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Small Intestinal Bacterial Overgrowth (SIBO)

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Abstract

In the healthy human being, there are a variety of intrinsic defense mechanisms that control the number of bacteria and its composition in various parts of the gastrointestinal tract. These defense mechanism include gastric acid secretion, preserved gastrointestinal motility (particularly phase III of the migrating motor complex), normal bacterial microflora, pancreatic biliary secretion, and an intact ileocecal valve, all of which protect against bacterial overgrowth. Any disturbance or alteration in the inherent defense mechanisms can lead to small intestinal bacterial overgrowth (SIBO); therefore, we can define SIBO as an increase in the number and/or an alteration in the type of bacteria found in the small bowel.

The etiology of SIBO is presumably multiefactorial and complex, including alternation of gastric acid secretion (primarily in the form of achlorhydria and pancreatic and biliary secretions insufficiency), chronic disease (e.g.renal failure, liver cirrhosis) and old age are among some of the different causes that result in competition between the host and overgrown bacteria for the ingested nutrients and catabolism of these nutrients which subsequently lead to release of toxic metabolites causing variable degree of injury to the proximal intestinal cells. The clinical features of SIBO are widely variable, including abdominal bloating, nausea, abdominal pain, chronic diarrhea, flatulence and weight loss; however, some patients have only subtle symptoms. For this reason, the diagnosis may often be overlooked.

Although the diagnosis of SIBO is complex;, there are a few different approaches that may be used to help establish the diagnosis in patients with suspected SIBO. The gold standard for diagnosis remains microbial investigation of jejunal aspirate. Non-invasive, indirect methods include hydrogen and methane breath testing (using either glucose or lactulose as a substrate). A third approach is the empiric treatment in patients with suspected SIBO with a trial of antibiotics with subsequent evaluation of symptomatic response and normalization of breath testing. The underlying principles of treatment of SIBO are complex and typically treated with a course of antibiotics as first line therapy along with addressing the underlying defect. Additionally, probiotics, herbals, and certain diets may also play a significant role in the treatment of SIBO in the future.

Keywords: Small intestinal bacterial overgrowth; SIBO

Introduction

Definition

SIBO is defined as increase number of bacteria and/or alteration of the type of these bacteria, typically resulting in subsequent nutrient malabsorption in the proximal part of small intestine. However, the most commonly cited definition is quantitative: 10^5 or more colonies forming units per milliliter (CFU/mL) of bacteria grown from small intestinal aspirate. The most common etiologies of SIBO include alteration of gastric acid secretion in the form of achlorhydria and pancreatic and biliary secretions insufficiency, anatomical abnormalities including, small intestinal obstruction, fistula, diverticula, ileo-cecal resection and surgical blind loop. SIBO usually presents with variable clinical manifestations including bloating, nausea, abdominal pain, chronic diarrhea, flatulence, nutritional deficiencies and weight loss.

Prevalence

The overall prevalence of SIBO in the general population is generally unknown and an extensive literature search is unable to identify the true incidence of SIBO, due to the inherent difficulty in establishing the diagnosis. Additionally, SIBO is presumably significantly underdiagnosed due to the non-specific nature of symptoms, asymptomatic individual, or because symptoms are often confused with functional bowel disease. A significant number of patients with SIBO may also not seek healthcare, for their symptoms. Additionally, the available data is also widely variable based on the disease being studied and diagnostic method being employed. In irritable bowel syndrome, SIBO has been reported in up to 78% of patients as compared to 20% in their controls based on hydrogen breath testing [1]. This number is significantly different as compared to other populations.

In celiac disease, a prevalence rate as high as 66% has been reported, again based on lactulose hydrogen breath testing [2]. A recent study found that SIBO was present in 43% of diabetic patients with chronic diarrhea, and 75% had a significant improvement in their symptoms after being treated with antibiotics [3].

Healthy populations

There is limited data available regarding the prevalence of SIBO in healthy populations. According to varying studies with the investigation of small sets of clinically healthy people as a control, findings consistent with SIBO were found in 2.5% to 22%.

