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Small intestinal bacterial overgrowth syndrome (SIBO) - clinical manifestations, diagnosis and therapeutic options

Krzysztof Dobrzeniecki
University Clinical Hospital of Poznan
Długa 1/2, 61-848 Poznań, Poland
krzysztof.dobrzeniecki@wp.pl
https://orcid.org/0009-0003-2743-2233

Natalia Olesińska
Voivodship Hospital for the Nervous and Mentally Ill in Boleslawiec
Aleja Tysiąclecia 30, 59-700 Bolesławiec, Poland
olesinskanat@gmail.com
https://orcid.org/0009-0004-5269-1488

Magdalena Pachla
Public Health Outpatient Care Network
Lipowa 4, 55-140 Żmigród, Poland
magda.p9803@gmail.com
https://orcid.org/0009-0005-0974-6284

Aleksandra Grzegorczyk
Non-Public Health Care Facility "San-Med"
Słowackiego 5, 49-200 Grodków, Poland
grzegorczykag@gmail.com
https://orcid.org/0009-0005-8057-1843

Katarzyna Muc
Jan Mikulicz-Radecki University Teaching Hospital
Borowska 213, 50-556 Wrocław, Poland
kasia.muc97@gmail.com
https://orcid.org/0009-0002-0381-132X

Natalia Hopej
Jan Mikulicz-Radecki University Teaching Hospital
Borowska 213, 50-556 Wrocław, Poland
nathopej@gmail.com
https://orcid.org/0009-0001-4553-6234

Kacper Turek
Provincial Specialist Hospital in Wroclaw
H. Kamieńskiego 73a, 51-124 Wrocław, Poland
turekkac@gmail.com
https://orcid.org/0000-0001-6551-8079

Abstract:

Small intestine bacterial overgrowth (SIBO) is a gastrointestinal disorder characterized by an abnormal growth of bacterial populations within the small intestine. These conditions disrupt the balance of microorganisms in the gastrointestinal tract, leading to a variety of clinical symptoms and complications.

Excessive bacterial proliferation in the small intestine often results from impaired motility, anatomical abnormalities or changes in the immune system. These factors contribute

to the fermentation of undecomposed carbohydrates, leading to the production of gasses and toxic by-products, causing symptoms such as abdominal pain, bloating, diarrhea and malabsorption. A variety of diagnostic methods, including breath tests and small bowel aspirate cultures, are used to accurately identify excessive bacterial growth. Treatment of SIBO involves a multidisciplinary approach, including dietary modifications, antibiotic therapy and prokinetic agents. Antibiotic treatment remains the cornerstone of therapy, but relapses require a focus on identifying and eliminating predisposing factors.

Keywords: SIBO, small intestinal bacterial proliferative syndrome, microbiota, dysbiosis

Introduction

Small intestinal bacterial overgrowth (SIBO) is defined as a form of dysbiosis with an increased number and/or abnormal type of bacteria colonizing the small intestine with features of the microbiota originating in the large intestine. The physiological small intestine is only marginally colonized, and bacteria residing in the large intestine should not colonize the jejunum and proximally located sections of the gastrointestinal tract. In healthy individuals, the number of bacteria colonizing the small intestine should not exceed 103 in 1 g or 1 ml of intestinal contents. [1, 2] In addition to the quantitative change, there is also a qualitative change in the bacteria residing in the small intestine with a predominance of gram-negative and anaerobic species. This results in excessive gas production in the small intestine, which leads to a feeling of bloating, abdominal pain, recurrent diarrhea and, consequently, problems with the absorption of nutrients from ingested food. [3] Numerous scientific studies indicate that there is a relationship between the intestinal bacterial flora and the health of patients. The richer, more diverse and healthy the microbiota, the longer and healthier a person's life, and disorders of the distribution of intestinal bacteria, both quantitative and qualitative, can predispose individuals to develop chronic diseases as well as small intestinal bacterial overgrowth syndrome [4].

There are many natural defenses designed to prevent abnormal colonization of the small intestine under physiological conditions. Endogenous defense mechanisms include

gastric acid secretion, intestinal peristalsis, the intestinal immune system, the ileocecal valve, pancreatic enzymes and the antimicrobial properties of biliary secretions. When any of these mechanisms fail, an overgrowth of the small intestinal bacterial flora can occur.

