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Progress in Diagnosis and Treatment of Small Intestinal Bacterial Overgrowth

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Abstract

Small intestinal bacterial overgrowth has been found to be associated with a variety of gastrointestinal disorders such as irritable bowel syndrome, inflammatory bowel disease, and, in recent years, diabetes mellitus and systemic sclerosis, among other extraintestinal diseases. Several novel diagnostic tools for small intestinal bacterial overgrowth have emerged in recent years, and several therapeutic approaches have been proposed. Therefore, it has become necessary to find an effective, safe, and simple diagnostic method and a safe treatment modality. This article provides a review of current diagnostic and therapeutic approaches to small intestinal bacterial overgrowth.

Keywords

Gastrointestinal Microbiome, Small Intestinal Bacterial Overgrowth, Hydrogen Breath Test, Jejunal Aspirated Culture, Review

1. Introduction

Small intestinal bacterial overgrowth (SIBO) is a clinical syndrome in which an imbalance in the type or number of bacteria in the small intestine causes gastrointestinal symptoms [1]. Under normal conditions, a small number of bacteria are present in the small intestine, mainly gram-negative aerobic and anaerobic bacteria, which break down carbohydrates entering the small intestine and produce gas. The exact prevalence of SIBO in the general population is unknown, with most studies reporting a prevalence of around 20% [2], and its prevalence fluctuates widely due to the lack of uniformity in the criteria for diagnostic tools. With the development of diagnostic tools, small intestinal bacterial overgrowth has been found to be associated not only with irritable bowel syndrome, inflammatory bowel disease, and gastrointestinal tumour, but also with

extra-intestinal diseases such as diabetes and systemic sclerosis [3]. Since its treatment is not identical to that of other diseases, the diagnosis and treatment of SIBO is particularly important.

2. Diagnosis of Small Intestinal Bacterial Overgrowth

2.1. Proximal Jejunal Aspirate Culture

Jejunal aspirated culture (JAC) is performed by endoscopic access to the proximal small intestine, by aspirating the contents of the small intestine using a sterile vacuum pressure syringe and immediately culturing them, and is diagnosed as small intestinal bacterial overgrowth when their colony count reaches 10^5 CFU/ml, which is considered a new standard for small intestinal bacterial diagnosis. Under normal circumstances, due to the digestion of bacteria in food by gastric acid and digestive enzymes in the stomach, as well as the autoimmune function and peristalsis of the intestine, the concentration of bacteria in the small intestine is usually less than 103 colony-forming units (CFU)/ml, whereas in various pathological states, an aspirate bacterial culture with a colony count higher than 10^5 CFU/ml is referred to as small intestine bacterial overgrowth. Although recent developments in endoscopic catheter design have minimized contamination, contamination of oral, oesophageal, gastric and duodenal contents can still lead to false positive results and the inability to aspirate more distant small bowel fluid for culture due to the length of the catheter can lead to false negative results. In addition, current clinical laboratory-based culture methods are only able to detect a small proportion of the extant flora, with a large proportion of bacteria remaining undetected. In a study by Sundin *et al.* [4], a study of bacterial abundance and numbers using high-throughput sequencing revealed that proximal small intestinal aspirate culture underestimated bacterial numbers and jejunal flora diversity. The limitations of proximal small bowel aspirate culture have limited its clinical application, but further studies can be conducted in conjunction with deep sequencing to assess bacterial concentrations in various segments of the small intestine of subjects with SIBO, and we look forward to their joint application to advance the development of diagnostic criteria for SIBO and further studies of the intestinal flora.