In a study of 294 non-hospitalized older adults in which 34 younger adults (mean age 33.6 years) served as healthy controls, the prevalence of SIBO, as determined by the glucose hydrogen breath test, was 5.9% in the control group versus 15.6% in the older group [4]. In another study of healthy older adults from Japan (mean age 74.7 years), they found that 0% of asymptomatic patients had SIBO based on a glucose breath test. An Australian study detected SIBO from duodenal aspirates in 0% of healthy controls (mean age 59), although 13% were positive for SIBO using a lactulose breath test. Healthy elderly volunteers from the United Kingdom had a 14.5% reported prevalence rate for SIBO based on a positive glucose breath test [5,6]. Finally, in a study of 111 patients with irritable bowel syndrome (IBS), 20% of healthy age- and sex-matched controls were found to have an abnormal lactulose breath test suggestive of SIBO [7]. In summary, although data are limited, the prevalence rates of SIBO in young and middle-aged adults appear to be low, whereas prevalence rates appear to be consistently higher in the older patient (14.5–15.6%); these rates, however, are dependent upon the diagnostic test used.

Etiology

The exact etiology of SIBO is complex including alterations of gastric acid secretion in the form of achlorhydria and pancreatic and biliary secretions insufficiency, renal failure, liver cirrhosis, older age, also anatomical abnormalities including small intestinal obstruction, fistula, diverticula, ileo-caecal resection and surgical blind loop. There are a variety of causes that lead to competition between the bacteria and the host cells for the ingested nutrients and it`s catabolism, which subsequently lead to release of toxic metabolites which cause a variable degree of injury for the proximal intestinal cells. Some patient have a single disease precipitating SIBO; however, the majority have more than one disorder causing SIBO and in the worst conditions, a vicious circle arises between the disease and the SIBO itself.

Achlorhydria: Achlorhydria is known to be one of the predisposing factors for developing SIBO due to atrophic gastritis and/or long term use of proton pump inhibitors (PPIs), which may predispose to increase the number of gastric and small intestinal bacteria. A large meta-analysis demonstrated a statistically significant association between PPI use and SIBO when the gold standard for diagnosis was used to establish the diagnosis (small bowel aspirate) [8].

Old age: Small bowel diverticulosis, reduction in gastrointestinal motility, achlorhydria and prior gastrointestinal surgery tend to be more prevalent in the elderly population and they are considered to be major risk factors predisposing to the development of bacterial overgrowth. SIBO can precipitate malnutrition in the older population as it is reported that it has been seen in the aging population with lower weight and body mass index (BMI) with observation of significant increase in weight following treatment with a course of antibiotics.

Diabetes mellitus: Small intestinal bacterial overgrowth is one of the most notable complications in the diabetic population, especially those with underlying neuropathy and delayed gastric emptying. In fact, nearly 50% to 70% of diabetic patients often complain of gastrointestinal symptoms with a predominance of abdominal pain and bloating. After SIBO progresses it may precipitate significant malnutrition of vitamins and essential nutrients among patients with diabetes, that is more profound as compared to healthier populations in which SIBO can develop.

Scleroderma: Scleroderma or systemic sclerosis is a multi-system, chronic connective tissue disease characterized by its effects on the skin and other internal organs by deposition of the connective tissue associated with both immunologic and microvasculature abnormalities. Gastrointestinal involvement in scleroderma tends to be diffuse and affects nearly 80% of patients. Scleroderma can affect any portion of the gastrointestinal tract and tends to cause small bowel dysmotility in an estimate 40-60% of patients. Its involvement in the small bowel, leading to small bowel dysmotility, commonly results in small intestinal bacterial overgrowth. Impressively, the prevalence of SIBO in the scleroderma population has been estimated to range anywhere between 43-56% [9,10] with diarrhea being the most common presenting symptom [11].

Cirrhosis: Small intestinal bacterial overgrowth among patients with cirrhosis has been observed at a very high frequency. The prevalence of SIBO has been estimated at up to 50% and 60% in patients with cirrhosis [12,13]. Deranged intestinal motility in the cirrhotic population is thought to be the main underlying cause for bacterial overgrowth. In one prospective study looking at 53 patients, the SIBO prevalence rate in cirrhotic patients using LBHT was 60.4% [14]. Patients with cirrhosis with associated with portal hypertension have a higher prevalence of SIBO and small bowel motility disorders given that portal hypertension subsequently changes the intraluminal environment of the small bowel. SIBO is one of the major risk factors for bacterial translocation; hence the reason why bacterial overgrowth in cirrhotic patients carry a significantly higher risk for developing the spontaneous bacterial peritonitis (SBP) due to impaired motility of the small intestine.

