemically acting agents. *Prokinetic agents (5-HT_4 receptor agonists).* Tegaserod was superior to placebo at improving CC symptoms but is no longer commercially available. Prucalopride has greater selectivity for the 5-HT_4 receptor compared with other 5-HT_4 agonists. Phase 3 RCTs have demonstrated that prucalopride (1, 2, and 4 mg) were effective at alleviating constipation symptoms. However, the 4-mg dose was not significantly more effective than the 2-mg dose for most endpoints and was associated with more GI side effects and therefore only the 1-mg and 2-mg doses are currently approved.[171] Diarrhea occurred in 11% to 19% of patients treated with prucalopride compared with placebo (3%–5%).

Other therapies. A phase 3 trial demonstrated that a vibrating colon capsule could improve CC symptoms, possibly by augmenting the circadian rhythm of colonic contractile activity.[172] Occasional use of enemas may be effective in patients with constipation. The long-term safety of chronic enema use is unknown. Transanal irrigation may improve symptoms in patients with medical refractory constipation. Subtotal colectomy with ileo-rectostomy is a therapeutic option for the rare patient with severe, medically refractory, colonic inertia. Proper patient selection is critical.[173]

C3. Functional Diarrhea

Definition

FDr is characterized by recurrent passage of loose or watery stools in the absence of an identifiable organic etiology. Patients with FDr should not meet criteria for IBS; although abdominal pain, discomfort, and/or bloating may be present, these are not the predominant symptoms. Symptom onset should occur at least 6 months before diagnosis, with symptoms present during the preceding 3 months.

Epidemiology

Prevalence of FDr varies widely from 1.5% to 17.0% depending on the diagnostic criteria used. In a population survey conducted in the United States, Canada, and the United Kingdom, prevalence of FDr was 4.7% using Rome IV criteria but decreased to 0.9% with Rome III.[2] The RFGES similarly reported a prevalence of 4.7%.[147] FDr often follows a chronic course, with 94% of patients remaining symptomatic at 12 to 20 months and 29% at 12 years. Data on HRQoL in China reported low HRQoL among individuals with FDr.[174]

C3. Diagnostic Criteria[a] for Functional Diarrhea

1. Loose or watery stools occurring in more than 25% of stools, and
2. Hard stools are rarely present without medication that can cause constipation

[a]Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis. The patients meeting criteria for IBS-D should be excluded.

Justification for change in criteria: Point 2 has been added for consistency with diagnostic criteria of CC.

Clinical Evaluation

Clinical history and alarm features. These are the same as in IBS-D and detailed in Figure 2.

Diagnostic tests. The utility of diagnostic testing in patients with FDr has not been as well studied compared with patients with IBS-D. Consequently, the yield of diagnostic tests for identifying the etiology of diarrhea in patients with symptoms of FDr remain uncertain.[175,176]

The Rome V BD Committee emphasizes that the diagnostic evaluation of patients with suspected FDr should be like IBS-D (Supplementary Table 5).[20–33,147,175,176]

Pathophysiology

The pathophysiology of FDr shares considerable overlap with IBS-D,[177] particularly in the secretory, osmotic, and motor disturbances that contribute to chronic diarrhea. Although the relative impact of individual mechanisms in FDr remains incompletely defined, bile acid diarrhea appears to be among the most common pathophysiologic disturbances in FDr.[178] A genome-wide association study meta-analysis demonstrated significant associations of stool frequency with 14 independent loci, suggesting a possible role for genetic contributions to FDr.[179–182] Few studies have addressed sensorimotor mechanisms of FDr separately from IBS. Early research reported increased fasting and postprandial colonic propagating contractions, as well as normal descending colonic tone during fasting and reduced tone postprandially in FDr.[180,181] Similar to IBS, FDr may develop following acute infectious gastroenteritis.[181,183] Although anxiety often accompanies IBS, psychological features specific to FDr remain less well characterized. Some data link chronic diarrhea to self-reported stress in population-based studies[182] and acute stress accelerates colonic transit.

