Pathophysiology, Evaluation, and Treatment of Bloating: Hope, Hype, or Hot Air?

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Abstract: Abdominal bloating is commonly reported by men and women of all ages. Bloating occurs in nearly all patients with irritable bowel syndrome, and it also occurs in patients with other functional and organic disorders. Bloating is frequently disturbing to patients and frustrating to clinicians, as effective treatments are limited and are not universally successful. Although the terms bloating and abdominal distention are often used interchangeably, these symptoms likely involve different pathophysiologic processes, both of which are still not completely understood. The goal of this paper is to review the pathophysiology, evaluation, and treatment of bloating and abdominal distention.

Patients from all disciplines of medicine frequently report symptoms of bloating. In a widely cited survey of the US population, 31% of respondents met Rome I criteria for functional bloating.[1] Other studies have shown that over 90% of patients with irritable bowel syndrome (IBS) have symptoms of bloating.[2] Given these high prevalence rates, clinicians might assume that the evaluation and diagnosis of bloating would follow a concise, evidence-based algorithm; that the pathophysiology of bloating and abdominal distention would be completely understood; and that treatment for both symptoms would be standardized. Unfortunately, none of these assumptions is true. The pathophysiology of bloating and abdominal distention is complicated and incompletely understood, although our knowledge of these highly prevalent disorders has expanded over the past decade due to a number of insightful experiments. Although no treatment is universally effective for bloating, several new therapies have become available during the past half-decade, which makes this review on the pathophysiology, evaluation, and treatment of bloating appropriate and topical.

Definitions

Bloating can be defined as a sense of gassiness or a sense of being distended; measurable distention does not have to occur. Rome III diagnostic criteria for functional bloating are listed in Table 1.[3] The term abdominal distention should be reserved for patients who show a visible increase in abdominal girth. Ambulatory monitoring using abdominal inductance plethysmography has shown that abdominal girth increases in healthy volunteers during the course of the day, particularly in the postprandial period, and decreases overnight to values that are comparable to those from the previous morning.[4] Changes in girth are greater in patients with IBS, and these patients are more likely to be symptomatic.[5,6]

Burping and belching, which are other common gastrointestinal (GI) complaints, reflect the expulsion of excess gas from the stomach. These complaints may or may not be related to bloating and abdominal distention. During an office visit, it is important to clarify the patient's symptoms, as belching and burping generally develop due to the swallowing of air (either consciously or subconsciously), rather than the processes described below that contribute to the symptoms of bloating and abdominal distention.

Epidemiology and Natural History

Epidemiologic studies have determined that 15–30% of the general US population experience bloating symptoms.[1,7-9] These surveys were limited by a lack of ethnic diversity, as most subjects (80–99%) were white. However, studies using similarly validated questionnaires in Asian populations reported comparable prevalence rates (15–23%).[10] Population-based studies have not conclusively shown a predisposition for bloating based on sex; however, in IBS studies, the prevalence of bloating ranged from 66% to 90%, and women typically had higher rates of bloating than men.[1,2,7-9,11,12] Constipation-predominant IBS patients tend to have a higher prevalence of bloating than patients with diarrhea-predominant IBS.[8,9]

Regardless of gender or underlying cause, bloating can create significant patient distress. In bloating patients who did not have IBS, over 75% of patients characterized their symptoms as moderate-to-severe, and over half stated that they had reduced their daily activities to some degree due to their bloating symptoms.[7] In IBS patients, bloating has been found to be an independent predictor of IBS severity.[13]

The natural history of bloating is poorly understood. A recent long-term follow-up study of patients with a diagnosis of functional dyspepsia (FD) found only a modest correlation among self-reports of bloating compared over 5 years.[14]

Table 1. Rome III Criteria for Functional Bloating

- Recurrent feeling of bloating or visible distention for at least 3 days per month
- Onset of symptoms at least 6 months prior to diagnosis
- Presence of symptoms for at least 3 months
- Insufficient criteria to establish a diagnosis of irritable bowel syndrome, functional dyspepsia, or any other functional gastrointestinal disorder

Modified from Longstreth GF, et al.[3]

Pathophysiology

The pathophysiology of gas and bloating is complicated. Understanding gut microflora, gas production, intestinal transit, intestinal propulsion of gas, and sensory function within the GI tract are essential for understanding symptom generation. Although not covered in this review, eating disorders and aerophagia may be associated with symptoms of gas and bloating, and these conditions should also be considered in the differential diagnosis (Table 2).[15,16]