Exocrine pancreatic insufficiency: Cystic fibrosis (CF) and chronic pancreatitis are also major risk factors for developing small intestinal bacterial overgrowth and may be responsible for persistent symptoms. The prevalence of SIBO in cystic fibrosis patients has been estimated to be as high as 56% [15], while the prevalence of developing SIBO in chronic pancreatitis ranges between 30% and 40% [16,17]. There are multiple risk factors hypothesized to predispose to SIBO development in this population including those with prior gastrointestinal surgery, exocrine pancreatic insufficiency with absence of anti-bacterial effect of the proteolytic enzymes.

Irritable bowel syndrome: There is massive overlap between small intestinal bacterial overgrowth and irritable bowel syndrome, and there are three different hypotheses to account for this. The first is that SIBO develops as primary event and irritable bowel syndrome (IBS) subsequently develops. The second opinion is the IBS is the primary event complicating by motor and visceral disturbances and dysfunction predispose to bacterial overgrowth to come as secondary event. There is a third opinion in the literature which suggests that SIBO and IBS and entirely different entities and are two distinct disorders with no overlapping pathophysiology [18]. Interestingly, some studies have suggested that SIBO is more prevalent in patients with constipation dominant IBS (IBS-C) as compared to the diarrhea dominant IBS (IBS-D) group [5]. Further research in this area ias needed.

Celiac disease: Patients with celiac disease who have persistently symptoms that do not respond to a strict gluten free diet may have underlying SIBO [19]. This is due to the fact that underlying chronic inflammation of the small intestinal mucosa predisposes to bacterial overgrowth and untreated SIBO is one reason why this patient population may have persistent symptoms. In celiac disease, a prevalence rate of SIBO as high as 66% has been reported [2].

Other diseases and disorders causing SIBO: Several other diseases and disorders have been implicated to predispose to small intestinal bacterial overgrowth including Crohns disease, short bowel syndrome, radiation enteropathy, connective tissue disorders, fibromyalgia, non-alcoholic steatohepatitis, and tropical sprue [20]. There are also some immune-deficiency disorders that predispose to SIBO such as HIV/AIDS and IgA deficiency syndrome. All anatomical pathology associated with small intestinal obstruction and stagnation predispose to SIBO such as strictures, adhesions, and tumors of the small bowel. Chronic small intestinal pseudo-obstruction and certain neurologic diseases also predispose to SIBO, such as Parkinson's disease and myotonic dystrophy.

Mechanism of Malabsorption in SIBO

Normal composition of the bacterial flora of the gastrointestinal tract plays a fundamental role for the preservation of its integrity and normal functioning in the human body, therefore any disturbance or alternation of this composition may lead to bacterial overgrowth. This in turn can lead to subsequent profound malabsorption in the proximal portion of the small bowel. Small intestinal bacterial overgrowth (SIBO) has three main pathways that result in nutrient malabsorption including vitamin deficiency such as vitamin A, D, E and vitamin B12 deficiency [21-25]. Some cases of SIBO have been reported to have associated thiamine and nicotinamide deficiency. Fat malabsorption may also occur resulting in steatorrhoea. Protein malabsorption is similiarly common in the SIBO population due to decrease absorption of the peptide and amino acids.

Clinical features

The clinical features of SIBO are highly variable and mainly are due to the malabsorptive nature of SIBO. Patients with SIBO who have fat malabsorption typically present with steatorrhea which predisposes to vitamin deficiencies, weight loss, abdominal bloating and discomfort. Abdominal bloating is often considered one of the cardinal symptoms of SIBO. Vitamin B12 deficiency also predisposes to megaloblastic anemia and peripheral neuropathy as well. Other types of anemia have also been described in SIBO patients including microcytic anemia, secondary to iron deficiency, and a normocytic anemia may also be observed in the setting of systemic or chronic illness. Some cases has also been reported of night blindness and metabolic bone disease due to vitamin A and vitamin D deficiency respectively. Many patients with SIBO have been erroneously diagnosed with fructose or lactose intolerance and/or diarrhea predominant Irritable bowel syndrome (IBS-D), as SIBO often presents with non-specific symptoms and may therefore be confused with functional bowel disease. Additional common, non-specific symptoms in patients with SIBO include nausea, abdominal distention, and fecal urgency.

Differential diagnosis

Small intestinal bacterial overgrowth (SIBO) remains frequently underdiagnosed in clinical practice as many intestinal disorders mimic small intestinal bacterial overgrowth and it is only confused with functional bowel disease. SIBO should therefore be differentiated from IBS-like symptoms (diarrhea, increase flatus, bloating, abdominal discomfort and abdominal pain) by evaluating either by breath testing or with microbial investigation of jejunal aspirate and should be treated if present. In patients with Crohn's disease, chronic pancreatitis and scleroderma who have progressive symptoms or deteriorating clinical status; SIBO should be suspected. SIBO should also be excluded also in any patient with celiac disease who is not responding to strict gluten free diet.

