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SMALL INTESTINE (D SACHAR, SECTION EDITOR)

The Spectrum of Small Intestinal Bacterial Overgrowth (SIBO)

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Abstract

Purpose of Review To critically review recent (past 3 years) literature on the definition, diagnosis, and management of small intestinal bacterial overgrowth (SIBO).

Recent Findings While various series continue to illustrate the occurrence of SIBO in disease states where well-known risk factors for its occurrence are present (hypochlorhydria, disorders of intestinal structure or motor function, pancreatic insufficiency, and chronic liver disease, for example), the current challenge is in defining the limits of SIBO. Is SIBO truly common among those with "functional" gastrointestinal symptoms where there is no evidence of maldigestion or malabsorption; the original hallmarks of SIBO? Our attempts to address this question continue to be hampered by the limitations of our diagnostic tool kit. There is hope—the application of modern molecular techniques to the study of the small intestinal microbiome, together with some innovative sampling techniques, such as real-time intestinal gas sampling, may soon allow us to truly define the spectrum of SIBO.

Summary SIBO, once removed from its original confines as a cause of malabsorption syndrome, has proven to be an elusive and moving target. Only the most rigorous studies employing validated methodologies will finally corral this mysterious entity.

Keywords Small intestinal bacterial overgrowth · Microbiome · Breath testing · Hydrogen methane · Rifaximin

Introduction

How we Got Here

Any attempt to define the spectrum of small intestinal bacterial overgrowth (SIBO) must begin with a definition of the entity—no easy task. In days of old this was simple and noncontroversial—SIBO was one of the causes of malabsorption and was sought among those who presented with diarrhea, weight loss, steatorrhea and nutritional impairment [1, 2]. Some combination of altered GI anatomy, hypochlorhydria, and dysmotility was the underlying cause of these instances of what might be referred to as "classical" SIBO. Based on studies among patients who had undergone gastrointestinal surgery, diagnostic criteria for SIBO were developed on the basis of cultures of jejunal aspirates and a cut-off for the diagnosis of SIBO of $> 10^5$ colony-forming units of bacteria per ml of jejunal juice established. All was well. The arrival of the endoscope, together with an increasing recognition of the relatively cumbersome, invasive, and technically challenging nature of jejunal aspiration prompted a number of innovations. First, gastroenterologists moved their aspirates in an orad direction and performed their cultures on juice obtained from the duodenum—an approach that was subject to contamination and whose diagnostic criteria were never validated. It must be pointed out that recent developments in per-endoscope catheter design have striven to minimize contamination—we look forward to their widespread application and the development of new diagnostic criteria [3]. Second, came the recognition that the intestine was the sole source of a number of gases, and of hydrogen, in particular, that were produced as a by-product of bacterial metabolism of unabsorbed or incompletely absorbed carbohydrates in the diet. In seminal studies, the ability of breath hydrogen assays to provide evidence of carbohydrate malabsorption and to

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measure oro-cecal transit opened a new era in noninvasive diagnostics. Not too long afterwards these same breath tests (typically using lactulose as the nonabsorbed carbohydrate substrate) were utilized as tests of SIBO and, in so doing, ushered in what remains a highly controversial expansion of the spectrum of SIBO. Anyone who could swallow a sugary syrup and provide a breath sample could be tested.