Gut Microflora

The term gut microflora (also called gut microbiome) refers to bacteria (and their byproducts) that inhabit the intestinal tract and their effects on both GI tract function and the body as a whole. Approximately 500 different species of bacteria reside within the colon, and nearly all of these species are anaerobes. Colonic microflora varies from individual to individual and reflects multiple factors, including diet, antibiotic use, and method of feeding as an infant. The number of bacteria in the GI tract is thought to exceed 10^{14}, which is more than the total number of cells in the human body.[17] Because less than 10% of these bacteria can be cultured, our understanding of them is limited. Research over the past decade has shown that these bacteria play a vital role in gut immune function, mucosal barrier function, metabolism of drugs, and production of short-chain fatty acids and vitamins. Even minor disturbances in gut microflora can lead to significant changes in gut function, including gas production. Although the overall volume of gas production may not significantly change from individual to individual, the content (methane [CH_4], hydrogen [H_2], or carbon dioxide [CO_2]) may vary greatly, potentially leading to changes in intestinal transit and visceral sensation.

Normal Intestinal Gas

At any time, the average individual has 100–200 cc of gas within the GI tract.[18-20] The volume of gas increases

Table 2. Differential Diagnosis of Abdominal Gas, Bloating, and Distention

- Aerophagia
- Anorexia and bulimia
- Gastroparesis
- Gastric outlet obstruction (partial or complete)
- Functional bloating
- Functional dyspepsia
- Dietary factors
  - Lactose intolerance
  - Fructose intolerance
  - Fructan consumption
  - Consumption of sorbitol or other nonabsorbable sugars
  - Carbohydrate intake
  - Gluten sensitivity
- Celiac disease
- Chronic constipation
- Irritable bowel syndrome
- Disturbances in colonic microflora
- Small intestinal bacterial overgrowth
- Abnormal small intestinal motility (eg, scleroderma)
- Small bowel diverticulosis
- Abnormal colonic transit
- Evacuation disorders of the pelvic floor

during the postprandial period, primarily in the pelvic colon.[20] Gastric distention and small bowel stimulation during the postprandial period accelerate gas transit.[21,22] Intraluminal lipids cause retention of gas, primarily within the proximal small intestine.[23,24]

Colonic gas production occurs primarily due to the metabolism of materials by colonic bacteria. Food products that are incompletely digested within the small intestine—such as lactose (in patients with lactase deficiency), fructose, sorbitol, legumes (ie, stachyose and raffinose), fiber, and complex carbohydrates (ie, wheat)—are broken down in the colon. Gas within the GI tract develops from several additional sources, including swallowed air, diffusion from the bloodstream, and a variety of chemical reactions within the GI tract. The 5 most common gases found within the GI tract are nitrogen (N_2), oxygen (O_2), H_2, CO_2, and CH_4. There are also trace amounts of other gases. Nearly all N_2 and O_2 within the upper GI tract come from swallowed air (Figure 1). CO_2 may come from swallowing air, drinking carbonated beverages, or neutralization of acids and alkalis in the upper GI tract. CO_2 is readily absorbed in the small intestine. A study of healthy volunteers found that the average individual produces approximately 700 cc of gas per day (primarily CO_2 and H_2 in the colon).[25] Most individuals also harbor some methane-producing (methanogenic) bacteria, which consume H_2 and release small amounts of sulfur-containing gas (hydrogen sulfide and methanethiol). Many colonic bacterial species consume both H_2 and CO_2, thereby reducing the gas content of the large intestine. Lastly, healthy human volunteers pass flatus 14–18 times per day, for a mean total volume ranging from 214 mL (on a low-fiber diet) to 705 mL (on a high-fiber diet) during a 24-hour period.[25] Contrary to popular belief, IBS patients usually do not produce more intestinal gas than other patients.

Abnormal Intestinal Gas

It is difficult to define an abnormal amount of intestinal gas for a number of reasons. No consensus has been reached on standardized definitions. For example, is it abnormal to produce 1,000 cc of intestinal gas per day? What about 2,000 cc per day? In addition, standardized tests cannot reliably distinguish normal gas production levels from abnormal levels. Although commonly used, abdominal radiographs do not provide any information regarding gas production, content, or evacuation, and breath H_2 tests have limited specificity and sensitivity.[26] Finally, as described below, bloating is primarily a sensory phenomenon, and the ability to accurately measure it in clinical practice is limited.

