NFH
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SMALL INTESTINAL BACTERIAL OVERGROWTH:

Clinical Presentation, Risk Factors, Diagnosis, and Treatment

Clinical Handbook

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Paving the Path to Optimal Health

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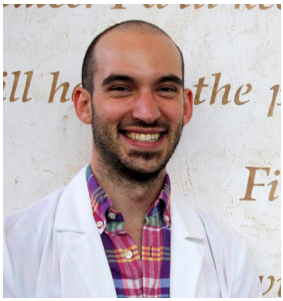
Dr Michael Traub obtained his undergraduate degree in biological sciences from the University of California, Irvine in 1976 where he conducted neurobiology research of learning and memory for Professor James L McGaugh. He graduated from the National College of Naturopathic Medicine in 1981 and completed a residency there in Family Practice and Homeopathy. He became board certified in homeopathic medicine by the Homeopathic Academy of Naturopathic Physicians in 1989. Dr Traub was recognized for his many years of service to the American Association of Naturopathic Physicians, including President from 2001-2003, when he was honored with the 2006 Physician of the Year Award. His father was a dermatologist, and this inspired Dr Traub to undertake extra study in this subject. He has taught dermatology at five of the seven accredited naturopathic medical schools in North America and is the author of “Essentials of Dermatologic Diagnosis and Integrative Therapeutics”. He is a recognized authority in the naturopathic profession on dermatology. He serves on the scientific advisory boards of several natural product companies, and has been actively engaged in clinical research for most of his career. Dr Traub has been medical director of Lokahi Health Center in Kailua Kona, Hawaii for the past 29 years. He is also board certified in naturopathic oncology by the American Board of Naturopathic Oncology.



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Maxwell Hunter Crispo was raised in Ancaster, Ontario, Canada. He graduated Bachelor of Arts and Science from the University of Guelph in 2013, with degrees in Nutritional and Nutraceutical Sciences and Ethics in the Life Sciences. He completed his naturopathic medical education at the Canadian College of Naturopathic Medicine. Dr Crispo graduated valedictorian of his class in 2018 and matched for an integrative oncology residency in Hawaii at Lokahi Health Center under the clinical direction of Dr Michael Traub, ND, FABNO. Dr Crispo is currently employed as a resident naturopathic physician at Lokahi Health Center in Kailua-Kona, where he offers Primary Care Medicine, as well as focused treatment in Naturopathic Integrative Cancer Care. At the completion of his residency, he will qualify for consideration and to write the exams to become a Fellow of the American Board of Naturopathic Oncology (FABNO). Dr Crispo is also a registered Integrative Yoga Therapy teacher, Ayurvedic Lifestyle Counsellor and has a University Certificate in Food Science. Max lives in Holualoa on the Big Island of Hawaii and in his free time enjoys exploring the many beaches of Hawaii, kayaking and cooking.

EDITOR'S INTRODUCTION

Diagnosis, prevention and treatment of small intestinal bacterial overgrowth (SIBO) represents a fast growing area for health care professionals. Indeed the gut microbiome in its larger sense is now being increasingly recognized as contributing to overall wellness. Optimization of the gut microbiota and SIBO are priority areas shared by our team at Nutritional Fundamentals for Health, which offers a cluster of products directed at this sector of patient care. Accordingly, the present Handbook is intended to serve as a practical clinical reference guide for practitioners interested in up to date contemporary approaches to prevent, treat and manage health concerns specific to SIBO. Written by Dr Michael Traub, a leading naturopathic doctor in this arena of health care readers can be assured that they are being provided the most comprehensive, informed recommendations available. It is our hope at NFH that this topic, along with the others in our ongoing 2020 Handbook series, will be positively received by practitioners in the natural health product space.

PREFACE

Small intestinal bacterial overgrowth (SIBO) is a common disorder, yet poorly recognized even within the conventional gastroenterology community. There is growing awareness of SIBO in North America since the 2006 publication of Pimentel's book "A New IBS Solution: Bacteria – The Missing Link in Treating Irritable Bowel Syndrome." SIBO tends to recur after initial treatment and successful ongoing management requires an understanding of risk factors, appropriate testing, and treatment strategies. The purpose of this Handbook is to provide a current evidence-based review of SIBO, predisposing factors, diagnostic tests, and therapies to educate physicians in its clinical management. The intention is to present the totality of the published data available, with a consideration of relative merits and limitations of available studies. Interventions should always be individualized to each patient's risk factors, history, goals, and current health status.

I would like to acknowledge my mentors in my evolving understanding of SIBO, especially Allison Siebecker ND, MSOM, LAc, Steven Sandberg-Lewis ND, DHANP, Mark Pimentel MD, Carmello Scarpignato MD, Leonard Weinstock MD, Satish Rao MD, PhD, and Angela Pifer MS, LCN, CN, FMN.

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KEY PRINCIPLES

Methods: The evidence and best practices summarized in this Handbook are based on relevant scientific publications, systematic reviews, and expert opinion where applicable.

Best practice advice:

1. A stepwise approach to rule-out SIBO and underlying disorders should be followed in IBS patients with persistent GI symptoms, including reliance on laboratory tests, breath testing, endoscopy with jejunal aspirate, and diagnostic imaging.
2. In those patients with initial positive response to treatment, clinicians may consider repeat breath test monitoring to facilitate anticipatory management.
3. Anatomic abnormalities or structural complications should be considered in patients with obstructive symptoms including abdominal distention, pain, nausea and vomiting, obstipation or constipation.
4. breath testing monitoringAntimicrobial therapy should be offered to patients who test positive for SIBO. Treatment of choice is rifaximin, 550 mg TID x 14 d, as well as non-pharmacologic antimicrobials such as allicin, berberine, oregano, Neem, and probiotics.
5. Low FODMAP and/or Elemental Diet may be offered for management of functional GI symptoms in SIBO with careful attention to nutritional adequacy. Patients should be screened and corrected for any nutritional deficiencies.
6. Prokinetic medication should be offered to SIBO patients for prevention of recurrence including prucalopride, low-dose erythromycin, low-dose naltrexone, ginger root, and Iberogast.
7. Psychological therapies including cognitive behavioral therapy, hypnotherapy, and mindfulness-based therapy should be considered in SIBO patients with functional symptoms.
8. Probiotics may be considered for treatment of functional symptoms in SIBO.
9. Structural therapies should be offered to SIBO patients, such as visceral therapy or pelvic floor therapy.
10. Physical exercise should be encouraged in SIBO patients with functional GI symptoms.