Taking our Breath Away

Their apparent simplicity in terms of performance and interpretation, acceptability to the patient and low cost led to the widespread use of breath tests in clinical practice, not only to diagnose SIBO but also to detect carbohydrate intolerance. Were that it was so simple [4]. Of the various breath tests proposed to detect SIBO, two have become by far the most widely employed—the glucose and lactulose breath tests. Nowadays, breath is assayed for both hydrogen and methane following the oral administration of one of these substrates. While considerable progress has been made in the performance of these tests in a manner that minimizes the impact of confounding factors, their interpretation continues to befuddle us. Various diagnostic criteria have been proposed: baseline hydrogen/methane excretion, early rise in gas excretion above baseline, and the presence of a "double peak" with the earlier of these believed to reflect abnormal fermentation of the substrate in a contaminated small intestine with the second, later, peak reflecting the arrival of the substrate in the cecum [5•]. As doubt came to be cast on the "double peak" the "early peak" gained ascendancy. Indeed, the recent North American consensus concluded that "a rise in hydrogen of ≥ 20 ppm above the baseline value by 90 min following substrate ingestion during glucose or lactulose breath test for SIBO was considered positive" [5•]. Despite this inter-American enthusiasm, the "early peak" has also had its detractors who contend that the "early peak" measures accelerated intestinal transit and not SIBO [6]. Employing simultaneous scintigraphy and breath testing, Yu and colleagues clearly showed that the rise in breath hydrogen regardless of its timing corresponded with the arrival of the substrate in the colon suggesting that rapid transit and not SIBO was responsible for many an "early peak" [6, 7]. In response, the defenders of breath tests assert that the false positive rate for hydrogen breath tests is only 15% and lower for glucose than lactulose tests [8]. This latter assumption that glucose-based tests are free from the influence of transit has also been questioned; Lin and colleagues noting that a radioisotope-labeled bolus of glucose reached the cecum before the appearance of a hydrogen peak [9]. The "early" peak may indeed be too "late" for the small intestine. Sundin and colleagues performed traditional cultures and a detailed analysis using high-throughput sequencing of jejunal aspirates and breath testing in the same individuals and came to a number of disquieting conclusions [10•]. First, and not surprising, they found that culture grossly underestimated bacterial numbers. Second, and in seeming contradiction of accepted dogma, breath test results and bacterial numbers did not correlate. Third, as they calculated that bacterial overgrowth at and above levels considered diagnostic of SIBO could not produce breath hydrogen levels that met diagnostic thresholds, they deduced that glucose malabsorption and not SIBO was behind a positive breath test [10•]. This study also reveals a major knowledge gap—human small intestinal microbiota. Despite the rapid evolution of our knowledge of various microbiota, our understanding of the normal bacterial population of the small intestine (not to mind how it may be altered in disease states) remains sketchy, to say the least. Access is clearly an issue and one that has led to all but a handful of human studies of gut microbiota being based on fecal sampling—hardly a useful approach to the diagnosis of SIBO [11].

Another recent and exciting innovation, a capsule-based technology that provides real-time measurements of the major intraluminal gases (hydrogen, carbon dioxide, oxygen, and methane) as it moves through the gut, has further shaken the weakened foundation on which breath tests are built [12•]. Their studies, albeit limited at present to experiments in normal volunteers, clearly showed that an oral glucose load of 40 g is, indeed, incompletely absorbed and will, therefore, undergo fermentation in the colon, resulting in a breath hydrogen peak (the infamous "early peak").

Our most commonly relied upon technology is clearly not as reliable as we thought it was—great care needs to be exerted; therefore, in the interpretation of studies that claim to "discover" SIBO as the cause of yet another ailment. New technology will, hopefully, rescue us from this morass—technologies that not only enumerate the normal bacterial population of the small intestine but also measure their various metabolites (other than the gases that we currently measure). How else can one explain how the elderly, widely considered to harbor a less diverse microbiota [13], are so much more likely to develop SIBO [14]. Bacterial function may be more important than mere numbers; in the long run, metabolomics may hold the key to SIBO.

The Prevalence and Spectrum of SIBO Today

Give all that has been said above on the limitations of current diagnostic technologies, it should come as no surprise that there are no reliable data on the true prevalence of SIBO in the general population or even in at-risk groups. Yes, the recent literature again supports the association of SIBO with certain risk factors. Most notable among these are as follows:

