# FUNCTIONAL BOWEL DISORDERS

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## INTRODUCTION

### Functional Bowel Disorders Classification

Functional bowel disorders (FBDs) are a spectrum of chronic gastrointestinal disorders, attributable to the middle or lower gastrointestinal tract, characterized by the following predominant symptoms or signs: abdominal pain, abdominal bloating, abdominal distension and bowel habit abnormalities (which include constipation, diarrhea, or mixed constipation and diarrhea). Functional bowel disorders (FBDs) can be classified into 5 distinct categories: irritable bowel syndrome (IBS); functional constipation (FC); functional diarrhea (FDr); functional abdominal bloating/distention (FAB/D); and unspecified FBD (U-FBD). Although categorized as distinct disorders, significant overlap exists, and in some cases it may not be possible to confidently distinguish them. The FBDs can be conceptualized in 3 ways (see Figure 1): 1. As distinct conditions that occur independently; 2. As distinct pathophysiologic conditions with symptoms that frequently overlap; and 3. As a spectrum of pathophysiologic disorders that frequently overlap and which are characterized by patient specific differences in the quantity, intensity and severity of symptom expression. The opinion of this committee is that the third conceptual framework is the one that best explains FBDs (Figure 1).

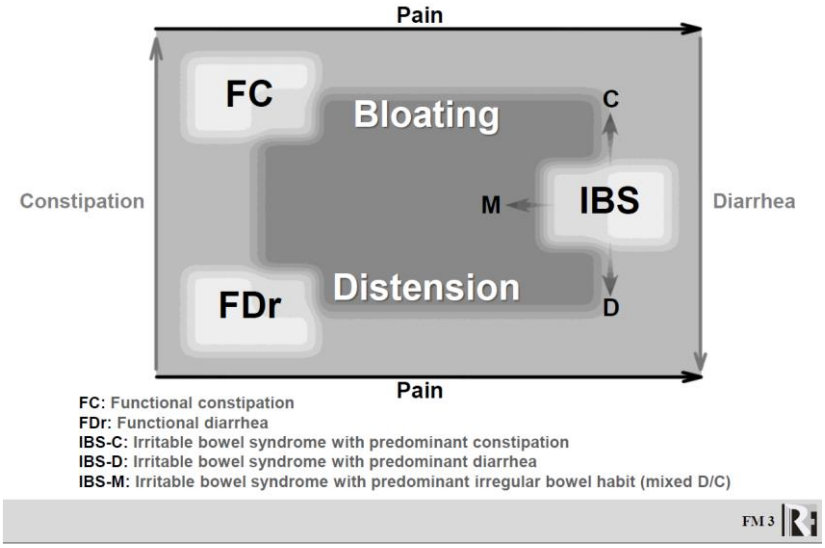


**Figure 1. Conceptual framework to explain Functional Bowel Disorders**

Patients with FBDs commonly transition from one FBD diagnostic group to another over time. This may be due to the natural history of the disorder, a response to therapy, or both. For clinical trials it is recommended that patients belong unequivocally to only a single diagnostic category, unless the investigation is focused specifically on overlapping FBDs. 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 (U-FBD).

The operational construct described below distinguishes FC and IBS with constipation as distinct disorders; cluster analysis studies support this separation.[1,2] Others believe, however, that both are part of a spectrum, with constipation as a predominant symptom and abdominal pain as a second symptom of variable intensity.[3-5] Considerable overlap exists between IBS-C and FC when mutual exclusivity is suspended.[6] Transition from FC to IBS-C, or *vice versa*, is common.[3, 7] The similarities of the 2 disorders suggest that IBS-C and FC should be considered separate ends of a spectrum[8] (Figure 1).

Functional diarrhea (FDr) and IBS-D represent a similar situation. In a minority of cases, diarrhea happens in the absolute absence of abdominal pain and should unequivocally be diagnosed as FDr. When mutual exclusivity was suspended, overlap between FDr and IBS-D occurred in 28% of cases.[6] The diagnosis of these 2 disorders should be made based on the predominant symptom: FDr if diarrhea is clearly the predominant symptom and IBS-D if diarrhea is present but abdominal pain predominates (Figure 1).

Functional abdominal bloating and distension are independent and specific FBDs only when present as the predominant symptom in the absence of other gastrointestinal symptoms. Functional abdominal bloating (FAB) and distension (FAD) should be classified as a single entity (FAB/D) although they encompass two different symptoms/signs: Abdominal bloating is the subjective sensation of abdominal pressure, fullness, and/or gassiness, while distention is the objective and measurable increase in abdominal girth. These conditions may

exist independently although they frequently coincide in the same individual.[9, 10] The distinct nature of these disorders is demonstrated by research showing that only 50-60% of patients with bloating have abdominal distension and the correlation between abdominal bloating and an increase in abdominal girth is poor.[11, 12] Further research may allow FAB and FAD to be considered separate entities.

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***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *FBDs are considered a spectrum of disorders rather than isolated entities.*
- *Distinguishing different FBDs may not be easy as overlap commonly exists.*
- *The transition from one FBD to another, or from one predominant symptom to another, is common and may occur due to the natural history of the disorder, a response to therapy, or both.*
- *Abdominal bloating and distention remain a single entity, although they do not always co-exist, and they likely have different pathophysiological origins.*

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**Patient Classification**

Subjects with FBDs can be divided into 2 major groups:

A. Non-patients. Those with mild symptoms (or not bothersome or worrisome enough) who have not sought medical attention for their FBD symptoms.

B. Patients. Those with symptoms severe enough (or bothersome or worrisome enough) to seek out medical attention for their FBD symptoms.

Not every individual with FBD symptoms should be considered a patient as these symptoms are frequent in the general population. The difference between patients and non-patients is related not only to symptom severity (e.g., intensity, frequency, unpredictability)

and medical consultation, but also to other factors such as fears and worries, impact on quality of life, co-existing medical and psychological disorders, learned behavior, and access to health care services.

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***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *Not every individual with FBD symptoms should be considered a patient.*
- *A clearer distinction between patient and non-patients is proposed. This is especially relevant for epidemiological studies.*

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## C1. IRRITABLE BOWEL SYNDROME

**Definition**

*Irritable bowel syndrome (IBS) is a functional bowel disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits. Disordered bowel habits are typically present (constipation, diarrhea or a mix of constipation and diarrhea), as are symptoms of abdominal bloating/distension.*

*Symptom onset should occur at least 6 months prior to diagnosis and symptoms should be present during the last 3 months.*

**Epidemiology**

Prevalence and incidence rates of IBS vary from country to country based on the survey population, the criteria used to define IBS and the type of survey instrument employed. A meta-analysis of 80 studies involving 260,960 subjects identified a prevalence rate of 11.2% (95% CI, 9-8%-12.8%).[13] Two separate longitudinal population studies lasting 10 and 12 years

reported the development of IBS symptoms in 15% and 16.2% of the population, yielding calculated incidence rates of 1.5% and 1.35%, respectively.[14, 15] Prevalence rates are higher for women than for men; younger people are more likely to be affected than those older than age 50.[13] There are insufficient data to assess the impact of socioeconomic status on the development of IBS symptoms.

A systematic review noted that 12-18% of patients became symptom free during a median follow-up period of 2 years, while 32-68% had unchanged or a worsening of IBS symptoms[16]. A longitudinal population study reported that 67% (95% CI, 61-73%) of patients symptomatic at baseline had persistent IBS symptoms, using Manning criteria.[14] Longitudinal population studies have shown that 32-68% of IBS patients have persistent symptoms at up to 12 years of follow-up[16].

**Diagnostic Criteria**

**C1. Irritable Bowel Syndrome**

***Diagnostic criteria****

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two 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

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *Abdominal discomfort has been deleted from the definition. It was the opinion of this committee that the imprecise nature of the term "discomfort" coupled with the fact that "discomfort" is not present in every language warranted its removal.*
- *Abdominal pain should be present at least 1 day per week on average during the preceding 3 months.*[1]
- *Bloating/distention are recognized as common symptoms.*
- *"… and with features of disordered defecation" has been replaced by "… disordered bowel habits are typically present (constipation, diarrhea or a mix of constipation and diarrhea)".*
- *"Criteria present for the last 3 months and onset at least 6 months prior to diagnosis" has been replaced by: "Symptom onset should occur at least 6 months prior to diagnosis and symptoms should be present during the last 3 months". The first criterion is meant to emphasize the specific FBD as a chronic disorder and to decrease the probability of an organic disease. The second criterion requires that symptoms be present recently.*

***Justification for Change in Criteria***

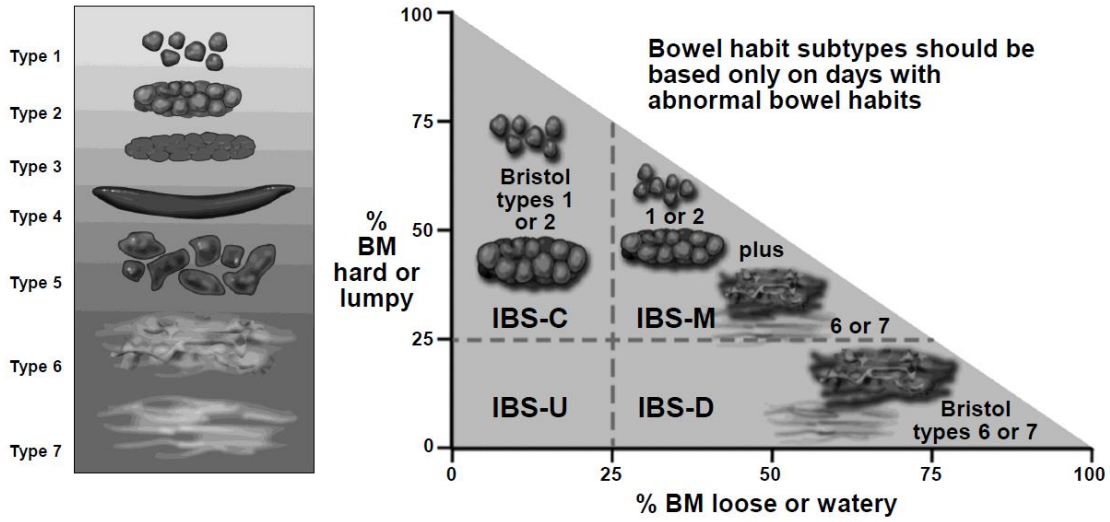
The presence of abdominal pain is mandatory to make the diagnosis of IBS. A diagnosis of IBS cannot be made if abdominal pain is absent. The term "discomfort" has been deleted from the current definition and diagnostic criteria because some languages do not have a word for discomfort or it has different meanings in different languages. Additionally, it is unclear whether the distinction between pain and discomfort is qualitative or quantitative. This is based on a study of IBS patients (n = 123) who reported that abdominal pain and discomfort were different,[17] but exhibited wide variations in their understanding of these terms. They reported that discomfort encompassed a wide range of symptoms such as bloating, gas,

[1] Based on data from the Report on the Rome Normative GI Symptom Survey. Whitehead, WE and Palsson, OS.

fullness, flatulence, sensation of incomplete evacuation or urgency. Another study concluded that "abdominal discomfort or pain" is an ambiguous term because no agreement could be reached on whether these are qualitatively different sensations.[18] In 328 IBS patients only one-half rated the frequency of pain alone (53%), and discomfort alone (55%), as identical in intensity. However, in 4 of 5 cases the same individual would be diagnosed with IBS regardless of which descriptor was used. Therefore, the current guidelines will not include the term abdominal discomfort, but will instead emphasize the more globally recognized term of abdominal pain. Non-pain symptoms should also be carefully specified rather than grouping them in this misleading term.

**IBS Subtypes**

IBS is classified into 3 main subtypes according to the predominant disorder in bowel habits: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D) and IBS with mixed bowel habits (IBS-M). The committee appreciates the complexity of subtyping IBS patients and for clinical practice suggests that subtyping be based on the patient's reported predominant bowel habit on days with abnormal bowel movements. IBS subtypes should be established according to stool consistency, using the Bristol Stool Form Scale (Figure 2).[19] For clinical trials the IBS subtype should be based on 14 days of daily diary reports. [20]




*Lewis SJ, Heaton KW. Scand J Gastroenterol 1997; 32:920*
*Heaton KW, O'Donnell LJ. J Clin Gastroenterol 1994; 19:28*

FM 11-12

**Figure 2. Bristol Stool Form Scale.**

**IBS Bowel Habit Subtype Criteria**

***Diagnostic criteria***

Predominant bowel habits are based on stool form on days with abnormal bowel movements.*

**IBS with predominant constipation (IBS-C):** > ¼ (25%) of bowel movements with Bristol stool types 1 or 2 and < ¼ (25%) bowel movements with Bristol stool types 6 or 7.

**IBS with predominant diarrhea (IBS-D):** > ¼ (25%) of bowel movements with Bristol stool types 6 or 7 and < ¼ (25%) bowel movements with Bristol stool types 1 or 2.

**IBS with mixed bowel habits (IBS-M):** > ¼ (25%) of bowel movements with Bristol stool types 1 or 2 and > ¼ (25%) bowel movements with Bristol stool types 6 or 7.

**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.

*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.

For clinical trials, subtyping based on at least 2 weeks of daily diary data is recommended.

***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *IBS remains divided into 4 subtypes (IBS-C, IBS-D, IBS-M and IBS-U), although it is recognized that pain or bloating/distention may predominate in some patients.*
- *Predominant bowel habits are based on stool form on days with abnormal bowel movements. 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.*
- *For clinical trials, subtyping based on at least 2 weeks of daily diary data is recommended.*

To have confidence in subtyping, patients should have at least 4 days of abnormal bowel habits each month.[2] Bowel habit subtypes should be based on Bristol Stool Form Scale (Figure 2) for days with abnormal bowel habits. Analysis of days without a bowel movement does not increase the specificity of bowel subtyping, while analyzing only days with abnormal bowel movements increases it.[2] 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 IBS patients have bowel movements that are within the normal range of stool consistency[3]. The diagnosis of IBS subtype should also take into account the patient's perception of their predominant bowel habits. Evaluation (subjective opinion and/or data from the Bristol scale) has to be performed with the patient off all therapies for bowel habit abnormalities (including laxatives and antidiarrheal agents).[21] The categories are considered mutually exclusive.

For clinical purposes, with the goal of providing a coherent treatment approach to health care providers, and for clinical trial design, the predominance of abdominal pain (P) and abdominal bloating/distension (AB/D) should be taken into account. Thus, although not included as classical IBS subtypes, some patients might be categorized as IBS-P or IBS-AB/D.

**Diagnosis of IBS**

IBS diagnostic criteria, like other diagnostic criteria, are not completely foolproof. The diagnosis of IBS requires common sense, physician thoughtfulness, limited diagnostic tests and careful follow-up. The decision to pursue diagnostic testing is predicated on a number of

[2] Based on data from the Report on the Rome Normative GI Symptom Survey. Whitehead WE and Palsson OS.

factors (e.g., alarm features, co-morbid conditions, refractoriness to therapy, cost of tests, insurance plans, etc.). 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, is perfect.[22] For example, it is now evident that some organic bowel disease may fulfill IBS criteria.[6]

Since a number of conditions have symptoms that can mimic IBS (e.g., inflammatory bowel disease [IBD], celiac disease, lactose 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.[23] Routine follow-up visits with targeted diagnostic studies for the persistently symptomatic patient appear cost-effective approach and may be more reassuring to the patient. The Rome IV committee encourages clinicians to make a positive diagnosis on the basis of symptoms and emphasizes that IBS is not a diagnosis of exclusion. It is worth emphasizing that when ordering a diagnostic test, clinicians need to consider the pre-test probability of the disease in question, based on the prevalence of the disease in symptomatic patients.

***How to Make the Diagnosis of IBS***

The diagnosis of IBS should be made based on four key aspects: 1. Clinical history; 2. Physical examination; 3. Minimal laboratory tests; and 4. Colonoscopy or other appropriate tests (when clinically indicated).

**1. Clinical History**

Main symptoms: ("Clinical diagnostic criteria")

Fulfilling diagnostic criteria is mandatory to make the diagnosis of IBS but it is not enough. Some organic diseases may also meet these criteria. Among more than 4000 patients with GI symptoms attending outpatient clinics 559 met Rome III criteria for IBS, an organic GI disease was present in 136 (24.3%), the commonest being Crohn's disease (n=10; 7.4%).[24] The prevalence of organic diseases was significantly lower in IBS-C (12.7%) versus IBS-D (32.1%) or IBS-M (23.8%; $p < .006$).[24] Incorporating the absence of alarm symptoms into the diagnostic criteria reduced the likelihood of organic disease only in IBS-D but, because alarm symptoms are so common, more than 60% of patients still have normal investigations (Figure 3).