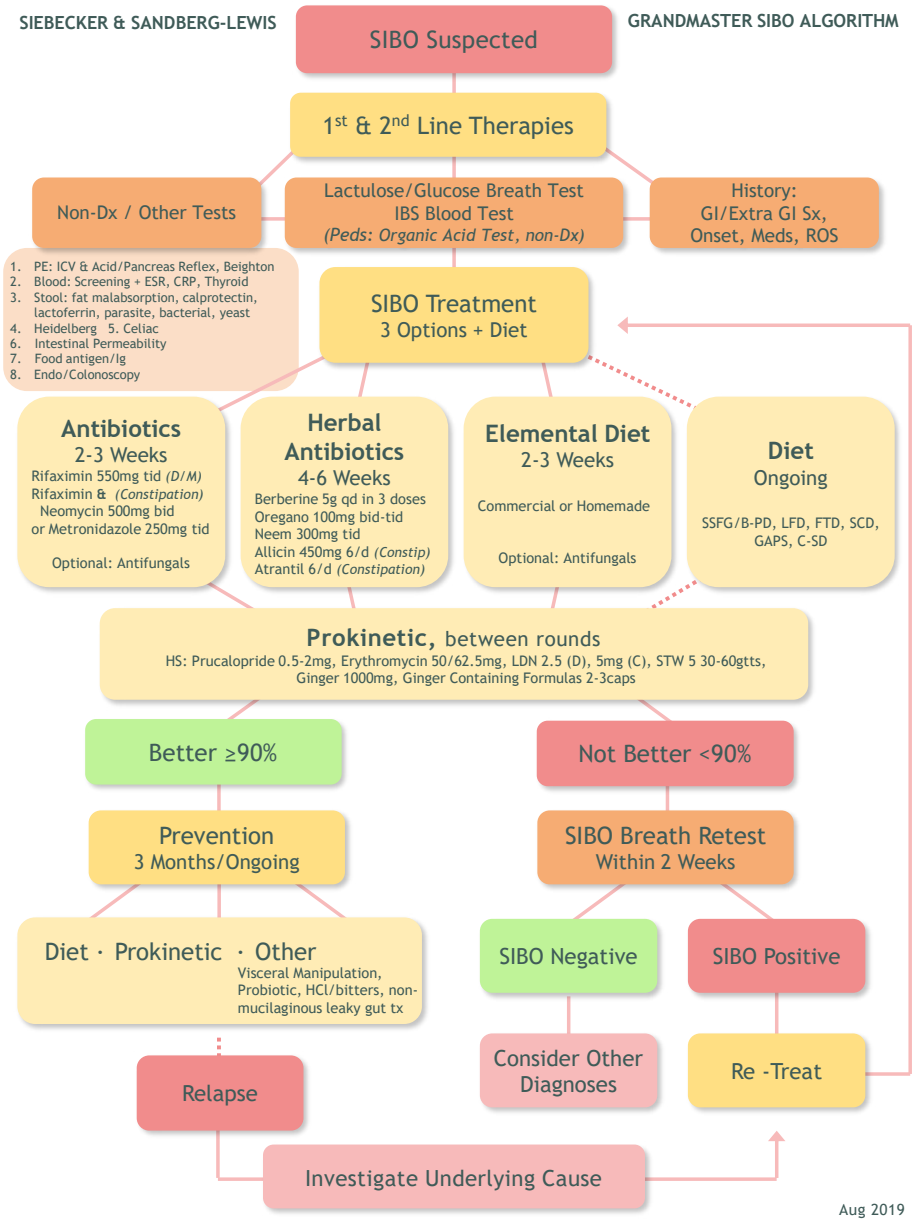
PURPOSE

Abdominal gas, bloating, distension, flatulence, discomfort, constipation and/or diarrhea are the cardinal symptoms of irritable bowel syndrome (IBS) and SIBO, but they do not necessarily predict positive diagnosis. A meta-analysis published in 2018 found that 40% of IBS patients had SIBO diagnosed by breath tests as a contributing cause of their symptoms (1). Females, older age, and IBS-diarrhea compared with other IBS subtypes increased the risk of SIBO; proton pump inhibitor use was not associated with SIBO in this review.

The overarching goal of this Handbook is to provide a pathway for clinicians to

help alleviate the considerable suffering and impact on quality of life for the many patients who present with the symptoms of IBS and SIBO. Siebecker and Sandberg-Lewis have developed an algorithm for this purpose:

Figure 1: Grandmaster SIBO Algorithm



Predisposing risk factors for SIBO include use of proton-pump inhibitors, abdominal surgery, IBD, hypothyroidism, Parkinson's disease, high carbohydrate diet, diabetes, dysmotility (e.g. history of C. jejuni infection, opioids, systemic sclerosis), spinal cord injury, traumatic brain injury, a history of food poisoning,

repeated courses of antibiotics, and anxiety. Small intestinal aspirate and culture with growth of 10^3-10^5 cfu/mL is accepted as the best diagnostic method, but its invasiveness and expense are limitations. Lactulose or glucose breath testing is non-invasive but indirect and needs further validation and standardization for SIBO. Antimicrobial treatment with antibiotics provides symptomatic benefit by decreasing bacterial overgrowth in the small bowel. Fifteen studies have demonstrated effectiveness and tolerability of rifaximin, a non-systemic antibiotic. Systemic antibiotics (neomycin and metronidazole) have shown efficacy in limited numbers of controlled trials. Herbal antimicrobials have demonstrated equivalent efficacy to rifaximin. Prokinetic medications are effective for preventing relapse after antimicrobial therapy. Low FODMAP and/or elemental diets are beneficial for symptomatic relief. With increased awareness of SIBO and more rigorous clinical trials, the outlook for successful management is bright (2).

INTRODUCTION

The gastrointestinal (GI) tract has the largest microbiota in the human body. The colon is where 38 trillion bacteria reside. The healthy duodenum typically has a low concentration of bacteria (numbers increase progressively along the course of the small intestine). SIBO is defined as an elevated amount of normal commensal bacteria in the small intestine, in addition to non-specific symptoms of gas, abdominal discomfort and abnormal bowel movements. Diagnosis is problematic in that symptom scores are not significantly different in patients who test positive or negative with duodenal aspirate or breath testing ($p=0.9$) (3).

CLINICAL PRESENTATION, PREVALENCE AND ETIOPATHOGENESIS

In the decades since irritable bowel syndrome was first described, millions of individuals have suffered for years, with lower quality of life and social isolation, as the attempt to find a cause proved fruitless. And like many illnesses that are not well understood, the tendency is to attribute the disease to the psychological condition of the patient.

The prevalence of IBS and SIBO varies with criteria used to define them, and among countries, from 1.1% to 40% for IBS. Globally, the pooled prevalence of IBS was 11.2% (4). Variability in patient populations and methods used to establish a diagnosis in studies has made prevalence of SIBO challenging to estimate (5).

One of the factors that plays a major role in SIBO is small intestinal dysmotility, which was found to be present in 86% of patients with IBS and SIBO versus 39% of patients with IBS without SIBO (p=0.02) (6). Dysmotility can be a sequelae of food poisoning, due to inhibition of the small intestinal migrating motor complex (MMC) by cytolethal distending toxin. Other conditions that can impair the MMC include diabetes mellitus, post-surgical or post-infections adhesions, and systemic sclerosis.

The evidence linking SIBO with use of proton-pump inhibitors (PPIs) is contradictory – some studies support such an association (7, 8) others do not (9, 10). The concern is that by inhibiting gastric acid, PPIs may allow overgrowth of small intestinal bacteria.

DIAGNOSIS OF SIBO

Endoscopic duodenal aspirate and culture is considered to be the best available diagnostic method for SIBO. A threshold of $>10^3$ cfu/mL is the accepted standard for a positive test. Aseptic technique is essential to minimize contamination from outside the duodenum. This can be accomplished with a 6F Liguory catheter with multiple holes in the sides of the tip for aspiration. The procedure is described in detail in Rao's 2019 paper (Rao, ibid). In addition to the potential for specimen contamination, the limitations of small bowel culture include the invasive procedure, cost, detection of only proximal SIBO, and the possibility of not detecting bacterial strains that do not grow well under standard culture conditions.

Breath testing is a noninvasive, relatively inexpensive method for diagnosing SIBO, but lacks a standardized methodology (Rezaie, ibid). Following appropriate preparation, the patient swallows a carbohydrate substrate such as glucose, lactulose, or fructose that GI microbes metabolize and then produce hydrogen and/or methane gas. Some of the gas is absorbed from the intestine and the breath specimens that are collected and analyzed provide an indirect measure of detecting SIBO (11).

The 2017 North American Consensus from the American Journal of Gastroenterology recommends the following for breath testing: 1) avoidance of antibiotics for four weeks and prokinetic medications and laxatives for one week before breath

testing (Rezaie ibid); 2) a strict diet of no fermentable carbohydrates for the day prior to specimen collection; 3) fasting for 8-12 hours prior to collecting specimens; 4) avoidance of smoking the day of the specimen collection; and 5) minimizing physical exertion during specimen collection.

The test dose is 75 g of glucose, 10 g of lactulose, or 250 mg of fructose, mixed in 250 mL of water. Specimens are collected at baseline and every 15-20 minutes following the test dose for 2-4 hours. Glucose and fructose are monosaccharides and absorbed in the proximal small bowel. Fructose is suitable for patients with diabetes. Lactulose is a non-absorbable disaccharide that reaches the colon. The specimens can be collected at home and are stable for 14 days. The analytical testing can be performed in the clinician's office or in a diagnostic laboratory.