Concomitant Symptoms of Bloating and Abdominal Distention

Healthy subjects generally tolerate intestinal gas quite well because they can propel and evacuate gas efficiently. A number of theories have been offered to explain why patients may have symptoms of both bloating and abdominal distention.

Increased Gas Production This theory has been largely discredited for a number of reasons. Several studies using different techniques (eg, argon washout and labeled sulphur hexafluoride) have not shown any significant differences in gas production between normal volunteers and IBS patients.[19,25,27-29] In addition, infusion of large amounts of gas (2,160 mL) into the intestinal tract of normal volunteers produces only a small change (<2 cm) in abdominal girth. In contrast, IBS patients show fairly large abdominal girth changes, even in the absence of gas infusion.[24-28]

Impaired Gas Transit Over 20 years ago, Kellow and colleagues demonstrated that some patients with IBS have abnormalities in intestinal transit, which could

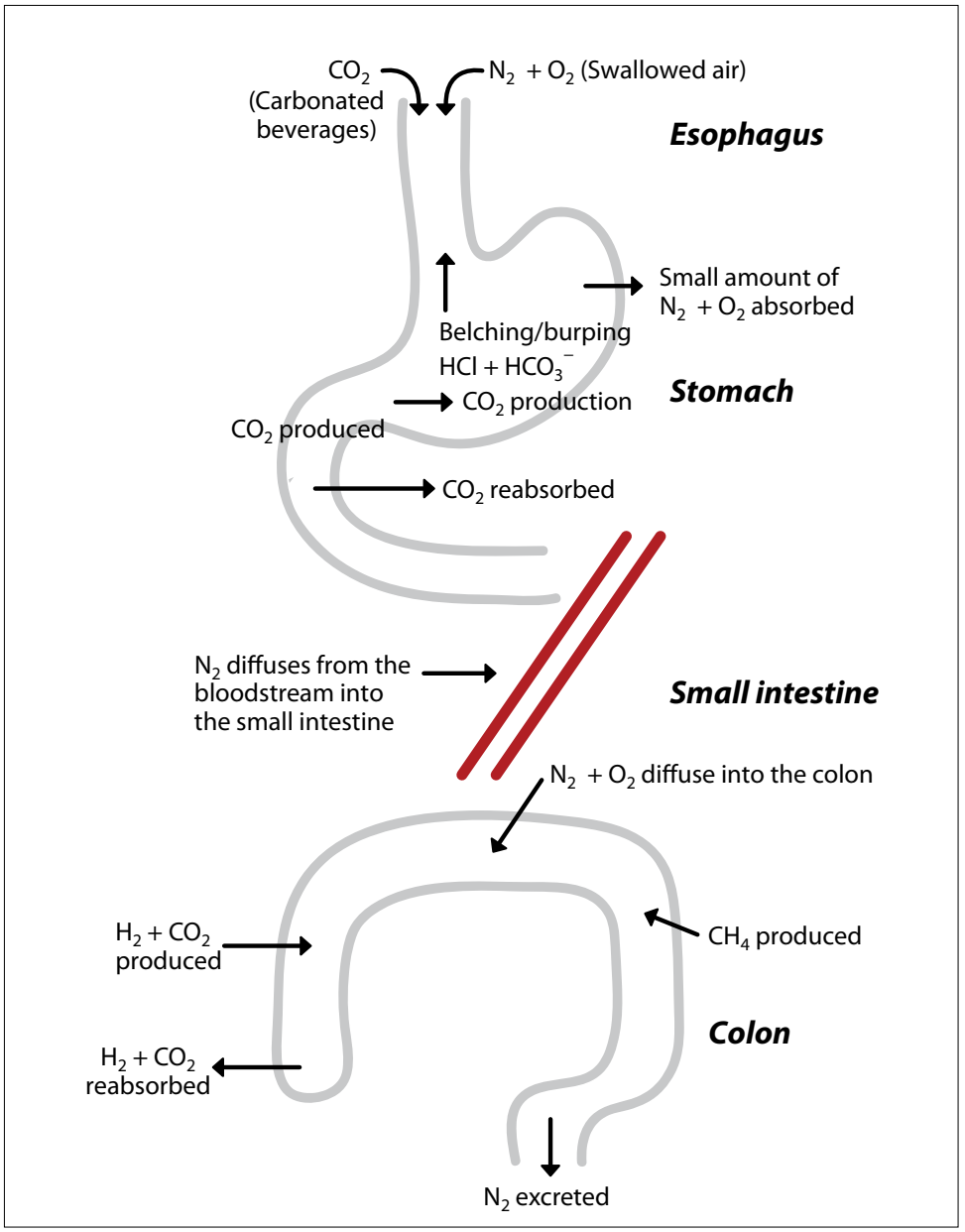

Figure 1. The physiology of intestinal gas, which develops primarily from food and drinks that are ingested or swallowed. Large amounts of carbon dioxide (CO_2) are produced in the small intestine as a byproduct of digestion, and much is reabsorbed in the small intestine. Hydrogen (H_2) and CO_2 are produced in large amounts within the colon, although much is reabsorbed. Methanogenic bacteria consume H_2 and release methanethiol and hydrogen sulfide.