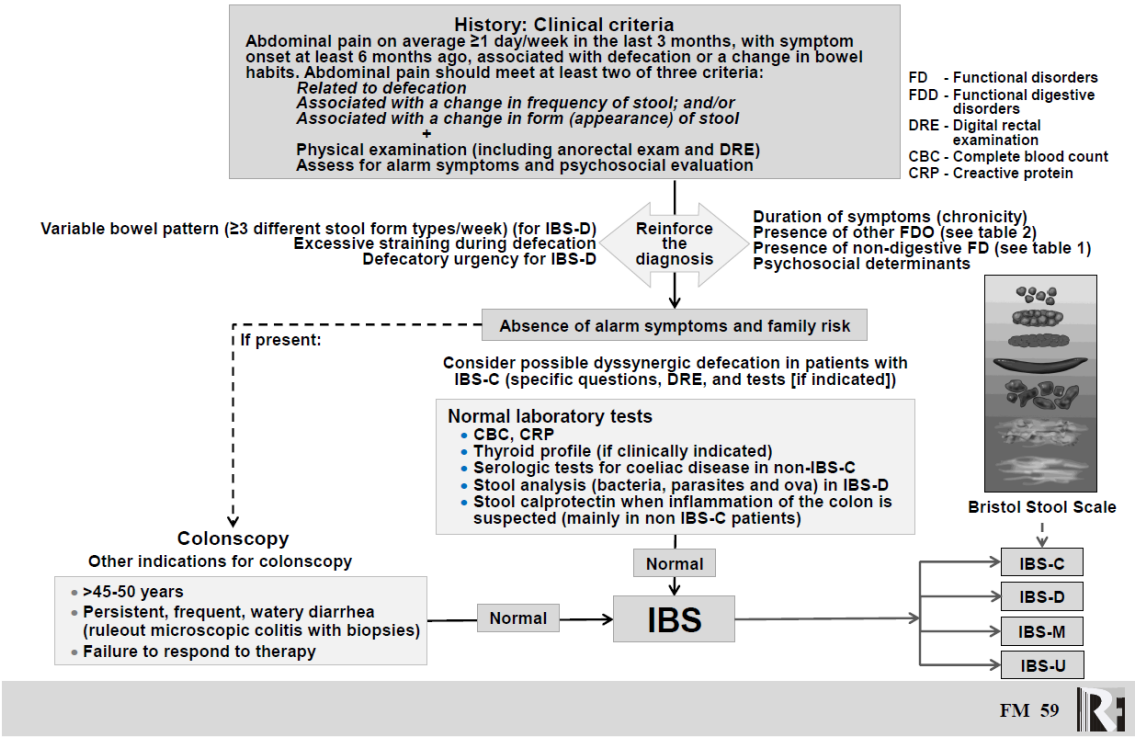



**Figure 3. Diagnostic algorithm for IBS**

In addition to these main symptoms, other GI and non-GI symptoms are also frequently present in IBS patients, and the presence of these concomitant symptoms lends further support to the diagnosis (see Table).[25-28]

**Table. Other gastrointestinal and non- gastrointestinal symptoms are also frequently present in IBS patients, and the presence of these concomitant symptoms lends further support to the diagnosis.** [25, 26]

| Other intestinal symptoms related to IBS | Other digestive symptoms frequently associated to IBS | Extraintestinal symptoms associated with IBS |
|---|---|---|
| *Mucus in feces* | *Heartburn* | *Fibromyalgia* |
| *Straining* | *Epigastric pain* | *Chronic fatigue syndrome* |
| *Urgency* | *Early satiety* | *Chronic pelvic pain* |
| *Feeling of incomplete evacuation* | *Postprandial fullness* | *Temporomandibular joint disorders* |
| | *Nausea* | *Headache* |
| | | *Neck and back pain* |
| | | *Muscle aches or soreness* |
| | | *Fatigue, tiredness, dizziness* |
| | | *Migraine* |
| | | *Palpitations, chest pain* |
| | | *Hot flushes* |
| | | *Sleep problems* |
| | | *Decreased sex drive* |
| | | *Dyspareunia* |
| | | *Increased urinary frequency and urgency, nocturia* |
| | | *Anxiety, depression* |
| | | *Breathing difficulties, asthma, cough* |
| | | *Pruritus* |
| | | *Bad breath/unpleasant taste in mouth* |

Unpredictable bowel pattern (≥3 different stool form types/week) reinforces the diagnosis of IBS in the diarrhea subtype;[29] it has not been tested in IBS-C or IBS-M. On the other hand, increasing the number of consecutive days without a bowel movement is associated with IBS-C.[30] 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), excessive straining during defecation, defecatory urgency, feelings of incomplete evacuation, and mucus with bowel movements, although common in IBS, are not specific.

IBS patients frequently report that symptoms are induced or exacerbated by meals, and about 50% with IBS-D complain of postprandial diarrhea.[31] Nevertheless, these findings are not specific enough to be part of the IBS diagnostic criteria. Other functional digestive disorders and non-digestive functional disorders may be present and these reinforce the diagnosis of IBS.[25, 26]

Absence of alarm symptoms and family risk

The presence of one or more lower-GI alarm features (a positive family history of colorectal cancer (CRC), rectal bleeding, weight loss, or anemia) does not improve the performance of IBS diagnostic criteria.[6, 32] However, from a clinical point of view, it is reasonable to include them in a directed clinical review. In support of this, recent data show that the absence of alarm symptoms reduced the likelihood of organic disease in subjects with IBS-D symptoms.[24]

Alarm features include: Unintended weight loss (> 10% in 3 months); blood in the stools not caused (confirmed) by haemorrhoids or anal fissures; nocturnal diarrhea; fever; and a family history of CRC (or polyposis syndromes), IBD or celiac disease.

Consider dyssynergic defecation (in patients with IBS-C)

It is important to distinguish dyssynergic defecation (DD) from other subtypes of constipation (including IBS-C) because DD has a distinct physiological mechanism and responds to different treatments. DD can be suspected based on a clinical history and physical examination.[33, 34] However, an accurate diagnosis requires tests that are associated with additional costs, may be invasive, and which may not be widely available (see Chapter 14).

Diet and psychosocial factors

A dietary history should be performed, with the help of a diary if necessary, with special attention paid to the intake of dairy, wheat, caffeine, fruits, vegetables, juices, sweetened soft drinks, and chewing gum, since these may exacerbate IBS symptoms or mimic IBS symptoms (see Chapter 4).

A brief psychosocial review should also be performed. Several available tests, including the HAD questionnaire and the PHQ12SS somatization score, may be useful (see Chapter 8).

**2. Physical Examination**

The intent of the physical examination is to reassure the patient and to exclude an organic basis for the patient's symptoms. A careful examination should include the anorectum and a digital examination with the following goals: 1. Identify anorectal causes of bleeding (mainly haemorrhoids and fissures) to avoid unnecessary diagnostic tests (i.e., colonoscopy); 2. Evaluate anal strength, (important in patients with IBS-D or IBS-M and incontinence) and inappropriate contraction of the puborectalis and/or anal sphincter (in patients with IBS-C), and 3: determine whether an abnormal pattern of abdominal wall contraction develops during simulated evacuation in patients with IBS-C.

**3. Laboratory Tests**

In almost every case of abdominal pain and bowel habit abnormalities a CBC and CRP should be performed. A systematic review and meta-analysis has shown that CRP and

calprotectin determinations are helpful in differentiating IBS from IBD.[35] Routine thyroid tests are not helpful, but can be checked in the appropriate patient if clinical suspicion is high. Serologic tests for celiac disease should be performed in patients with IBS-D and IBS-M who fail empiric therapy. Older studies demonstrated a higher prevalence of celiac disease in subjects with IBS symptoms than in the general population,[36-38] although a large, multicenter trial did not confirm this.[39] Upper gastrointestinal endoscopy with duodenal biopsies should be performed if serologic tests are positive or if clinical suspicion is high; biopsies can also be used to identify tropical sprue, which can mimic IBS symptoms.[40]

Stool analysis (bacteria, parasites and ova) may be useful if diarrhea is the main symptom, especially in developing countries where infectious diarrhea is prevalent.

As discussed previously, fecal calprotectin may be useful to help distinguish IBS from an inflammatory process (mainly in non IBS-C patients younger than 50 years). Each laboratory should identify its own cut off values.[41] When borderline values are obtained the clinician should repeat the fecal calprotectin before performing colonoscopy (if no other indication for colonoscopy exists).[42]

A screening colonoscopy is indicated in all patients ≥ 50 years in the absence of warning signs (45 years in African-Americans). Colonoscopy is also indicated for: the presence of alarm symptoms or signs; a family history of colorectal cancer (according to individual risk: patient age, type of symptoms, specific familial background, etc.); watery diarrhea; and > 6-10 bowel movements/day and/or persistent diarrhea that has failed empiric therapy (consider microscopic colitis - mainly in women > 50 years of age). Biopsies of different segments of the colon are required.[43, 44]

When diarrhea is present, especially if watery, with more than 4-6 bowel movements per day and/or associated urgency, bile acid malabsorption and carbohydrate malabsorption should be suspected. Given the high prevalence of bile acid malabsorption (BAM) and

increased BA synthesis in patients with IBS-D symptoms an empiric therapeutic trial with a BA sequestrant (cholestyramine or colesevelam) is reasonable.[45, 46] Scintigraphic evaluation by the $^{75}$SeHCAT test or postprandial C4 (7a-hydroxy-4-cholesten-3-one) serum determination are diagnostic options, although neither are widely available.

Carbohydrate (e.g., lactose, fructose, sorbitol) malabsorption is another frequent cause of liquid/watery diarrhea.[47, 48] Breath tests are helpful in the diagnosis but if not available a 4-week trial free of the suspected carbohydrate is recommended to evaluate the clinical response.

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***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *The diagnosis of IBS should be made following several steps, according to the clinical diagnostic citeria, but not only based on the criteria. Test indications are more clearly specified.*
- *The main criteria have been reworded:*
    - *Related to defecation; and/or*
    - *Associated with a change in frequency of stool; and/or*
    - *Associated with a change in form (appearance) of stool*
- *Symptoms that cumulatively support the diagnosis of IBS are more clearly explained*
- *Indications for tests are included*
- *Calprotectin is recommended in IBS non-C (< 50 years of age)*

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**Physiological Features**

IBS is a multifactorial disorder with a complex pathophysiology. There appear to be factors which increase the vulnerability to developing IBS and factors that are associated with

symptom generation and flares. A unifying theme is that these factors lead to dysregulation of the "brain-gut axis" resulting in diverse pathophysiological mechanisms, which appear to generate some IBS symptoms. 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 gastroenteritis, food intolerances, chronic stress, and surgeries. The resulting pathophysiologic mechanisms include, but are not limited to, altered GI motility, visceral hyperalgesia, increased intestinal permeability and immune activation and altered microbiota (Figure 4). Symptom clusters of IBS may arise from several etiologies that can differ within subgroups of patients.

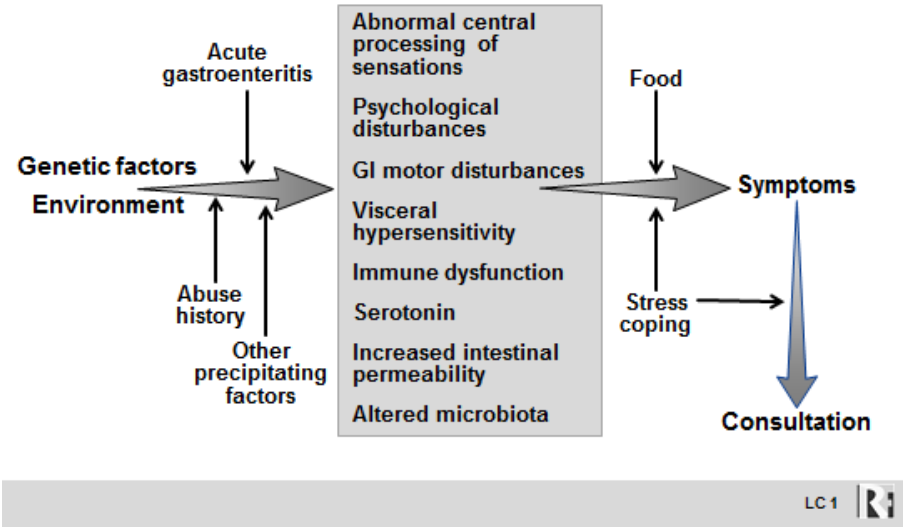


**Figure 4**. **Proposed pathophysiology of IBS.**

**Genetics**

IBS tends to cluster in familes and patients' relatives are more likely to report IBS symptoms than unrelated controls [49]. Twin studies have been used to try to ascertain the relative contribution of environment versus genetics but these cohorts were never set up to assess IBS and so subject classification is variable and important methodological differences have resulted in widely varying heritability estimates from 57%[50] in an early small study of 686

twins to virtually zero in a much larger study of 4,480 twin pairs[51]. The Virginia twin study of 10,699 twins found a much greater concordance for self-reported IBS in monozygotic twins (17%) than dizygotic twins (8%)[52]. However, it also showed having a mother with IBS was a stronger predictor than having a dizygotic twin with IBS, suggesting that social learning is a more important influence than genes. An alternative approach is to study the association of IBS with single nucleotide polymorphisms (SNPs) in candidate genes as has successfully been done in Crohn's disease. A recent genome wide association study (GWAS) using >11,326 Swedish twins identified the previously unrecognised association of IBS with two genes KDELR2 (KDEL endoplasmic reticulum protein retentionreceptor 2) and GRID2IP (glutamate receptor, ionotropic, delta 2 (Grid2) interacting protein) suggesting new avenues for research.[53] Previous candidate gene studies have typically been much smaller and rarely replicated. Since the strongest stimulus to develop IBS is an episode of gastroenteritis[54] there have been several attempts to identify SNPs which predicted the development of post-infective IBS (PI-IBS). Studies of individuals infected in the Walkerton outbreak of enteric infection in 2007 suggested genes related to gut permeability (*Cadherin-1*, *CDH1),* immune response (*Interleukin-6* (IL-6)) and response to bacterial DNA (*Toll-like receptor 9* (TLR-9)), but this study was underpowered and has yet to be validated in a larger cohort. Others have examined genes controlling the inflammatory response, particularly the key cytokine tumour necrosis factor-α (TNFα). IBS patients were more likely to be heterozygous for the -308 (G/A) SNP which predicts high production of TNFα than controls (46% versus 26%)[55]. Possession of both the high producer TNF-α SNP and low producer IL-10 allele (-1082 A) were also more prevalent in IBS patients (9%) versus controls (3%). More recently the G allele of SNP rs4263839 in the Crohn's associated proinflammatory gene *TNFSF15* has been demonstrated to increase the risk of IBS (odds ratio (OR) =1.37) [56] as has another closely linked SNP in the same gene.[57] This same study also supported the earlier report linking TNF-α to PI-IBS[56]. A meta-analysis of 5 studies suggested that the high producing GG genotype of the IL-10 (-1082

G/A) SNP reduces the risk of IBS[58]. Serotonin (5-HT) plays a pivotal role in both brain and gut physiology and many studies have examined the 5-HT transporter- linked polymorphic region (5-HTTLPR) within the promoter region of the serotonin transporter (SERT) gene *SLC6A4*. The short version (*ss*) which would be predicted to reduce the amount of SERT and hence increase serotonin availability at the synapse has been associated with IBS-D in some[59-62] but not all studies[63, 64]. The *ss* polymorphism reduces SERT function when expressed in transformed lymphoblasts although changes in SERT expression in intestinal mucosa in IBS have been inconsistent, some finding a decrease[65,66] while others did not[67, 68]. Measuring SERT function in platelets is technically easier and several studies have linked impaired platelet SERT to symptoms in IBS-D [66 69]. Animal studies have shown that the ss allele confers increased anxiety and susceptibility to behavioral pathology in response to psychosocial stress [70], however, the previously reported gene-environment interaction between the *s* allele and stressful early life events leading to depression[71] could not be replicated[72]. More recently, it has been shown that an uncommon functional SNP in the untranslated regions (UTR) of the $5HT_3$ receptor subtype E gene (*HTR3E*) which alters the response to micro-RNA-510 is linked to IBS-D with an overall OR of 5.4 (95% confidence interval (CI) 1.9-15.3). [73]

An alternative approach has been to study SNPs in candidate genes identified from gene expression in IBS colonic biopsies. Studies using a microarray have shown a molecular signature which distinguished IBS from healthy controls involving genes controlling the host mucosal immune response to microbial pathogens[74]. The most recent study from this group showed a link between genetic tendency to inflammation and colonic transit which suggested that these genetic polymorphisms do have a functional effect[75]. Overall the evidence from genetic studies is inconclusive because of inadequate power and poor phenotype definition but the recent GWAS studies show that with much larger cohorts progress can be made.