Treatment

Few studies have specifically evaluated treatment in patients with FDr. Most therapeutic recommendations are extrapolated from studies in related conditions like IBS-D, which limits the ability to provide evidence-based recommendations. In general, the reader is referred to the IBS-D treatment section.[21]

As abdominal pain is not predominant, neuromodulators used in IBS-D should not be considered as initial therapy. Management should include a careful review of medications, including over-the-counter agents, supplements, and alternative therapies, as these may contribute to diarrhea (eg, magnesium, proton pump inhibitors). Loperamide slows colon transit and improves stool frequency and consistency; it can be used routinely (2–4 mg; up to 4 times a day) without the need for laboratory monitoring. Empiric treatment with a bile acid sequestrant (eg, cholestyramine, colesevelam, colestipol) for a minimum of 4 weeks is reasonable if testing for BAM is not available. Ondansetron, a 5-HT_3 antagonist, improves stool consistency and frequency and reduces urgency, but not abdominal pain, in patients with IBS-D. Given the predominant antidiarrheal effect of ondansetron, it may be effective in FDr, although it has not been studied specifically in this population.

C4. Functional Abdominal Bloating

Definition

FAB is characterized by recurrent abdominal fullness, pressure, or a sensation of trapped gas (bloating), and/or a measurable, visible increase in abdominal girth (distension). FAB should not meet diagnostic criteria for other disorders of gut–brain interaction (DGBI), although patients may have coexisting but less bothersome symptoms characterized by bowel habit abnormalities (either constipation or diarrhea) and abdominal pain or discomfort (usually when abdominal distention is at its worst). However, these symptoms should not predominate in frequency or severity. Symptom onset should be at least 6 months before diagnosis, and the predominant symptom (bloating or distension) present during the preceding 3 months.

Although abdominal bloating and distention represent distinct phenomena—bloating being a subjective sensation of abdominal pressure, fullness, and/or gassiness, and distension an objective, measurable increase in abdominal girth—they are classified together under FAB (Figure 5). At the present time there is insufficient research to support separating these entities.

Epidemiology

Bloating is common in the general population, more prevalent in women, and increases with age. Reported prevalence rates range from 11% in East Asia to 20% in Latin America.[184] Bloating and/or distension is nearly universally reported by those with IBS (96.6%) and functional dyspepsia (88.9%) compared with 53.8% without DGBI. The global prevalence of individuals meeting criteria for FAB in the RFGES was 3.5%.[2] Cross-cultural research on FAB presents challenges, as the term “bloating” lacks a direct translation in Spanish and other Latin languages, whereas “distension” refers to an objective sign that can measured. In these populations, pictograms may be more effective than verbal descriptors.[185]

C4. Diagnostic Criteria[a] for Functional Abdominal Bloating

Must include both of the following:

1. Recurrent abdominal bloating and/or visible distension on average at least 1 d/wk; abdominal bloating and/or visible distension predominant over other symptoms.
2. There are insufficient criteria for the diagnosis of IBS, CC, FDr, and the postprandial distress syndrome subtype of functional dyspepsia.

Mild pain or discomfort related to bloating and minor bowel movement abnormalities may be present but do not predominate.

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

Clinical Evaluation

This is like the previously discussed BDs and is detailed in Figure 5.[186]

Role and indication for diagnostic testing. Evidence-based guidelines for diagnostic testing of patients with suspected FAB are currently lacking. In clinical practice, evaluation should follow principles similar to those applied to suspected IBS and CC.[186]

Pathophysiology

The pathophysiology of bloating remains incompletely understood and is likely heterogeneous both across different DGBI and among patients within the same disorder. Potential causes include visceral hypersensitivity, abnormal intestinal gas transit, impaired evacuation of rectal gas, colonic fermentation of different food products, small intestinal bacterial overgrowth, altered gas homeostasis, changes in the gut microbiota, and an abnormal abdomino-diaphragmatic reflex. Contrary to popular belief, most patients with DGBI do not have more intestinal gas than healthy volunteers. One key mechanistic finding is abdominophrenic dyssynergia, which is a phenomenon whereby distention of the luminal intestinal tract leads to abnormal contraction of the diaphragm along with relaxation of the abdominal wall muscles, resulting in visible abdominal distension.[187] The underlying cause of this abnormal reflex is not known, although one study in patients with IBS suggested an association with increased wall tension. Psychological factors, including anxiety and depression, are frequently associated with the presence and severity of abdominal bloating, suggesting a gut–brain interaction component.[188]

Treatment

Data on the treatment of FAB primarily come from studies involving patients with IBS or CC. The recommendations that follow should be taken with the caveat that large RCTs evaluating the therapeutic efficacy of diets or medications have not been performed in patients with FAB.[189]

Diet. Some patients note symptom improvement with a diet low in FODMAPs, whereas others note benefits by reducing gluten (see section on IBS).

