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Conventional, Complementary, and Controversial Approaches to Small Intestinal Bacterial Overgrowth

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Small intestinal bacterial overgrowth (SIBO), classically understood as an excess of bacteria and their associated byproducts in the small bowel, has become in recent years a progressively credible explanation for a variety of gastrointestinal symptoms. At the same time, clinical presentations associated with this entity are wide-ranging and overlap substantially with other heterogeneous diagnoses like irritable bowel syndrome. This ambiguity is compounded by a lack of standardized testing and treatment modalities, which can be frustrating for providers and patients alike. Herein we outline a contemporary understanding of SIBO pathophysiology, diagnosis, and therapy, with particular attention to their interface with diet and nutrition.

Once a highly contested diagnosis, small intestinal bacterial overgrowth (SIBO) has gained traction over the past several years as a reasonable explanation for a variety of gastrointestinal symptoms. This traction is attributable not only to an accumulating foundation of empiric evidence, but also to a growing general interest in the role of gut microbiota in health and illness. At the same time, persistent ambiguities surrounding SIBO with respect to clinical hallmarks, diagnostic testing, and preferred treatment approaches leave providers vulnerable to setting thresholds of suspicion that may be too high or too low. Likewise, patients frustrated by a lack of definitive answers may be prone to perseverating upon this clinical entity given its elusive, protean, and faddish qualities.

Classically, the pathophysiology of SIBO has been understood as an excess of bacteria in the small intestine beyond the conventional cutoff value of 10^5 colony forming units per milliliter (CFU/mL). This excess of bacteria, along with their associated metabolic processes and byproducts, leads in theory to various forms of maldigestion. More recent refinements in the SIBO disease model suggest that it may also involve the presence of inappropriate microbial species in particular

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regions of the small intestine. In a healthy state, proximal small intestinal microbiota are comprised primarily of Gram-positive aerobes, whereas the distal small bowel favors mostly facultative anaerobes in a gradient leading toward to the dense and almost exclusively anaerobic population of the colon.[1] Alongside bacterial overgrowth in absolute numbers, then, disturbances in these usual ratios have been suggested as potentially problematic.

Recent work has also focused on delineating qualitative distinctions among the various microbiota that might account for SIBO symptoms in any given individual. Elaborations in breath testing modalities have facilitated scrutiny of organisms producing methane and hydrogen sulfide as metabolic byproducts in response to an oral carbohydrate load, though the quantitative parameters for identifying them are subject to ongoing refinement.[2] Recognizing that bacteria are not the only microorganisms present in the body, some investigators have suggested that a parallel process of small intestinal fungal overgrowth (SIFO) may account for the persistence of symptoms in patients treated adequately for SIBO.[3,4] While such added layers of detail represent exciting avenues for future research, these distinctions remain difficult to draw clinically and thus, as speculation, can be clarifying and confounding in equal measure.

Clinical Features

Still, amidst these controversies, clinical patterns do exist to guide thinking about SIBO rationally. According to aggregated case series, among patients with SIBO, the most commonly reported symptoms tend to be diarrhea, abdominal pain, and abdominal bloating.[5] In large individual studies, however, symptom prevalence and severity have been shown to be poor predictors for the presence of SIBO as defined by hydrogen breath testing. Such analyses have considered a wide variety of gastrointestinal symptoms, including heartburn, chest pain, nausea, bloating, belching, flatulence, abdominal pain, constipation, and diarrhea, suggesting that while none is predictive of SIBO, any might in theory be associated with it.[6] That said, attention to alternative fermentative byproducts has yielded more significant associations. Methane production, for instance, is tied to constipation, perhaps by virtue of delayed gut transit.[7] Recently presented data on hydrogen sulfide production, meanwhile, suggest an association with diarrhea and abdominal pain.[8]

The overlapping presentations of irritable bowel syndrome (IBS) and SIBO have been scrutinized heavily, and the shifting relationship between these two categories can contribute to uncertainty on the part of both patients and providers. Recognizing that IBS is a diagnosis predicated on clinical criteria, SIBO is likely a mechanism contributing to symptoms in a subset of IBS cases, though not necessary an exclusive explanation. Prevalence data vary widely, with a recent meta-analysis suggesting that approximately one-third of IBS patients tested positive for SIBO by conventional, non-invasive methods.[9] SIBO has also been hypothesized to contribute to other clinically defined diagnoses, like functional dyspepsia, though experimental data to prove this link are thus far limited.[10]

Risk factors for excessive or otherwise altered small bowel microbiota include disturbances of small bowel anatomy or motility, predisposing in turn to bacterial stasis (including diverticula, post-operative adhesions, blind limbs, chronic opiate use, diabetic enteropathy, or underlying connective tissue disease such as systemic sclerosis) and impairments in the normal biochemical clearance mechanisms for bacteria in the small bowel (including hypochlorhydria mediated by proton pump inhibitors, for example, or reduced pancreaticobiliary secretions in the setting of chronic pancreatitis) (Table 1). Incompetence or surgical absence of the ileocecal valve has also been studied as a potential risk factor for SIBO, presumably by virtue of inappropriate reflux of colonic microbiota into the small intestine.[11] Given the imperfect nature of available diagnostics, as will be discussed below, recognizing clinical risk factors becomes a valuable means of establishing pre-test probability for SIBO before committing to a potentially protracted series of iterative therapies.