2.2. The Breath Test

The breath test is an indirect test based on the production of gases by bacterial metabolism. The basic principle is that carbohydrates ingested by the body are rapidly fermented by overgrown bacteria in the small intestine, producing gases such as short-chain fatty acids, hydrogen (H_2) and carbon dioxide (CO_2). The breath test is easy to perform, inexpensive and non-invasive, and is now a commonly used test for SIBO. Current substrates include glucose, lactose, fructose, sorbitol, sucrose and inulin. In the latest North American consensus on breath tests criteria are set for hydrogen breath tests to diagnose small bowel bacterial overgrowth [5]. The most commonly used breath tests are the lactose hydrogen

breath test and the glucose hydrogen breath test. Human cells cannot produce H_2 and CH_4 by themselves, and the exhaled H_2 and CH_4 are produced exclusively through anaerobic fermentation of carbohydrates by intestinal flora. H_2 is produced in the intestine mainly by the breakdown of fermented carbohydrates by gram-negative anaerobic bacteria. It was later discovered that CH_4 bacteria in some individuals consume H_2 to produce CH_4, resulting in an increased rate of leakage from a single test for hydrogen, which led to the inclusion of a test for methane in subsequent tests. It is important to note that only 20% - 30% of the human intestinal flora contains CH_4-producing bacteria. As two commonly used substrates, glucose and lactulose have their own advantages and limitations. The lactulose breath test is more sensitive than the glucose breath test, but can be affected by blind oral transmission time and lead to false positive results. In contrast, the glucose breath test is more specific but less sensitive as glucose is absorbed by the proximal jejunum and can only detect proximal SIBO [6]. In addition, there are also hydrogen sulfide breath tests and carbon dioxide breath tests that can be used to diagnose small intestinal bacterial overgrowth through the detection of different substrates and exhaled gases, but their usefulness and validity are still lacking compared to hydrogen breath tests.

2.3. High-Throughput Sequencing

High-throughput sequencing technology, also known as next-generation sequencing, involves processing specimens through nucleic acid extraction, followed by complementary DNA synthesis, then amplification using primers specific to a given range of organisms, and finally identification of different species and relative abundance of bacteria using hybridisation arrays based on fluorometric measurements or melting curve analysis of genomic DNA or PCR products [7]. In contrast, genomics-based on high-throughput sequencing technology, which can further sequence all DNA fragments in a sample to identify specific strains of bacteria and their abundance, has become a new approach for the study and diagnosis of SIBO, with the advantages of high accuracy and sensitivity. Choong-Kyun Noh and Kwang Jae Lee performed a hydrogen breath test in patients with functional abdominal distension and a hydrogen breath test by The results showed no significant difference in the relative abundance of microbiota at the genus level between SIBO negative patients and healthy controls, but the proportion of Prevotella (21.2% vs 4.5%, P = 0.024) and Ekaterina (16.1% vs 3.1%, P = 0.002) was significantly higher in SIBO-positive patients [8]. O H Sundin *et al.* [4] performed a glucose hydrogen breath test and a bacterial culture and gene amplification technique on jejunal aspirates by colonoscopy the following day in 18 patients with symptoms of SIBO and showed that a higher signal in the hydrogen methane breath test was significantly associated with lower jejunal bacterial viability. The combination of bacterial culture and high-throughput sequencing for the diagnosis of SIBO would be a developmental direction and a guide to the treatment of SIBO. However, high-throughput se-

quencing is a relatively time-consuming and expensive method that is not suitable for routine clinical application.

2.4. Gas-Sensitive Capsule Technology

In recent years, a new type of gas-sensitive capsule technology can monitor the concentration of gas in the intestine in real time with the gastrointestinal movement after taking, and periodically send the concentration of gas in the intestine to the receiver. Kyle J. Berean *et al.* [9] compared a gas-sensitive capsule with a glucose hydrogen breath test and showed that the capsule measured hydrogen values that were consistent in magnitude with the breath test values but not in time consistent, and that the capsule was sensitive in measuring hydrogen concentrations in the gut, provided information on the site of gas production in the gut, was safe and reliable, and had the potential to improve the diagnostic accuracy of diseases such as small intestinal bacterial overgrowth.