An increase in hydrogen concentration of >20 ppm from baseline within 90 min and/or an increase of methane of >10 ppm within two hours are considered positive tests for SIBO. This sounds straightforward, however, accurate interpretation of breath test results requires some training and experience. A negative duodenal aspirate and culture and/or negative breath test would rule out SIBO and leave the patient with a diagnosis of IBS. Symptoms are similar, but IBS can exist without SIBO. A serologic test has recently been developed that can be used to develop some types of IBS (IBSchek – to be described in the following section). A recent systematic review and meta-analysis of 14 breath test studies for SIBO compared lactulose (LBT) and glucose (GBT) sensitivity and specificity and yielded the following results: pooled sensitivity and specificity of LBT and GBT were 42.0%/70.6% and 54.5%/83.2%, respectively (12). A cut-off of H2 < 20 ppm gave a slightly better result than >20 ppm, and breath tests were better predictors of SIBO in patients with surgical reconstructions of the GI tract.

Rao et al published a study in 2019 to determine the diagnostic utility of breath tests that assess for SIBO, fructose or lactose intolerance, and the predictive value of symptoms in 1230 patients (13). The prevalence of SIBO was 33%, fructose intolerance 34%, and lactose intolerance was 44%. Hypersensitivity was found with a prevalence of 16% and 9%, respectively, during fructose and lactose breath tests. Although gas (89%), abdominal pain (82%), and bloating (82%) were highly prevalent, pretest symptoms or their severity did not predict an abnormal breath test, but symptoms during the breath test facilitated diagnosis of SIBO, fructose, and lactose intolerance and hypersensitivity.

The glucose breath test has good specificity but low sensitivity in that it detects only proximal SIBO since the glucose is completely absorbed in the proximal jejunum. Lactulose provides higher sensitivity, but has a high risk of false positive results since the rise in breath hydrogen can reflect the arrival of lactulose in the cecum. There is a need for better substrates, standardized methodology, and validation for breath testing to be reliable. When breath test results are not definitive when SIBO is suspected, additional testing may be needed. New approaches to breath testing have been explored. One involves glucose administration via endoscopy rather than orally. Two orally ingested capsules have also been developed, but they require further clinical trials and validation (Rao, ibid). Another limitation of breath testing is that it fails to identify SIBO when patients have "non-hydrogen and non-methane-producing colonic bacteria,

which yields a flat line on breath testing. Bacterial gas kinetics is a complex process that must be taken into account when breath gas results are interpreted. Gas exchange between hydrogen producers and hydrogen consumers, such as methanogens and sulfate-reducing bacteria, is a process in which the availability of hydrogen depends on both its production and removal. Hydrogen sulfide (H_2S) is a crucial gas involved in this process as it is a major hydrogen-consumptive pathway involved in energy exchange.

It has recently been discovered that elevated levels of H_2S in exhaled breath are found in IBS-D individuals with both positive and negative SIBO testing arising from the activity of intestinal sulfate-reducing bacteria as well by multiple host detoxification mechanisms (14, 15).

H_2S may contribute to the pathogenesis of SIBO, help us better interpret breath testing, and may as such be a useful biomarker.

Practical Clinical Tips:

Lactulose may be a good option for testing SIBO patients with constipation, since it has a laxative effect. Glucose may be a better option for SIBO patients with diarrhea, as lactulose may significantly aggravate their diarrhea.

Methanogenic SIBO and mixed methane/hydrogen SIBO patients are generally more resistant to treatment than those with hydrogen SIBO. It may be more appropriate to call methane SIBO by the term “methanogen syndrome” or “methanogen bloom”. Methanogenic organisms tend to be Archea, not bacteria, and prescription antibiotics are not as effective when used as monotherapy. It is common that as methanogen overgrowth decreases and less hydrogen is consumed, hydrogen levels rise. (Siebecker, A. 2019 personal communication).

Risk Factors in Developing SIBO

Conditions that can predispose to SIBO are numerous. Various clinical studies have investigated these associations of SIBO in disease states where well-known risk factors for its occurrence are present. Such factors include diarrhea-predominant IBS [IBS-D], hypo-chlorhydria, narcotic intake, low hemoglobin, disorders of intestinal structure or motor function, pancreatic insufficiency, and chronic liver disease (16).

The author reviewed 112 publications in PubMed using the search terms “small intestinal bacterial overgrowth and risk factors.” Practitioners must use their clinical judgement in addition to the available evidence to assess and address underlying susceptibility factors that are essential to optimal management of SIBO. Some key papers from that review follow.

A 2017 paper categorized 1809 patients who had undergone hydrogen breath testing to rule out SIBO. Suspected contributors were weighted and ranked based on four pathophysiological pathways including i) impaired gastric acid barrier, ii) impaired intestinal clearance, iii) immunosuppression, and (iv) miscellaneous factors including thyroid gland variables (17).

Impairment of the gastric acid barrier (gastrectomy, odds ratio: OR = 3.5, PPI therapy OR = 1.4), impairment of intestinal clearance (any resecting gastric surgery

OR = 2.6, any colonic resection OR = 1.9, stenosis OR = 3.4, gastroparesis OR = 3.4, neuropathy 2.2), immunological factors (any drug-induced immunosuppression OR = 1.8), altered thyroid gland metabolism (hypothyroidism OR = 2.6, levothyroxine therapy OR = 3.0) and diabetes mellitus (OR = 1.9) were associated significantly to SIBO. Any abdominal surgery, ileocecal resection, vagotomy or IgA-deficiency were found not have any influence, and a history of appendectomy decreased the risk of SIBO. Multivariate analysis revealed gastric surgery, stenoses, medical immunosuppression, and levothyroxine to be the strongest predictors.

Levothyroxine therapy, as a proxy for hypothyroidism, was the strongest contributor in a simplified model. The most important contributors for the development of SIBO in this largely unselected cohort in descending order were levothyroxine use, impairment of intestinal clearance, immunosuppression, and impairment of gastric acid barrier.

Dysfunctional Gastric Acid Barrier

Gastric acid is an effective barrier against the invasion of ingested microorganisms. Although available data are contradictory, several meta-analyses and systematic reviews have reported that patients treated with PPIs, as well as post-gastrectomy patients, have a higher frequency of SIBO compared to patients who lack the aforementioned conditions. Reduction of the acid barrier function is expected in atrophic gastritis (18), use of proton pump inhibitors (19), and gastrectomy (20).

In a 2018 study performed at Indiana University evaluating 76 patients with suspected SIBO, 37 presented with a positive culture of small bowel aspirate (based on > 10^3 cfu/mL) and 39 presented with a negative culture. Conditions ($p=0.02$) and surgery ($p<0.01$) associated with decreased gastric acid were associated with SIBO (21).

Impaired Intestinal Clearance and Dysmotility

Anatomical pathologies are associated with small intestinal stagnation and obstruction, e.g. strictures, adhesions, small bowel tumors, duodenal and jejunal diverticula, but there are little data to support these hypotheses. (Brechmann, ibid.) The existence of blind loops might be the common mechanism. Conditions that allow for stool reflux, such as ileocecal resection or low ileocecal valve pressure, are also considered to confer predisposition to SIBO (22).

Evidence does exist supporting the role that impaired motility plays in SIBO (23), such as diabetes (24), small intestinal pseudo-obstruction, and neurological diseases, including Parkinsonism (25) and multiple sclerosis (26).

Diabetic GI complications are termed diabetic enteropathy (DE) with symptoms of diarrhea, fecal incontinence, constipation, dyspepsia, nausea and vomiting. The long-held belief that vagal autonomic neuropathy is the primary cause of DE has recently been replaced by new findings that hyperglycemia and the ensuing oxidative stress on neural networks, including the nitrergic efferent nerves and interstitial cells of Cajal (ICC), have major roles in the development of DE (27).

DE occurs in most patients with diabetes, yet early diagnosis and treatment to prevent irreversible detrimental effects on the small bowel are lacking. Delay in

diagnosis is compounded insofar that DE symptoms are similar to gastroparesis and adverse effects from diabetes medications. Current diagnostic methods such as manometry, wireless motility capsules, and scintigraphy are not regularly available to clinicians. Rifaximin can, however, be helpful in relieving symptoms of DE.