**Stressful Life Events**

Increasing evidence suggests that chronic, sustained stressors experienced in childhood or adulthood are associated with the onset of, and symptom flares, in IBS.[76] Early adverse life events (EALs) have been found to increase the risk of developing IBS.[77, 78] More than 40% of patients referred to gastroenterologists for functional gastrointestinal disorders, including IBS, are reported to have been physically and/or sexually abused.[79, 80] Based on animal and human studies, EALs may increase the susceptibility to IBS by increasing visceral sensitivity, intestinal permeability, colonic motility, and stress responsiveness.[81] Military deployment has been shown to be associated with multi-symptom reporting, including symptoms of IBS.[82, 83]

**Gastrointestinal Motor Disturbances**

IBS has long been considered a disorder of disturbed gastrointestinal motility, but uniform motility patterns in IBS have been hard to define. Even though exaggerated motility induces diarrhea, decreased motility induces constipation, and intestinal "spasms" may cause abdominal pain, it has been difficult to relate specific motility findings to the key symptoms of IBS, especially abdominal pain.[84] No specific colonic motility pattern for IBS has been defined, but an increased frequency of high-amplitude propagating contractions (HAPC) and colonic propulsive activity have been found in non-constipated IBS patients,[85-87] with an association between the occurrence of HAPCs and pain episodes.[85, 88] Somewhat more consistent has been the finding that IBS patients seem to have an exaggerated and prolonged postprandial colonic motor response compared with healthy volunteers,[85, 89] and a recent large IBS study showed an abnormal rectal tone response in IBS patients compared with healthy controls and this was unrelated to bowel habit, but associated with the presence of rectal hypersensitivity.[90] Colorectal compliance has also been evaluated in several studies where the general theme seems to be a tendency towards reduced compliance, but with no consistent association with the predominant bowel subtype.[90] Motility disturbances in the GI tract have also been

demonstrated indirectly in transit studies, with rather uniform findings with accelerated GI transit in IBS with diarrhea and delayed transit in constipation,[91, 92] with an association between the bowel habit and colonic transit demonstrated using both scintigraphy[93] and radiopaque markers,[94] with approximately 20-30% of patients with FBDs displaying abnormal colonic transit. Abnormal motor function has been demonstrated in other parts of the GI tract, suggesting the presence of a generalized GI motor abnormality in some IBS patients[84] (the reader is referred to the section on bloating and distention for a discussion of other important mechanisms such as abnormal intestinal gas transit).

**Visceral Hypersensitivity and Abnormal Peripheral and Central Processing of Sensations**

Enhanced visceral perception, also referred to as visceral hypersensitivity, has been demonstrated in IBS and can be due to a greater sensitivity of visceral afferent pathways and/or a central amplification of visceral afferent input.[95] Factors including *hyperalgesia* (increased pain ratings or lowered pain thresholds to noxious stimuli) and *hypervigilance* (increased attention or bothersomeness to a noxious stimulus) contribute to increased visceral perception in IBS. [96-98]

Visceral perception in IBS has been quantified predominantly by pain and discomfort thresholds or sensory ratings in response to rectal or colonic distension, usually administered by a barostat (computerized distension device). Visceral perception in IBS can be influenced by gender,[99] bowel habit,[100] and cognitive and emotional factors.[98, 101] The presence of visceral hypersensitivity or hyperalgesia has been found in 8 to 60% of patients.[90, 102]

Peripheral mechanisms, such as transient gut inflammation, may enhance visceral sensitivity. Release of inflammatory mediators results in peripheral sensitization due to the increased firing of primary sensory afferent nerves.[103] Animal models have shown that acute inflammation alters the neurochemical coding and innervation of the myenteric plexus and submucosal nerves,[104] changes which have been associated with enhanced sensitivity to

stimulation.[105] Recent studies have shown increased numbers of TRPV1 positive neurons in rectal biopsies[106] and increased staining of the pan-neuronal marker PGP9.5 and brain derived neurotrophic factor (BDNF) in enteric nerves in IBS patients[107] and these measures correlated with severity of pain.

The importance of central sensitization in enhanced visceral perception in IBS is demonstrated by a recent meta-analysis of neuroimaging studies conducted in IBS patients with visceral distension. IBS was associated with greater engagement of brain regions involved in emotional arousal and endogenous pain modulation and less in areas associated with processing visceral afferent information.[108] Neuroimaging studies in IBS support the role of the CNS in the cognitive, affective and motivational dimensions of the perceptual (including pain) experience. More detailed information is in the Central Disorders of GI Pain chapter.

In addition to abnormalities in visceral perception, there are recent studies that demonstrate evidence of somatic hyperalgesia.[109] These findings help to explain the relatively frequent coexistence of IBS and functional somatic pain syndromes.[110]

**Autonomic Function and Hypothalamic-pituitary Adrenal (HPA) Axis Function**

An imbalance in the autonomic nervous system (ANS) with increased sympathetic and/or decreased vagal tone, which is also seen in chronic stress states, has been found in subsets of IBS patients compared with healthy subjects.[111] Altered ANS tone has been reported in IBS patients at rest[112] and during visceral stimulation, including a meal,[113] rectosigmoid distension,[114] sigmoidoscopy,[115] and during mental stress.[116] Factors that affect ANS tone, particularly increased sympathetic tone and/or decreased vagal tone, include male gender,[114] IBS bowel habit subtype,[117] more severe disease and a history of anxiety and depression.[118]

The corticotrophin releasing factor (CRF)-HPA axis system provides an integrated neurobiologic response to physiologic and psychological stress along with the ANS and

immune system. Activation of central and peripheral CRF signaling pathways has been implicated in the alterations in GI motility, permeability, and stress-induced visceral hyperalgesia in IBS.[119] Studies show evidence of HPA axis dysregulation in IBS, although results are varied.[81] More studies have demonstrated increased basal levels of cortisol as well as an enhanced response to somatic and visceral pain stimuli, psychological stress or hormone challenge in IBS patients compared with healthy controls. However, there are a few studies that have found normal or blunted responses in IBS.

Taken together, studies support dysregulation of the ANS and HPA axis systems in IBS. These findings give further credence to the clinical observations of stress-sensitive symptoms in IBS and provide evidence that stress plays a pathophysiologic role in IBS, via central and peripheral mechanisms.

**Post-Infectious IBS**

Postinfectious IBS (PI-IBS) is IBS developing in someone previously free from IBS symptoms, immediately after an episode of infectious gastroenteritis characterised by an acute illness with $\geq 2$ of the following clinical features: fever, vomiting, diarrhea and a positive stool culture [120]. The proportion of patients developing IBS following intestinal infections varies widely from 3.7%-36% and appears to be dependent on the severity of the initial illness. The highest figures were reported from the Walkerton outbreak, when the municipal water supply was simultaneously contaminated by both *Campylobacter jejuni* and *Escherichia coli O147*. Meta-analyses indicate that bacterial gastroenteritis increases the risk of developing IBS at 12 months post infection 6.4 fold (95% CI 2.6-15.4), declining to 3.9 fold (3.0-5.0) at 24-36 months [54]. Prognostic studies suggest that more than half last longer than 5 years.[121] These and other studies show that gastroenteritis is one of the strongest known risk factors for developing IBS.[122]

<u>Impact of type of infection</u>

The type of infection influences the severity of mucosal damage with invasive organisms and those producing cytotoxins such as *Campylobacter jejuni*, *Salmonella enteritidis* and *Shigella flexneri* being most commonly implicated in PI-IBS.[123] [124] Viral gastroenteritis, though much more common that bacterial gastroenteritis, produces less tissue damage and immune activation is restricted to lymphocyte infiltration with no overt ulceration[125]. Viral gastroenteritis appears to be associated with a lower risk of developing PI-IBS compared with bacterial infections[126]. Postviral IBS is usually[127] but not always[128] transient. PI-IBS has also been reported after giardiasis with an OR of 4.0 (3.5-4.5).[129] These patients had lower somatic comorbidity than expected in IBS[130] supporting the idea that psychological factors may be less important in PI-IBS than in unselected IBS as other have reported.[131] PI-IBS has also been reported after an acute infection with the nematode worm Trichinella britovi.[132]

Typical symptoms after PI-IBS

Six months after gastroenteritis around 25% of patients report looser, more frequent stools, but only around 10% also report abdominal pain diagnostic of IBS [123]. Typical associated symptoms include urgency, bloating, excess mucus and loose frequent stools. A survey of 840 cases of *C. jejuni* enteritis reported 103 cases who developed PI-IBS using the Rome I criteria, 63% of whom were classified as diarrhoea predominant[120].

The strongest risk factors relate to the type and severity of infection. Thus, prolonged initial illness[123], weight loss[133], rectal bleeding[133], and the production of cytotoxin[134] give relative risks (RR) of 11.5, 1.8, 1.7, and 12.8 respectively. Other risk factors include the nature of the host response assessed using rectal mucosal lymphocyte and enterochromaffin (EC) cell counts [120]. Adverse host factors include female gender, younger age and smoking[135]

**Immune Dysfunction**

Several studies have analyzed various aspects of gut, as well as of systemic immune function in IBS, and the results differ between studies. However, the majority of studies have demonstrated at least some abnormalities in line with low-grade inflammation and/or abnormal immune function. [136] Increased innate immune function has been found in subpopulations of IBS patients, and the main focus has been on mast cells and monocytes.[136] Increased numbers of mast cells in the gut mucosa of IBS patients have been demonstrated in the majority of studies[137-139] but there are also studies with no difference[140] or even lower number of mast cells[141] in IBS patients compared with controls. However, of potentially greater interest than the actual number of cells are what they produce, and higher levels of mast cell mediators, such as tryptase, trypsin and histamine have been documented in biopsy supernatants from IBS patients,[138, 142, 143] and mediators of colonic mast cells in patients with IBS, but not in healthy individuals, excite visceral neurons.[142] Mast cells may be distributed throughout the mucosa and submucosa, however colonic mast cell infiltration and mediator release in close proximity to mucosal innervation (within 5 microns) may contribute to abdominal pain perception in IBS patients, possibly.[142] Regarding monocytes and macrophages, the majority of studies have assessed these indirectly by measuring levels of cytokines primarily produced by these cells in blood or mucosa with conflicting results.[140, 144, 145] The implication that an activated adaptive immune response is involved in the pathogenesis of IBS is supported by reports of increased number of T cells in various compartments of the intestinal mucosa.[139, 146] Moreover, IBS patients seem to have more activated T-cells in blood samples, but not altered function or frequency of regulatory T cells [147] Also, B cells in the blood of IBS patients seem to have an increased activation level compared with control subjects.[148]

**Serotonin**

As previously mentioned, changes in SERT expression in intestinal mucosa in IBS have been inconsistent[65 66 68]. Several studies have linked impaired SERT function in platelets to IBS

physiology and IBS-D symptoms[69] [66]. The key mediator is likely to be the local release of serotonin which has been hard to assess. Measuring serotonin in platelet-depleted plasma after a test meal has suggested increased release in PI-IBS and IBS-D[149] [150] and a decrease in IBS-C [149, 151]. The levels correlate with sigmoid motility both fasting and postprandially[152], but the technique is difficult since platelets contain 1000 times the concentration of 5-HT as plasma, so any minor activation can confound results. The benefits of $5HT_3$ receptor antagonists and $5HT_4$ agonists are the best evidence that deranged 5-HT metabolism underlies the symptoms.

**Abnormal Intestinal Permeability**

By using oral probe excretion assays, abnormal intestinal permeability has been demonstrated in IBS patients, primarily, but not solely, in PI-IBS[153, 154] Biopsies have shown evidence of abnormal intestinal integrity and disruption in tight junctions in IBS patients relative to controls, although it appears largely unrelated to IBS subtype.[138, 155] Several factors may be responsible for the impaired intestinal barrier function seen in IBS patients, including food constituents such as gluten, immune abnormalities, and also psychological factors (e.g., stress).[155-158]

**Gut Microbiota**

The GI tract microbiota may have an important role in the onset and maintenance of IBS, particularly postinfectious IBS.[159] Several studies have already described the microbiota composition in IBS patients and although differences from controls have been described, these are inconsistent and so far no specific species have consistently been associated with IBS.[160] A finding that has been seen in several studies is a gut microbial composition enriched with *Firmicutes* together with a reduced abundance of *Bacteroidetes* in IBS patients compared to healthy individuals.[161, 162] Moreover, another frequent finding is reduced fecal microbial diversity in IBS patients compared to controls or at least in a subset of IBS patients.[163] To date,

a specific "IBS microbiota" has not yet been defined. The relevance of small intestinal bacterial overgrowth (SIBO) in IBS remains to be proven, as initial reports using the lactulose hydrogen breath test suggesting an important role for SIBO in IBS,[164] have been hard to replicate.[165, 166] Further, by using the gold standard for diagnosing SIBO, i.e. culture of jejunal aspirate, and commonly used cut-off levels for small intestinal bacterial counts for diagnosing SIBO, no evidence for SIBO in IBS have been detected,[165] even though a mild increase of small intestinal bacteria has been noted in patients with IBS in two studies.[165, 167] However, the relevance for IBS symptomatology is still debated and not proven.

**Role of Diet**

One community survey suggested minor differences in diet between IBS patients and healthy controls, with IBS patients eating slightly more fat and less carbohydrate [168]. A larger study found a tendency for higher intake of fruit to be associated with more severe symptoms in IBS-D [169]. In one large study systematic exclusion diets were shown to benefit 36% of 200 IBS patients studied, and importantly, of those who responded, 37% remained well on the diet a mean of 15 months later [170]. The commonest foods implicated in causing symptoms were onions (35%) followed by milk (32%) and wheat (30%). Similar foods were identified in a survey of Swedish IBS patients which also reported that beans, fruit and fatty foods aggravated symptoms in >20% [171]. Patients often believe they are "allergic" to some foods and epidemiological studies do suggest a link between respiratory allergy and IBS,[172] #830}[173] but the largest study of 91,237 asthmatics in the UK reported the lowest risk with an OR of only 1.2 (1.0-1.5)[174]. Objective testing of reported food allergy by double blind challenge[175] only confirms this in around 10%[176]. Atopic individuals with IBS who self-refer because of perceived food allergy are more likely to have increased serum IgE and increased mucosa IgE positive cells. However, their numbers did not correlate with IBS symptoms[175].

Initial interest in the role of IgG and particularly the subtype of IgG4 antibodies, which can activate mast cells, was stimulated by one uncontrolled report [177] and one randomised trial[178] from secondary care that antibody-directed diets could improve IBS symptoms. However, the commonest antibodies were to wheat and milk, and thus the trial was essentially one of wheat and dairy exclusion, which is known to be effective, at least in some IBS patients probably because of exclusion of FODMAPs (see below). More recently a large community based survey has shown that the incidence of IgG food antibodies is no different in IBS from controls when controlled for food intake[179].

**Role of Gluten**

Gluten is the part of wheat protein which gives dough its elasticity and traps gas to make bread rise, giving it its light texture. Public demand has led to the development over the last century of flour with higher gluten content. While true celiac disease is uncommon with an incidence of < 1% in those of Northern European descent, many patients with IBS claim benefit on a gluten-free diet (GFD), despite not meeting standard criteria for celiac diagnosis. An early study of an open label GFD in IBS-D reported that patients with IBS-D had a higher than normal incidence of HLADQ2/8 positivity (39%), and that those that were positive were more likely to respond to the GFD, 60% versus just 12% who were HLDQ2/8 negative[180].

Such patients, who do not meet strict criteria for celiac disease but in whom wheat-induced symptoms have been confirmed using a double blind wheat challenge have been reclassified as having non-celiac wheat sensitivity (NCWS). Studies of these patients suggests that there are at least 2 subgroups within NCWS, one with features suggestive of occult celiac disease (anaemia, duodenal lymphocytosis) and one with allergies to multiple foods and duodenal and colonic eosinophilia[181]. These conditions must be distinguished from the very rare wheat dependent exercise-induced anaphylaxis characterised by urticarial and

anaphylactic collapse,[182, 183] which has been linked to the presence of IgE to a range of specific gliadin subtypes.[184]

Gliadin is known to be somewhat resistant to peptic digestion and in animal studies has been shown to be toxic to enterocytes, releasing zonulin and increasing permeability possibly *via* binding to the chemokine receptor CXCR3[185]. A recent placebo-controlled trial in IBS patients showed that a GFD decreased stool frequency and small bowel permeability, an effect again more obvious in HLADQ2/8 positive patients[157]. The apparent benefit of GFD may be due to the low FODMAP content since wheat accounts for around two-thirds of dietary fructans and oligofructose in both the United Kingdom[186] and the US[187].

**Mechanism of FODMAP-induced Symptoms**

Anecdotal clinical experience had long suggested that some patients respond to restricting poorly absorbed carbohydrates but it was not until a rigorous chemical approach [188] identified the key components, which were then given the acronym FODMAPs[189] (see text box). Such substances escape absorption in the small intestine where the small osmotically active ones induce water secretion and accelerate transit delivering large boluses of water and rapidly fermentable substrate to colonic bacteria, which respond by producing gas and short chain fatty acids. It is believed that the ensuing distension stimulates colonic contractions, and in a hypersensitive individual, abdominal pain and frequent defecation.

**Psychological Features**

Psychological disturbance is associated with IBS, especially in patients who seek medical care,[190] and psychosocial factors affect outcome.[191] Regardless of care-seeking status, IBS is associated with more psychiatric distress, sleep disturbance, “affective vulnerability” and “over-adjustment to the environment”.[192] Moreover, in a recently published 12-year prospective study, support for a bidirectional interaction between the gut and the brain in

patients with IBS was suggested, as anxiety and depression at baseline could predict the development of IBS at follow-up, but the presence of IBS at baseline could also predict more severe anxiety and depression at follow-up.[193] For more detailed information, please see the chapter on Psychosocial factors.