Diagnostic Evaluation

There are multiple modalities available for SIBO testing, though all are subject to important limitations. Quantitative culture of aspirated small bowel fluid is formally considered to be the diagnostic gold standard, though cost, invasiveness, and technical limitations (including

Table 1. Risk Factors for Small Intestinal Bacterial Overgrowth

Structural Abnormalities	Motility Abnormalities	Biochemical Abnormalities
• Post-operative adhesions • Small bowel diverticula • Small bowel strictures • Blind intestinal loops • Incompetent ileocecal valve	• Chronic intestinal pseudo-obstruction • Connective tissue disease (e.g. scleroderma) • Diabetes mellitus • Medications (e.g. opiates, anticholinergics)	• Hypochlorhydria (e.g. atrophic gastritis, proton pump inhibitor use) • Chronic pancreatitis • Common variable immunodeficiency

variations in bacterial concentration according to the region of small bowel sampled) make it impractical for routine clinical use.[12] By virtue of its relative convenience, breath testing has become a much more widespread surrogate technology for establishing a diagnosis of SIBO, though debate continues to surround basic questions of methodology and interpretation.

Breath tests are performed by asking patients to ingest a pre-specified carbohydrate substrate before quantifying exhaled gases at regular intervals as an indirect measure of small bowel bacterial metabolism. The choice of substrate is an important variable, since glucose is natively absorbed by the small bowel whereas lactulose is not; as such, glucose can be predisposed to more false negative results, while lactulose can lead to more false positives.[13] A recently published North American consensus document has formalized cutoff values for abnormality with regard to exhaled hydrogen and methane, a helpful frame of reference for an often subjective study.[14] A number of experts explicitly disagree with these values, however, citing conflicting data, flawed assumptions about carbohydrate transit through the small intestine, and the lack of a reliable diagnostic gold standard.[15]

Supportive data can be gathered from other laboratory parameters, most of which surround the nutritional implications of SIBO. Severe SIBO is classically associated with reductions in Vitamin B12, due to either competitive bacterial uptake or inhibited absorption, and excesses in folate, a byproduct of bacterial metabolism.[16] While certain bacterial species produce Vitamin B12, the majority are consumers, leading to a functional state of Vitamin B12 malabsorption.[17] In certain circumstances, elevations of methylmalonic acid may be a useful surrogate biomarker of SIBO even when the serum Vitamin B12 level is normal.[18] Fat malabsorption and deficiencies in the fat-soluble vitamins (Vitamins A, D, E, and K) have also been rarely reported, sometimes with clinically significant implications, including reduced bone density, night blindness, neuropathy, and coagulopathy.[19] These metrics are neither sensitive nor specific in isolation, of course, but can be useful points to remember with respect to pattern recognition.

Conventional Therapy

Given the inherent limitations of the tests discussed above, many providers consider empiric treatment for SIBO as a diagnostic modality in its own right. In this context, the most common approach is to utilize a course of antibiotics to reduce bacterial burden and evaluate for symptom improvement thereafter. This strategy errs on the side of overtreatment; however, increasing the number of patients exposed to the potential risks of antibiotic therapy, including medication side effects, precipitation of *C. difficile* colitis, and the development of resistant organisms.

A variety of antibiotics have been studied with roughly equivalent rates of success, suggesting that targeting specific bacteria may not always be necessary to facilitate the collapse of synergistic, polymicrobial colonies.[20] The studied dosages and durations of these antibiotics have also varied. Recent practice has favored the use of rifaximin, a poorly absorbed antibiotic, in part due to its reduced toxicity profile and in part due to a relatively more

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robust base of evidence, including randomized controlled trial evidence for its utility in IBS with diarrhea, a diagnosis that is often simultaneously entertained.[21,22] For methane-predominant SIBO, certain investigators have advocated using a combination of neomycin and rifaximin, which small data sets suggest is superior in this context to either antibiotic alone.[23]

Underlying risk factors for SIBO will predispose to recurrence after a successful course of antibiotic therapy and thus should be mitigated wherever possible. Such maneuvers might include optimizing blood glucose control, withdrawing gut-slowing or acid-suppressing medications, and perhaps even selectively instituting prokinetic drugs.[24] Even common risk factors can be potentially significant; some estimates suggest that proton pump inhibitors at daily dosing increase the small intestinal bacterial burden by 50- to 100-fold.[25] In situations where risk factors are significant and cannot be reversed, SIBO treatment may obligate the indefinite long-term use of multiple antibiotics in cycling fashion.