Since 1977 it has been known that a subset of patients with SIBO show reduced motility with fewer contractions of the migrating motor complex (MMC) (28) and Pimentel showed that successful treatment of SIBO improves motility (29). Gastroparesis has been shown to be associated with SIBO. In one study, 39% of patients with gastroparesis had evidence of SIBO by LBT (30).

Little is known about SIBO and drugs used to decrease intestinal motility, although opioids are recognized as a contributing factor (31).

Hypothyroidism is associated with altered GI motility including impairment of intestinal clearance or constipation, and is commonly seen in patients with SIBO. Hypothyroid patients with chronic GI symptoms should be evaluated for the possibility of SIBO. Hypothyroidism can thus be grouped with these other conditions that impair intestinal clearance and impair motility.

Post-Infectious Gastroenteritis

The theory that many cases of SIBO result from post-infectious gastroenteritis is based primarily on research in rat models. Host anti-cytolethal distending toxin B (CdtB) is common to all pathogens causing gastroenteritis. Pimentel et al. demonstrated in a 2015 study that anti-CdtB antibodies cross-react with vinculin in the interstitial cells of Cajal (ICC) and myenteric ganglia in a rat model, disrupting normal gut motility, and the circulating antibody levels and loss of vinculin expression correlate with Campylobacter jejuni exposures and SIBO (32).

In 2017, Pimentel and colleagues found that anti-CdtB and anti-vinculin titers and positivity rates are higher in IBS-D and IBS-M, and lower in IBS-C subjects, and suggested that IBS-C is pathophysiologically distinct from IBS subtypes with a diarrhea component (33).

This led Pimentel and his group to develop the IBSchek, the first clinically validated blood test (ELISA-based) to positively diagnose IBS based on the presence of antibodies to CdtB and vinculin (34). Based on the 2017 validation study of nearly 3000 patients, the test is over 90% specific and approximately 40% sensitive. The test was developed so that if it is positive, the patient has IBS and if it is negative, the patient may not. This test prevents the need for multiple investigations, which have inherent risks, and prevents the wasting of time and health resources to diagnose IBS. Providers often order multiple and different procedures because they do not feel comfortable with the diagnosis of IBS. Having a single test that says whether or not a patient has the condition helps the provider and patient feel confident about the diagnosis. A study showed that it takes an average of more than six years of seeing physicians and undergoing tests to reach a definitive diagnosis of IBS from the onset of symptoms (35). In contrast, this blood test takes only a few days to establish a diagnosis. The test is not perfect, but it is a good start to at least identify a subset of patients with IBS. Although it is helpful for identifying patients with IBS-D and -M, it is not useful in

the setting of IBS-C. There is also some criticism about the low sensitivity of the test. However, the test was designed to diagnose specifically the subgroup of IBS that is derived from gastroenteritis, not every subgroup of IBS.

Liver Disease

SIBO is often found in patients with cirrhosis as a result of impaired intestinal motility and delayed transit time, both of which are worsened the more severe the liver disease. Additional risk factors for SIBO commonly seen in cirrhotic patients include coexisting diabetes, autonomic neuropathy, and alcohol abuse. In cirrhotic patients, the presence of SIBO can lead to dire consequences due to increased intestinal permeability and bacterial translocation into the systemic circulation. SIBO thus poses a significant risk for both bacterial peritonitis and hepatic encephalopathy in cirrhotic patients (36).

In a meta-analysis of 19 case-control studies of chronic liver disease (CLD), SIBO was found in 35.8% of cases compared to 8% of controls with breath tests, and 68.3% of CLD patients compared to 7.9% of controls with small intestinal culture (37).

In a case-control study of 372 patients who had an abdominal imaging study and a glucose breath test, those who tested positive for SIBO had an increased risk for hepatic steatosis (38).

Obesity is thought to alter small bowel motility, leading to susceptibility to SIBO. Although obesity was significantly associated with SIBO in one study, the findings suggested small bowel transit time (SBTT) did not account for the obesity-SIBO relationship (39). However, a recent systematic review and meta-analysis of five studies and 515 patients found that in Western countries, the risk of SIBO was significantly three times higher among obese patients compared to those who were not obese (40). There was no significant difference in non-Western patients.

Patients with colectomy have a significantly higher prevalence of SIBO/SIFO and greater severity of gastrointestinal symptoms (Rao 2018, ibid).

A systematic review and meta-analysis to determine the prevalence of SIBO in 1175 adult patients with IBD and 407 controls found a substantially higher prevalence of SIBO in IBD patients compared to the controls. Prior surgery and the presence of fibro-stenosing disease were risk factors for SIBO in IBD (41).

SIBO is a common, difficult to treat complication of systemic sclerosis (42).

Impaired Immunity as a Causative Factor for Sibo

Data about the role of the immune system in SIBO are limited and contradictory. A higher bacterial load of jejunal aspirates was shown in ten children with IgA deficiency and seven with other rare immunodeficiency syndromes (43). Although pharmacotherapy is the most common reason for immunosuppression in adults, data are scarce for immunosuppressed adult SIBO patients. However, immunosuppressive medication in patients with Crohn's disease was shown to have no association with SIBO (44), while corticosteroids did predispose to SIBO in one cohort (45).

Miscellaneous Factors

Various other diseases and disorders have been described as being associated with or complicated by SIBO, such as alcohol consumption, chronic pancreatitis, pancreatic cancer, microscopic colitis, cystic fibrosis, spinal cord injury, and traumatic brain injury.

Alcoholics are reported to have higher rates of SIBO, as diagnosed by jejunal aspirate. A retrospective chart review, completed for 210 consecutive patients who underwent the LBT, found that moderate alcohol consumption was a strong risk factor for SIBO. Cholecystectomy appeared to be protective against SIBO. Neither PPI use nor tobacco use was associated with an increased risk of SIBO (46).

SIBO is more common in patients with chronic pancreatitis, both alcoholic and idiopathic (47).

A recent study found a high prevalence of SIBO in pancreatic carcinoma and cholangiocarcinoma. SIBO also correlates positively with toll-like receptor 4 (TLR-4) expression, suggesting that SIBO could be a risk factor for the pathogenesis of pancreatic carcinoma and cholangiocarcinoma, in which TLR-4 signaling may be involved (48).

Patients with IBS/SIBO refractory to treatment should undergo colonoscopy to rule out microscopic colitis (49).

Some patients with celiac disease continue to experience GI symptoms months after adopting a gluten-free diet, despite optimal adherence. A study of 15 of such patients found that ten of them tested positive on lactulose H2-BT. After rifaximin therapy at 800 mg/day for one week, all patients were symptom-free (50).

Patients with cystic fibrosis are more likely to have elevated fasting breath hydrogen levels compared with controls, suggestive of a high prevalence of small bowel bacterial overgrowth in CF patients. Medications commonly used by CF patients may influence intestinal health. The use of azithromycin is associated with an increased risk of a positive breath test. Use of laxatives and inhaled ipratropium are associated with a decreased risk of a positive breath test (51).

Visceral Hypersensitivity

In the last decades, several studies have shown that, compared to healthy volunteers, IBS patients have an increased sensitivity to colonic distension (52, 53). Fecal metabolites, including organic acids and amino acids, may increase visceral sensitivity and exacerbate symptoms of IBS (54).

This so-called visceral hypersensitivity, now recognized as an important pathophysiological mechanism underlying symptom generation in IBS, is present in 33 to 65% of IBS patients (55). Multiple neurological mechanisms are involved in the sensitization of visceral pain, leading to increased perception of luminal stimuli. Early-life adverse events create a predisposition to visceral hypersensitivity later in life, which are subject to epigenetic control and modulated through gut microbiota and the gut-brain axis (56). This is an active

area of research in regards to IBS, but there are currently no PubMed references specific to SIBO and visceral hypersensitivity.