**Other Factors**

Bile acids entering the colon stimulate motility and secretion and may therefore be of relevance in IBS patients, especially for bowel habits of patients. In a systematic review bile acid malabsorption was found to be a common finding in IBS-D patients and in patients with functional diarrhea.[45] Recently, increased bile acid synthesis was demonstrated in patients with IBS-D, but not in IBS-C,[158] and an association between the excretion of unconjugated bile acids and the stool characteristics has been seen in IBS, and these effects were independent of colonic transit.[194] Moreover, by using the $^{75}$SeHCAT test, another recent study in a mixed group of IBS patients found an abnormal test (SeHCAT retention <10% on day 7) in 18% of IBS patients, and abnormal tests were predominantly seen in non-constipated IBS and associated with more frequent stools and accelerated colonic transit time.[195]

**Treatment**

***General aspects***

The type and severity of symptoms (digestive and non-digestive) and the nature of associated psychosocial issues determine treatment. In addition to allaying fear of serious disease, the physician should assess the impact of IBS symptoms on patient's quality of life and level of daily functioning, taking into account the patient's personality, recent life stress, anxiety and depression. A patient's reaction to their IBS symptoms may be more important than the symptoms themselves, and psychological factors may alter symptom perception and lead to multiple consultations, unjustified and hazardous investigations, and even unneeded surgery [196] The cornerstone for any effective therapy is a strong physician-patient relationship, which can improve IBS symptoms [197] and reduce health care utilization[198].

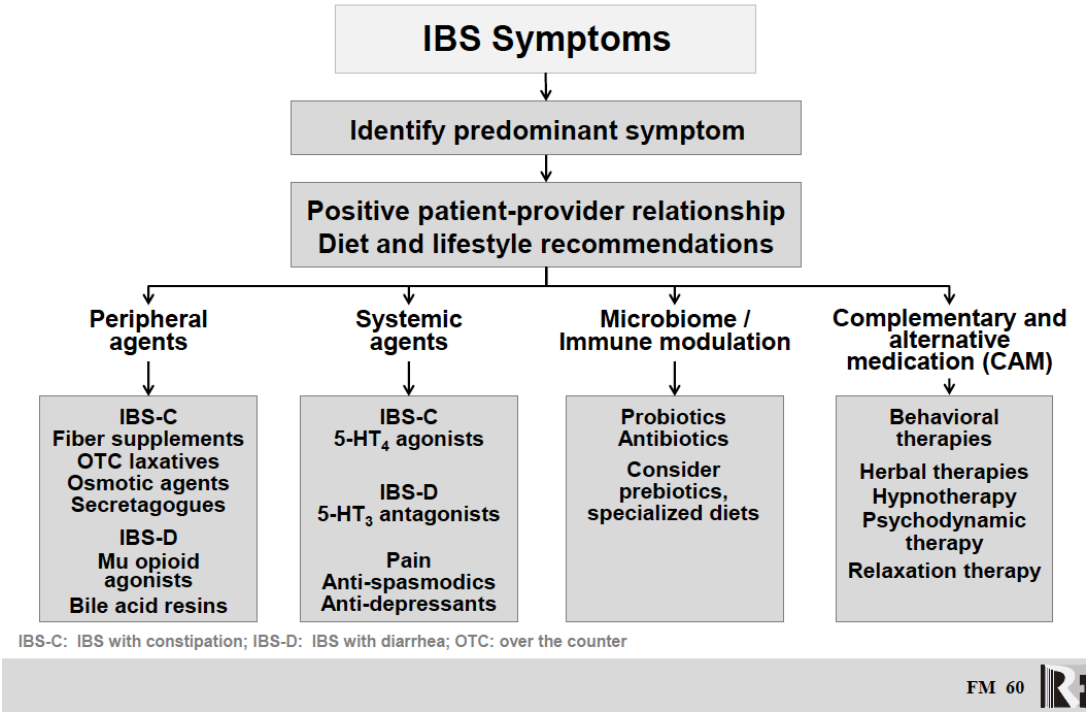


**Figure 5. Treatment of IBS**

***Dietary and Lifestyle Modification***

While the benefits of exercise to general well-being as well as co-morbid conditions commonly encountered in IBS patients including psychological distress and fibromyalgia [199] has been well established only recently has moderate to strenuous exercise been shown to

improve IBS symptoms [200]. Therefore, it seems logical for providers to incorporate exercise into the treatment of most IBS patients[199, 200].

Dietary recommendations in IBS have moved far beyond just fiber supplementation and avoidance of common "culprit" foods such as fatty/greasy foods or those that contain lactose[201]. While such recommendations can still be of benefit to selected individuals, it is clear that they are not a panacea for most IBS patients.

Dietary fiber supplementation remains a cornerstone of IBS management although its optimal use in clinical practice can be more nuanced than is often appreciated[202Ford, 2014 #454]. A recent systematic review and meta-analysis identified 12 trials comparing fiber with control and found a only marginal difference in the proportion of IBS patients with persistent symptoms after any type of fiber vs. the control intervention (52% vs. 57%, RR 0.87; 95% CI 0.76 to 1.00, NNT = 11)[135] When only the 7 higher quality studies were analyzed, there was no treatment benefit for fiber vs. control (RR of persistent symptoms = 0.90, 95% CI = 0.75 to 1.08). Subgroup analysis suggested that benefits for IBS symptoms were confined to soluble (psyllium/ispaghula husk) as opposed to insoluble (bran) fiber. These findings were more recently confirmed by a comparative effectiveness trial which assessed the benefits of psyllium, bran or rice flour placebo in IBS patients[203]. Thus, when fiber is recommended for IBS, soluble supplements such as psyllium or ispaghula are best supported by the evidence. Fiber should be started at a modest dose and slowly increased over the course of several weeks to a target of 20-30 grams of total dietary and supplemental fiber per day. Certain forms of fiber and particularly bran, which contain large amount of non-absorbed, highly fermentable fructans, can exacerbate problems with abdominal distension, flatulence, constipation and diarrhea in IBS patients[204].

Other dietary interventions, such as gluten-free and low fermentable oligo-, di-, monosaccharides and polyols (FODMAP) diets, have become increasingly popular as primary or

adjunctive treatment strategies for IBS.[135] Recent data from clinical trials suggests that a gluten free diet can lead to significant symptom improvement in a subset of IBS sufferers[205]. In a randomized controlled 4-week trial involving 45 patients with IBS-D without celiac disease, a gluten-free diet reduced bowel frequency and decreased small bowel permeability as measured by the lactulose:mannitol ratio. IBS-D patients who were HLA-DQ2/8-positive were more likely to be responders than those who did not have the gene associated with celiac disease [157]. Further evidence supporting a gluten-free diet in IBS patients is found in a double-blind, randomized, placebo-controlled rechallenge trial. In this study reintroduction of gluten in a blinded manner in IBS patients who had response to a gluten-free diet was associated with an increase of symptoms in 68% of IBS patients compared with 40% of those IBS patients who remained on a gluten free diet. Individual symptoms such as bloating, abdominal pain, and tiredness were more likely to increase in patients receiving gluten than those who remained on a gluten-free diet[205]. Adding a gluten-free diet to IBS patients already on a low FODMAP diet does not offer additional benefit[206].

Whether the clinical benefits observed are the consequence of gluten [157], other wheat proteins[181], highly fermentable short chain carbohydrates [206], or the nocebo effect [204] remain to be elucidated. It is clear that non-celiac wheat intolerance is not a single condition but rather, represents the symptom experience arising from one or more pathophysiological pathways. If one chooses to recommend a gluten-free diet to patients with IBS symptoms, it is critical to appropriately screen for celiac disease before instituting a gluten-free diet.

There is accumulating evidence from retrospective and prospective controlled trials that dietary FODMAP restriction is associated with reduced fermentation and significant symptom improvement in a subset of IBS sufferers [207] [208, 209]. It appears that restriction of both fructose and fructans is necessary to achieve the full clinical benefits of this dietary intervention [210]. 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 Austrialian diet (22.8 vs. 44.9; range 0-100, $p<0.001$). Patients of all IBS subtypes had greater satisfaction with stool consistency while on the low-FODMAP diet, but IBS-D (n=10) was the only subtype with improvement in altered stool frequency [209].

Response to FODMAP restriction is usually assessed after 4-6 weeks. Responders then engage in a structured reintroduction of FODMAP-containing foods which allows the individual to tailor his/her diet. The complexity of the low FODMAP diet and the need for a structured food reintroduction phase emphasizes the critical role of a properly trained dietician in the team caring for IBS patients. Other groups have assessed empiric food elimination diets [211] as well as the potential role of food additives (e.g., histamine and salicylates) in the pathogenesis of IBS symptoms [212].

***Peripherally Acting Agents***

**Laxatives**

Though commonly recommended to patients with IBS-C because of their wide availability, low costs and perceived safety, there are few clinical trials in patients with IBS-C. A randomized, placebo controlled trial conducted in adults with IBS-C confirmed the benefits of PEG (13.8-41.4 grams/day for 4 weeks) for stool frequency, stool consistency, and straining but not for abdominal symptoms such as abdominal pain or bloating [213]. Overall, PEG was well tolerated in these studies. The most commonly reported adverse events were abdominal pain and diarrhea, both of which occurred in less than 5% of patients. A second randomized, controlled trial in adolescents reported similar results[214.]

**Prosecretory Agents (Secretagogues)**

Current prosecretory drugs exert their effects *via* chloride channels located on the apical surface of enterocytes. Further details can be found in Chapter 5. Lubiprostone is a luminally-acting prostone which selectively activates type 2 chloride channels (ClC-2).[215,216] Active secretion of chloride ions leads to secondary passive paracellular movement of sodium and water. The resultant luminal distension stimulates gastrointestinal (GI) tract motility with attendant effects on intestinal and colonic transit).[215] Lubiprostone may also stimulate smooth muscle contraction through prostaglandin E1 receptors, suggesting a direct effect on GI motility[217]. Currently lubiprostone has been approved for the treatment of adult women with IBS-C (8 µg twice daily) in a number of continents and countries. In a large, placebo-controlled, randomized study involved over 1,100 IBS-C patients, lubiprostone (8 ug twice daily) resulted in significantly higher overall response compared with placebo (17.9% vs. 10.1%, P=0.001) over 12 weeks of treatment[218]. A subsequent extension study followed IBS-C patients taking lubiprostone for up to 52 weeks. The most common adverse effects were nausea (8% v. 4% placebo) and diarrhea (6% v. 4% placebo)[219]. Lubiprostone should be dosed with food to reduce the incidence of nausea.

Linaclotide is a 14 amino acid peptide that acts on the guanylate cyclase C (GC-C) receptor located on the luminal surface of intestinal epithelial cells. GC-C receptor activation leads to the production of intracellular cGMP and subsequent activation of CFTR with resultant chloride secretion; the increase in extracellular (basolateral) cGMP increases the threshold for colonic nociception and is believed to thereby reduce sensation of pain[215]. Linaclotide is approved in the US, Canada, Mexico, Switzerland and the EU for adults with IBS-C at a dose of 290 mcg daily. In 2 large phase III trials linaclotide was found to be more effective than placebo at improving bowel and abdominal symptoms in IBS-C patients [220-222]. A 6 month, double-blind, placebo-controlled phase III trial utilized a combined end point which required improvement of ≥ 30% from baseline in average daily worst abdominal pain score as well as an increase of ≥ 1 complete spontaneous bowel movement (CSBM) from baseline for ≥ 6/12

weeks. Linaclotide resulted in a response rate of 33.7% vs. 13.9 % for placebo-treated patients (P < 0.0001, number needed to treat (NNT) = 5.1, 95 % CI: 3.9, 7.1). Diarrhea was the most commonly reported adverse event with linaclotide (19.7% vs 2.5% placebo). Other than diarrhea, the incidence of adverse events was similar between treatment groups. Linaclotide should be taken on an empty stomach at least 30 minutes prior to the first meal of the day.

A second GC-C agonist, plecanatide, is currently in development. In a dose ranging trial plecanatide improved abdominal pain and bowel habits in IBS-C at 3.0 and 9.0 mg dosing (41.9% and 40%, respectively, compared to 24.7% for placebo for the FDA Endpoint for IBS-C). [223]

**Bile Acid Modulation**

Modulation of bile acids in the GI tract has recently gained interest as a treatment of functional bowel disorders. Bile acids such as chenodeoxycholic acid (CDCA) elicit dose dependent increases in stool frequency[224, 225] and a double-blind, placebo-controlled study found that sodium CDCA accelerated colonic transit and improved bowel function in 36 females with IBS-C [226]. More than 40% of patients treated with CDCA experienced lower abdominal cramping/pain (P = .01). Further studies are required and CDCA has yet to receive approval.

A recent systematic review found bile acid malabsorption to be common in IBS-D type patients [45]. In this study 10% of patients had severe bile acid malabsorption as determined by SeHCAT while 32% had moderate bile acid malabsorption. The more severe the bile acid malabsorption the more likely patients were to respond to a bile acid sequestrant. In a pharmacodynamics study of 24 IBS-D patients, colesevelam, a bile acid sequestrant, delayed emptying of the ascending colon compared with placebo, and was associated with greater ease of stool passage (p = 0.048) and somewhat firmer stool consistency (p = 0.12) [227]. Several bile acid binders are widely available including cholestyramine, colesevelam and colestipol.

**Mu-opioid Agonists**

Loperamide is a synthetic peripheral mu-opioid receptor agonist which decreases colonic transit, and increases water and ion absorption. In a small placebo-controlled study of 25 IBS-D patients (21 completed), Lavo and colleagues found loperamide improved stool consistency, pain, urgency and subjective overall response [228]. In another study [229], loperamide improved stool consistency, reduced bowel frequency, and reduced intensity of pain though it increased nightly abdominal pain. Finally, in a small group of IBS-M patients (n=21), Hovdenak [230] found improvement in stool frequency and consistency as well as fewer painful days during loperamide treatment. Clinically, loperamide is used to reduce rectal urgency and frequency. Constipation may develop and therefore dose titration may be necessary.

***Systemically Acting Agents***

**Antispasmodics**

Antispasmodics are either anticholinergic or direct smooth muscle relaxants that reduce contractions within the gastrointestinal tract. A meta-analysis involving 12 different anti-spasmodics found a RR of persistent symptoms after treatment of 0.68 (CI 95% 0.57-0.81) with a NNT to prevent symptoms of 5 (CI 4-9)[202]. Likewise, enteric-coated peppermint oil also has anti-spasmodic properties and has been extensively studied in IBS. A recent meta-analysis found peppermint oil treatment to be significantly superior to placebo for global improvement of IBS symptoms (RR 2.23; 95% CI 1.78-2.81) and improvement in abdominal pain (RR 2.14; 95% CI 1.64-2.79). The most commonly reported adverse event was heartburn [231].

**Antidepressants**

Tricyclic antidepressant agents (TCAs) (e.g., amitriptyline, desipramine) are frequently used to treat patients with IBS, particularly those with IBS-D because of the potential for the anti-cholinergic effects of TCAs to cause constipation. In general TCAs appear to be effective in

treating IBS symptoms (RR of remaining symptomatic 0.66 (95% CI 0.56-0.79), NNT of 4 (95% CI 3 to 6)), however, only one clinical trial[232] included only IBS-D patients. In this study, which included 52 patients with IBS-D, after 2 months 10 mg amitriptyline resulted in reduction in the incidence of loose stool and feeling of incomplete defecation as well as complete response (defined as loss of all symptoms) in 68% of patients compared with 28% complete responders with placebo. At this dose of amitriptyline side effects were similar between the groups.

A recent systematic review and meta-analysis summarized the efficacy data for selective serotonin reuptake inhibitors. Seven trials were included which showed a RR of remaining symptomatic of 0.68 (95% CI 0.51-91, NNT = 4 (95% CI 2.5-20).[202] There are few studies which have evaluated selective norepinephrine reuptake inhibitors in IBS. At present, it is difficult to draw any conclusions regarding efficacy based upon the limited available data. Further studies are clearly needed.

The most common adverse events reported with antidepressants were drowsiness and dry mouth, particularly in patients receiving TCAs.

**Prokinetic Agents**

Prucalopride is a selective 5-HT4 receptor agonist that has been found to be effective in the treatment of patients with chronic constipation but, to date, has not been subjected to randomized, placebo controlled trials in IBS-C patents.