CH_4=methane; HCl=hydrochloric acid; HCO_3^-=hydrogen carbonate; N_2=nitrogen; O_2=oxygen.

contribute to symptoms of gas and bloating.[30,31] This finding makes clinical sense, particularly in IBS patients with constipation, who have an increased prevalence of bloating and abdominal distention. Although a small study involving intestinal gas infusions failed to show differences in small bowel motility in patients with IBS (n=10) compared to healthy volunteers (n=10), patients with IBS experienced more pain during actual gas infusions and sham gas infusions than healthy volunteers.[32] In a larger study of 20 patients with IBS (75% women) and 20 healthy volunteers, 90% of patients with IBS developed intestinal gas retention compared to only 20% of control subjects (P<.01).[28] Abdominal distention correlated with gas retention in these patients. Patients with IBS also had impaired gas clearance from the proximal colon (as opposed to the distal colon)

compared to healthy volunteers; this finding is similar to that of earlier studies showing that patients with IBS had impaired small intestinal gas clearance.[33-35] Impaired gas transit in patients with IBS may reflect abnormalities in intrinsic reflexes (as discussed below) or sensitivity to lipids.[35]

Impaired Evacuation Some patients cannot effectively evacuate gas, resulting in prolonged intestinal gas retention and symptoms of bloating and pain. Patients with IBS, functional bloating, and constipation are less able to effectively evacuate infused gas and are much more likely to develop symptoms of abdominal distention.[23,29,36-38] Some of these patients appear to have a deficiency in a normal rectal reflex involved in intestinal gas propulsion.[39]

Abnormal Abdominal-Diaphragmatic Reflexes Over 60 years ago, Alvarez raised the possibility of an abnormal abdominal wall reflex in patients with symptoms of bloating.[40] In healthy adults, intestinal gas infusion increases muscle activity in the abdominal wall.[41] Gas infusion in bloating patients leads to decreased contraction of the abdominal wall muscles concurrent with inappropriate relaxation of the internal oblique muscles. This abnormal viscerosomatic reflex activity in patients with bloating means that abdominal wall muscles relax, rather than contract, with gaseous distention of the GI tract, emphasizing luminal gas. In contrast to healthy volunteers, the diaphragms of bloating patients descend while the ventral abdominal wall muscles relax, leading to an increase in abdominal girth.[42,43]

Abnormalities in Posture Some clinicians have reported that patients with significant complaints of bloating and abdominal distention appear to unconsciously change their body position and adopt a more lordotic position. Although this issue has not been well studied, patients with IBS do not generally appear to adopt a more lordotic position compared to other patients.[44]

Abnormal Sensation or Perception Patients with IBS are more sensitive to stretch and distention of the GI tract compared to healthy volunteers.[45,46] In a study of 58 patients with IBS (based on Rome II criteria), those with bloating alone had lower thresholds for abdominal pain compared to those who also had symptoms of abdominal distention.[47] Clinically, impaired transit of gas and ineffective evacuation of gas could lead to distention of the intestine in a hypersensitive patient, thereby causing significant bloating and pain out of proportion to the amount of gas trapped within that segment of the intestine.

Psychosocial Aspects

In women with IBS, the most common symptom complaint (and one of the most severe) is intestinal gas.[7,48,49] The prevalence and severity of bloating symptoms have been associated with increased healthcare utilization and decreased quality of life, and these negative impacts are particularly evident in women with IBS.[8,9,50] Bloating symptoms are also common and often severe in patients with gastroparesis. The severity of bloating has been shown to be inversely correlated with patient-rated quality of life according to both the generic SF-36 survey and the disease-specific Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life questionnaire.[51]

Psychosocial distress may contribute to the perceived severity of bloating.[52,53] Women with moderate-to-severe bloating more frequently report a history of major depression and more severe depression and anxiety.[50] In one study, patients with moderate-to-severe bloating had significantly higher Symptom Checklist–90R scores for anxiety, depression, and somatization compared to women with minimal or mild bloating symptoms. The Global Symptom Index of psychological distress was also elevated in patients with moderate-to-severe bloating symptoms.[54] However, other studies have failed to find a significant relationship between bloating and psychological distress.[6,11] Additionally, the association between bloating and psychological distress does not appear to be as convincing in patients with FD.[55] Although further studies are needed to fully understand the relationship between bloating symptoms and psychosocial distress, it is clear that treatment strategies that address psychological comorbidities are likely to be most effective.