Mood Disorders

Psychological factors and low-grade mucosal inflammation are believed to contribute to the pathogenesis of IBS (57, 58). There is only one published article at the time of this writing specifically addressing SIBO and psychological factors (59). In this Chinese study, published in 2016, 89 patients with IBS and 13 healthy volunteers underwent lactulose HBT with concurrent ^{99m}Tc scintigraphy. The prevalence of SIBO was 39% in IBS patients and 8% in controls. Patients with IBS had higher anxiety, depression and Life Event Stress scores, but these measures were not significantly different in SIBO-positive and SIBO-negative IBS patients. Psychological disorders were not associated with SIBO. Serum IL-10, a cytokine associated with severe anxiety and depression, was significantly lower in SIBO-positive than SIBO-negative IBS patients. Similar well-designed studies with larger numbers and other populations are necessary to better understand any association of mood disorders and SIBO, although the mechanisms are likely similar to those found to be true for IBS.

Finally, a provocative study conducted at the Cleveland Clinic published in 2018 showed a significantly increased risk of coronary artery disease (CAD) among patients testing positive for SIBO, identified using the glucose hydrogen/methane breath test. This result lends support to a possible role of gut bacteria and their metabolic by-products in the development of CAD, and that in the presence of risk factors, patients with SIBO may benefit from assessment for CAD (60). Such risk factors may include the previously described conditions associated with SIBO such as obesity, hepatic steatosis, and diabetes. In addition, the number of pathogens to which an individual has been exposed (pathogen burden) has been linked to CAD risk, and this association is modulated by variations in serum IL-6 levels dependent on the IL6/G-174C polymorphism (61).

From the preceding section on SIBO risk factors, SIBO is clearly a condition in which it is incumbent on the responsible practitioner to establish a comprehensive differential diagnosis. The author learned this lesson well when he obtained an abdominal ultrasound for a patient who was not responding adequately to treatment for SIBO, which revealed a 5 cm mass on the head of the pancreas, subsequently leading to the diagnosis of stage IV pancreatic carcinoma. The patient died less than three months later.

Identifying and addressing contributing factors to SIBO at the outset will hopefully afford patients the optimal chance of recovery.

TREATMENT OF SIBO

Pharmacologic Antibiotics

Once the diagnosis of SIBO is made, the treatment plan consists of four essential components:

1. Antimicrobial therapy (pharmacological and botanical)
2. Therapeutic diet

3. Prokinetic medication
4. Addressing underlying factors

And 4 optional components:

5. Psychological therapy
6. Probiotics
7. Structural therapy
8. Physical exercise

These components are briefly summarized below and then discussed in greater detail.

1. Antimicrobial therapy options are as follows:
   a. Rifaximin 550 mg TID x 14 d
   b. Botanical antimicrobials: allicin, berberine, oregano, Neem BID x 4-8 wk
   c. Elemental diet x 14-21 d
2. Therapeutic Diet:

   Low FODMAP diet with careful attention to nutritional adequacy.

3. Prokinetic medication;
   a. Prucalopride 0.5-1 mg at bedtime (qhs)
   b. low-dose erythromycin 50-62.5 mg qhs
   c. low-dose naltrexone 1.5-5 mg qhs
   d. ginger root 1000 mg qhs
   e. Iberogast 20 drops TID
4. Addressing underlying factors: Individualized treatment for obesity, diabetes, adhesions, or IBD.
5. Psychological therapies, including cognitive behavioral therapy, hypnotherapy, mindfulness-based therapy, should be considered in SIBO patients with functional symptoms.
6. Probiotics may be considered for treatment of functional symptoms in SIBO.
7. Structural therapies should be offered to SIBO patients including visceral therapy and pelvic floor therapy.
8. Physical exercise should be encouraged in SIBO patients with functional GI symptoms.

Antimicrobial Therapy

Rifaximin

Rifaximin, a modification of rifamycin, is a nonabsorbable antibiotic that is approved for the treatment of IBS-D. It is widely used in the treatment of SIBO and in clinical trials. Gatta and Scarpignato published a systematic review with meta-analysis in 2017 on the safety and effectiveness of rifaximin in SIBO (62). These authors included 32 studies involving 1331 patients. The authors rated the quality of the studies as poor: 75% of the studies were conducted in Italy. Most were not randomized. In the 10 studies that allowed for analysis, improvement or resolution of symptoms in patients with eradication of SIBO was 67.7%. Adverse effects were seen in 4.6%, but only 0.47% of them had to discontinue therapy.

Rifaximin dose and co-therapy with soluble and insoluble fibers and probiotics, including Lactobacilli and Bifidobacteria, were independently associated with an increased eradication rate (63).

Rifaximin fulfills all the criteria for the ideal antibiotic for GI infections (64), lacks drug-drug interactions, and is considered an antibiotic with eubiotic properties as it does not negatively alter beneficial intestinal flora (65), does not cause yeast overgrowth, nor create resistance (66). The branded formulation of the drug is preferred, as it contains only the crystal polymorph -α, while a higher systemic bioavailability has been demonstrated for the generic formulation containing an amorphous form of the molecule.

Neomycin

Neomycin is also not systemically absorbed and has historically been used in patients with infectious diarrhea. With a short course, side effects are rare. Neomycin has a high antibiotic resistance rate, but rifaximin effectively prevents resistance to neomycin.

A retrospective chart review of patients treated at Cedars-Sinai Medical Center in Los Angeles was performed on IBS-C patients with methane on their lactulose breath test (> or =3 ppm) who for ten days received rifaximin alone, neomycin alone, or the combination (67). Those receiving the combination (n=27) had an 85% clinical response and 87% eradication rate on follow-up breath test, compared with 63% response/ 33% eradication in the neomycin only group and 56% response/ 28% eradication in the rifaximin only group. The eradication rate difference was highly significant (p=0.001).

Metronidazole

Metronidazole is a systemic antibiotic that has been used for SIBO. It has a lower decontamination rate than rifaximin, comparatively poor tolerability, and can engender antibiotic resistance. It can be considered as a third line treatment option (68, 69).

Practical clinical tip: Rifaximin is often tolerated better by sensitive patients than herbal antibiotics or an Elemental Diet.

Dosage for antibiotics:

Rifaximin: 550 mg TID x 14-21 days for IBS-D, IBS-M, or H_2S
Neomycin 500 mg BID x 14-21 days for IBS-C, H_2S, with rifaximin
Metronidazole 250 mg TID x 14 days for IBS-C, with rifaximin

Herbal Antimicrobial Therapy (Habx)

There are two primary strategies with herbal antimicrobial therapy for SIBO:

1) combination therapy with two single herbs or 2) combination formulas with multiple herbs

Advantages to using two single herbs are to more easily identify the source of adverse reactions for sensitive patients, and for higher gas levels on breath testing since multiple rounds of treatment may be needed and resistance can develop. Advantages to combination formulas are to target yeast overgrowth and

parasites in addition to SIBO and for patients with lower levels of gas where it is less likely to need to reserve herbs for future use. Clinical resistance with herbal antimicrobials is commonly seen after six weeks of treatment. There is little benefit for continuing to use the same herbs for longer than 8 weeks, as relapse frequently occurs. There are primarily four single herbal medicines that are used in treating SIBO: berberine, Oregano, Neem, and allicin.

Berberine is typically sourced from *Hydrastis canadensis, Mahonia aquifolium, Berberis vulgaris, Phellodendren amurense, Coptis chinensis, and Anemopsis californica*. Berberine and' Oregano are typically used with Neem for hydrogen-producing bacteria and diarrhea.
Allicin is typically used for methanogens and constipation.

Berberine is a broad-spectrum antimicrobial, with both positive and negative impacts on the gut microbiome, and is also beneficial for increased intestinal permeability (70). It has herb-drug interactions with loratadine and erythromycin.

Dose: Berberine 1500 mg TID x 4-8 wk

Practical clinical tip: Do not use low-dose erythromycin as a prokinetic agent concomitantly with berberine.