**5-$HT_3$ Antagonists**

Antagonism of 5-$HT_3$ receptors, which are found on enteric motor and sensory neurons and in central locations such as the vomiting center, has been shown to reduce visceral pain, colonic transit and small intestinal secretion. Alosetron, a highly selective 5-HT3 antagonist, has been shown to relax the colon, and increase thresholds for visceral sensation in IBS patients and decrease intestinal transit, particularly in women[233]. Alosetron has been shown

to be effective in relieving pain, reducing stool frequency and rectal urgency in women with IBS-D.[202, 215,] Alosetron was initially approved by the FDA at a dose of 1 mg twice daily for the treatment of women with IBS. However, due to safety concerns (ischemic colitis and complications of constipation) it was removed from the market and then subsequently reintroduced under an ongoing risk management plan. Currently, alosetron is approved only in the U.S. for women with severe IBS-D beginning at a lower dose (0.5 mg twice daily). Since its reintroduction, the incidence rates have been 4 and 2 cases per 1000 patients for ischemic colitis and complications of constipation, respectively (i.e., 0.95 and 0.36 cases per 1000 patient-years, respectively)[234]. To date one study has evaluated the effects of the lower dose of alosetron (0.5 mg qd) in women with severe IBS-D. In this study 0.5 mg q.d. of alosetron resulted in significant improvements in symptoms and health-related quality of life, restriction of daily activities and treatment satisfaction over placebo [235]. Recent studies have found ramosetron and ondansetron to be effective in the treatment of IBS-D.[236, 237]

***Microbiome and Immune-modulators***

**Probiotics**

Probiotics may benefit IBS patients through multiple mechanisms including modification of gut bacterial communities, mucosal immune function, mucosal barrier function, function of neuroendocrine cells, and fermentation[238]. Bifidobacterium infantis 35624 led to significant improvements in abdominal pain/discomfort, bloating/distention, and/or bowel movement difficulty compared with placebo ($P<0.05$) in two randomized, placebo-controlled trials conducted in IBS patients[239 240]. A fermented dairy product containing Bifidobacterium lactis DN-173 010 also resulted in reduced symptomatology and significant gastrointestinal transit improvement in patients with IBS-C[241].

In a recent meta-analysis which included 43 clinical trials, the RR of IBS symptoms persisting was 0.79 (95% CI 0.70-0.89). Probiotics were found to offer benefits to global IBS symptoms, pain, bloating and flatulence[242]. Given the data to date, it is reasonable to speculate that some single and multi-strain probiotics will offer clinical benefits to patients with IBS, however, adequately powered, methodologically rigorous, randomized, controlled trials will be needed to clarify the appropriate type, dose and duration.

**Antibiotics**

Several antibiotics have been studied for the treatment of IBS. However, the best studied antibiotic is rifaximin, a non-absorbable antibiotic, which is available in the U.S. and several other countries. In two large clinical trials, 2 weeks of treatment with rifaximin 550 mg three times daily in patients with non-constipated IBS resulted in significantly more patients reporting adequate relief of global IBS symptoms (40.8% vs. 31.2%, P=0.01) and bloating (39.5% vs. 28.7%, P=0.005)[243] during the first 4-weeks of follow-up. Improvement in symptoms persisted for the 10 weeks followup period. A meta-analysis that included five clinical trials found rifaximin to be more efficacious than placebo for global IBS symptom improvement (OR=1.57; 95% CI=1.22, 2.01; therapeutic gain=9.8%; NNT = 10.2), with mild heterogeneity (P=0.25, I(2)=26%)[244]. Adverse events with rifaximin were similar to placebo. Repeat treatment with rifaximin appears to offer similar efficacy to an initial course of therapy.[245]

**Mast Cell Stabilizers**

Disodium cromoglycate reduces the release of mast cell mediators such as histamine, leukotrienes and cytokines such as TNF-alpha. In a study of 120 IBS-D patients (55% had concomitant food intolerance assessed by skin prick test) with a positive reaction to at least one food, an exclusion diet in association with disodium cromoglycate 250 mg q.i.d. for four months provided improvement in symptoms compared with an exclusion diet alone[246].

Ketotifen, another mast cell stabilizer, has been shown to prevent mucosal mast cell stimulation induced by cholecystokinin and increased the threshold pressure for induction of discomfort by rectal balloon distension in 30 IBS patients with visceral hypersensitivity but not in normosensitive IBS patients[141]. In this study, ketotifen significantly decreased abdominal pain and other IBS symptoms and improved quality of life.

**5-Aminosalicylic Acid**

Early small trials suggested possible benefits of mesalamine for IBS[247-249]. More recent studies in post-infectious IBS-D and two larger phase 2 trials failed to show significant efficacy [250, 251].

**Other Potential Treatments**

Medical foods are a new category of treatments defined by the US Food and Drug Administration as "a food…formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Serum-derived bovine immunoglobulin isolate offers a potentially unique treatment option but requires evaluation in rigorous, appropriately powered clinical trials.[252, 253]

Fecal microbial transplantation for IBS has been reported in case reports and small uncontrolled series. Preliminary reports appear promising but the efficacy and safety of FMT requires validation in randomized, controlled trials[254].

***Complementary & Alternative Medicine (CAM)***

Complementary and alternative medicine therapies are growing increasingly popular amongst IBS patients for a number of reasons (cost, ease of use, perceived safety). Survey

studies demonstrated that one-third to one-half of patients with functional GI disorders or IBS use CAM therapies [255, 256].

**Herbal Therapies**

One of the most extensively studied herbal therapies for IBS is "Tong xie yao fang (TXYF)". A systematic review of 12 randomized trials which included over 1000 IBS patients found that TXYF was more effective than control treatments (RR of 1.35, 95% CI 1.21–1.50, p <0.05)[257]. Unfortunately, most of the studies were of poor quality undermining any conclusions that can be drawn from this analysis.

A recent high quality, randomized, controlled trial found that St John's Wort was less effective than placebo for IBS symptoms providing a vivid reminder that supplements perceived to be "safe" are not necessarily effective[258].

**Acupuncture**

Randomized controlled trials have consistently failed to show benefit of acupuncture compared with sham acupuncture[259]. However, sham acupuncture appears to be more effective than no treatment[260].

**Behavioral Therapies**

The efficacy of psychological/behavioral therapies including cognitive behavioral therapy (CBT) or hypnotherapy is discussed in detail in Chapter 8 but appears to be agnostic to IBS subgroup. A recent systematic review and meta-analysis identified 11 randomized, controlled studies which defined IBS by the Rome criteria (I-III) and found that the majority of studies reported statistically significant improvements for the primary study endpoint with CBT (6 studies) or hypnotherapy (5 studies). These trials tended to enroll all subgroups of IBS patients but did not report treatment outcome based upon IBS subgroup[261].

## C2. FUNCTIONAL CONSTIPATION

## Definition

*Functional constipation (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 prior to diagnosis, and symptoms should be present during the last 3 months.*

* It should be noted that patients with FC, as well as those with IBS-C, have constipation of functional origin and these disorders are considered a continuous spectrum.

---

**KEY POINTS**

***The following points highlight notable changes from Rome III:***

- *"Persistently" has been deleted (chronicity is part of the general FBDs definition).*
- *It is specified that abdominal pain and/or bloating may be present but are not predominant (i.e., the patient does not meet criteria for IBS).*
- *"Criteria present for the last 3 months and onset at least 6 months prior to diagnosis" has been replaced with "Symptom onset should occur at least 6 months prior to diagnosis and symptoms should be present during the last 3 months".*
- *It is noted that when referring to patients with constipation of functional origin both FC and IBS-C should be considered parts of a spectrum.*

---

**Epidemiology**

Few studies have evaluated the incidence of chronic constipation of functional origin in adults. Most epidemiologic studies have focused on patients with chronic constipation who may or may not meet strict criteria for FC. One study reported onset rates of 40/1,000 person years when patients were resurveyed a median of 14.7 months after the initial survey.[262] Using modified Rome II criteria a community study identified a 12-year cumulative incidence of constipation of 17.4%.[263]

Accurately measuring the prevalence of constipation is problematic because researchers have used a variety of definitions and questionnaires, while patients' self-reporting of symptoms is subjective, influenced by societal customs, and correlates poorly with stool frequency. In adults the mean prevalence rate of chronic constipation is approximately 14%, with rates that range from 1.9 to 40.1%.[264] A large postal survey study of Australian women (41,724) identified self-reported prevalence rates of constipation of 14.1% in young women (ages 18-23), 26.6% in middle-aged women (ages 45-50), and 27% in older women (ages 70-75).[265] The prevalence rate of post-infectious FC was 127 / 100,000 patient years during an eight-year period; this was seven times higher in women compared with men (480 versus 67 / 100,000 patient years).[126] Self-report rates of constipation are generally higher compared with use of Rome criteria. Risk factors for FC include female gender, reduced caloric intake, and increasing age.[266, 267]

The natural history of FC is unclear. One study found that 89% of adults were still symptomatic when surveyed 12-20 months after the initial diagnosis.[262] However, larger population studies reported that symptoms of FC resolved in 77.8% of patients (n = 1365) over a 12-year follow-up period,[15] and that only 3% of patients (n = 2835) had persistent symptoms over a 20-year follow-up period, although an additional 21% had intermittent symptoms of constipation.[268]

***KEY POINTS***

- *Evaluation of symptoms should ideally be done when off of laxatives and medications and supplements known to cause constipation.*

**Diagnosis of FC**

**C2. Functional Constipation**

***Diagnostic criteria****

1. Must include *two or more* of the following:
    a. Straining during at least ¼ (25%) of defecations;
    b. Lumpy or hard stools (Bristol Stool Form Scale 1-2) at least ¼ (25%) of defecations;
    c. Sensation of incomplete evacuation at least ¼ (25%) of defecations;
    d. Sensation of anorectal obstruction/blockage at least ¼ (25%) of defecations;
    e. Manual maneuvers to facilitate at least ¼ (25%) of defecations (e.g., digital evacuation, support of the pelvic floor);
    f. Fewer than three SBM per week.
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

** Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis*

Constipation can be established by both subjective and measurable variables: infrequent bowel movements, hard stools, excessive straining, feelings of incomplete evacuation, daily stool weight <35 g/day, prolonged colonic transit, or evidence of outlet obstruction. None of these individual variables alone is ideal to define constipation, and the combination of

symptoms and quantifiable measures – when needed – seems to be the most useful approach. Rome IV FC diagnostic criteria has maintained the 25% (1/4) rule for all six features because it is easy to remember and useful in clinical practice; however, figures have been revised based on surveys of the U.S. population to identify a symptom as abnormal only if it occurs more often than the 90$^{th}$ percentile for the population (see spefic figures for each FC symptom in the appendix of this chapter). When these criteria are used in countries where the frequencies of these symptoms are known to differ from Western Europe and North America, different frequency thresholds may be substituted based on the 90$^{th}$ percentile for that population. Colonic transit time can be estimated by evaluating stool form using the Bristol Stool Form Scale – stool forms 1 & 2 are associated with slower transit, while stool forms 6 & 7 are associated with more rapid transit.[19]

A survey of US adults that evaluated patient perspectives of chronic constipation showed 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%).[269] Thus, the diagnosis of FC needs to be established according to the diagnostic criteria but also in conjunction with the patient's opinion. This evaluation should be performed, if possible, while the patient is not taking laxatives.

In contrast to the Rome III classification, the last AGA technical review did not use the term "functional constipation" because a subset of patients with symptom criteria for FC have slow colonic transit.[270] Importantly, the AGA and Rome III criteria both emphasize the need to identify defecatory disorders.[202] It is the opinion of this committee that all cases with no evidence of structural or metabolic abnormalities to explain the symptoms should be considered under the umbrella of FC (mainly for epidemiological studies, where it is not easy to differentiate among different types of chronic constipation). We acknowledge that a

diagnosis of slow transit constipation or defecatory disorders requires diagnostic tests (see below), which may alter treatment strategies.

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. Chronic constipation can be divided into three broad categories: normal-transit constipation, slow-transit constipation, and defecatory or rectal evacuation disorders (Figure 6).

***Diagnosis of FC***

The diagnosis of FC should be made uing five consecutive steps: 1. Clinical history; 2. Physical examination; 3. Minimal laboratory tests; 4; Colonoscopy or other tests (in specific cases where available); 5. Specific tests to evaluate constipation pathophysiology (when needed and if available).

**1. Clinical History**

Main symptoms: ("Clinical diagnostic criteria")

It is important to determine what the patient means when reporting constipation. A detailed history should include the duration of symptoms, frequency of bowel movements, and associated symptoms such as abdominal pain, bloating or distention should be obtained. The history should also include an assessment of stool consistency, stool size, and degree of straining during defecation. The presence of warning symptoms or signs, such as unintentional weight loss, rectal bleeding, change in stool caliber, severe abdominal pain, and a family history of colon cancer should be elicited. A long duration of symptoms that have been refractory to conservative measures is suggestive of a functional colorectal disorder. By contrast, the new onset of constipation may indicate a structural disease.[271]

Clinical trials have used complete spontaneous bowel movements (CSBM) as an endpoint; however, its utility in the diagnosis of FC in clinical practice is unclear.

Absence of alarm symptoms and family risk

Specific descriptors of alarm features include: unintentional weight loss (> 10% in 3 months); blood in the stools not caused (confirmed) by hemorrhoids or anal fissures; fever; and a family history of CRC (or familial polyposis syndromes).

It is important to distinguish dyssynergic defecation (DD) from other subtypes of constipation because DD has a distinct pathophysiological mechanism and responds to specific treatments. However, the diagnosis currently depends on tests which carry some costs and risks, and which may not be widely available. However, DD can be suspected by questionnaire and physical examination.[33, 34]

**2. Physical Examination**

The general physical examination should exclude major central nervous system disorders, especially spinal lesions. The abdomen should be examined for distention, hard stoolin a palpable colon, or an inflammatory or neoplastic mass. The rectal examination is paramount in evaluating a patient with constipation. Painful perianal conditions and rectal mucosal disease should be excluded, and defecatory function should be evaluated. The perineum should be observed both at rest and after the patient strains as if to have a bowel movement. A digital rectal examination should be performed to evaluate the patient for the presence of a fecal impaction, anal stricture, and rectal mass. It is also crucial to evaluate contraction of the puborectalis and/or anal sphincter during digital examination.

**3. Laboratory Tests**

TSH (thyroid stimulating hormone) and serum calcium should be performed when clinically indicated (e.g., suspected hypothyroidism or diseases inducing hypercalcaemia).

**4. Indications for colonoscopy:**

All patients aged ≥ 50 years (≥ 45 in African-Americans (or Blacks)) should have a screening colonoscopy. The presence of alarm symptoms (unintentional weight loss, hematochezia, anemia) or family history of colorectal cancer (according to individual risk: patient age, type of symptoms, specific familial background, etc.) should prompt earlier intervention.

**5. Specific Tests to Evaluate Constipation Pathophysiology**

The chronicity, severity and nature of symptoms may indicate the need for specialized tests. For example, straining with soft stools and manual maneuvers to assist defecation suggest anorectal dysfunction, which can be identified by anorectal manometry.[270, 272] An estimate of transit time can be obtained from the Bristol Stool Form Scale.[19]

Testing for slow colonic transit and/or DD is neither required nor justified in all patients. Moreover, most physicians do not have the ability to perform these evaluations. Patients who do not respond to reasonable trials of empiric therapy (e.g. fiber and/or osmotic laxatives; see below) should undergo diagnostic evaluation to identify physiological subgroups.

*Measurement of Colon Transit*

Using radiopaque markers, measurement of whole gut transit time (primarily colon transit) is inexpensive, simple and safe.[273, 274] A radioisotope technique involves less radiation than x-ray studies and may provide more information,[275] although it is available in very few centers.

*Additional Studies*

To confirm DD, anorectal manometry and balloon expulsion testing may help.[276] Defecography may detect anatomical etiologies, such as intussusception and rectocele with stool retention. Defecography also identifies the failure to decrease the anorectal angle with straining and abnormal pelvic floor descent, features that are typical of dyssynergic

defecation.[277] Electromyography and pudendal nerve latency testing are adjunctive techniques (See *Anorectal Disorders*).

**Pathophysiology**

**Etiology**

Recent meta-analyses show chronic constipation major risk factors to be female gender, increasing age and lower socioeconomic status [264] [278]. The strongest risk was female gender with an OD of 2.22; 95 % CI: 1.87 – 2.62. Before puberty the incidence of constipation shows no consistent gender effect [279] [280].

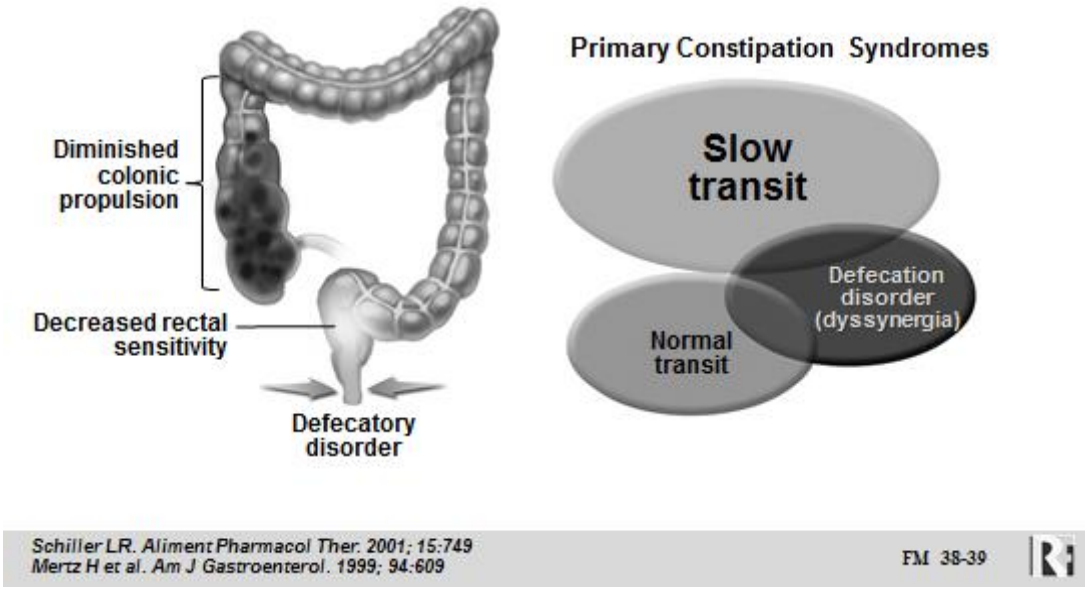


**Figure 6. Pathophysiology of FC**

***Genetics***

Several studies suggest constipation shows familial clustering[281, 282] Moving from familial clustering to finding a genetic association is rendered more difficult when the phenotype is poorly characterized or there are multiple mechanisms leading to the same phenotype as there are with constipation. These mechanisms include diet, microbiota,

absorption, secretion and motility as well as behavior and beliefs. The association of Hirschsprung's disease, a cause of constipation not of functional origin, with mutations in the *RET* gene is well recognised [283]. Studies of familial slow transit constipation found no mutations in the *RET* proto-oncogene [284]or neurturin (*NRTN*) [285]. Several SNP associations with FC have been reported including the bile acid receptor TGR5 SNP rs11554825,[286] thought to be important in mediating bile acid related peristalsis. More recently the loss of function NaV1.5 channelopathy, found in 2% of IBS patients, has been associated with constipation[287]. A recent meta-analysis suggests that the L-variant of the 5HTTLPR is associated with IBS-C in Asian populations but not in Caucasian subjects[288]. Due to the similarities of FC with IBS-C, it is plausible to hypothesize similar findingns in non-IBS constipatied patients.