Diagnosis

Although bloating can cause significant patient distress, it generally represents a benign condition. Evaluation of a patient with bloating should begin with a careful history and physical examination to rule out an organic disorder as the cause of the patient's symptoms. Patients should be questioned about alarm features such as anemia and unintentional weight loss, as these symptoms may be a sign of a malabsorptive process. If these symptoms are present, the clinician may initiate the evaluation by ordering a complete blood count, celiac sprue serology, and an upper endoscopy with duodenal biopsies. Patients complaining of bloating along with another symptom should be evaluated accordingly. For example, patients with coexisting nausea and vomiting may require small bowel imaging and a gastric-emptying scan, whereas patients with diarrhea can initially be evaluated via stool studies and a colonoscopy. Aside from ruling out an obstructive process or a condition that could predispose the patient to bacterial overgrowth,

imaging studies have little utility for establishing the diagnosis of bloating. In one study, a computed tomography scan did not find any differences between bloating patients and healthy controls in terms of the amount of intestinal gas.[56] At this stage in the evaluation of a patient with bloating, most clinicians initiate treatment. However, many healthcare providers are concerned that symptoms of bloating and abdominal distention are signs of small intestinal bacterial overgrowth (SIBO) and often initiate empiric therapy for bacterial overgrowth. This complicated and contentious topic is briefly reviewed below.

Small Intestinal Bacterial Overgrowth

The diagnosis of SIBO remains controversial. Many authorities believe that the gold standard for diagnosis of this condition involves obtaining a culture of the small intestine via an orojejunal tube or sterile endoscopic aspiration. Historically, total bacterial counts over 10^5 colony-forming units (CFU)/mL have been considered diagnostic of SIBO, although other studies have used values from 10^4 CFU/mL to 10^7 CFU/mL.[26] Aspiration of the small intestine has several limitations, as the procedure is time-consuming, invasive, and costly. Additionally, many laboratories do not culture small intestinal aspirates. For these reasons, most healthcare providers now attempt to diagnose SIBO via noninvasive measures.

Imaging Small intestinal imaging is recommended by many clinicians to identify structural abnormalities that could predispose a patient to SIBO. A recent study found that the odds of having SIBO were increased 7-fold in patients with small bowel diverticula.[57] A 4-hour solid-phase gastric-emptying scan can identify bloating patients with underlying gastroparesis.[51]

Endoscopy There is currently no role for routine endoscopy in the diagnosis of SIBO aside from sterile aspiration of the small intestine, as previously discussed. Biopsy of the duodenum may show villous blunting; however, this finding is neither sensitive nor specific for the diagnosis of SIBO.[58]

Laboratory Evaluation No serologic test is diagnostic of SIBO, although vitamin levels may provide clues as to its presence. SIBO may cause malabsorption of vitamin B_{12} and vitamin D; therefore, it is reasonable to check the levels of these vitamins in appropriate patients. Elevated folate levels may also point to the diagnosis of SIBO, as upper intestinal tract bacteria are capable of synthesizing folate.

Breath Testing Breath testing is the most widely used diagnostic test for SIBO. Breath testing is based on the principle that bacteria produce H_2 and CH_4 gas in response to nonabsorbed carbohydrates in the intestinal tract; H_2 gas can then freely diffuse to the bloodstream, where it is exhaled by the patient. A carbohydrate load, typically lactulose or glucose, is administered to the patient, and exhaled breath gases are analyzed at routine intervals. With lactulose, a normal response would be a sharp increase in breath H_2 (and/or CH_4) once the carbohydrate load passes through the ileocecal valve into the colon. In a normal small intestine, glucose should be fully absorbed prior to reaching the ileocecal valve; therefore, any peak in breath H_2 or CH_4 is indicative of SIBO. There is significant laboratory-to-laboratory variation as to what constitutes a positive breath test; generally, an increase in H_2 of 20 parts per million within 60–90 minutes is considered to be diagnostic of SIBO.[26,59] Elevated fasting levels of H_2 and CH_4 have also been shown to be highly specific, but not sensitive, for the diagnosis of SIBO.[26,59] Earlier studies have demonstrated that 14–27% of subjects will not excrete H_2 in response to varying loads of lactulose; however, these nonproducers of H_2 were found to have significantly higher levels of CH_4 after lactulose ingestion. Thus, the addition of CH_4 analysis may increase the sensitivity of the H_2 breath test.[60]