Abdominophrenic biofeedback. A recent RCT in patients with meal-triggered visible abdominal distention (n = 42) demonstrated that thoracoabdominal wall motion–guided biofeedback using inductance plethysmography improved abdominal distention scores; these effects were not observed in the placebo group.[190]

Pharmacological treatments. *Over-the-counter agents.* Simethicone, an antifoaming agent, may improve symptoms of gas and bloating in some patients, whereas α-galactosidase may benefit some patients who ingest foods high in oligosaccharides. Peppermint oil, taken 2 to 4 times daily before meals, may improve bloating and distention in some patients.

Secretagogues. A meta-analysis of RCTs found that secretagogues were superior to placebo for treating bloating.

Neuromodulators. In patients with moderate to severe DGBI, desipramine in conjunction with CBT resulted in an improvement in bloating, although the effects of desipramine alone on bloating remains unclear. Low-dose amitriptyline led to some improvement in bloating in a prospective trial of amitriptyline in patients with IBS. A small, crossover trial with citalopram showed an improvement in the number of days without bloating at 3 and 6 weeks, whereas pregabalin improved bloating symptoms in a 12-week prospective study in adult patients with IBS.

Prokinetic agents. Post hoc analysis of phase 3 and 4 studies with prucalopride in patients with CC who had moderate to severe bloating demonstrated a greater improvement with prucalopride (2 mg once daily) compared with placebo (62% vs 50%).

Microbiome and immune modulation. *Probiotics.* A systematic review and meta-analysis of combination probiotics for the treatment of IBS found a low certainty of evidence for the benefit of combination probiotics over placebo. It is important to note that some patients report a worsening of bloating with probiotics.

Antibiotics. In a double-blind, RCT of 124 patients with predominant bloating and excessive flatulence with negative lactulose hydrogen breath tests, rifaximin (400 mg by mouth twice daily for 7 days) improved global symptoms and bloating scores compared with placebo. Rifaximin (400 mg 3 times daily for 10 days) also reduced bloating severity during a 10-week follow-up period.[191] In the 2 phase 3 trials in patients with nonconstipated IBS, rifaximin at a dosage of 550 mg 3 times daily for 14 days provided greater adequate relief of bloating compared with placebo (40% vs 30%).[115] Similarly, a retreatment trial evaluating multiple courses of rifaximin in patients with IBS-D found that rifaximin (550 mg 3 times daily) led to a greater improvement in overall IBS symptoms, including bloating, compared with placebo.[116]

C5. Unclassified Bowel Disorders

Definition

U-BD was previously referred to as unspecified functional bowel disorder in Rome IV. The change in nomenclature more accurately reflects that these individuals do not meet other classifications of Rome diagnoses and deleting the functional descriptor.

C5. Diagnostic Criteria[a] for Unclassified Bowel Disorders

Must include the following:

1. Bothersome bowel symptoms are not attributable to structural abnormalities and not fully meeting criteria for IBS, CC, FDr, or FAB disorders.

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

Clinical Evaluation

In a single-center tertiary care study, among 813 patients meeting Rome IV criteria for a BD, 13.1% met criteria for U-BD. Compared with other BDs, patients with U-BD reported lower overall symptom severity including abdominal pain, constipation, and diarrhea; however, health care utilization, anxiety, depression, and sleep disturbances were similar to those observed in other BD subtypes.[192] These findings suggest that U-BD lies on a continuum with other BDs, reflecting significant clinical and psychosocial overlap. Furthermore, among patients initially meeting criteria for U-BD, only 40% continued to meet this diagnosis at 1-year follow-up, whereas the remainder transitioned to other BD criteria, most commonly IBS.[193]

C6. Opioid-Induced Constipation

Definition

OIC is part of a spectrum of opioid-induced BDs that encompasses a range of GI disturbances resulting from the effect of opioids both on the GI tract and in the central nervous system. The reader is also referred to the appropriate sections for a discussion on narcotic bowel syndrome.

Epidemiology

In the RFGES, the prevalence of OIC was 1.6% in internet-surveyed countries and 0.9% in household surveys.[2] Rates were higher in women than in men and increased with age only in the household population. A more recent study in the United States reported that 1.7% for OIC and 0.4% for opioid-exacerbated constipation.[194] There are limited data on the incidence of OIC.