Oregano oil is used as an herbal antimicrobial for all types of SIBO. Its primary active antimicrobial components are carvacrol and thymol. Carvacrol (CV) is a phenolic monoterpenoid found in essential oils of oregano (*Origanum vulgare*), thyme (*Thymus vulgaris*), pepperwort (*Lepidium flavum*), wild bergamot (*Citrus aurantium bergamia*), and other plants (71). Carvacrol antimicrobial activity exceeds that of other volatile compounds present in essential oils due to its free hydroxyl group, hydrophobicity, and phenol moiety. It has particular efficacy against food-borne pathogens, including *Escherichia coli, Salmonella,* and *Bacillus cereus*. An emulsified dry tablet of oregano oil is a more tolerable form than the oil extract.

Dose: Oregano oil 100 mg TID x 4-8 wk

Allicin is an active component of garlic and effective against methanogens. Antibacterial activity of garlic is mainly due to the broad-spectrum antimicrobial compound allicin. Allicin exerts antimicrobial effect by inhibiting thiol-containing enzymes in microorganisms, and facilitates rapid reaction of thiosulfinates with thiol groups. Allicin specifically inhibits other bacterial enzymes such as the acetyl-CoA–forming system, (acetate kinase and phosphotransacetyl-CoA synthetase) (72, 73). Allicin does not impact beneficial flora and when used in combination with antibiotics will reduce the risk of antibiotic resistance (74). Allicin is well tolerated whereas whole garlic and garlic oil often aggravate the symptoms of SIBO. Since it is sulfur-containing, Allicin is not used for H_2S SIBO.

Dose: Allicin SAP 2 caps BID

Neem leaf (*Azadirachta indica*)

Published clinical research on Neem in humans is mostly focused on reduction of oral pathogens in gingivitis and periodontitis, as well as in the treatment of parasitic infections (75). Although Neem has become a popular adjunctive antimicrobial to employ in the treatment of SIBO, there are no published clinical

trials substantiating the efficacy in intestinal infections or dysbiosis. Perhaps the study that most closely approaches this indication is a 2009 trial that tested the efficacy reducing Streptococcus mutans contamination of the toothbrush with 3% Neem in comparison to 2% triclosan, 0.2% chlorhexidine gluconate and 1% sodium hypochlorite, with distilled water as the control (76).

This was a double-blind, crossover, within-group comparative controlled trial enrolling 40 children 12-15 y old. Toothbrushes were collected after 5 days of use and soaked for 12 hours in the five solutions in separate phases. The brushes were then cultured for *S. mutans*. Mean colony-forming units (CFUs) of *S. mutans* for distilled water were not significantly different from baseline ($p=0.17$). The four other disinfecting solutions demonstrated significant reductions in mean CFUs from baseline ($p<0.001$). The percentage of mean CFUs was highest in the Neem solution (86%). The fact that Neem had higher efficacy than the other disinfectants is impressive. However, whether this experimental model would translate to small intestine bacterial overgrowth is purely speculative. Yet there is some evidence that Neem exerts favorable effects in gastrointestinal conditions.

The efficacy of Neem bark extract as an anti-ulcer agent in humans was the subject of a paper published in 2004 (77). Gastric acid secretion was significantly suppressed with administration of Neem extract at 30 mg twice daily for 10 days. Treatment with Neem at 30–60 mg twice daily for ten weeks was also found to nearly completely heal duodenal ulcers. One case of esophageal ulcer and one case of gastric ulcer were also completely healed by the administration of Neem bark at 30 mg twice daily for six weeks.

Dose: Neem SAP 650 mg TID

Combination formulas for SIBO

A multi-center study, including The Johns HopkinsHospital, found “herbal therapies are at least as effective as Rifaximin” with “similar response rates and safety profiles” (78). The investigators used two herbal combination formulas together, at a dose of two capsules twice daily for four weeks. The formulas were: Candibactin AR: This mixture is composed of oregano oil, thyme oil, sage, and lemon balm and Candibactin BR: berberine and proprietary blend of Coptis (*Coptis chinensis*) Root & Rhizome, Chinese Skullcap (Scutellaria baicalensis) Root, Phellodendron (*Phellodendron chinense*) Bark, Ginger (*Zingiber officinale*) Rhizome, Chinese Licorice (*Glycyrrhiza uralensis*) Root, Chinese Rhubarb (*Rheum officinale*) Root & Rhizome.

Dose:
Candibactin AR 2 caps BID x 4 wk
Candibactin BR 2 caps BID x 4 wk
Other patients in the study took FC Cidal and Dysbiocide.

FC Cidal is proprietary blend of:
French Tarragon (*Artemisia dracunculus*) (leaf)
Indian Tinospora (*Tinospora cordifolia*) (stem & root)
Horsetail (*Equisetum arvense*) (whole herb)
Thyme (*Thymus vulgaris*) (leaf)
Pau D’ Arco (*Tabebuia impetiginosa*) (inner bark)

Stinging Nettle Extract (*Urtica dioica*) (root)
Olive (*Olea europaea*) (leaf)

Dysbiocide: This mixture contains dill (*Anethum graveolens*) (seed), Stemona (*Stemona sessilifolia*) (root) (powder and extract), Wormwood (*Artemisia absinthium*) (shoot & leaf) (extract), Java Brucea (*Brucea javanica*) (fruit) (powder & extract), Chinese Pulsatilla (*Pulsatilla chinensis*) (rhizome) (powder & extract), Jamaica Quassia (*Picrasma excelsa*) (bark) (extract), Cutch Tree (*Acacia catechu*) (heartwood & bark) (powder & extract), Hedyotis (*Hedyotis diffusa*) (aerial part) (powder & extract), and Yarrow (*Achillea millefolium*) (leaf & flower) (extract).

Dose:
FC Cidal 2 caps BID x 4 wk
Dysbiocide 2 caps BID x 4 wk

Practical clinical tip:
Add allicin for methane when using combination formulas.

Hydrogen sulfide SIBO treatment:

Bismuth is used to treat patients with H_2S as its mechanism of action is to bind sulfide (79, 80). See dosage recommendations below.

Zinc acetate: This mixture is used to treat H_2S and has been shown to decrease H_2S in rats by 5-fold (81). Dose: 50 mg qd

Molybdenum: No more than 150 mcg bid assists in detoxication of sulfur.

Hydroxycobalamin: This particular form of vitamin B12 is able to bind H_2S and render it less biologically toxic (82). It can be given both intramuscularly (1 mg IM qwk) and as an oral therapy (5000 mcg TID x 10d, then 15,000 mcg once monthly).

Korean red ginseng: In addition to improving fatigue, this form of ginseng has been shown to suppress the activity of sulfur metabolizing enzymes in mice, thus reducing production of hydrogen sulfide internally (83). This can obviously play an important dual role in those SIBO patients who struggle with fatigue or who have compromised adrenal function. Dose: 1000-1500 mg qd.

Epsom salt baths: Use 400 grams (about 4 cups) of Epsom salts, soaking for 20 minutes nightly for seven nights in a row increased sulfate levels in the blood to a steady state in an unpublished study (84). This alone can sometimes dramatically improve digestive symptoms in SIBO patients. A shower rinse after the bath is recommended.

Consumption of sulfur-rich foods should be reduced including milk, cheese, eggs, coconut oil, palm oil, garlic, onions, sulfites (wine, dried fruits), and carrageenan.

Meat increases fecal sulfide (FS) 15x that of a vegetarian diet (85). However, fecal sulfide is not toxic nor available for H_2S production when bound and a high meat diet "likely reflects its ability to provide fecal sulfide binders as opposed to its ability to increase production" (86).

One small study showed decreased H_2S bacteria in healthy subjects after eating cruciferous vegetables, supporting the theory that inorganic sulfate in these foods is not a determining factor in H_2S production (87).

Sulfur-containing supplements should be avoided including berberine sulfate, glucosamine sulfate, methylsulfonylmethane (MSM), Sacromyces cerevisiae (produces H_2S), sulfur-containing amino acids such as NAC, cysteine, glutathione, methionine, homocysteine, taurine, as well as an Elemental Diet.