Symptoms reported by patients are vague, complaining of abdominal pain, bloating, diarrhea and a feeling of overflow in the abdominal cavity. In many cases, the clinical picture consists of more than one cause and the symptoms overlap with many other disease entities, making a correct diagnosis and finding the source of the problem sometimes difficult.

Prevalence, pathophysiology and risk factors

The exact prevalence of SIBO is not known, it is thought that it can range from 2.5% to 22% and depends on age and comorbidities. [5] Difficulties in determining the prevalence are due to the fact that the symptoms of SIBO are uncharacteristic and that an asymptomatic course is possible. The clinical manifestation of SIBO often accompanies systemic diseases (e.g. diabetes) and is not initially considered in the differential diagnosis. [6]

An overload or lack of properly functioning defense mechanisms, results in a disturbance of homeostasis and may become the cause of the development of SIBO. Among the factors involved in the pathogenesis of SIBO, a distinction is made between intrinsic and extrinsic factors. Intrinsic factors include: impaired secretion of hydrochloric acid (deficiency may be due to atrophic gastritis or gastrectomy), bile and pancreatic enzymes (e.g. in cystic fibrosis or chronic pancreatitis, exocrine pancreatic insufficiency); disorders of gastrointestinal motility (resulting in impaired intestinal cleansing may be due to primary visceral neuropathy, myopathy or neuropathy secondary to e.g. diabetes, Parkinson's disease); disorders of natural cellular and humoral immunity of the intestinal mucosa (e.g. AIDS or insufficient secretion of immunoglobulin A), anatomical abnormalities of the gastrointestinal tract (e.g. strictures, tumours, post-operative conditions, adhesions and interloop fistulas, diverticula). Extrinsic factors include diet, gastric juice inhibitors (e.g. proton pump inhibitors), drugs that modulate the intestinal flora (pre- and probiotics), antibiotics and drugs that interfere with gastrointestinal motility (e.g. opioids, anticholinergics and antidiarrhoeals). [5,6,7] When studying patients presenting with gastrointestinal complaints, a significant correlation was observed with cigarette smoking [odds ratio (OR) = 6.66], the appearance of bloating (OR = 5.39), abdominal pain (OR = 4.78) and the presence of anaemia (OR = 4.08) [8]. The risk of SIBO in patients increases with age [OR = 1.04, 95% confidence interval (CI): 1.01-1.07], due to impaired intestinal motility and reduced gastric acid production, and is

independent of gender and race[8,9]. Risk factors also include the co-occurrence of irritable bowel syndrome (IBS). For patients with IBS, rates of SIBO are up to seven times (51.7 to 78%) higher compared to a group without IBS. [6,11]

Clinical features and pathoetiology

The clinical picture of bacterial overgrowth of the small intestine is uncharacteristic, the reported symptoms are variable and some patients are asymptomatic. Patients present with symptoms of abdominal pain, flatulence, excessive gas accumulation, feelings of fullness in the abdominal cavity, belching, altered bowel habits (diarrhea, less commonly constipation).[9,28] Constipation occurs when the main cause of bacterial overgrowth is methanogenic bacteria, e.g. *Methanobrevibacter smithii*. [12] In more severe cases, patients may develop fatty diarrhea, resulting in malabsorption with excessive weight loss and malnutrition. Impaired absorption of fat-soluble vitamins, as well as vitamin B_{12} and iron, is mainly observed. These deficiencies may result in the development of macro- or microcytic anemia, polyneuropathy and bone metabolism disorders. In most patients, folic acid and vitamin K deficiencies are not observed, as they are products of bacterial metabolism. [7] Ignoring the symptoms of SIBO can lead to changes in the amount of digestive enzymes produced, leading to a decrease in pregnancy weight, malnutrition and inflammation of the body. [13,14]

Diagnosis

Breath tests are used to diagnose small intestinal bacterial overgrowth syndrome. Commercially available are the hydrogen and hydrogen-methane test, which measure the level of hydrogen or methane in the air exhaled by the patient after ingestion of a lactulose or glucose solution. Carbohydrates are a substrate for bacteria, which metabolize them to produce the above-mentioned substances. An increase in the level of exhaled hydrogen or methane of at least 20 ppm of the baseline value (measured on a fasting basis) 90 minutes after the ingestion of a polysugar allows the test result to be interpreted as positive. [15] The sensitivity of the test using glucose is estimated at 20-93% and the specificity at 45-86%. [16] Using lactose, the test has a sensitivity of 17-68% and a specificity of 44-86%.