C6. Diagnostic Criteria for Opioid-Induced Constipation

Must include both:

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 (Bristol Stool Form Scale 1–2) in more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation in more than one-fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage in 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 SBMs per week
2. Loose stools are rarely present without the use of laxatives

Clinical Evaluation

A similar diagnostic approach recommended for IBS-C and CC can be considered, but there are no conclusive data regarding the yield of diagnostic tests in patients with OIC.[195]

Pathophysiology

Opioid-induced bowel disorder occurs when opioid receptors (eg, mu, kappa, or delta) in the GI tract or central nervous system are activated by either exogenous or endogenous opioids leading to decreased propulsive activity; increased nonpropulsive contractions and fluid resorption; decreased pancreatic, biliary, and gastric secretions; and increased anal tone. These physiological changes may lead to abnormalities in esophageal peristalsis, gastric emptying, small intestine and colon transit, and anorectal function.[195]

Treatment

The treatment of OIC mirrors that of CC in large part, except for the use of peripheral acting mu-opioid receptor antagonists (PAMORAs).[196]

Prescription medications. If lifestyle modifications and over-the-counter agents are not effective, then prescription medications are the next step. These can be classified into non-PAMORAs and PAMORAs.

Non-PAMORAs. Lubiprostone is the only secretagogue currently approved by the Food and Drug Administration for the treatment of OIC. Although the initial 2 studies with lubiprostone in OIC were negative, a third RCT, excluding patients on methadone, found that lubiprostone (24 μg twice daily) was more effective than placebo at improving OIC symptoms (27.1% vs 18.9% for the primary endpoint).[197] Two separate phase 2 studies evaluated prucalopride and linaclotide and demonstrated benefits, but large phase 3 RCTs have not been performed.[197]

PAMORAs. Methylnaltrexone, a quaternary derivative of naltrexone, is available as a subcutaneous injection (8 or 12 mg) or an oral tablet (150 mg). In a prospective, placebo-controlled RCT (n = 460), daily or every other day (alternating with placebo) subcutaneous methylnaltrexone was superior to placebo at improving SBMs without the need for rescue medication within 4 hours of injection.[198] Oral methylnaltrexone was evaluated in a 12-week RCT study involving 803 patients with OIC and found to be superior to placebo at the recommended dosage of 450 mg daily.

Naloxegol is a pegylated conjugate of the opioid antagonist naloxone. In 2 phase 3 12-week RCTs, 1352 patients with noncancer pain with OIC were randomized to naloxegol (12.5 and 25 mg) or placebo. Patients randomized to 25 mg were more likely to meet the primary endpoint in both trials (44.4% and 39.7%, respectively) compared with those randomized to placebo (29.3%).[199] In an open-label, crossover trial comparing PEG with the PAMORA naloxegol, no difference was found between these 2 groups (n = 246) during the 2-week active treatment period and patients did not prefer one over the other.

Naldemedine, a derivative of naltrexone, was studied in two 12-week phase 3 RCTs in patients with noncancer pain with OIC. The primary endpoint was met by patients with OIC randomized to naldemedine (0.2 mg) in the first study and 52.5% of patients in the second, compared with an average of 34% of patients randomized to placebo. AEs were like other PAMORAs—diarrhea and abdominal pain.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2026.02.003.

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Correspondence
Address correspondence to: Maura Corsetti, MD, PhD, Nottingham Digestive Diseases Biomedical Research Centre, Queens Medical Centre – E Floor, West Block, Derby Road, Nottingham, NG7 2UH, United Kingdom. e-mail: maura.corsetti@nottingham.ac.uk.

Conflicts of interest
These authors disclose the following: Maura Corsetti is a consultant for Mayoly, PROMEDCS, Biocodex, and Sanofi/Opella. Andrea Shin is a consultant for Ardelyx and ModernGut; and on the advisory board of Gemelli Biotech and Salix Pharmaceuticals. Brian E. Lacy is a consultant for GSK, Lilly, and Renexxion. Brooks D. Cash is a consultant for Ardelyx, AbbVie, and Viscera Labs. Magnus Simrén is a consultant/advisory board member of Biocodex, Tillotts, BioGaia, Renapharma, and AlfaSigma; and on the speakers bureau of Tillotts, Takeda, Biocodex, Sanofi, AbbVie, Janssen Immunology, Pfizer, BioGaia, Renapharma, Mayoly, and Bromatech. Max J. Schmulson is member of the Advisory Council of Daewoong South Korea, Gemelli Biotech Inc, Moksha 8 Mexico, Pro.Med.CS. Praha a.s., and Prometis México; and is a speaker for Alfa Sigma Mexico, Daewoong South Korea, Biopas Colombia, Moksha 8 Mexico, and Prometis Pharma Mexico. Anthony Lembo is a consultant for Ironwood, Takeda, Ardelyx, BioAmerica, and Pfizer. The remaining author discloses no conflicts.

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