Diagnosis

The diagnosis of SIBO is complex; however, it can be approached in a few different ways [26]. The first approach is microbiological investigation of jejunal aspirate for quantitative cell count and culture, which remains the gold standard of diagnosis. A second approach is a non-invasive, indirect method including hydrogen and methane breath testing (typically using either glucose or lactulose as a substrate). A third approach is empiric treatment in patients with suspected SIBO with a trial of antibiotics with subsequent evaluation of symptomatic response and resolution of symptoms. Among these approaches, breath testing is the most commonly employed .due to the non-invasive and inexpensive aspect of this approach.

Breath Testing: The currently used breath tests for SIBO are founded on the ability of the small intestinal bacteria to produce carbon dioxide, hydrogen and/or methane gas after metabolizing ingested lactulose, glucose or D-xylose.

Breath testing is considered to be a simple, non-invasive, safe and relatively inexpensive test. Lactulose is starch that is not absorbed by the small intestine in the healthy human being, but is cleared by bacteria in the proximal colon into hydrogen producing a late peak after 90 minutes. In patients with SIBO there is an early rise of hydrogen peak within the first 90 minutes due to the presence of bacterial overgrowth in the small intestine. The glucose breath test is the most widely used test in the United States [27,28]. In patients with SIBO, glucose is metabolized into hydrogen or methane in the proximal part of small bowel while it`s completely absorbed without producing hydrogen or methane in the small bowel of a healthy individual. The sensitivity and specificity of hydrogen breath test are 62.5% and 82% after glucose administration and 52% and 86% after lactulose administration respectively; therefore, the hydrogen breath test tends to be considered more accurate than the methane breath test in diagnosis of SIBO.

Formal diagnostic criteria:

Glucose Hydrogen breath testing: An increase of 12 ppm above basal

Lactulose HBT: The conventional double peak (>10 ppm increase over baseline with a decrease of > 5ppm before the second peak) (OR) 20 ppm above basal at 90 minutes.

There are several disadvantages that are considered to be significant limitations of breath testing in the diagnosis of SIBO. First, many patients can have a false positive test, especially those who have rapid small bowel transit. Examples of this include patients who spoke tobacco, have underlying lung disease, along with patients who have performed recent vigorous exercise at the time of their test [29]. Additionally, breath testing also cannot be used as a tool of

differentiation for bacterial colonies in the small bowel. The breath test also may overestimate the presence of SIBO, as oropharyngeal flora may contribute in certain patients resulting in a confusing early peak. The acidic environment in the colon also inhibits bacterial carbohydrate metabolism, producing inaccurate values for the lactulose and glucose metabolism. Lastly, in patients with gastroparesis and severe delay in gastric emptying time, false negative test results may also occur [29].

Quantitative cell count and culture of small bowel aspirate

Quantitative cell count and culture of small bowel aspirates remains the gold standard for diagnosis of SIBO [30]. Prior studies have suggested that that the presence of more than 105 CFU/mL of coliform gram negative bacilli or strict anaerobes bacteria is diagnostic for SIBO [31]. Other studies have illustrated that the optimal site for sampling is the proximal jejunum [32,33]. Unfortunately, obtaining jujenal aspirates is an invasive, costly, and time consuming approach as it requires endoscopy to perform and a microbiology lab that is equipped to perform quantitative cell count and culture. Another major potential problem with jejunal aspirate is that there is a high rate of false negative results with small bowel sampling [34]. Technical issues may also occur and can confound the results, such as contamination of the jujenal aspirates with the oropharyngeal flora and other issues with the transport and culturing [35].

Treatment

Antimicrobial treatment: The underlying principles of treatment of SIBO are complex. SIBO is typically treated with a course of antibiotics as first line therapy along with addressing the underlying defect or disease. Additionally, probiotics, herbal therapies, and certain diets have shown promise in this disorder and play a significant role in the treatment of SIBO in the future.

A recent meta-analysis comparing the efficacy of antibiotic therapy and placebo effect in a population of patients with SIBO found that the antibiotics appear to be significantly more effective than placebo in both breath test normalization as well as in relieving the clinical symptoms [36].