***Onset of Constipation and Life Style Factors***

Constipation often begins in childhood but unfortunately there are few studies in children (see pediatric section). Risk factors appear similar to adults possibly because diet and behavioral habits are established early in life. Studies of younger children (3-5 years) from Hong Kong show constipation in around one-third with lower fiber intake being a risk factor[289] and fluid intake > 800 ml and a preference for fruit and vegetables reducing the risk[290]. Studies in Korea[291] and the USA reported constipation in around 1 in 10 schoolchildren[292]. Children's parents felt that poor diet and refraining from using the school toilet was important[280].

The marked diurnal variation in colonic motility with peak activity on awakening and after large meals [293] means that these are optimal times for defecation. Many constipated patients report postponing defecation because of lack of time or opportunity to respond to these physiological stimuli. There is good evidence that education and changes in behavior can often substantially improve constipation[294]. Furthermore, deliberately avoiding defecation in return for a reward can induce all the symptoms of constipation including hard infrequent stools [295].

Diet is also a key risk factor. The Nurses Health Study of 62,036 women aged 36-61 years showed that "high fiber" intake reduced the risk of constipation[267]. More recent studies support this association[296]. Regular exercise is associated with a significantly reduced risk of constipation[267, 297]. Such surveys are of course not controlled studies and are subject to confounding by other factors such as comorbidities and drugs. However, one small RCT of 12 weeks exercise program showed a significant benefit[298].

An influential nursing home survey found that decreased fluid intake was a risk factor for developing constipation following admission[299]. However, decreased fluid intake is associated with many other factors including general frailty and inadequate food consumption. Several small RCTs have shown that while severe water restriction (2500 ml/day reduced to <500 ml/day) reduces stool weight by around 30%[300] there is no benefit in increasing fluid intake in those who are normally hydrated[301].

**Motility / Transit**

Transit studies in constipated subjects, using different techniques, have shown that overall transit of colonic contents is slow compared with healthy controls,[93, 302] but it should be noted that a substantial proportion of patients with severe constipation demonstrate normal colonic transit.[303] In constipated patients with slow transit, affected colonic regions differ substantially, with approximately a normal rate of movement of contents in the ascending colon and hepatic flexure but delayed transit in the transverse and left colon in some patients, whereas other patients show slow transit in both the right and left sides of the colon.[304] In some patients with severe constipation there are more widespread transit alterations in the GI tract. Moreover, by using pancolonic spatiotemporal mapping it was recently possible to show regional deficiencies in, and disorganization of, colonic propagating pressure waves in severe constipation.[305]

**Visceral Sensitivity**

Visceral perception is increased in a subset of IBS patients but is less well studied in patients with FC. Sensory thresholds and compliance to rectal barostat testing were evaluated in FC patients (Rome III criteria; n=11), and IBS-C patients (n=23) and compared with healthy volunteers (n=23).[5] No group differences in perceptual thresholds for first sensation and stool sensation were identified, but there was a significant difference in pain threshold. IBS-C patients had a lower pain threshold (i.e., increased rectal sensitivity) compared with patients with FC and controls. Although there was no significant difference between the latter two groups, three (27%) of the constipation patients were considered "hyposensitive" based on the 2.5 and 97.5 percentiles for controls. The remainder were within the normosensitive range. Taken together with other studies, compared with some IBS patients, FC patients do not have increased rectal sensitivity and some may be hyposensitive. Limited data suggests that rectal sensitivity does not differ between normal transit and slow transit constipation.[303]

**Enteric Nervous System / Interstitial Cells of Cajal**

Disorders of smooth muscle, the ENS, its neurotransmitters and receptors, or the CNS-ENS axis may cause severe constipation. In a proportion of patients with severe slow transit constipation, clinical signs of autonomic dysfunction can be seen.[306] Some patients have morphological changes within the myenteric and submucosal plexus,[307] and there are also histologic studies showing abnormal numbers of myenteric plexus neurons involved in excitatory or inhibitory control of colonic motility, with decreased amounts of the excitatory transmitter substance P[308] and increased amounts of the inhibitory transmitters vasoactive intestinal polypeptide (VIP) or nitric oxide (NO).[309] Other studies have demonstrated reduced numbers of colonic enteroglucagon- and serotonin-containing endocrine cells in constipated patients.[310]

Interstitial cells of Cajal (ICCs) are the intestinal pacemaker cells and play an important role in regulating gastrointestinal motility.[311] Confocal images of ICCs in patients with slow-

transit constipation show not only reduced numbers but also abnormal morphology of ICCs, with irregular surface markings and a decreased number of dendrites. In patients with slow-transit constipation, the number of ICCs has been shown to be decreased in the sigmoid colon[312] or the entire colon.[313, 314] Pathologic examination of colectomy specimens from patients with severe intractable constipation revealed decreased numbers of ICCs and myenteric ganglion cells throughout the colon.[315]

**Serotonin**

Higher combined fasting and postprandial platelet-depleted plasma serotonin concentrations were identified in FC patients compared with IBS-C patients and, to a lesser extent, healthy controls.[5] Overall, serotonin concentrations correlated positively with rectal sensory thresholds and inversely with stool frequency. These findings suggest that, in addition to playing a role in colonic transit, serotonin's influence on rectal sensitivity may play a role in decreasing perception and evacuation of rectal contents in patients with FC.

**Dyssynergia**

Dyssynergic defecation is a defecatory disorder that causes constipation symptoms due to a failure to effectively empty the rectum because of an inability to coordinate abdominal, rectoanal, and pelvic floor muscles. Some patients inappropriately contract the external anal sphincter and puborectalis muscles when bearing down, while in other patients, these muscles incompletely relax during defecation. In addition, there may be inadequate rectal propulsive forces needed to expel stool.[270] The cause of dyssynergia is not well understood but is thought to be due to maladaptive learning of sphincter contraction that could develop from avoiding pain and discomfort associated with the passage of large, hard stools. In one study, 50-60% of patients were found to have impaired rectal sensation[316]. In addition to dyssynergia, chronic constipation can be caused by other defecatory disorders including rectocele, descending perineum syndrome, intussusception and rectal prolapse.

Further details can be found in the Anorectal Disorders chapter.

**Psychological 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.[317] Patients with severe constipation and normal intestinal transit often have increased psychological distress,[317] and may have misperceptions about their bowel frequencies.[318] Moreover, abnormal illness behavior and locus of control is more common in patients with chronic constipation compared with non-patients.[319]

Constipation behavior can be learned in early life. A child may learn to contract the sphincters to retain stool to avoid defecation.[317] Some data also suggest that faulty toilet training produces anorectal disorders such as pelvic floor dyssynergia and encopresis.[320] Deliberate suppression of defecation leads to reduced stool frequency and weight and increased transit time.[295] Suppression of defecation is common, and in a quarter of subjects the urge may not return for several hours.[321]

**Treatment**

***General Measures***

Rendering a confident diagnosis, while providing both education and reassurance are the cornerstones of management, particularly in a patient who fears that failure to evacuate is harmful or represents an underlying life-threatening disease such as colon cancer. Other measures such as acting on the call to defecate and in some cases scheduling visits to the toilet are often suggested, although no data from controlled trials exists to support these recommendations. Defecation may be facilitated by elevating the feet with a foot stool or using a toilet that is lower to the ground. There is indirect evidence that increased fluids and physical exercise is beneficial in patients with constipation[322.] It is important to carefully

scrutinize a patient's supplements (i.e., vitamins, herbs) as well as over-the-counter and prescription medications for potential causes of constipation.

When empiric medical treatment fails after an appropriate clinical trial (i.e., 4-8 weeks), detailed physiological testing should be performed to identify the most appropriate treatment. For example, a patient with dyssynergic defecation by anorectal manometry and balloon expulsion test would be most appropriately treated with anorectal biofeedback.

***Peripherally Acting Agents***

**Fiber Supplementation and Bulk Laxatives**

Most treatment guidelines recommend a trial with dietary fiber or a fiber supplement if dietary and lifestyle modifications are not effective, before considering laxative therapies or physiological testing[202, 270] Differences in solubility and fermentation are linked to different proposed mechanisms by which fiber influences GI function and in turn, symptoms[323]. Insoluble, non-fermentable fiber accelerates transit by increasing stool biomass leading to direct stimulation of secretion and motility. Soluble, more fermentable forms of fiber are thought to accelerate transit though their water holding properties and as a consequence of the osmotic effects of fermentation by-products, most notably, short chain fatty acids. Secondary effects of fiber and its fermentation on the fecal microbiome, mucosal immune activation, and /or permeability could also modulate GI function and sensation[323].

Many patients with mild constipation improve with fiber. Total fiber intake of 20-30 grams per day is recommended. For fermentable fiber, dose-dependent bloating, distention, and flatulence can affect tolerability and compliance. It is important to instruct patients to "start low and go slow", up-titrating the dosage of fiber in increments over the course of weeks. There is limited data to suggest that constipated patients with severely delayed colon transit and/or obstructed defection are less likely to improve with fiber.[202, 270]

**Osmotic Laxatives**

Osmotic laxatives create an intraluminal osmotic gradient which encourages net water and electrolyte secretion resulting in reduced stool viscosity and increased fecal biomass with secondary effects on peristalsis. These physiological effects underlie improvements in constipation[270]. Given the efficacy, safety, and relatively low cost, many authors consider osmotic laxatives as the next most logical choice after fiber for patients with CC[202, 270].

*Unabsorbed mono/disaccharides and sugar alcohols*: The osmotic properties of lactulose, lactitol, mannitol and sorbitol benefit patients with constipation[324 325]. These agents, which are not absorbed by the human small intestine, are rapidly fermented by colon bacteria to short-chain fatty acids[326] The best evidence supporting the use of these agents exists for lactulose, which at doses of 15-30 ml once to twice a day can improve symptoms of mild to moderate constipation.[201] Side effects include dose-dependent abdominal cramping and bloating[325]. Lactulose appears to be a safe choice for pregnant women with constipation.

*Saline Laxatives*: Incompletely absorbed salts such as magnesium citrate, magnesium sulphate, and sodium & disodium phosphate cause the flux of water into the small intestine and colon. Though there is little evidence from randomized, controlled trials, these agents are commonly used by patients and generally safe when used in recommended doses. Excessive use may lead to electrolyte imbalances, particularly in the elderly or among patients with renal impairment[327].

Polyethylene glycol (PEG) creates an osmotic gradient which draws fluid and electrolytes into the intestinal lumen. Evidence from high quality, randomized, controlled trials of up to 6 months demonstrate its efficacy in patients with chronic constipation [328] Low doses are superior to placebo [329] and lactulose [330] in adults and children[331]. A recent trial found that PEG was non-inferior to the prokinetic agent, prucalopride [332]. PEG is generally well tolerated; the adverse events most commonly reported include distention and diarrhea.

**Stimulant Laxatives**

Stimulant laxatives include diphenylmethane derivatives, such as bisacodyl, sodium picosulfate and conjugated anthraquinone derivatives, including cascara sagrada, aloin and senna. They decrease water absorption and stimulate intestinal motility and prostaglandin release[333-335]. Sodium picosulphate (bisacodyl conjugated with sulphate) and the anthraquinone derivatives are cleaved by bacteria in the colon, where the active agent may stimulate enteric nerves. High quality, 4 week, randomized, controlled trials have demonstrated clinical benefits for stool frequency and other constipation associated symptoms with bisacodyl and sodium picosulphate in patients with chronic constipation[336, 337]. No large randomized, controlled trials have evaluated anthraquinones for the treatment of chronic constipation. At recommended doses, these drugs appear to be generally safe although no long term safety data is available. The most common side effects are abdominal pain (24.7% v. 2.5% placebo) and diarrhea (53.4% v. 1.7% placebo)[336, 337]. Melanosis coli, a brown mucosal discoloration, is a harmless, reversible consequence of prolonged anthraquinone intake that results from apoptosis of colonic epithelial cells and deposition of pigment in macrophages [338-340].

**Prosecretory Agents (Secretagogues)**

In 4 week, randomized controlled trials of patients with chronic constipation, lubiprostone (24 mcg twice daily with food) proved superior to placebo for increasing stool frequency, improving stool consistency, reducing straining and overall constipation symptoms[341-343]. The most common adverse events reported in the clinical trials were nausea (31% of patients) and diarrhea.

In 12 week, randomized, controlled trials, linaclotide 145 mcg once daily was more effective than placebo at increasing stool frequency, improving stool consistency, straining and overall constipation symptoms in patients with chronic constipation[344]. The most common treatment associated side effect was diarrhea (16% v. 5% placebo)[344].

Results from a dose ranging trial with plecanitide suggest that 3 mg once daily may also be effective for functional constipation.[345]

**Bile Acid Modulation**

Elobixibat is a nonabsorbed, small molecule that inhibits ileal bile acid transporters, thereby increasing delivery of bile acids to the proximal colon which exerts effects on colonic secretion and motility. Elobixibat has been found to improve stool frequency and other constipation associated symptoms in patients with chronic constipation. The most commonly reported adverse events have been dose-dependent abdominal pain and diarrhea[346-348]. Elobixibat is undergoing evaluation in chronic constipation and IBS-C patients in North America in phase III trials.

**Enemas and Transanal Irrigation**

Enema volume stimulates the rectum to defecate and may be effective in patients with constipation due to disordered defecation or megacolon [349]. Phosphate enemas also have an intracolonic osmotic effect. Whether phosphate enemas offer any benefit over tap water enemas has not been evaluated. The long-term safety of chronic enema use is unknown.

Transanal irrigation is a technique in which scheduled water irrigation sessions are utilized to evacuate stool from the rectum and distal colon. This technique has demonstrated benefits in patients with medically refractory constipation, most commonly in the setting of spinal cord injury or neurogenic bowel disorders (i.e., multiple sclerosis or Parkinson's disease)[350, 351].

**Surgery**

Subtotal colectomy with ileorectal anastomosis is a therapeutic option in the rare patient with severe, medically refractory, colonic inertia. However, these cases should not be considered as FC. Moreover, normal gastric emptying, small bowel motility and anorectal function should be established prior to surgery. Approximately 50% to 90% of these patients

note symptom improvement, although complications are common, including small bowel obstruction (approximately 1/3 of patients), diarrhea, incontinence, and recurrence of constipation. Although stool frequency often improves, other symptoms including bloating and abdominal pain may not [352] [353]. Therefore, abdominal colectomy with ileorectal anastomosis should only be performed in patients with normal gastric and small bowel motility when all non-surgical treatments have been exhausted.

***Systemically Acting Agents***

**Prokinetic Agents**

5-$HT_4$ receptor agonists stimulate peristalsis [354] and accelerate gastrointestinal transit [355, 356]. Tegaserod, a highly selective, partial 5-$HT_4$ receptor agonist, was found to be superior to placebo at improving stool frequency and other constipation associated symptoms [357, 358]. Tegaserod was withdrawn from the USA 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. Randomized, controlled trials have reported that prucalopride (1-4 mg daily) improves chronic constipation symptoms including stool frequency, stool consistency, and straining. The most common adverse events of headaches (25-30% v. 12-17% placebo), nausea (12-24% v. 8-14% placebo), and diarrhea (11-19% v. 3-5% placebo) tended to occur within 24 hours of initiating treatment and were often transient [359, 360].

The prostaglandin $E_1$ analog, misoprostol (1200 µg/day), was effective in a 3-week study, but its long-term efficacy remains unproven. It is contraindicated in pregnancy. [361]

***Complementary and Alternative Medicine (CAM)***

CAM therapies are being increasingly utilized by patients with chronic constipation. Dried plums (prunes) contain fiber and non-absorbable carbohydrates including sorbitol and

fructans. In an 8-week single-blind, randomized study, prunes (50 grams or roughly 6 prunes twice daily) improved stool frequency and consistency when compared with psyllium ($p < 0.05$) [362]. Hemp seed extract, a Chinese herbal medicine evaluated in patients with FC for 8 weeks (7.5 g twice daily), significantly improved stool frequency as well as relief of constipation severity and straining when compared with placebo. No serious adverse events were reported [363].