Another method, which allows a much more accurate diagnosis, is the culture method for bacterial cultures taken from the intestine during endoscopic examination, as well as taking sections of the small bowel wall for histopathological examination. Due to the

invasiveness of the examination, the higher cost and time investment, the tests are rarely performed.

Clinical symptoms appear in patients when invasive strains of bacteria cause inflammation through the toxins and enzymes produced, damaging the epithelium of the intestinal wall. The most common pathogens detected when diagnosing SIBO are *Escherichia coli*, *Aeromonas*, *Klebsiella* sp. Endoscopic and histopathological findings typically appear normal. Non-specific symptoms that have been seen in patients on the aforementioned examinations include redness, swelling of the mucosa, ulceration, abnormal vascular pattern, eosinophilia and an increased number of lymphocytes detected on histopathology. [17]

Treatment

SIBO therapy must be individualized and should address all causes, symptoms and complications. The mainstay of SIBO treatment is pharmacotherapy, which aims to modify the microflora of the small intestine, leading to symptom relief. In clinical practice, the first line of treatment is antibiotic therapy to eliminate aerobic and anaerobic bacteria, which usually remains empirical. Several broad-spectrum antibiotics have been proven to be effective, such as metronidazole, rifaximin, doxycycline, ciprofloxacin or amoxicillin with clavulanic acid. Currently, rifaximin is the preferred agent due to its reduced toxicity and side-effects comparable to placebo. [26] Its spectrum of action includes aerobic, anaerobic Gram-positive and Gram-negative bacteria.[18] SIBO relapses have been observed in 43% of patients after antibiotic therapy. [19] Re-antibiotic therapy may be associated with bacterial resistance, diarrhea including *Clostridoides* infection, and dysbiosis of the intestinal microflora. The advantage of rifaximin is that it does not induce bacterial resistance and can therefore be used during relapses. However, an interval of four weeks must be maintained between two-week courses of antibiotic therapy.

Diet also deserves special attention in the treatment of SIBO. Unfortunately, there is limited literature addressing dietary management in SIBO patients, however, dietary recommendations have been carefully analyzed in patients diagnosed with IBS. Up to 78% of patients with irritable bowel syndrome have been found to be SIBO-positive [20], hence recommendations aimed at this group of patients should be considered.

The primary dietary recommendation is a low FODMAP diet. The acronym is derived from the English words Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols, i.e. products rich in short-chain carbohydrates that are poorly absorbed and rapidly

fermentable with high osmotic pressure. These include fructose found in fruit and honey, lactose, fructans found in wheat, onions, garlic, galactans found in legumes and polyols, which include mannitol, sorbitol, xylitol. Patients suffering from both SIBO and IBS should avoid consuming the above-mentioned products, which will have the effect of reducing abdominal pain, the feeling of bloating and the occurrence of recurrent diarrhoea. [20,27]

Table 1. Products that should be avoided in the low-FODMAP diet.

monosaccharide: fructose	**oligosaccharides: fructans**	**polyols: sorbitol**
apple	onion	stone fruits
honey	garlic	pear
mango	artichokes	apple
watermelon	legumes	cauliflower
pear	wheat and rye products	mushrooms

Another pillar used in substitution treatment is the use of probiotics, particularly those containing a single strain of bacteria, and dietary fiber supplementation. Both products allow the regulation of intestinal peristalsis, reducing intestinal discomfort and improving the clinical picture of sufferers [21,22]. However, there is a need to choose the probiotics individually and with high precision, depending on specific properties and the intended effect of supplementation [29].

In a study led by García-Collinot conducted on patients with diagnosed SIBO, the efficacy of specific bacterial strains against the symptoms of the disease was investigated. Supplementation with *Sacharomyces boulardii* (CNCM I 745) in patients diagnosed with SIBO and systemic scleroderma was shown to result in significantly better bacterial eradication and a reduction in the amount of hydrogen exhaled in the hydrogen test compared to patients treated with metronidazole alone. [23] A beneficial effect was also shown when the strain *Lactobacillus reuterii* (DSM 17938) was used for 4 weeks [30]. Supplementation allowed a significant reduction in the level of methane produced and even a complete absence of the gas (less than 5 ppm during the expiratory test) observed in 55% of the subjects. [23] A

strain with an adverse effect on the progression of SIBO was also identified. Only a two-week supplementation with *Bifidobacterium infantis* strain 35624 caused an increase in methane levels in the lactulose breath test and led to a positive test result. [23] This strain should therefore be avoided when supplementing patients, as it could exacerbate the symptoms of the disease and worsen the patient's clinical condition.

