An Overview of Irritable Bowel Syndrome and its Relation to Small Intestinal Bacterial Overgrowth

Irritable bowel syndrome (IBS) impacts a large proportion of our population and a large proportion of healthcare costs are attributed to this disease process. Previously thought to be a diagnosis of exclusion, it is now clear that IBS can be safely diagnosed at the time of an initial patient encounter by a gastroenterologist. Small intestinal bacterial overgrowth (SIBO) and IBS are intimately related and treatment options are now targeted to reduce the bacterial load below a threshold, which may cause symptoms. While the gut microbiome is complex, in 2018, the pathophysiology of IBS based on alterations of the gut microbiome has taken a front seat in understanding this condition.

INTRODUCTION: UNDERSTANDING IMPACT OF DISEASE
It is thought that irritable bowel syndrome (IBS) affects up to 45 million people in the United States alone and is more prevalent in females than in males.1 Up to 40% of visits to the gastroenterologist are due to IBS symptoms. This disease causes significant burden to patients and their families alike, at times with symptoms so severe that their quality of life may be impaired. In addition, it is estimated that in the United States alone, direct healthcare costs due to IBS near $1 billion and another $50 million is attributed to indirect costs.2

IBS is characterized by alterations in bowel habits and associated abdominal discomfort. In particular, based on Rome IV criteria for the diagnosis of irritable syndrome, patients must have recurrent abdominal pain (not discomfort) weekly for at least 3 months and is associated with change in bowel habits (either stool form or frequency); symptoms must have started at least 6 months before establishing a diagnosis. Depending on the predominant bowel pattern type, there are various subtypes of the disease including IBS-D (diarrhea predominant), IBS-C (constipation predominant) or IBS-M (mixed diarrhea and constipation).3

Over the last 2 decades a number of theories have been proposed for IBS and have centered around the role of pain. However, evidence from this last decade has found that the microbiome
An Overview of Irritable Bowel Syndrome and its Relation to Small Intestinal Bacterial Overgrowth

May play a key role in symptoms in this condition. While various microbiome alterations have been described, one dominant theme is the finding of small intestinal bacterial overgrowth (SIBO) in a large subset of IBS. Studies suggest that this bacterial alteration could explain the majority of IBS patients, which is thought to be the prevailing etiology of IBS and is found in greater than 75% of IBS patients based on initial studies. In SIBO, the microbiome are altered such that the normally minimally colonized small bowel of humans now has an overabundance of non-pathogenic bacteria. The most accepted current definition is based on a recent North American consensus suggesting that coliform counts >10^3 cfu/mL define SIBO. Bacteria and their products in SIBO have the potential to produce bloating, abdominal pain and alterations in stool form and these symptoms are also typical of IBS.

SIBO and IBS: Are They Related?

Prior studies have suggested that >60% of patients with IBS-D in fact have a component of small intestinal bacterial overgrowth. This is based on breath testing and recent meta-analysis. While this had been controversial for many years, mounting evidence has shown the likelihood of small bowel bacteria causing IBS to be high. This is based now on data from intestinal culture, deep sequencing and trials that demonstrate the benefits of the antibiotic, rifaximin.

While there is now a large body of evidence to support this, the reason for the SIBO in IBS remains incompletely understood. One of the main risk factors for the development of SIBO includes alterations in the migrating motor complex (MMC), or impaired motility of the GI tract. Stagnation of the gut will ultimately lead to a form of dysbiosis. This is reminiscent of classic forms of SIBO such as scleroderma or diabetes. However, in IBS there is growing evidence for the role of acute gastroenteritis in the development of IBS and SIBO. A large meta-analysis published in 2017 has now concluded that a major cause of IBS is acute gastroenteritis. Based on animal studies, it is now believed that IBS and SIBO originate from this acute gastroenteritis. There is speculation that this transient food poisoning event or stressful stimulus permanently alters the MMC, and this stasis then serves as a nidus for bacterial overgrowth.

Whenever considering SIBO, it is also important to rule out other causes besides IBS. Prior intra-abdominal surgical interventions, particularly those involving the ileocecal valve, are particularly notorious for precipitating SIBO in addition to prior mechanical obstructions, adhesive disease, and even Celiac or inflammatory bowel diseases (particularly in stricturing or fistulizing disease). Various immune and pancreatic exocrine deficiencies may be implicated as well. It should be noted that none of these risk factors may be present despite clinical suspicion of these conditions.