Probiotics might be of benefit to patients with FC, however the quality of the available evidence is marginal and the results reported have been conflicting. A systematic review that included the results of five RCTs concluded that probiotics may increase stool frequency and improve stool consistency in patients with chronic constipation - organisms studied included *B. lactis* DN-173 010, *Lactobacillus casei* Shirota and *E. coli* Nissle 1917 [364].

## C3. FUNCTIONAL DIARRHEA

**Definition**

*Functional diarrhea (FDr) is a functional bowel disorder 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 prior to diagnosis and symptoms should be present during the last 3 months.*

---

***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *The term "mushy" has been deleted; it was redundant.*

- *It is specified that abdominal pain and/or bloating may be present but are not predominant symptoms (i.e., patients do not meet criteria for IBS).*

**Epidemiology**

The incidence and prevalence of FDr has not been well investigated, in part because it is frequently not distinguished from IBS with diarrhea. 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.[126]

Reported prevalence rates for FDr range from 1.5% to 17%. Using Rome II criteria, prevalence rates for out-patients in Iran were 2%, compared with 3.4% for healthy volunteers in Mexico City, and 1.54% in Chinese adults,[365-367] Using the validated Bowel Disease Questionnaire and excluding patients who met criteria for IBS, one survey study (performed at 2 time points, 12 years apart), identified prevalence rates of 5.6% and 5.7%,[15] while another survey study reported a prevalence rate 17%.[368] Using Rome III criteria a cross-sectional household survey of 18,180 adults conducted in Tehran province identified a prevalence rate of 11.1%,[369] while a survey study of 4,275 adults in Taiwan identified a prevalence rate of 2.2%.[370]

The natural history of FDr has not been well characterized. One study reported that 94% of patients with chronic diarrhea remained symptomatic after 12-20 months of follow-up.[262] In contrast, a 12-year follow-up study reported that only 29% of patients remained symptomatic.[15]

**C3. Functional Diarrhea**

***Diagnostic criteria****

Loose or watery stools, without predominant abdominal pain or bothersome bloating, occurring in at least 25% of stools.

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *75% of stools being loose has been changed to > 25%.*

**Diagnosis of FDr**

The diagnosis of FDr should be made based on three key aspects: 1. Clinical history; 2. Physical examination; 3. Diagnostic tests.

**1. Clinical History**

Main symptoms ("Clinical diagnostic criteria")

Diarrhea occurs with many gastrointestinal disorders, and is a common reason for consulting a physician. Diarrhea should be defined by stool form, not frequency, as stool consistency correlates well with colon transit.[19] The evaluation should start with a careful history. Erratic bowel habits with episodes of constipation, in the presence of abdominal pain and/or bloating, is highly suggestive of IBS. A stool diary incorporating the Bristol Stool Form Score helps verify stool consistency and excludes pseudodiarrhea.[371] A dietary history should be taken to exclude lactose and fructose intolerance, and ingestion of excess amounts of fiber or poorly absorbed carbohydrates. Post-prandial diarrhea can occur in both FDr and IBS patients; however, other disorders (e.g.: celiac disease, Crohn's disease, rapid colonic response

to feeding, food allergies, food sensitivities, carbohydrate maldigestion, SIBO) may cause similar symptoms and may warrant evaluation. [47]

Alarm features, such as unintentional weight loss, diarrhea awakening the patient, tenesmus (painful urge to defecate), recent antibiotic use, hematochezia (in the absence of bleeding hemorrhoids or anal fissures), high-volume diarrhea (>250 ml/day), > 6-10 bowel movements per day,[1, 372] evidence of malnutrition, or a family history of colorectal neoplasia, celiac disease, or inflammatory bowel diseases should prompt further investigation.

**2. Physical Examination**

The physical examination of a patient with FDr should be normal. The clinician should look for signs of anemia, clubbing and abdominal tenderness. An abdominal mass suggests Crohn's disease in the young and cancer in the elderly. A careful anorectal examination should be performed to assess anal sphincter tone (especially important in patients with incontinence) and if the patient has a history of hematochezia (to assess for the presence of hemorrhoids or a fissure).

**3. Diagnostic Tests**

A CBC and CRP should be checked in all patients with chronic diarrhea. A thyroid profile can be performed if there is clinical suspicion of hyperthyroidism. Serology for celiac disease should be checked in those that fail empiric therapy (and consider EGD with duodenal biopsies if antibody tests are positive or if clinical suspicion is high), stool analysis (bacteria, parasites and ova) in endemic areas, and fecal calprotectin if clinical suspicion for an inflammatory process is high. Giardiasis and tropical sprue should be excluded especially when there is a history of acute onset.

For patients with persistent symptoms, stool specimens can be analyzed for fecal elastase-1 and fat, not only because these may identify maldigestive process with moderate

sensitivity, but also because a negative test is useful to exclude the need for further consideration of maldigestive disorders.[48] Colonoscopy can be considered in those who have failed empiric therapy, in those with alarm symptoms, and in all patients over age 50 for screening purposes (>age 45 in African-Americans). If performed, random biopsies should be obtained from both the right and left colon to rule out microscopic colitis. Bile acid malabsorption (BAM) is significantly under-recognized and may account for approximately 30% of diarrhea previously diagnosed as IBS-D or FDr.[373] Unfortunately, confirmatory testing is not available in most institutions and requires stool collection and the gammagraphic measurement of whole body retention of 75Se-homocholic acid taurine ($^{75}$SeHCAT).

**Usefulness of Diagnostic Tests**

In patients with chronic watery diarrhea the functional origin should be considered with caution, since in many cases there is an organic cause that justifies diarrhea. This is highlighted by the results of a study involving 62 patients with chronic watery diarrhea who were carefully investigated using a series of tests; afterwards BAM was considered to be the cause of diarrhea in 28 (45%) patients, sugar malabsorption in 10 (16%), gluten-sensitive enteropathy in 10 (16%), and both BAM and sugar malabsorption in 2 patients; 12 (19%) patients remained without a specific diagnosis and were considered to have functional diarrhea. Diarrhea stopped in the 50 patients after specific treatment was initiated, and all were without relapse after 12-months of follow-up. [47]

Given the high prevalence of BAM in patents with watery diarrhea an empiric therapeutic trial with a BA sequestrant (e.g., cholestyramine or colesevelam) is reasonable. Scintigraphic evaluation by the 75SeHCAT test is another option but is not available in many countries. Clues to the diagnosis of BAM are sudden-onset, urgency and nocturnal diarrhea, as well as increased stool weight,[374] but clinical suspicion should not be limited to these cases.

Similarly, microscopic colitis (collagenous colitis and lymphocytic colitis) should be suspected, especially in the presence of watery diarrhea and/or persistent diarrhea that has failed empiric therapy (mainly in women > 50 years of age). There is considerable symptomatic overlap between IBS-D, FDr and microscopic colitis. In a population based study of 131 patients with microscopic colitis, 33% had previously been diagnosed with IBS.[44] Positively identifying microscopic colitis is relevant since anti-inflammatory therapy, e.g. with budesonide[375] is effective.

Carbohydrate (e.g., lactose, fructose, sorbitol) malabsorption is another frequent cause of liquid/watery diarrhea.[47, 376] Breath tests can be used to make the diagnosis, but if not available, then dietary exclusion of the suspected carbohydrate (e.g., 3-4 weeks) is recommended.

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***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *It is emphasized that patients with chronic diarrhea require a thoughtful evaluation before making the diagnosis of FDr.*
- *Indications for colonoscopy (and biopsies) have been added*
- *When diagnostic tests are not available, then an empiric therapeutic intervention is reasonable.*

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**Physiologic Features**

No single pathophysiological abnormality can explain the cause of FDr in every patient. As in other FBDs, diverse mechanisms seem to contribute, including altered gastrointestinal motility, brain-gut disturbances, genetic and environmental factors, prior infections and psychosocial factors, among others.[377] In fact, IBS-D and FDr overlap in 28% of cases when

mutual exclusivity is suspended.[378] However, patients are more likely to be younger, female, anxious and report somatization-type behavior in IBS-D, whereas only loose, mushy or watery stools are more common in FDr. [378]

Genetic susceptibility similar to that found in IBS-D is present in FDr, although data is limited. For example, the tryptophan hydroxylase 1 (TPH1) promoter SNP-347C/A differentially binds EGR-1 and this correlates with IBS bowel habit subtypes; the CC genotype is more prevalent in IBS-D (47%) than in IBS-C (25%) and IBS-M (37%) subtypes.[379] Conversely, genetic variants in CDC42 and NXPH1 are susceptibility factors for IBS subtypes: Rs2349775 (NXPH1) and rs17837965 (CDC42) were associated with IBS-D and IBS-C, respectively, in two independent cohorts.[380]

Gastrointestinal motor disturbances are thought to be the main cause of FDr. However, few studies have specifically addressed the pathophysiology of FDr or even considered it as distinct from IBS. More than 20 years ago it was reported that fasting and postprandial colonic propagating contractions are increased in FDr, whereas nonpropagating contractions are increased in healthy volunteers but minimally in patients with diarrhea.[381] Unlike IBS, no studies of rectal sensation have been performed in FDr, although a pilot study showed normal left colonic tone during fasting and a reduced duration of increased colonic tone postprandially.[382]

Similar to IBS, where approximately 7% of acute infectious gastroenteritis patients later develop IBS, either a bacterial or viral infection can lead to post-infectious FDr.[128, 383] Unlike IBS-D, however, no studies have investigated the role of disrupted tight junctions or mast cell activation in FDr patients.[138]

**Psychological Features**

While anxiety often accompanies IBS, few data apply specifically to FDr. Epidemiologic research identified an association between chronic diarrhea and self-reported stress in the general population. Moreover, acute stress accelerates colonic transit in humans and animals,[384] but the relevance of this finding to chronic stress, and to FDr patients, is uncertain. One study indicated that anxiety tends to precede IBS onset, particularly if diarrhea predominates.[385]

**Treatment**

There are very few studies which have evaluated treatment in patients with FDr. Data from studies in patients with other conditions like IBS-D tend to be extrapolated to the treatment of patients with FDr.

***Diet***

A thorough diet history and diary is critical to help identify potential triggers. Clinicians often employ specialized diets (e.g. elimination diet), or diets designed to treat IBS symptoms (e.g. gluten-free or low FODMAP), although none of these have been tested in FDr patients.[157, 209, 210, 376, 386-391]

***Peripherally Acting Agents***

**Fiber**

Some patients may note improvement in stool consistency using methylcellulose or fiber products, although appropriate studies to guide clinical care have not been performed in the FDr population.

**Opiates**

The synthetic peripheral opioid agonist loperamide reduces intestinal transit thereby increasing intestinal water and ion absorption. Loperamide improves stool frequency and consistency as well as urgency and incontinence in patients with FDr and IBS-D.[228-230] Loperamide may result in some improvement in anal sphincter tone, given the effects of opioids on smooth muscle tone (please see OIBD section for a discussion of physiology).

**Bile Acid Binders**

Cholestyramine improves diarrhea symptoms in patients with bile acid malabsorption but may also be effective in some patients without bile acid malabsorption [225, 392] Colesevelam, improves IBS diarrhea symptoms and may be better tolerated, although it has not been assessed in FDr patients[225] [225].

***Systemically Acting Agents***

**Antidepressants**

Tricyclic antidepressant agents (TCAs) have anticholinergic effects which slow intestinal transit time and therefore may be effective in patients with FDr, although studies have not been conducted.

**5-$HT_3$ Antagonists**

The 5-$HT_3$ antagonist alosetron has been proven to be effective in treating women with IBS-D. [393] Another 5-$HT_3$ antagonist, ondansetron, which is widely used as an antiemetic, was recently shown to improve stool consistency, frequency, and reduce urgency but not abdominal pain in patients with IBS-D.[236] Although theoretically enticing, neither of these agents have been studied in FDr.

***Microbiome and Immune Modulators***

**Probiotics**

Probiotics appear to improve symptoms associated with IBS, including diarrhea[242], though their effects in FDr remain unclear.

**Antibiotics**

A meta-analysis of 5 clinical trials with rifaximin found improvement in global IBS symptoms and bloating, but no significant effect on bowel function.[202] The role of rifaximin, as well as other antibiotics, in FDr remains unclear.

## C4. FUNCTIONAL ABDOMINAL BLOATING/DISTENSION

**Definition**

*Functional abdominal bloating/distension (FAB/D) is characterized by symptoms 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 functional bowel disorders although mild abdominal pain and/or minor bowel movement abnormalities may co-exist.*

*Symptom onset should be at least 6 months prior to diagnosis and the predominant symptom (bloating or distension) should be present during the last 3 months.*

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***KEY POINTS***

***The following points highlight notable changes from Rome III:***

- *"Abdominal fullness, pressure or a sensation of trapped gas" has been included*

---

**Epidemiology**

Bloating is a commonly reported symptom, both in the general community and in patients with other functional gastrointestinal disorders (FGIDs). The incidence of functional bloating has not been evaluated in large prospective studies. The prevalence of bloating is better described. A large (n = 2,510) telephone survey of U.S. adults reported that 15.9% had symptoms of bloating or distension in the month prior to the interview.[394] Women were more likely to report bloating than men (19.2% vs. 10.5%), and were twice as likely to rate their bloating as severe (23.8% vs. 13%). Older individuals (> 60 years of age) were less likely to report symptoms of bloating and distention than younger individuals. Two other large prospective studies of US adults identified similar prevalence rates of bloating (21% and 19%).[395, 396] Using Rome III criteria, the prevalence of functional bloating in the general population of Iran was reported to be 1.5%. This figure is likely much lower than other reported studies as patients with other FBDs were excluded.[369]

Patients with FGIDs are more likely to report co-existing symptoms of bloating. In the IBS population, 66% to 90% of patients report bloating.[397-399] Bloating is typically more common in patients with IBS-C than IBS-D and is more prevalent in women than men.[396, 399-401] In a cross-sectional study of over 16,000 Chinese adults, bloating was more prevalent (21%) in patients with functional constipation than those without constipation symptoms (OR = 8.44; 95% CI 6.9-10.2).[402]

**C3. Functional Abdominal Bloating/Distension**

***Diagnostic criteria****

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

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

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

## Diagnosis of FAB/D

FAB/D should be diagnosed based on three aspects: 1. Clinical history; 2. Physical examination; 3. Minimal/limited diagnostic studies.

### 1. Clinical History

Main symptoms ("Clinical diagnostic criteria")

The evaluation of a patient with abdominal bloating and/or distension should begin with a careful history, which includes the onset of symptoms, the relationship to diet (e.g., wheat, dairy, fructose, fiber, non-absorbable sugars) and bowel habits, and the presence of symptoms suggestive of other functional GI disorders. Alarm features, such as anemia and unintentional weight loss, should be assessed, as these symptoms may be a sign of a malabsorptive process. If present, the clinician may initiate a diagnostic evaluation (see

below). Patients complaining of bloating along with another symptom should be evaluated accordingly.

Sufferers of bloating and/or distension typically report worsening as the day progresses, particularly after meals, but with alleviation of symptoms overnight.[403, 404] In tape measure studies of abdominal girth to assess distension, diurnal worsening of bloating is accompanied by increased girth.[405] Studies performed with abdominal inductance plethysmography, which permits objective ambulatory measurement of abdominal girth throughout the day, have confirmed that abdominal girth increases during the day in most patients with IBS and to a greater extent than in healthy volunteers.[406] However, the symptom of bloating only correlates with increased abdominal girth in constipated patients,[10] suggesting different, constipation-related pathophysiological mechanisms. Thus, functional bloating is typically diagnosed after constipation and sugar maldigestion are excluded. Bloating alone (not bloating with distension) is associated with rectal hypersensitivity, whereas bloating with distension (but not bloating alone) is associated with prolonged colonic transit relative to patients with bloating alone.[407, 408] In addition, reduction in abdominal girth overnight,[11] as well as difficulties with rectal gas expulsion[409] in patients with bloating, suggest there may be a significant contribution of abnormal rectal gas evacuation to symptoms of bloating.

**2. Physical Examination**

Bloating (subjective) and distension (objective) should be differentiated. The term abdominal distension 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.

**3. Diagnostic Tests**

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 be performed to evaluate for possible obstruction. A serum IgA and TTG antibody can be used to evaluate for celiac disease. Small intestinal bacterial overgrowth can be evaluated by culturing the jejunal aspirate or by performing a breath test, preferably with glucose.[409] A CBC should be performed if there are warning signs of anemia. If the clinical suspicion for celiac disease is high, upper endoscopy with duodenal biopsies should be performed.

**Physiologic Features**

Bloating and distension are commonly thought of as synonymous terms. However, accumulating evidence has demonstrated that these processes have different pathophysiologic underpinnings and thus should be considered distinct entities, although they commonly overlap.[408] It is important to note that research in this area has been problematic in part due to linguistic differences. Thus, for the purpose of this monograph, bloating and distention will be defined as noted above.