1. *Altered anatomy* and, especially, any change that promotes stasis or exposure to colonic contents [15]. Though rare, jejunal diverticulosis is frequently complicated by SIBO [16].
2. *Hypochlorhydria*, including acid suppression. Here, much has been made of the role of proton pump inhibitors; yes, they slightly increase the risk for SIBO [14, 17] but the odds ratio calculated in a recent meta-analysis for SIBO with these widely used medications was only 1.71 [17].
3. *Dysmotility and hypomotility*. Any significant disturbance of small intestinal propulsion [15, 18, 19] be it hypomotility, as in scleroderma [20, 21] or disordered motility, including absence of the migrating motor complex [22]. It has also been suggested that ileocolonic sphincter hypotension may also predispose to SIBO [18]. The relationship between SIBO and motility may be bidirectional as there is some evidence to suggest that excessive production of methane may delay intestinal transit [23].
4. *Immune deficiencies*. SIBO has been described in association with hypogammaglobulinemia, both in inherited and acquired forms, as well as in disorders of cellular immunity, such as human immunodeficiency virus infection (HIV). Interestingly, vagal neuropathy has also been invoked in the causation of SIBO in relation to HIV infection [24].
5. *Small intestinal disease* and, especially, any disease that impairs defense mechanisms and/or promotes stasis, such as radiation enteritis or inflammatory bowel disease (IBD). A number of studies in recent years have revisited the prevalence of SIBO in IBD. SIBO has been described in up to 62% of patients with IBD (both ulcerative colitis and Crohn's disease) and its presence associated with symptoms suggestive of disease activity [25–27] and elevated levels of calprotectin in the stool [26]. Symptoms and indices of disease activity improve with antibiotic therapy alone [25, 27•]. Not surprisingly, SIBO, in Crohn's disease, has been associated with stricturing disease [26]. In a meta-analysis of available studies, the mean prevalence of SIBO in celiac disease was 20% [28] and was associated with persistence of symptoms despite institution of a gluten-free diet.
6. *Multifactorial*. Important examples include SIBO in association with chronic pancreatitis and liver disease.

   (a) In *chronic pancreatitis*, relevant factors include the loss of pancreatic enzymes, a decrease in intestinal motility consequent upon the inflammatory process, the effects of narcotics on gut motility, and the presence, in some instances, of intestinal obstruction. In a meta-analysis, the average prevalence of SIBO among those who suffered from chronic pancreatitis was 36% [29•]. In one study, the presence of SIBO was linked to an alcoholic etiology for chronic pancreatitis, the presence of diabetes, being on a proton pump inhibitor and requiring enzyme replacement therapy [30]; in others, relationships to clinical features were less clear-cut [31, 32]. SIBO has also been described in patients with acute pancreatitis and linked to disease severity [33].

   (b) SIBO has also been frequently documented in association with *liver disease*; another recent meta-analysis estimated an average prevalence of SIBO in chronic liver disease which ranged from 36 to 68% depending on test modality. They also noted similar prevalence rates in those with and without cirrhosis [34•]. In cirrhosis, SIBO has been linked with the occurrence of encephalopathy, both overt and subclinical [35], systemic endotoxemia, and spontaneous bacterial peritonitis [36]. Altered motility, impaired immunity and gut barrier function, as well as changes in the intraluminal milieu are among the factors that might contribute to SIBO in the context of liver disease.
7. *Relationship to SIBO unclear or yet to be defined*. An almost endless list of diseases and disorders has been linked, at one time or another, with SIBO.

   (a) Given the proposed metabolic role of the microbiome and the volume of experimental data to support its contribution to the genesis of *obesity* [37], it should come as no surprise that several studies have examined the prevalence of SIBO in obesity and related disorders, such as type II diabetes and nonalcoholic liver disease [38–44]. Data on the prevalence of SIBO in obesity, per se, are conflicting with one study, employing the lactulose breath hydrogen test, describing SIBO in 89% of obese subjects [40] and another noting an inverse relationship between SIBO and obesity among nonconstipated irritable bowel subjects [45]. Among individuals with type II diabetes the presence of SIBO has been associated with delayed orocecal transit [42]; this relationship does not appear to hold for obesity, in general [40]. SIBO has been shown to increase the risk for NAFLD among obese children [41] and more recent studies [43, 44] provide further support for a role for SIBO in NAFLD and nonalcoholic steatohepatitis (NASH) in adults. Here, mechanistic studies have identified a pathway involving bacterial engagement with Toll-like receptor 4 (TLR-4) and the pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) [37, 44]. The Roux-en-Y gastric bypass procedure appears to increase the occurrence of SIBO in obese subjects

while the adjustable gastric band has no such effect [39]. In a retrospective analysis of breath test database, SIBO was linked to the occurrence and severity of coronary artery disease [46]; a small prospective study provided some evidence to suggest that SIBO might promote atherosclerosis [47].