Alternative and Nutritional Therapy

A variety of alternative management options for SIBO have been proposed from within and beyond the physician community (Table 2). Among patients with a high threshold of suspicion for SIBO who are intolerant of, or unresponsive to, antibiotic medications, alternative interventions may be seen as attractive options despite a relative paucity of supporting data. Likewise, given the frequent link between food intake and symptom exacerbation, nutrition can be an avenue of native interest for patients with SIBO, though again the available evidence for any individual dietary strategy is sparse.

Diets proposed for SIBO tend to focus on reducing or eliminating foods easily fermented by bacteria and leading in turn to gaseous and osmotically active metabolic byproducts. The low FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet is perhaps the best known of these diets, but it should be noted that its effectiveness has been studied particularly in the context of IBS, not SIBO. Extrapolation regarding the potential benefit of this diet in SIBO rests on the known overlap between these two clinical entities, but to our knowledge, the evidence to support this extrapolation remains largely anecdotal.[26] Other popular diets proposed for bacterial overgrowth, under names like "the biphasic diet," "the fast tract diet," and "the SIBO specific diet," among others, are even less driven by published data but seem to function as *ad hoc* variations on the same basic theme of reducing intake of highly fermentable carbohydrates.

The identification and elimination of dietary triggers may be viewed as a relatively low-harm exercise to the extent that patients with SIBO understand that it represents a short-term and essentially palliative maneuver. Misapprehensions that dietary modification can treat bacterial overgrowth, or that dietary indiscretion can lead to worsening dysbiosis, should be avoided. Symptoms may be mitigated, but the underlying risk factors for SIBO remain. Providers should also counsel patients to keep their exclusions temporary and minimally restrictive, given the risk of developing disordered eating habits (that is, "orthorexia nervosa") and the potentially deleterious effects of carbohydrate restriction on the gut microbiome overall.[27,28] Registered dietitian involvement can be instrumental in facilitating healthful approaches to dietary optimization, including the identification and repletion of developing micronutrient and macronutrient deficiencies.

Beyond dietary modification, nutritional supplements have also been explored as alternative therapies for SIBO. A recent meta-analysis suggested that probiotics trend toward effectiveness in reducing bacterial burden and symptoms associated with SIBO, though interpretation is limited by heterogeneity in study methodology and the probiotic products under investigation.[29] By way of caution and contrast, however, a recent small study suggested that symptomatic SIBO could in fact be provoked by probiotic supplementation.[4] Herbal compounds for the treatment of SIBO are widely available, and at least one study has suggested comparable efficacy with rifaximin as measured by a negative follow-up breath test.[30] Again, however, variations in the composition of these commercial preparations limit the extent to which these findings are clinically actionable.

Table 2. Various Management Strategies for Small Intestinal Bacterial Overgrowth

Management Strategy	Examples	Caveats
Antibiotics	• Rifaximin • Neomycin • Ciprofloxacin • Metronidazole	• Studies vary with respect to dose and duration • Few formal studies for many antibiotic regimens • Specific agents associated with specific side effects (e.g. ototoxicity from neomycin) • Risk of precipitating antibiotic-associated complications (e.g. C. difficile colitis)
Probiotics	• Lactobacillus • Bifidobacterium • Saccharomyces boulardii • Mixed compounds	• Data are limited • Commercially available products vary significantly in bacterial composition and quantity • SIBO may be precipitated by probiotic use in rare cases
Dietary Intervention	• FODMAP reduced diet • "Biphasic diet" • "Fast tract diet"	• Data are extremely limited (and in many cases absent)
Herbal Supplements	• FC-Cidal™ (Biotics, Rosenberg, TX) • Dysbiocide™ (Biotics, Rosenberg, TX) • Candibactin-AR® (Metagenics, Aliso Viejo, CA) • Candibactin-BR® (Metagenics, Aliso Viejo, CA)	• Data are extremely limited • Commercially available preparations vary in composition and are minimally regulated
Address Underlying Predispositions	• Reduce acid suppression • Remove other offending medications (e.g. opiates) • Consider prokinetic medications where appropriate	• Prokinetic use in the small intestine is usually off-label • Weaning symptom-oriented medications can be difficult and often requires a bridging plan to alternative therapies • Certain risk factors (e.g. small bowel dysmotility in scleroderma) are irreversible

CONCLUSION

Approaching the question of SIBO responsibly requires acknowledging the persistent ambiguities surrounding the clinician's standard diagnostic and therapeutic tools. Recognizing clinical patterns can help determine how aggressively to query for SIBO when initial diagnostic and therapeutic modalities are unproductive. Furthermore, literacy with alternative strategies promoted to general audiences can facilitate more meaningful counseling in recognition of patients' pre-existing health attitudes and behaviors. ■

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