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Analytical Review: Small Intestinal Bacterial Overgrowth Syndrome in Clinical Practice

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ABSTRACT

This article presents current information on the pathogenesis, clinical presentation, and diagnostic methods of Small Intestinal Bacterial Overgrowth syndrome (SIBO) from the perspective of the systemic influence of the microbiota on the patient's body (the "gut-organ" axis). Particular attention is paid to the standardization of diagnostic breath tests, the interpretation of their results depending on the type of gas produced (hydrogen/methane), and a differentiated approach to evidence-based antibacterial therapy.

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Introduction: Relevance of the Topic, Goals and Objectives Glossary: The Topic Contains Specific Vocabulary

Small Intestinal Bacterial Overgrowth (SIBO) is a disease characterized by an imbalance in the small intestinal microbiota, manifested by altered intestinal motility, malabsorption, and impaired local and systemic immune responses [1]. This definition is included in the International Classification of Diseases, 11th Revision (ICD-11), which includes the nosological entity DA96.00 – SIBO.

SIBO Research Intensity (2015–2025) General Status and Research Trends

Small Intestinal Bacterial Overgrowth (SIBO) is currently under active study. The ScienceDirect database alone contains 109 key findings for the specified period. Research has shifted from simply recognizing SIBO as a pathology to a deeper understanding of the mechanisms by which it influences systemic diseases via the gut-organ axis (liver, brain, kidneys).

Key Research Areas

SIBO is recognized as a specific variant of human microbiome and/or microbiota disorders. Metabolomics results in a group of patients with IBS revealed a link between certain bacteria and bile acid derivatives: 3-hydroxy-cis-5-tetradecenoylcarnitine, cholyltryptophan, and nutriacholic acid. These metabolites are involved in the transport and metabolism of fatty and bile acids, which is believed to contribute to the development of pathology. In the group of patients with SIBO, a link was observed between certain bacteria and metabolic components such as epiandrosterone and homogentisic acid. It is noted that functional impairments in the group of patients with SIBO are primarily associated with disturbances in amino acid and energy metabolism. Enrichment of gas-producing bacteria in SIBO may affect tyrosine metabolism and energy regulation, leading to symptoms such as bloating and constipation. A recent study further elucidates differences in disease pathogenesis from a gut microbiome perspective. Gut microbiota and metabolites may serve as clinical biomarkers for differentiating IBS and SIBO [Lu S, Chen Y, Guo H ... Differences in clinical manifestations and the fecal microbiome between irritable bowel syndrome and small intestinal bacterial overgrowth. Digestive and Liver Disease, 2024; 56, 2027-2037].

Etiology and Pathophysiology of the Disease or Condition (Group of Diseases or Conditions)

Stress, defined as an acute threat to homeostasis, has both short-term and long-term effects on gastrointestinal function. Exposure to stress leads to alterations in brain-gut communication (the "brain-gut axis"), ultimately leading to the development of a wide range of gastrointestinal disorders, including Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS) and other functional gastrointestinal diseases, adverse reactions to food antigens, peptic ulcer disease, and Gastroesophageal Reflux Disease (GERD). The main consequences of stress on gut physiology include: 1) changes in gastrointestinal motility; 2) increased visceral sensing; 3) changes in gastrointestinal secretion; 4) increased intestinal permeability; 5) negative effects on gastrointestinal mucosal regenerative capacity and mucosal blood flow; and 6) negative effects on the gut microbiota.

Mast Cells (MCs) are important effectors of the brain-gut axis, transducing stress signals into the release of a wide range of neurotransmitters and proinflammatory cytokines that can significantly influence gastrointestinal physiology.

The gastrointestinal microbiota is a vital component of healthy human well-being. Key functions of the gut microbiota include protecting the body from pathogens, maintaining immune regulation, participating in nutrient metabolism, and synthesizing

a number of essential metabolites and vitamins (e.g., short-chain fatty acids, secondary bile acids, B vitamins, and vitamin K).

Key Points for the Clinician

- **Substrate Asymmetry (3:1):** Clearly demonstrates why the glycoconjugate pool bears the brunt of bacterial deconjugation.
- **Detergent Effect:** Shows that free bile acids act as chemical membrane damaging agents by physically shedding disaccharidase complexes.
- **Qualitative Contribution of Taurine ((H{2}S)):** Despite its smaller volume, this pathway generates highly toxic hydrogen sulfide, which perpetuates the vicious cycle of small intestinal villus alteration.