Empiric Antibiotics A direct test for SIBO is an empiric course of antibiotics, an approach that is similar to a trial of proton pump inhibitors for patients with acid reflux symptoms. The use of empiric antibiotics is limited by their adverse effects, which include the potential to cause pseudomembranous colitis; however, these risks have decreased in recent years with the advent of poorly absorbable antibiotics such as rifaximin (Xifaxan, Salix). Few trials to date have evaluated an empiric trial of antibiotics for SIBO, although this approach would be reasonable for any patient with symptoms consistent with SIBO and/or any condition that would predispose the patient to this condition (ie, scleroderma or previous surgery involving the ileocecal valve). Empiric antibiotic trials are not without risks, due to the potential for promoting drug resistance and other side effects, including nausea, abdominal pain, and upper respiratory infections. However, a number of studies have shown that rifaximin has rates of adverse effects that are similar to those associated with placebo.[61,62]

Treatment

There is no evidence-based algorithm for treating patients with bloating and abdominal distention; thus, each patient requires an individualized treatment plan. Gastroenterologists generally follow a stepwise approach, formulating the treatment plan with the patient in order to improve compliance. The first step is to identify the chief symptom(s): bloating, abdominal distention, or both. This step may

provide some insight into the underlying pathophysiologic mechanism. The next step is to educate the patient regarding the possible pathophysiologic processes that might produce these symptoms. Gastroenterologists then try to reassure the patient that these symptoms, although uncomfortable and frustrating, are usually benign. Finally, specific and reasonable goals are identified. The following section provides the best evidence currently available from the literature (Table 3). No large, randomized, controlled studies have been performed in patients with functional bloating; thus, much of the data have been obtained from patients with IBS.

Table 3. Treatment Options for Bloating

- Diet
- Exercise and posture
- Over-the-counter medications
- Probiotics
- Antibiotics
- Smooth muscle antispasmodics
- Osmotic laxatives
- Prokinetic agents
- Chloride channel activators
- Tricyclic antidepressants

Diet

A careful dietary history should be taken from each patient, with an emphasis on food products that readily ferment within the colon (eg, dairy, fructose, fructans, fiber, and sorbitol).[63] A recent study showed that bloating improved in IBS patients who avoided these fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.[64,65] Gastroenterologists usually direct patients to remove one possible offending substance at a time (ie, dairy first, then fructose-containing liquids, then fiber, and so on); however, some patients with severe bloating and abdominal distention prefer to begin with a strict elimination diet consisting of only water, broth, boiled chicken, and egg whites, and then they slowly add in different food groups. Some patients have noted symptom improvement after minimizing carbohydrates and gluten, although this approach has not been well studied.[66,67]

Exercise and Posture

A study of 8 patients with bloating found that physical exercise (ie, using a stationary bike) improved intestinal gas clearance and reduced symptoms of bloating.[68] As gas retention is worse in the supine position than the upright position, patients should be counseled to exercise and minimize recumbent periods during the day to reduce symptoms of gas and bloating.[69]

Over-the-Counter Medications

A study of 5 healthy volunteers showed that activated charcoal (0.52 g/dose 4 times daily) did not change gas production nor improve abdominal symptoms.[70] Simethicone is an antifoaming agent that improved symptoms of upper abdominal bloating in one small study, although this agent has not been evaluated in a prospective fashion using Rome-classified patients.[71] α-galactosidase has been shown to improve gas and flatus production in healthy volunteers who were fed a meal high in oligosaccharides.[72] Mechanistically, this approach should not improve gas and bloating symptoms that are due to ingestion of lactose, fructose, fructan, or fiber.