Choosing the appropriate antibiotic should ideally be according to the antibiotic sensitivities of the small bowel bacterial overgrowth based on small bowel aspirate and culture. At present, there are no consensus guidelines regarding the initial antibiotic regimen that should be used in patients with SIBO.

To date, numerous studies have been performed to determine the efficacy of various antibiotics in the treatment of SIBO. Thus far, several studies have suggested that Rifaximin may be the most efficacious antibiotic, given its extensive spectrum of coverage including gram-positive, gram-negative, aerobes and anaerobes [37-42]. Rifaximin has been reported in several studies to improve symptoms in up to 92% of patients and additionally to eradicate bacterial overgrowth in up to 80% based on normalization of breath testing [39,40]. The recommendation regarding dosing and duration of treatment varies widely from one study to the next; however, it has been reported that higher dosing (1200 or 1600 mg daily) is more effective as a treatment course as compared to conventional dosing [38,41].

Tetracyclin has also been suggested as an initial therapy for SIBO (1000 mg daily for a 7 day course) and has been shown to result in both normalization of hydrogen breath testing and resolution of symptoms [42]. In another study by Castiglione et al., patients with Crohn's disease and concomitant SIBO were found to be effectively treated with a combination of Ciprofloxacin and Metronidazole [43].

Due to the malabsorptive nature of SIBO; vitamin A, B12, D and E levels should be routinely obtained and replaced if indicated. Pancreatic enzyme supplementation should also be considered in those patients with severe bacterial overgrowth and evidence of fat malabsorption.

Small bowel prokinetics, such as Octeriotide, has also been shown to play a significant role in symptom improvement, especially in those with scleroderma and underlying connective tissue disease. It has additionally been shown to decrease the hydrogen excretion as well as it induces the peristaltic wave of the small intestine [44].

Dietary manipulation may play a fundamental role in the treatment of SIBO. The main concept is to provide a diet that consists of nutrients readily absorbed in the small bowel and leaving fewer calories for bacterial metabolism [45]. As carbohydrates are the primary source for bacteria, a low (FODMAP) diet, which refer to low intake of carbohydrates in the form of (fermentable Olig-Di-Monosaccharaides And Polyps), has been shown to significantly relieve symptoms, particularly in those with IBS [46].

Probiotics, herbals, and certain diet may also play a significant role for relieving and treating SIBO. Chedid et al recently reported that herbal therapies appear to be as effective as antibiotic therapy in the treatment of SIBO based on resolution of hydrogen breath testing [47]. Probiotics are bacterial preparations that alter the bacteria in the bowel to cause beneficial effect. The primary role for probiotics is to strengthen the barrier function of the gut, to modify the inflammatory response of the bowel, and to potentially decrease visceral hypersensitivity as well [48,49]. Recent studies have also shown beneficial effects in the setting of treating SIBO patients with enteric-coated peppermint oil [50].

Lastly, long term use of proton pump inhibitors (PPIS); have been postulated to predispose to an increase in the number of bacteria in the stomach and the small bowel. Therefore, stopping unnecessary acid suppressive therapy (which is often prescribed erroneously) may play a significant role in relieving the symptoms for SIBO.

Prognosis

The recurrence rate of SIBO is unfortunately high and depends on many different risk factors including old age, chronic use of PPIS, and history of appendectomy [51]. Lauritano et al. reported that SIBO has a high recurrence rate after a nine month of treatment course with Rifxamin [51-57]. Thus, the prognosis of SIBO may depend on the severity of the underlying disease more than the bacterial overgrowth itself.

Conclusion

Small intestinal bacterial overgrowth remains an underdiagnosed and clinically significant problem with symptoms ranging from mild to the most severe end of the spectrum, often resulting in profound malabsorption and consequent nutritional deficiencies. The etiology of SIBO is often multifactorial while the underlying pathophysiological defect remains unaddressed. The diagnosis of SIBO is complex. While the gold standard for diagnosis remains microbial quantitative cell count and culture of jejunal aspirate, this approach is fraught with

challenges and has a significantly low specificity with a high rate of false negatives. Non-invasive, indirect diagnostic methods more commonly employed include hydrogen and methane breath testing (using either glucose or lactulose as a substrate). The underlying principles of treatment of SIBO remain challenging and typically first line therapy includes a course of antimicrobial therapy along with addressing the underlying etiology (e.g. small bowel inflammation). Lastly, probiotics, herbal therapy, and certain dietary modification (e.g. low FOD MAP diet) may play a significant role in the treatment of SIBO as we move forward in targeted, tailored therapies.

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