Dysbiosis and Constipation

It should be noted that previously SIBO was considered only in the setting of unexplained diarrhea, though if this were the case, it would be difficult to implicate intestinal dysbiosis in the pathogenesis of IBS, in which about half of patients

<table>
<thead>
<tr>
<th>Studies to Consider Ordering for the Work Up of IBS and SIBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Tests</td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>TSH</td>
</tr>
<tr>
<td>Celiac serologies</td>
</tr>
<tr>
<td>Stool studies</td>
</tr>
<tr>
<td>Inflammatory markers</td>
</tr>
<tr>
<td>• ESR</td>
</tr>
<tr>
<td>• CRP</td>
</tr>
<tr>
<td>• Fecal calprotectin</td>
</tr>
<tr>
<td>CdtB and vinculin antibodies</td>
</tr>
<tr>
<td>Cross-sectional imaging</td>
</tr>
<tr>
<td>CT scan</td>
</tr>
<tr>
<td>KUB</td>
</tr>
<tr>
<td>Endoscopic evaluation</td>
</tr>
<tr>
<td>Upper endoscopy (to exclude Celiac disease)</td>
</tr>
<tr>
<td>Colonoscopy (to exclude microscopic colitis or IBD)</td>
</tr>
<tr>
<td>Hydrogen/methane breath testing</td>
</tr>
<tr>
<td>Glucose or lactulose substrates</td>
</tr>
</tbody>
</table>
An Overview of Irritable Bowel Syndrome and its Relation to Small Intestinal Bacterial Overgrowth

DISPATCHES FROM THE GUILD CONFERENCE, SERIES #14

studies may also help aid in the diagnosis. IBS is no longer a diagnosis of exclusion but should be considered in the differential in a patient with altered bowel habits and associated abdominal pain.

A detailed history is essential in making the diagnosis of IBS. Physicians should look out for the so-called ‘alarm signs’ such as unintentional weight loss, symptoms that awake patients from their sleep, blood in stool, family history of colon cancer or onset of symptoms at an older age. Patients’ medications should also be reviewed as various agents may contribute to their symptoms. Surgical history and dietary habits should also be inquired.

Generally, IBS patients will have some abdominal tenderness with palpation but no other abnormalities are identified; if hepatosplenomegaly or ascites are noted, certainly other diagnoses should be considered. A digital rectal exam is essential before making the diagnosis of IBS as well to ensure no palpable masses, especially in patients with IBS-C.

In addition, the altered gut microbiome can also induce immune mediated cytokines that not only may precipitate dysmotility and augment nociceptive signaling and visceral hypersensitivity.

As a result, it is thought SIBO is on the pathway to the development of IBS (Figure 1).

**Testing: How to Come to the Diagnosis**

Diagnosis requires comprehensive clinical history, a focused physical exam and depending on the type of IBS, laboratory, radiographic and endoscopic studies may also help aid in the diagnosis. IBS is no longer a diagnosis of exclusion but should be considered in the differential in a patient with altered bowel habits and associated abdominal pain.

A detailed history is essential in making the diagnosis of IBS. Physicians should look out for the so-called ‘alarm signs’ such as unintentional weight loss, symptoms that awake patients from their sleep, blood in stool, family history of colon cancer or onset of symptoms at an older age. Patients’ medications should also be reviewed as various agents may contribute to their symptoms. Surgical history and dietary habits should also be inquired.

Generally, IBS patients will have some abdominal tenderness with palpation but no other abnormalities are identified; if hepatosplenomegaly or ascites are noted, certainly other diagnoses should be considered. A digital rectal exam is essential before making the diagnosis of IBS as well to ensure no palpable masses, especially in patients with IBS-C.

The American College of Gastroenterology (ACG) guidelines suggest that in the absence of red flags, basic screening labs may not be needed be performed in patients with a new diagnosis of IBS at time of initial visit. However, there is some reassurance in negative studies and some studies that offer that reassurance include a complete blood count and thyroid studies. In patients with diarrhea predominant stools, Celiac disease serologies should also be performed although stool studies for common pathogenic bacteria, ova and parasites and inflammatory markers (serum erythrocyte sedimentation rates, C-reactive protein and/or fecal calprotectin) are less useful.

(continued on page 40)

![Figure 1. A large part of IBS is related to SIBO. Cytokine release due to intestinal dysbiosis may precipitate visceral hypersensitivity.](image)
As of 2016, new biomarkers for IBS-D and IBS-M have also been developed. There is an enzyme-linked immunosorbent assay (ELISA), which detects antibodies to cytolethal distending toxin B (CdtB); these antibodies have also been found to have cross-reactivity with vinculin, a protein in the intestine. This ELISA utilizing antibodies to both CdtB and vinculin is now commercially available and attempts to identify antibodies to the toxin which can be found as a result of food poisoning as well as autoantibodies to vinculin, hence its utility in post-infectious IBS patients with predominant diarrhea.16