2.5. Other Diagnostic Techniques

In recent years, it has been found that the 5-HT pathway of tryptophan metabolism may play a role in the pathogenesis of SIBO [10]. The main metabolites of tryptophan, 5-HT and urinary 5-hydroxy indole acetic acid (5-HIAA), are significantly elevated in patients with SIBO; with a positive correlation between 5-HIAA and LHBT, they can be considered as non-invasive markers of SIBO and provide new ideas for the diagnosis of SIBO. A urinary excretion test has also been used in the diagnosis of SIBO. The bile acid coupling formed is orally administered and then hydrolysed in the intestinal lumen by bacterial bile acid (or bile acylglycine) hydrolases. The cleaved coupling fraction (PABA, 5ASA) is absorbed by the membrane and part of it is metabolised in the intestine and liver before entering the urine. The time course of measuring the rate of urinary excretion of PABA or 5-ASA, including their metabolites, as a measure of intestinal bacteria has shown the usefulness of bile acid couples as diagnostic substrates for SIBO, despite the small number of clinical trials using this urinary excretion test [11]. Whereas recently reported gas chromatography-thermal conductivity assays for collecting components of intestinal exhaust [12], and the use of cluster analysis with the aid of artificial intelligence techniques [13] have also been used to diagnose SIBO, these studies are still in the developmental stage and their validity needs further confirmation.

The diagnosis of small intestinal bacterial overgrowth is more commonly made by culture of proximal small intestinal aspirates and the hydrogen breath test, which is widely used in the clinical setting to diagnose an increasing number of patients with SIBO, and the ensuing treatment is indispensable.

3. Treatment of Small Intestinal Bacterial Overgrowth

3.1. Antibiotic Treatment

It has been proposed that SIBO should be diagnosed and treated based on the

response to antibiotics. However, the symptoms of SIBO are non-specific and tend to overlap with other diseases, so its irregular use of antibiotics poses a risk to patients, but antibiotic therapy remains the mainstay of SIBO treatment.

Rifaximin is a non-absorbed oral antibiotic that has local intestinal antibacterial activity, low risk of systemic toxicity, low resistance, as well as a high safety profile for repeated use. Rifaximin treatment has better efficacy and fewer adverse effects than other antibiotics. A recent meta-analysis showed that rifaximin is effective and safe in the treatment of SIBO, is dose dependent and is usually associated with improvement in gastrointestinal symptoms and underlying disease [14]. In contrast, there is no clear consensus on the choice, dose and duration of antibiotics for the treatment of SIBO, clinicians often use empirical dosing covering aerobic and anaerobic Enterobacteriaceae bacteria [15], which then results in a reduction in the overall gut microbiota, leaving patients at risk of developing antibiotic resistance and leading to opportunistic bacterial infections such as Clostridium difficile and fungi [16]. Recurrence of SIBO after successful antibiotic treatment is common, with a recurrence rate of approximately 44% within 9 months of initial treatment in patients with SIBO, with higher rates in the elderly, post-appendectomy and in patients on long-term proton pump inhibitors. It has been suggested that recurrent SIBO can be treated with a cocktail of combined antibiotics or alternating antibiotics [17], but comparative studies of treatment outcomes are lacking.

3.2. Probiotic and Prebiotic Therapy

Probiotics and prebiotics are now widely used in digestive diseases, not only to enhance the barrier function of the intestine, inhibit a variety of pathogens, modify the inflammatory response of the intestine and reduce the hypersensitivity of the body, but also to produce branched-chain fatty acids and affect the absorption of vitamins. Bustos Fernandez, L. M. *et al.* [18] collected 54 patients with diarrhoeal irritable bowel syndrome and treated them with probiotics and showed that in patients with SIBO, Salmonella burgdorferi was associated with dietary advice to reduce bacterial overgrowth and improve digestive symptoms while restoring the intestinal microbiota. In addition, a study by Rosa Rosania *et al.* [19] showed that sequential antibiotic-probiotic/prebiotic administration had good outcomes in patients with SIBO. Compared to the disruption of intestinal flora brought about after the broad-spectrum bactericidal effect of antibiotics, probiotics are milder and do not disrupt the balance of intestinal flora causing fungal or Clostridium difficile infections, with better long-term results, and their sequential treatment with antibiotics may become a novel treatment option.