Table 1: Dosages for herbal antimicrobials:

Gas/Type	Agent	Dose x 4-6 wks
• Hydrogen • Hydrogen & Methane Diarrhea predominant • Diarrhea (w/either gas)	**Berberine + Neem**	1500 mg tid + 600 mg tid
	Berberine + Oregano	1500 mg tid + 100 mg tid dry tablet oregano dose
	Oregano + Neem	100 mg tid + 600 mg tid
• Methane • Hydrogen & Methane Constipation predominant • Constipation (w/either gas)	**Berberine + Allicin**	1500 mg tid+900 mg tid
	Neem + Allicin	600 mg tid + 900 mg tid
	Oregano + Allicin	100 mg tid + 900 mg

Practical clinical tips:

For methane:

• Elemental Diet
• Rifaximin + Neomycin/ or metronidazole/ or allicin
• Nitazoxanide 1000-2000 mg/day, in 2-3 divided doses x 7-14 days (88, 89)

Bismuth: Use 524 mg qid (2000 mg/d) x 14-28 d for H_2S, with Abx or HAbx

OTC Bismuth PILLS:
"Up and Up 5 Symptom Digestive Relief" (as *bismuth subsalicylate*)
"Peptigard" 8/day (meant for ulcers with mucilaginous herbs)
"Biofilm Phase 2 Advanced" 10/d (meant for antibiofilm with ALA, black cumin)
"Biosolve-PA": DMPS 25 mg/d alpha lipoic acid and 100 mg/d bismuth subnitrate 200 mg

OTC Bismuth LIQUID or CHEWABLE:
Pepto Bismol (as *bismuth subsalicylate* with sugar alcohol)

Prescription Bismuth PILLS:
Compounded Bismuth Subnitrate or citrate: 700 mg in one large capsule, dose: TID

Elemental Diet

A third treatment option to reduce SIBO is to limit the delivery of nutrients to the small bowel by providing an Elemental Diet consisting of predigested micronutrients that are readily absorbed in the proximal small intestine (90).

Elemental Diets have been shown to reduce enteric flora. In a 2004 retrospective review, Pimentel and colleagues evaluated the ability of an elemental diet to normalize the LBT in SIBO patients with abnormal breath test findings. Consecutive subjects with SIBO based on abnormal LBT underwent a 2-week

exclusive elemental diet consisting of Vivonex Plus in a quantity based on individual caloric requirement. On day 15, prior to solid food, subjects returned for a follow-up breath test and those with an abnormal LBT were continued on the diet for an additional seven days. The ability of an elemental diet to normalize the LBT was determined for day 15 and 21. A chart review was then conducted to evaluate any clinical benefit one month later. Of the 93 subjects available for analysis, 74 (80%) had a normal LBT on day 15 of the elemental diet. When those who continued to day 21 were included, five additional patients normalized the breath test (85%). Subjects who successfully normalized their breath test had a 66.4 +/- 36.1% improvement in bowel symptoms, compared to 11.9 +/- 22.0% in those who failed to normalize ($P < 0.001$). Disadvantages of an elemental diet are a lack of palatability and the unwillingness on the part of patients to subsist without other food for 2-3 weeks. Dextrose-free Physicians Elemental Diet is formulated to improve palatability.

Practical clinical tip:
The initial choice of treatment for SIBO should be a matter of informed consent, documented in the patient's chart, after a full discussion in which the proposed treatment, alternatives, and risks are discussed, and the patient has the opportunity to ask questions and have them answered.

The patient should be given the choice to express their preference of prescription antibiotics, herbal antibiotics, or Elemental Diet.

Therapeutic Diets

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) has been shown in many published articles to be beneficial in IBS (91).

The diet is based on the theory that decreasing exposure of small intestinal microbes to carbohydrate and its fermentation products will inhibit bacterial growth, affect luminal transport and/or alter gas production. There is a lack of published data on therapeutic diets specifically for SIBO, yet clinicians with experience in treating SIBO almost universally recommend one of several well-described diets low in fermentable carbohydrates, such as the:

(i) SIBO-Specific Food Guide (92),
(ii) SIBO Bi-Phasic Diet (93),
(iii) Low FODMAP Diet (94),
(iv) Cedars-Sinai Diet (95),
(v) Fast Track Diet (96), or
(vi) Specific Carbohydrate Diet (97).
Siebecker has surveyed six SIBO specialists regarding therapeutic diets for SIBO and has provided their estimates of symptom reduction as follows (personal communication 2019):

SIBO specific food guide/BiPhasic Diet: 75-90% improvement

Cedars-Sinai Diet: 60-80% improvement

Specific Carbohydrate Diet: 60-75%; 84% remission in IBD, 100% remission in pediatric IBD (98, 99, 100)

Low FODMAP Diet: “hit or miss”; good relief in 75%; 86% in IBS; 50-75% in IBD cases (101, 102, 103, 104)

These diets recommended for SIBO:

- Include carbohydrate and can potentially trigger symptoms
- Help decrease symptoms
- Individual customization of diet gives best results – diets are guidelines, not hard and fast rules, not legal or illegal. Fanatical adherence to a diet may encourage food phobia, feelings of deprivation, loss of food pleasure, excessive weight loss and at worst, outright malnutrition.
- Ask patient to experiment to determine which carbohydrate foods are tolerated and which are triggers
- Portion size of carbohydrate matters
- White rice is better tolerated than brown rice
- White bread is better tolerated than whole wheat bread
- Sourdough bread is sometimes better tolerated (105)
- Onions, garlic and apples worsen GI symptoms
- Bone broth or ribs may worsen GI symptoms (cartilage, skin and bones contain carbohydrates: mucopolysaccharides/glycosaminoglycans)
- Allow protein (eggs, meat, poultry, seafood)
- Allow fats
- Many are gluten-free (except Cedars-Sinai, Fast Track, Low FODMAP)
- Exclude sucralose, sugar alcohol sweeteners (polyols), and lactose (the most universally difficult carbohydrate for SIBO patients (106). One study found 86.6% regression of lactose intolerance after SIBO eradication (107).
- SIBO Specific Food Guide and SIBO Bi-Phasic Diet:
- Combine the best of both Low FODMAP and Specific Carbohydrate Diets
- An introductory phase I diet is optional while waiting for test results and before antibiotic, herbal antibiotic or elemental diet. Phase II is done with antimicrobial treatment
- No snacking between meals, space meals 3-5 hours apart to allow MMC to clear bacteria; overnight fast 10-12 hours with no eating two hours before bedtime
- SIBO Cookbooks

Several by Rebecca Coomes are very helpful resources for patients. To order: http://www.breathtests.com/patientstore.html

The SIBO Diet Plan, by Kristy Regan (available on amazon.com)

Critique of the FODMAP diet:

Pifer, a clinical nutritionist with expertise in SIBO, published a two part review article on the Low FODMAP (LFD) diet in the newsletter “Today’s Practitioner,” Sept. 30, 2019, and made some provocative conclusions: “there is a pervasive misunderstanding of what the FODMAP diet does and does not do, and how it should be used in a clinical setting.” She points out there are diverse dietary interventions in the results of a pubmed.gov search for the term “low FODMAP”. Most adherence is self-reported. Although there is agreement across studies

that low FODMAP diets improve symptoms of bloating, diarrhea, and quality of life, there are high risks of bias (only one study is double-blinded), intervention periods ranging from two days to six weeks and only one with a six month follow-up, and heterogeneous control diets with limited established efficacy (108).

Pifer points out that methane levels did not change in response to a LFD nor a High FODMAP diet intervention in all studies that have measured methane (109), although there are three studies that show a change in hydrogen (110). However, the subjects in one study were healthy – they did not have IBS or SIBO. They did not prepare properly for the test. In the randomized trial of children with IBS (reference 99 above), as well as in the third study, there was no proper preparation, the subjects ate during the test, and specimens were collected for 14-15 hours rather than two or three hours as intended with SIBO breath testing. Pifer has made a valuable contribution by bringing to our attention these weaknesses of studies using breath testing for IBS and SIBO.

Prokinetic Medications

A prokinetic agent is prescribed immediately after following the first course of a treatment such as an antibiotic, herbal antimicrobial, or Elemental Diet, to improve small bowel motility and thereby improve clearance of bacterial overgrowth (111).