Probiotics

Probiotics are defined as live microorganisms that confer a health benefit on the host when administered in adequate amounts. Although probiotics are commonly used, most have not been adequately evaluated in randomized, placebo-controlled trials. A recent prospective study of the probiotics *Lactobacillus acidophilus* and *Bifidobacterium lactis* in patients with nonconstipated functional bowel disorders (n=60) found an improvement in bloating severity during an 8-week trial period.[73] A prospective trial of 77 patients with IBS compared *Bifidobacterium infantis* 35624, *Lactobacillus*, and placebo. The authors found that patients randomized to *B. infantis* 35624 experienced improvement in abdominal pain/discomfort and bloating in the setting of a normalized interleukin (IL)-10/IL-12 ratio.[74]

A follow-up study evaluated the efficacy of *B. infantis* in women with IBS (based on Rome II criteria; all subgroups). Subjects were randomized in a blinded fashion to placebo or 1 of 3 daily doses of *B. infantis* for a 4-week trial period. *B. infantis*, at a dose of 1×10^8 CFU/mL, improved abdominal pain and discomfort significantly more than placebo (P=.023); the other 2 *B. infantis* doses were not better than placebo. Bloating symptoms were also significantly better with the 1×10^8 CFU/mL *B. infantis* dose than placebo.[75]

In a randomized, placebo-controlled study of children with diarrhea-predominant IBS (n=25), the probiotic formulation VSL#3 reduced bloating more than placebo (P=.05).[76] A follow-up, double-blind, placebo-controlled study of 48 adult patients who met Rome II criteria and reported significant bloating showed that flatulence and relief of bloating were better in the VSL#3 group than the placebo group (P=.014).[77] Finally, in a prospective study of 59 children (mean age, 12.5 years), VSL#3 (450 billion bacteria per capsule) improved bloating more than placebo during a 6-week study period (P<.001).[78]

Prescription Medications

Antibiotics Rifaximin, a gut selective antibiotic that is not systemically absorbed, is one of the best-studied antibiotics for the treatment of bloating. In a double-blind, randomized, placebo-controlled trial, 81 patients with IBS (based on Rome I criteria) were assigned to receive either rifaximin (400 mg 3 times daily) or placebo for 10 days.[79] Patients who received rifaximin reported improvement in global IBS symptoms as well as bloating symptoms compared to patients who received placebo (P=.010). A randomized, placebo-controlled trial of 124 bloating patients evaluated the effects of rifaximin (400 mg by mouth twice daily) during 3 separate 10-day periods: at baseline, during treatment with rifaximin or placebo, and after treatment.[80] All patients had a normal lactulose H_2 breath test result on study entry. At the end of the treatment period, the rifaximin group noted a statistically significant improvement in symptoms (41.3% vs 22.9%; P=.03). This improvement was maintained in 28.6% of patients at the end of the study (compared to 11.5% of the placebo group; P=.02). An analysis of 2 large, double-blind, placebo-controlled studies involving 1,260 patients with nonconstipated IBS (TARGET 1 and TARGET 2) found that patients treated with rifaximin (550 mg by mouth 3 times daily) were more likely to have adequate relief of bloating compared to patients who received placebo (P<.001).[62]

Tricyclic Antidepressants Tricyclic antidepressants (TCAs) are frequently used to treat functional abdominal pain.[81] Data from a randomized, controlled trial comparing desipramine with cognitive behavioral therapy demonstrated an improvement in patients with functional abdominal pain as well as an improvement in bloating.[82] An ongoing research study (the National Institute of Health's Functional Dyspepsia Treatment Trial) may provide further information on the efficacy of TCAs for the treatment of bloating associated with FD.

Smooth Muscle Antispasmodics Smooth muscle antispasmodics are routinely used by clinicians to treat abdominal pain that is associated with IBS. Although several trials in Europe have shown an improvement in symptoms in patients treated with these drugs, data from clinical trials in the United States are limited, and these medications (eg, mebeverine, otilonium, and trimebutine) are not available in the United States.[83] Because these medications relax smooth muscle, they have the potential to cause further gas accumulation within the GI tract and to delay transit of gas through the GI tract. Thus, although these agents are commonly used to treat cramps and spasms within the GI tract, they have the potential to worsen symptoms of gas and bloating; therefore, they cannot be recommended for routine use.

Osmotic Laxatives These agents, the most common of which is polyethylene glycol, improve symptoms of constipation.[84] One prospective study found that symptoms of bloating improved when patients with chronic constipation were treated with a polyethylene glycol solution.[85] These agents have not been studied in patients who complain predominantly of bloating.

Prokinetic Agents

Neostigmine Neostigmine is a potent cholinesterase inhibitor that is used in the hospital setting to treat acute colonic pseudo-obstruction. In a prospective study of 28 patients with abdominal bloating who underwent jejunal gas infusion, intravenous neostigmine induced significant and immediate clearance of retained gas compared to placebo.[29] A randomized, placebo-controlled study using pyridostigmine in patients with IBS and bloating (n=20) demonstrated only a slight improvement in symptoms of bloating.[56] The small sample sizes of these studies and the need to use neostigmine in a carefully supervised setting limit the applicability of these results.