(b) The advent of the concept of the microbiota–gut–brain axis has provoked interest in the potential role of gut microbes in *neurodegenerative and neuroinflammatory diseases* [48]. SIBO has been described in association with Parkinson's disease [49–51] and multiple sclerosis [52]. In Parkinson's disease, SIBO prevalence appears to be related to disease severity [49, 50] but, as yet, the impact of SIBO eradication on motor or nonmotor symptoms has not been defined [51].

(c) In the recent literature, SIBO has been described in association with *environmental enteropathy* [53•], *deep venous thrombosis* [54], *Helicobacter pylori infection and its eradication* [55], *familial Mediterranean fever* (where its eradication seems to augment the response to colchicine) [56], and *gall stones* [57], as well as following *partial colectomy* [58, 59] and *cholecystectomy* [60].

8. *Irritable bowel syndrome* (*IBS*). By far the greatest controversy related to SIBO over the past decade and a half has been the proposal that SIBO is linked to irritable bowel syndrome (IBS). In the latest systematic review and meta-analysis, Chen and colleagues calculated a pooled prevalence for SIBO in IBS of 38%; diagnostic modality (breath test vs jejunal aspirate), older age, female sex, and diarrhea predominant symptomatology but not proton pump inhibitor (PPI) use were predictors of SIBO [61•]. Others, documenting this same association found SIBO occurrence was independent of PPI use [62], linked to immune activation [63] but unrelated to gastrointestinal symptomatology or psychiatric comorbidity [63]. Recent studies on therapies effective against SIBO do not help to clarify the issue with the response to antibiotic therapy appearing to be unrelated to the presence or absence of SIBO [64, 65]. Others, indeed, have identified mechanisms, other than its antibiotic effect, whereby rifaximin, which is widely used in both SIBO and IBS, might impact on symptoms [66]. Many factors serve to confound any attempt to interpret the literature on this proposed association: the nonspecific nature of IBS symptoms, the aforementioned limitations of the more commonly used diagnostic methods, variability in patient selection, shortcomings in study design, confounding factors, and the absence of convincing data to indicate that the eradication of SIBO has a long-lasting impact on the natural history of the disease. My own impression is that SIBO is not common in IBS but may be relevant to an IBS subgroup, such as postinfection IBS [67•]. I agree with the conclusion of Aziz, Tornblom, and Simren: "the SIBO-IBS hypothesis lacks convincing evidence but remains under scrutiny" [68•].

Complications of SIBO

The many clinical manifestations of SIBO have been described in detail elsewhere [2]. The recent literature provides further examples of an association between SIBO and malnutrition [69], coagulopathy [70], venous thromboembolism [71], and hyperammonemic encephalopathy [72].

Management

When one searches for high-quality evidence on which to base therapeutic decisions in SIBO one soon finds that the literature is scant and, in general, of low quality. Yes, rifaximin is effective in eradicating SIBO and resolving symptoms [73] and antibiotics are effective in those with scleroderma and SIBO [21], but beyond this, there is little to guide the clinician. Evidence to date suggests that probiotics may promote eradication but do not appear to be effective in preventing SIBO [74].

Summary

SIBO is not a new concept—it began life decades ago as a well-characterized cause of maldigestion and malabsorption. Now, it has morphed into a many-headed monster that seems to engulf all before it. Due to the absence of a true gold standard for the diagnosis of SIBO [75•], all of the literature on its prevalence in, and impact on, various disease states is somewhat suspect. In reviewing the literature from the past few years, I was struck by how similar rates for SIBO prevalence were across a host of disparate disorders (30–40%, typically). Are we merely detecting an epiphenomenon of simply being sick and tested? Responses to treatment are also inconclusive; not only is the evidence base scant but other impacts of our therapies could also be operative. Indeed, it is far from clear what exactly our commonly utilized antibiotics are doing. We desperately need a validated and reliable diagnostic methodology followed by high-quality clinical trials; only then will the true spectrum of SIBO be revealed. The "monster" that we now perceive SIBO to be may be no more than a phantom.

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Compliance with Ethical Standards

Conflict of Interest Eamonn M M Quigley reports consultancies with and/or research support from 4D Pharma, Alimentary Health, Allergan, Axon Pharma, Biocodex, Glycyx, Ironwood, Pharmasierra, Salix, Shire, Takeda, Vibrant, and Zeeland.

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