In patients with red flag symptoms or in elderly patients, those having pain out of proportion to physical exam and those with sudden onset of symptoms or significant weight loss, further imaging should be considered. While endoscopic evaluation is not necessary prior to making the diagnosis of IBS, colonoscopy should be performed if there is a suspicion for inflammatory bowel disease and to exclude microscopic colitis (in the correct demographic such as over 50 years old with new onset of symptoms). All patients should be up to date with general colorectal cancer screening guidelines, and a sudden change in bowel habits without a clear precipitating factor, particularly in the elderly, should prompt colonoscopy.17

There is also a role for breath testing in patients with risk factors for SIBO, especially since there is >90% reproducibility of symptoms with lactulose or glucose substrates.18 This breath testing identifies both hydrogen and methane produced by the small intestinal bacteria; both of these innate gases are not traditionally made unless intestinal dysbiosis is present. The glucose substrate is particularly effective for diagnosing proximal SIBO where it is predominantly absorbed. Previously, small bowel aspirates were being obtained at the time of upper endoscopy but yield of SIBO is lower and the process of obtaining these samples has proven to be difficult both from implementation and cost perspectives.19

Medical Therapies: Understanding Current Treatment Options

Non-Pharmacologic Treatment Strategies
Treatments are largely aimed at reducing symptoms associated with IBS. Determining what to advise a patient really requires an individualized approach depending on their preferences and predominant symptoms. Non-pharmacologic techniques including adherence to a low-FODMAP diet are often recommended as first line therapy. However, recent data suggest extreme diets need supervision and may produce nutrient deficiencies.20 Peppermint oil, probiotics, and various soluble fibers have also been suggested before considering prescription therapies. However, these have had limited success in small randomized controlled trials. In the case of probiotics, bloating may also be a side effect.21

Pharmacologic Treatment Strategies
As SIBO is thought to be a direct consequence of altered gut flora, it should be acknowledged that antibiotics may be an effective therapy for patients with this condition. Rifaximin, a non-absorbable antibiotic initially used for travelers’ diarrhea, has now proven to be beneficial in SIBO patients and has been approved by the Food and Drug Administration (FDA) for IBS-D. Neomycin and metronidazole, though not FDA approved for this indication, have been shown to be beneficial when added to patients with methane predominant SIBO in those with underlying IBS-C and reduction in methane may in fact treat the constipation as well.22 In addition, patients must understand that if there is truly a component of intestinal dysbiosis, symptoms will certainly improve but will not resolve entirely. However, in the TARGET 3 trial 36% of subjects who responded to rifaximin did not need any further treatment. Nevertheless, relapse of symptoms can be seen in many patients who initially respond to rifaximin.22 In patients who had clinical evidence of IBS and abnormal hydrogen breath testing using a glucose substrate, treatment with rifaximin resulted in normalization in breath testing; however, >40% patients had recurrence of symptoms 9 months after the initial course of rifaximin and again abnormal breath testing.22 Thus it is reasonable to conclude that the degree of small intestinal bacteria re-accumulation correlates with degree of symptoms. Use of a pro-kinetic such as erythromycin, at low nocturnal dosages, after successful treatment of IBS with an antibiotic delayed relapse of SIBO from 59 to 138 days;23 it is interesting to recognize that at low dosages,
erythromycin does not exhibit antimicrobial properties but can be useful in stimulating the MMC.23

Aside from antibiotics, other FDA-approved drugs for IBS-D include eluxadoline (mu-opioid agonist) and alosetron (5-HT3 antagonist), the latter approved for women in particular. It should be noted that alosetron has the rare but reported risk of ischemic colitis and in fact inducing severe constipation. Bile acid sequestrants and anti-diarrheal agents (lomotil, loperamide), though not FDA approved, work in a small proportion of patients with IBS-D and thus are often tried in addition to and in conjunction with the above therapies. For IBS-C, lubiprostone (intestinal chloride channel activator) and linaclotide (cyclic guanosine monophosphate [cGMP] activator) are FDA approved therapies.

Given the gut-brain connection, various studies have also demonstrated effectiveness of tricyclic antidepressants, selective serotonin receptor inhibitors (SSRIs) and selective serotonin and norepinephrine receptor inhibitors (SNRIs) in the treatment of IBS whereby pain is the predominant symptom. However, these drugs are not FDA-approved for this indication.

SUMMARY

Irritable bowel syndrome is a complex disease process and no longer considered a diagnosis of exclusion. It is thought that small intestinal bacterial overgrowth plays an important role in the pathogenesis of IBS and the intestinal dysbiosis may precipitate symptoms such as visceral hypersensitivity due to nociceptive stimulus. In the presence of ‘alarm’ symptoms such as unintentional weight loss, blood in stool, or sudden onset in symptoms, further work up may be warranted and entails a combination of laboratory, radiologic, and endoscopic testing. Treatment options are aimed at targeting the prevailing symptom in IBS, but further research is required to treat the underlying etiology now that the pathophysiology of the disease has been definitively established.

References