The pathophysiology of bloating remains incompletely understood for a number of reasons (see Figure 7 below). One, the underlying pathophysiologic process (or processes) is likely different amongst the various FGIDs. Two, the etiopathophysiology of bloating varies from patient to patient, even within the same FGID subcategory. Three, bloating is a complex process and frequently represents a number of different processes, all of which produce the same symptom. Potential causes of functional bloating include visceral hypersensitivity, abnormal intestinal gas transit, impaired evacuation of rectal gas, colonic fermentation of different food products, small intestine bacterial overgrowth, an abnormal abdomino-diaphragmatic reflex, and disorders (both qualitative and quantitative) of the gut microbiota.[267] Contrary to popular opinion, most patients with FGIDs do not have more

intestinal gas than healthy volunteers.[410] However, IBS patients report more bloating and distension than healthy volunteers with similar levels of intestinal gas infusion, and IBS-C patients may retain gas longer than IBS-D patients.[411, 412] These studies highlight the facts that visceral hypersensitivity[407] and impaired intestinal transit and evacuation are responsible for bloating symptoms in some FGID patients.

The pathophysiology of abdominal distension in patients with FGIDs is better understood due to innovations in technology, including abdominal inductance plethysmography, a novel technique that can measure abdominal distention. Elegant studies from several research groups have demonstrated that an abnormal viscero-somatic reflex, involving the diaphragm and the abdominal wall muscles, is responsible for the symptom of distension in many FGID patients. Specifically, stretch and distention of the luminal intestinal tract - from gas, liquids, or solids - leads to an abnormal contraction of the diaphragm (rather than relaxation) along with relaxation (rather than contraction) of the abdominal wall muscles (the rectus and external oblique). This abnormal reflex causes visible abdominal distension, in contrast to healthy volunteers, where diaphragmatic relaxation and contraction of the abdominal wall muscles prevents or minimizes abdominal distension.[413] The precise etiology of this abnormal viscero-somatic reflex is not known; one study of IBS patients identified a relationship with rectal hyposensitivity.[407] Abdominal distension in FGID patients frequently occurs in conjunction with sensations of bloating, although it may occur independently. Other factors play a role in visible abdominal distension, most notably slower intestinal transit,[406] in addition to the factors responsible for bloating symptoms (see above).

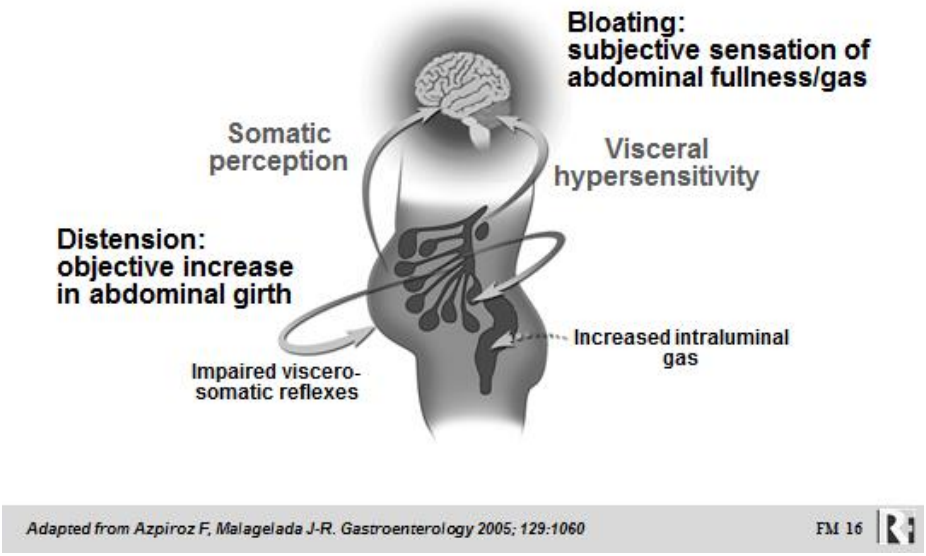


**Figure 7. Pathophysiology of functional abdominal bloating and distension.**

**Psychological Features**

Large questionnaire studies to identify co-morbid psychological disorders in patients with FAB/D are not available.

**Treatment**

Most studies have evaluated abdominal bloating in patients with other FGIDs and therefore may not have been sufficiently powered to detect significant differences.

**Diet**

Foods that are poorly absorbed and highly fermentable are commonly associated with increased gas and bloating. Some patients with IBS and bloating note an improvement in symptoms when placed on a diet low in FODMAPs.[209, 210] Similarly, some IBS patients note an improvement when treated with a gluten free diet. Neither approach has been used specifically in patients with functional bloating.[205, 414]

### *Peripherally Acting Agents*

#### Laxatives

A recent trial in IBS-C patients using polyethylene glycol plus electrolytes for 28 days found no significant reduction in bloating compared with placebo (p=0.06).[213]

#### Prosecretory Agents (Secretagogues)

In 2 phase III studies in IBS-C patients bloating improved with lubiprostone (8 mcg twice daily) compared with placebo[218]. Similarly, linaclotide also improved bloating symptoms in the phase III studies for chronic idiopathic constipation[344] and IBS-C[220, 221]. A recent trial with CC patients who had predominant bloating showed significant reductions in bloating symptoms[415].

#### Gas Reducing Substances

Simethicone, an anti-foaming agent, was reported to improve the frequency and severity of gas, distension and bloating in one small study involving 41 patients with upper gastrointestinal symptoms[416]. α-galactosidase, derived from *Aspergillus niger* mold, acts to break down non-absorbable oligosaccharides before they are metabolized by colonic bacteria. In healthy volunteers fed a meal high in oligosaccharides, α-galactosidase improved symptoms of gas and bloating.[417] In pediatric patients (age range 4-17 years) complaining of gas-related symptoms, α-galactosidase reduced global distress, the number of days with moderate to severe bloating, and the proportion of patients with flatulence compared with placebo [418]

### *Systemically Acting Agents*

#### Antispasmodics

Among the antispasmodics, peppermint oil has been most extensively studied. One study demonstrated that peppermint oil, taken three to four times a day, 15-30 minutes before meals for four weeks, resulted in a significant decrease in abdominal distention compared with placebo[419]. In another study peppermint oil twice daily for 4 weeks decreased bloating and distention[420].

**Antidepressants**

In patients with moderate to severe functional bowel disorders, desipramine in conjunction with cognitive behavioral therapy resulted in an improvement in bloating although the effects of desipramine alone on bloating remain unclear[421]. A small, crossover-trial with citalopram showed an improvement in the number of days without bloating at 3 and 6 weeks[422].

**Prokinetic Agents**

In a study of 28 patients with abdominal bloating, intravenous neostigmine caused immediate clearance of infused jejunal gas compared to placebo[411]. However, in patients with IBS and bloating, pyridostigmine (p.o.) provided only minimal improvement in bloating [423].

***Microbiome and Immune Modulation***

**Probiotics**

A recent meta-analysis of probiotics in IBS found overall improvement in symptoms of bloating. Bloating scores were significantly reduced with probiotics (SMD = −0.15; 95% CI −0.27 to −0.03), with no significant heterogeneity between individual study results ($I^2$=16%, $P$=0.26)[242]. However, the optimal strain, dose, frequency and duration of probiotic use remains unclear.

Significant improvements in objectively measured abdominal girth as well as reduced symptomatology were observed in a randomized, double-blind, controlled, parallel group study comparing a fermented dairy product containing Bifidobacterium lactis DN-173 010 and a control product in IBS-C patients.[241]

In women with IBS, *Bifidobacterium infantis* 35624 at a dose of $1 \times 10^8$ CFU/mL improved bloating symptoms more than placebo[240]. Similarly, in patients with non-constipated functional bowel disorders, *Lactobacillus acidophilus* and *Bifidobacteriumlactis* reported improvement in bloating severity [424]. The combination probiotic VSL#3 has been shown to reduce bloating in children, although the results in adults have been less impressive [425-427].

**Antibiotics**

In a double-blind, randomized, placebo-controlled trial of 124 patients with predominant bloating and excessive flatulence with negative lactulose hydrogen breath tests, rifaximin (400 mg p.o. twice daily for 7 days) improved global symptoms and bloating scores compared with placebo [428]. Rifaximin (400 mg three times daily for 10 days) also reduced bloating severity during a 10-week follow-up period [429]. Finally, 2 phase III trials found that rifaximin, at a dose of 550 mg three times daily for 14 days in patients with non-constipation IBS, provided greater adequate relief of bloating compared with placebo (40% vs. 30%, $p<0.05$)[243].

## C5. UNSPECIFIED FUNCTIONAL BOWEL DISORDERS

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

**C5. Unspecified Functional Bowel Disorder**

***Diagnostic criteria****

Bowel symptoms not attributable to an organic etiology that do not meet criteria for the four previously defined functional bowel disorders

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

## OPIOID-INDUCED BOWEL DISORDERS

Since the Rome III criteria were published significant advances have been made in the area of opioid-induced bowel disorders (OIBD). These disorders are becoming more prevalent with the increasing use of opioids. Although this committee does not consider OIBD a functional gastrointestinal disorder, we recognize that OIBD may overlap with any of the FBDs described above. In addition, further advances in knowledge over the next decade may elucidate shared pathophysiologic or psychologic processes. For these reasons, a brief description of OIBD is provided below (the reader is also referred to the appropriate sections for a discussion on narcotic bowel syndrome (NBS) and cannabis hyperemesis syndrome (CHS)).

**Definition**

Opioid induced bowel disorders (OIBD) refers to a spectrum of disorders, which develop as a result of opioids acting both on the gastrointestinal tract and in the central nervous system. With the exception of nausea and vomiting, which are at least in part centrally mediated, symptoms and signs of OIBD reflect the segment of the GI tract involved. One of the most common OIBDs is opioid-induced constipation, which is defined and described below.

Criteria for OIBD: A symptom complex that develops with opioid use and which reflects the impact of opioids on the GI tract, including hard stools, infrequent stools, incomplete evacuation, bloating, abdominal pain, nausea and vomiting.

**Opioid Induced Constipation**

***Diagnostic criteria***

I.New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy, that must include *two or more* of the following:

a. Straining during at least ¼ (25%) of defecations;
b. Lumpy or hard stools (Bristol Stool Form Scale 1-2) at least ¼ (25%) of defecations;
c. Sensation of incomplete evacuation at least ¼ (25%) of defecations;
d. Sensation of anorectal obstruction/blockage at least ¼ (25%) of defecations;
e. Manual maneuvers to facilitate at least ¼ (25%) of defecations (e.g., digital evacuation, support of the pelvic floor);
f. Fewer than three SBM per week.

II. Loose stools are rarely present without the use of laxatives.

Opioids are increasingly being used to treat cancer- and non-cancer related chronic pain. As opiate use has increased, so has the recognition that these agents have a number of adverse effects on the GI tract. 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. However, given the high prevalence of FGIDs it is important to recognize that not all gastrointestinal symptoms in a patient taking opioids are directly related to opioids. Thus,

functional constipation may overlap with, or exacerbate, opioid-induced constipation (OIC; and *visa versa*). The marked rise in the prevalence of opioid-induced disorders clearly signals a need for a heightened awareness for all health care providers. The following sections provide a brief overview of this issue.

Adverse effects of opioids on the GI tract can be broadly classified into NBS and OIBD. NBS is characterized by an increase in the severity of chronic abdominal pain despite the use of continuous or increasing doses of opioids prescribed for abdominal pain.[430] NBS is mediated, to a large degree, *via* changes in the central nervous system (see Chapter 12).[431-433] OIBD represents a broad spectrum of disorders which can involve any segment of the gastrointestinal tract. OIBD occurs when opioid receptors (e.g., mu, kappa, or delta) in the GI tract or CNS are activated by either exogenous or endogenous opioids leading to a decrease in propulsive activity, an increase in non-propulsive contractions, a decrease in pancreatic, biliary and gastric secretions, and an increase in anal tone. These physiologic changes may lead to abnormalities in esophageal peristalsis, gastric emptying, small intestine and colon transit, and anorectal function. Thus, depending upon the gut segment involved (e.g., esophagus, stomach, small intestine, colon, anorectum), symptoms of OIBD can include reflux, dysphagia, nausea, vomiting, early satiety, bloating, distention and constipation.

The most common OIBD is OIC, which has recently been defined by an expert panel as a change, when initiating opioid therapy, from baseline bowel habits and defecation patterns, that is characterized by any of the following: a) reduced bowel frequency; b) development or worsening of straining; c) a sense of incomplete evacuation; or d) a patients´ perception of distress related to bowel habits.[434] The occasional patient may also develop fecal impaction with overflow incontinence, while others may report symptoms compatible with overlapping OIBD (e.g., reflux, nausea, bloating). The reported prevalence of OIBD ranges from 60- 90% in cancer-related opioid use to 40-60% in non-malignant pain patients.[435, 436] Not surprisingly,

patients with OIC report a significant reduction in quality of life.[437, 438] The treatment of OIC is similar in many ways to the treatment of functional constipation (see functional constipation section above. Laxatives are recommended for both the prophylaxis and management of OIC in patients with cancer by the European Association for Palliative Care.[439] Lubiprostone, a chloride channel activator, was approved for the treatment of OIC in adults with non-cancer pain in 2013. [440]

Additional treatment options for patients with OIC involve the use of opioid receptor antagonists which block opioid actions either centrally or peripherally, thereby minimizing or preventing the negative effects of opioids on intestinal secretion and colonic propulsion. [441] Naloxone and nalbuphine are 2 medications classified as centrally active agents. Since these agents cross the blood-brain barrier they may precipitate opioid withdrawal symptoms.[442, 443] 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.

Agents that specifically block peripheral opioid receptors in the GI tract and not central receptors would be clinically advantageous, since they would not lead to symptoms of withdrawal. Three such peripherally acting μ-opioid receptor antagonists (PAMORA) are currently available. Subcutaneous methylnaltrexone is approved for OIC in patients with chronic non-cancer pain and for patients with advanced illness receiving palliative care who have had an inadequate response to laxative therapy.[444, 445] The European Association for Palliative Care (EAPC) guidelines recommend subcutaneous methylnaltrexone as a second-line treatment option for OIC in patients with chronic cancer pain when traditional laxatives are not effective.[439] Alvimopan, available in the United States, but not in Europe, is a PAMORA indicated only for preventing or shortening the course of postoperative ileus after bowel resection and is therefore available only for hospital use.[446] It is not currently approved for use in OIC in either Europe or the US. Naloxegol, an oral PEGylated derivative of naloxone, was

approved by the FDA for the treatment of OIC in adult patients with non-cancer pain in September 2014 (cite 470).

**Drugs in Development for the Treatment of OIC**

Several additional PAMORA agents with the potential to not compromise pain relief in patients taking opioids are currently in development for OIC.[441] One randomized, controlled trial has demonstrated the efficacy of the 5-$HT_4$ agonist prucalopride (2 mg p.o.) in the treatment of OIC.[440] An oral formulation of methylnaltrexone is under investigation, and the currently available subcutaneous formulation is under consideration for OIC in patients with chronic non-cancer pain. Two other medications currently under development for OIC in patients with chronic non-cancer pain include: Bevenopran, TD-1211, and N-aldemedine (S-297995). Large, prospective, multinational, randomized, placebo-controlled trials are needed to assess the efficacy and safety of these agents.

## Key Questions for Future Research in Functional Bowel Disorders

1. What is the validity of the Rome IV FBDs criteria for both clinical research and patient care?

2. How does the new method of Rome IV subtyping for IBS predict response to treatment?

3. Are FBDs individual disorders or do they represent a spectrum of disease?

4. What is the temporal relationship between food ingestion and bowel movements with abdominal pain in IBS patients, and does it differ between IBS subtypes?

5. What are the relative roles of motility, permeability, immune activation, microbiome, visceral hypersensitivity and brain-gut interactions in FBDs and how do they interact?

6. What is the clinical utility of current biomarkers for FBDs?

7. Can biomarkers be used to identify patients most likely to respond to specific treatments for FBDs?

8. Which new biomarkers will aid in the diagnosis and treatment of FBDs in clinical practice and clinical trials?

9. Can genetic subtyping predict clinical phenotype and response to therapy?

10. What are the predictors (e.g. genetics, psychological, physiological, metabolic) of long-term outcomes in FBDs?

11. What are the roles of diet and lifestyle in FBDs?

12. What are novel treatment targets for abdominal symptoms of FBDs (e.g., abdominal pain and bloating)?

13. What is the relationship of opioid induced constipation (OIC) with FC and can Rome IV criteria for FC be used to accurately define OIC?

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**Appendix**

Functional constipation features according to the frequency thresholds based on the occurrence of these symptoms in the general population. These constipation symptoms are notoriously variable in frequency of occurrence in normal people (derived from the Rome Survey of the Normal Population).

a. Straining during more than 30% of defecations
b. Lumpy or hard stools (Bristol Stool Form Scale 1-2) on more than 30% of defecations
c. Sensation of incomplete evacuation on more than 30% of defecations
d. Sensation of anorectal obstruction/blockage on more than 20% of weeks
e. Manual maneuvers to facilitate more than 10% of defecations
f. Fewer than three SBM per week for more than 20% of weeks