Cisapride Cisapride is a mixed 5-HT_3/5-HT_2 antagonist and 5-HT_4 agonist that was previously used to treat reflux, dyspepsia, gastroparesis, constipation, and IBS symptoms. The drug was withdrawn from the US market in July 2000. In a study of FD patients, cisapride improved symptoms of bloating in some patients, although the benefits were not overwhelming.[86-88] Cisapride did not improve bloating in patients with IBS and constipation.[89]

Domperidone Domperidone is a dopamine antagonist used to treat FD, gastroparesis, and chronic nausea.[90-92] Although this drug may improve dyspeptic symptoms (including upper abdominal bloating) in some patients, its routine use in clinical practice is precluded by the absence of prospective, randomized, controlled studies evaluating its efficacy in patients with functional bloating.

Metoclopramide Metoclopramide is a dopamine antagonist approved for treatment of diabetic gastroparesis.[90] Patients with FD and gastroparesis frequently have symptoms of bloating.[51,92] One small study found that metoclopramide did not improve symptoms of abdominal distention in dyspeptic patients.[93]

Tegaserod Tegaserod is a 5-HT_4 (serotonin type 4) receptor agonist that stimulates GI peristalsis, increases intestinal fluid secretion, and reduces visceral sensation.[94] In July 2002, this drug was approved by the US Food and Drug Administration for the treatment of IBS with constipation in women, as studies showed an improvement in bloating symptoms with the drug.[95-98] Although tegaserod has since

been withdrawn from the US market, it is still available for emergency use. Other 5-HT_4 agonists (ie, prucalopride) may become available in the United States in the future.

Chloride Channel Activators

Lubiprostone Two phase III studies evaluated the safety and efficacy of lubiprostone (Amitiza, Sucampo) in patients with IBS and constipation.[99] A total of 1,171 adults (91.6% women) who had been diagnosed with constipation-predominant IBS (based on Rome II criteria) were randomized to receive either 12 weeks of twice-daily lubiprostone (8 mcg) or placebo. The primary efficacy variable was a global question that rated overall IBS symptoms. Patients who received lubiprostone were nearly twice as likely as those who received placebo to achieve overall symptom improvement (17.9% vs 10.1%; P=.001). Secondary endpoints, including bloating, were significantly improved in the lubiprostone group compared to the placebo group (P<.05 for all endpoints). The most common treatment-related side effects were nausea (8%) and diarrhea (6%); these side effects occurred in 4% of the placebo group.

Linaclotide Linaclotide is a 14-amino-acid peptide that stimulates the guanylate cyclase receptor. Lembo and colleagues conducted a multicenter, placebo-controlled study of 310 patients with chronic constipation (based on modified Rome II criteria).[100] Patients were randomized to receive 1 of 4 linaclotide doses (75 µg, 150 µg, 300 µg, or 600 µg) or placebo once daily for 4 weeks. Patient measures of bloating were significantly better for all linaclotide doses compared to placebo. A multicenter, double-blind, placebo-controlled, dose-ranging study of 420 patients with constipation-predominant IBS (based on modified Rome II criteria; <3 complete spontaneous bowel movements [CSBMs]/week) compared daily linaclotide (75 µg, 150 µg, 300 µg, or 600 µg) to placebo during a 12-week study period.[101] The primary endpoint was the change in CSBM frequency, while other bowel symptoms (eg, abdominal pain and bloating) were secondary endpoints. A total of 337 patients (80%) completed the study. Using a strict intention-to-treat analysis, all doses of linaclotide were shown to significantly improve stool frequency (P<.023 or better) as well as improve symptoms of straining, bloating, and abdominal pain (all with P<.05, except for the 150-µg dose and bloating, which was not statistically better than placebo).

Summary

Bloating and abdominal distention are very common symptoms that cause significant patient distress. Although these terms are often used interchangeably, bloating and abdominal distention should be considered separate disorders with different pathophysiologic mechanisms. A careful history and examination and a few simple tests can usually differentiate bloating from abdominal distention by distinguishing between an organic process and a functional disorder. Reassurance and education are critical steps in the treatment of these chronic disorders, and a step-by-step therapeutic approach involving diet, probiotics, and medications usually leads to symptom improvement.

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