3.3. Dietary Therapy

In patients with SIBO, fermentation of carbohydrates by intestinal bacteria leads to excessive production of intestinal gas, causing gastrointestinal distention, abdominal pain and constipation. A FODMAPs diet is the intake of fermentable

oligosaccharides, disaccharides, monosaccharides and polyols, which produce gas under the fermentation of intestinal bacteria, which allows the intestinal lumen to dilate in patients who are already viscerally hypersensitive, causing a range of symptoms. Martyna Więcek *et al.* [20] treated IBS patients in remission with a diet low in FODMAPs and showed an improvement in gastrointestinal symptoms in 2/3 of patients. Although the available literature suggests that optimal dietary patterns play an important role in the treatment of SIBO [21], the existing literature is not conclusive on the efficacy of diet in the treatment of SIBO, and a large number of controlled trials are still needed to clarify the efficacy and determine the dietary regimen for treatment.

3.4. Faecal Flora Transplantation (FMT)

FMT is a treatment to restore the gut microbiota barrier in patients by transplanting functional flora from the faeces of healthy subjects into the patient. Fenghua Xu *et al.* [22] treated 55 patients with SIBO with faecal flora transplantation and showed a significant improvement in gastrointestinal symptoms in patients with SIBO treated with FMT compared to the placebo group, and However, there are few trials of FMT for SIBO in existing studies, and the sample sizes of the above trials are small and the evidence is insufficient, so a large number of randomised controlled trials are still needed to clarify its efficacy, but its future as a treatment option for SIBO remains objective.

3.5. Herbal Treatment

Herbal therapy is the use of herbs found in nature for treatment, and the main rationale is still that the herbal components in them have some antibacterial activity. Victor Chedid *et al.* [23] gave 1200 mg of rifaximin daily and herbal treatment respectively to 104 patients positive for SIBO and showed that herbal treatment was at least as effective as rifaximin. Another recent meta-analysis on the use of alternative treatments for SIBO showed [24] that herbal salvage therapy was as effective as triple antibiotic therapy for SIBO non-responders. Herbs with antibacterial activity include garlic, black cumin, cloves, cinnamon and thyme, all of which can be used therapeutically, and with such a wide range of herbs available for treatment, it will be important to standardise them in future studies.

3.6. Other Treatments

Since slowed bowel motility causes SIBO and the methane in the gas produced by SIBO causes a vicious cycle of slowed migratory complex motility of the bowel [25], accelerating bowel motility through medication is a new treatment modality. Yeon-Ji Kim *et al.* [26] showed no significant difference in effect between mosapride or rifaximin alone and the combination of the two, with rifaximin having the advantage of reducing gas and mosapride helping to reduce respiratory hydrogen concentrations, suggesting that pro-gastrointestinal drugs

are more effective in the treatment of SIBO. It has also been found that lovastatin extended-release can reduce CH_4 production and improve constipation symptoms by inhibiting enzymes in the CH_4-producing bacterial pathway, which can be used to treat CH_4-positive SIBO patients [27].

4. Outlook

SIBO, as an intestinal flora disorder, causes symptoms such as abdominal distension, abdominal pain, diarrhoea, malnutrition, etc. It is associated with a variety of diseases inside and outside the digestive system, and cannot be diagnosed directly based on the symptoms alone SIBO. In the treatment of SIBO, antibiotics are currently the most effective treatment method, but they can greatly affect the balance of the intestinal flora, and fecal flora transplantation therapy also has the prospect of development, while probiotics, diet and other complementary therapies can be an important supplement to prevent the recurrence of SIBO. As the understanding of intestinal flora improves and molecular biology advances, diagnostic tools and more effective treatments for SIBO will be improved.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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