Prescription prokinetics include prucalopride, low-dose erythromycin, and low-dose naltrexone. There are also non-pharmaceutical agents that have prokinetic properties. A trial discontinuation of prokinetic medication after at least 3 months is suggested, but continued long-term use may be needed. Tolerance to prokinetics is frequently observed, and for this reason it is recommended to alternate prokinetic agents every two months.

Prucalopride is a serotonin 5-HT4 receptor agonist that received FDA-approval in December 2018 (112). Suicides, attempts and ideation have been reported across various clinical trials of prucalopride, but there is no evidence of a causal association between this drug and increased risk for suicidal ideation and behavior. It is also an unlikely cause of cardiovascular risks (113) or liver injury (114).

Dosage: Brand names: Motegrity/Resolor 0.5-1 mg qhs

Low-dose Erythromycin (LDE): Use 50 mg at bedtime (115). LDE is a motilin receptor agonist that stimulates gastric phase II contractions (116). Compounding may be necessary for this low dose, or quarter a 250 mg pill to get 62.5 mg. Contraindicated with berberine and escitalopram (QT interval prolongation can cause increased risk of arrhythmia).

Low-dose Naltrexone (LDN): Blocks opioid receptors, displacing endorphins and enkephalins such as Opioid Growth Factor (OGF). This has three effects:

- Receptor (Rc) upregulation- more Rc to catch more OGF
- Increased Rc sensitivity- ditto, to catch more
- Increased production of OGF- feedback

LDN blocks the Rc for 4-6 hours, then releases, freeing up the Rc to interact with

the newly formed OGF in a rebound effect. There is emerging evidence that opioid receptor antagonists may also have prokinetic actions, reversing pathological states of gastrointestinal hypomotility that are due to overactivity of the enteric opioid system (117, 118, 119, 120).

- Dose 1.5-5 mg qhs. Taper upwards to 2.5 mg for diarrhea types or 5 mg for constipation type.
- Side effects: sleep disturbance, vivid dreams (usually fades), headache, nausea

Non-Prescription Prokinetics:

Ginger Root

The prokinetic effect of ginger root (*Zingiber officinalis*) on the stomach has been shown in a number of animal studies (121, 122).

There is one small trial showing that ginger root and artichoke leaf significantly promoted gastric emptying in healthy volunteers with no adverse effects (123). Ginger root dose: 1000 mg qhs.

Iberogast

Also known as STW 5, Iberogast is an herbal formula in use for over 50 years consisting of *Iberis amara* (Bitter candytuft), German Chamomile (Matricaria recutita) flower, Angelica (Angelica archangelica) root and rhizome, Caraway (Carum carvi) fruit, Lemon balm (Melissa officinalis) leaf, Celandine (Chelidonium majus) aerial part, Licorice (Glycyrrhiza glabra) root, and Peppermint (Mentha piperita) leaf. It has been proven to be effective and safe in the management of functional gastrointestinal disorders in five controlled, randomized double-blind studies of functional dyspepsia and in one trial conducted in patients with IBS (124). One study comparing STW 5 to the effect of the prokinetic medication cisapride on dysmotility-related symptoms found them to equally effective, with STW5 having a superior safety profile (125). Iberogast is currently only commercially available in the US on Amazon.com.

Dosage is 20 drops (1 mL) TID

Probiotics

Probiotic therapy is a controversial area in the management of SIBO. Some patients benefit from probiotic supplementation, others do not. A 2017 meta-analysis of 18 studies concluded that probiotics led to significantly increased resolution of SIBO compared with six studies that excluded probiotics (126).

Probiotics are known to improve GI function through several mechanisms, including production of short-chain fatty acids (127) and enzymes (128), support for intestinal barrier integrity (129), modulation of genetic expression (130), immunity (131) and hormones (132), stimulation of the enteric nervous system and reduction of visceral pain (133), and improve gut transit time (134).

Constipation is strongly associated with the presence of intestinal methanogens, which may directly inhibit motor activity. Two recent studies performed on adults and children affected by chronic constipation showed that the supplementation

with *L. reuteri* significantly improved bowel movements. A retrospective review of the data from 20 adults (12 females) affected by functional constipation, treated with the probiotic *L. reuteri* (DSM 17938) for four weeks who performed a H_2/CH_4 lactulose breath test (LBT) showing a CH_4 production higher than 5 ppm, were retrospectively analyzed (135).

Four weeks of *L. reuteri* administration was associated with a significant reduction of mean CH_4 production determined by LBT from 20.8 +/-15 to 8.9 +/- 8.6; $p < 0.0001$ CI 95% and of AUC value (from 5101.5 +/- 3571.13 to 2128.4 +/- 2110.8; $p < 0.0001$ CI 95%). A total disappearance of CH4 production (< 5 ppm at LBT) was seen in 11 patients. There was no significant reduction of H_2 production. An investigation of whether probiotic supplementation could be predicted to be effective based on composition of the gut microflora would be helpful.

Prebiotics are contraindicated in SIBO, as they are typically fructo-oligosaccharides or other fermentable carbohydrates.

Practical clinical tip: consider *L. reuteri* for CH_4 SIBO.

Physical Therapies

These include cognitive behavioral therapy, hypnotherapy, as well as mindfulness-based therapy and should be considered in SIBO patients with functional symptoms, insofar that stress and mood disorders can play a role in the disorder (136).

The Wurn Technique is manual therapy directed to relieve small bowel obstruction and release post-surgical adhesions and supported by several published papers (see referenced below). It should be considered for patients with SIBO who have a history of abdominal or pelvic surgery or trauma. Therapists who have completed training in the technique can be found throughout North America and the UK at www.clearpassage.com

Results of a 57-year review of the side effects of surgery (137) concluded: “Adhesions occur in more than 90% of the patients after major abdominal surgery and in 55-100% of the women undergoing pelvic surgery. Small-bowel obstruction, infertility, chronic abdominal and pelvic pain, and difficult re-operative surgery are the most common consequences of abdominal and pelvic adhesions” (138, 139, 140, 141, 142)

Exercise

A systematic review of the effect of yoga in IBS analyzed 6 randomized controlled trials with a total of 273 patients. There was evidence for a beneficial effect of a yogic intervention over conventional treatment in IBS, with significantly decreased bowel symptoms, IBS severity, and anxiety. Significant improvements were also seen after yoga in quality of life, global improvement, and physical functioning compared with no treatment (143).

Body Awareness Therapy consists of simple structured movement exercises that are incorporated into the care of patients with IBS in European countries (Eriksson, ibid).

A randomized controlled neuroimaging trial is underway in China comparing Tai Chi and aerobic exercise for functional constipation (144).

CONCLUSION

This evidence-based review of SIBO leaves the impression that although it is an active field of research that has yielded valuable information in understanding, preventing and treating SIBO through the various means available, more must be learned to better diagnose and manage this disorder.

A fundamental problem with SIBO, and one that allows controversy to simmer, is the lack of a universally accepted and applied gold standard for its diagnosis. 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 that 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. SIBO, once removed from its original confines as a cause of malabsorption syndrome, has proven to be an elusive and moving target. Meanwhile, therapy remains, for the most part, empirical and is based on the correction, wherever possible, of any underlying causes, and the use of antibiotics (both pharmacological and herbal), prokinetics and therapeutic diet. Only the most rigorous studies employing validated methodologies will finally corral this mysterious entity.

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Diagnosis, prevention and treatment of small intestinal bacterial overgrowth (SIBO) represents a fast growing area for health care professionals. Indeed the gut microbiome in its larger sense is now being increasingly recognized as contributing to overall wellness. Optimization of the gut microbiota and SIBO are priority areas shared by our team at Nutritional Fundamentals for Health, which offers a cluster of products directed at this sector of patient care. Accordingly, the present Handbook is intended to serve as a practical clinical reference guide for practitioners interested in up to date contemporary approaches to prevent, treat and manage health concerns specific to SIBO. Written by Dr. Michael Traub, a leading naturopathic doctor in this arena of health care, readers can be assured that they are being provided the most comprehensive, informed recommendations available. It is our hope at NFH that this topic, along with the others in our ongoing 2020 Handbook series, will be positively received by practitioners in the natural health product space.

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