Studies have shown a link between fiber supplementation and the occurrence of positive modifications in the composition of the intestinal microflora. The use of a 7-day psyllium treatment in constipated patients resulted in an increase in beneficial microorganisms such as *Lachnospira*, *Faecalibacterium* and *Roseburia*. [22] In a study by Holscher et al, a positive effect of agave inulin supplementation on the intestinal microflora was demonstrated, with an increase in *Actinobacteria* and *Bifidobacteria* and a decrease in *Desulfovibrio* observed. [24] A one-week dietary change in 16 healthy volunteers from a high-fiber to a low-fiber diet was associated with gastrointestinal symptoms in each subject. Two participants were diagnosed with SIBO after this short-term intervention. [25] Dietary fiber should be considered an essential component of a healthy diet as a nutrient for prebiotic organisms residing in the gut.

The increasing amount of scientific research on the subject of SIBO highlights the significant challenges clinicians face in diagnosing and selecting appropriate treatments for this condition. [31]

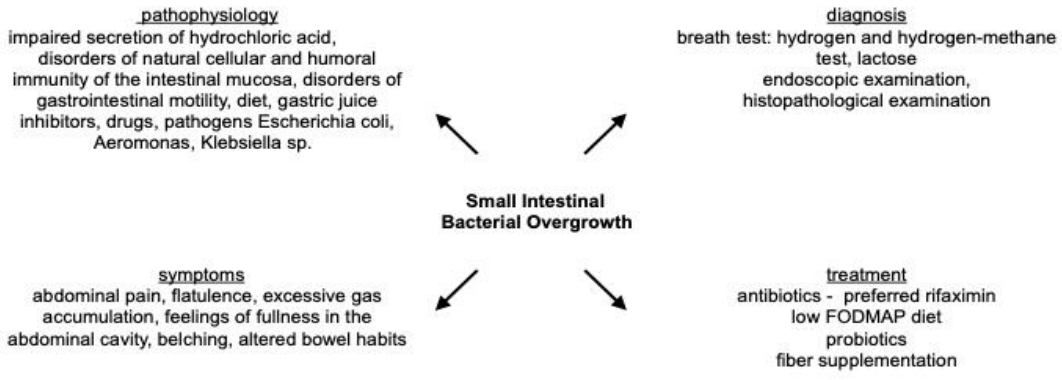

Figure 1. Summary of pathophysiology, symptoms, diagnosis and treatment of small intestinal bacterial overgrowth (SIBO).

Conclusions

SIBO is a heterogeneous syndrome characterized by a pathological overgrowth of microflora of colonic origin in the small intestine. It can cause numerous non-specific

gastrointestinal complaints that bring patients to primary care facilities. Non-invasive hydrogen breath tests are most commonly used to diagnose SIBO. The mainstay of therapy is the use of gastrointestinal-selective antibiotic therapy. Treatment should also address the underlying disease. A proper, tailored diet, the use of probiotics and the elimination of risk factors should also be considered.

Disclosure:

Authors' contribution:

Authors' contribution:

Conceptualization: Kacper Turek, Magdalena Pachla, Krzysztof Dobrzeniecki

Methodology: Natalia Olesińska, Aleksandra Grzegorczyk

Software: Katarzyna Muc, Magdalena Pachla

Check: Krzysztof Dobrzeniecki, Katarzyna Muc

Formal Analysis: Kacper Turek, Aleksandra Grzegorczyk

Investigation: Krzysztof Dobrzeniecki, Aleksandra Grzegorczyk, Natalia Olesińska

Resources: Natalia Hopej, Aleksandra Grzegorczyk

Data Curation: Natalia Olesińska, Katarzyna Muc, Krzysztof Dobrzeniecki

Writing-Rough Preparation: Natalia Olesińska, Krzysztof Dobrzeniecki

Writing-Review and Editing: Krzysztof Dobrzeniecki, Natalia Olesińska, Magdalena Pachla, Aleksandra Grzegorczyk, Katarzyna Muc, Natalia Hopej, Kacper Turek

Visualization: Katarzyna Muc, Natalia Olesińska

Supervision: Krzysztof Dobrzeniecki, Magdalena Pachla, Aleksandra Grzegorczyk

Project Administration: Natalia Hopej, Krzysztof Dobrzeniecki

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