Changes in assessment methodology. The disparity in knowledge about the human intestinal microbiota has been induced by the predominantly culture-based method of assessing the composition of microflora. As noted in numerous studies, this approach is painstaking, labor-intensive, and limited in scope, as most fecal microorganisms are anaerobic (die in an aerobic environment) and cannot be cultured using standard microbiological methods, or the microorganisms are not rendered viable during processing of the study material [1, 2].

To further assess the presence of high-ranking publications, the academic.research.microsoft.com portal was used. A total of 21,990 publications were found. The top five journals with the largest number of publications are:
Scientific Reports, Frontiers in Microbiology, PLOS ONE, bioRxiv, and Microbiome. The top five institutions by ranking are: 1. Harvard University, 2. University of Copenhagen, 3. University College Cork, 4. Wageningen University and Research Centre, 5. University of Gothenburg. The keyword "Gastrointestinal Microbiome" yielded 1,997 publications. Journal rankings: Scientific Reports, PLOS ONE, Gut microbes, Microbiome, World Journal of Gastroenterology. Institution rankings: 1. Harvard University, 2. University of Colorado Boulder, 3. Washington University in St. Louis, 4. Broad Institute, 5. University of Copenhagen.

The International Prospective Register of Systematic Reviews (PROSPERO) database identified 167 reviews on the gut microbiome. The review topics cover virtually all areas of medicine: exercise, obesity, weight management, Alzheimer's and Parkinson's disease, diabetes, multiple sclerosis, miscarriage, dermatitis, gastrointestinal diseases, and more. However, only five reviews were completed. It is important to note the presence of internationally accepted terms and concepts that have significant practical significance.

Microbiota is the microbial community, including bacteria and viruses, that inhabits a given habitat. In 2014, the Medical Subject Headings (MeSH) of the PubMed database introduced the following definition of microbiota: the complete set of microbes (bacteria, fungi, viruses, etc.) that naturally exist in a specific biological niche, such as an organism, soil, water, etc.

Microbiome

The community of microorganisms associated with the human body, with their collective genes constituting the metagenome (of microbial genomes). In recent years, microbiome has commonly been used to refer to the collective genomes of members of a given microbial community. In 2018, the PubMed Medical Subject Headings (MeSH) database introduced the term "gastrointestinal microbiome"—all microorganisms that naturally exist in the gastrointestinal tract.

Additionally, definitions are provided for the following terms: Dysbiosis, Phylotype, Taxon, Biocenosis, Commensals, Nutrients, Enterotypes, Permeable Intestine, and Small Bowel Bacterial Overgrowth (SIBO). Two points should be noted. First, the key terms were introduced in the last five years; therefore, searching in more recent years will not yield objective results. Second, there are partial inconsistencies in the definitions of microbiota and microbiome with those specified in the human microbiome/metagenome project, compared to medical subject headings. Furthermore, the World Health Organization (WHO) approved the new International Classification of Diseases and Causes of Death, 11th revision (ICD-11), which includes the disease entity DA96.00 – SIBO.

The development of the Human Microbiome/Metagenome (HM) project has been accompanied by the accumulation of a significant number of studies on the human microbial community. However, during the implementation of the HM, it became clear that a change in the methodological approach to assessing the microbiota (microbiome) was required. First and foremost, a rather complex methodology was developed for identifying and detailing the characteristics of the totality of human microorganisms in various anatomical regions of the body (microbiome). This resulted in a critical assessment of the currently used microbiological culture methods.

The main disadvantages of culture-based microbiological methods are primarily related to the impossibility of culturing more than 50% of the human microbiota. When this is possible, the high cost of classical culture-based and biochemical approaches to characterizing microbial communities significantly limits their applicability in large-scale studies. Furthermore, these methods are almost always based on obtaining and studying pure microbial cultures, which completely precludes the possibility of understanding the microbial community as a system. The presented results dictate the need to reconsider the use of culture-based methods for diagnosing intestinal microbiota disorders in clinical practice.

The use of genetic platforms such as GS FLX (Roche), HiSeq 2000 (Illumina), and SOLiD™ 4 System (Applied Biosystems) enables in-depth metagenomic studies not only based on 16S rRNA gene analysis but also on the results of complete sequencing of microbial genes, their plasmids, and viruses. This significantly facilitates the creation of a holistic picture of the human body's interactions with the intestinal microbiome as a whole through a complete metabolic reconstruction of interactions within this system. Results from this approach show that microbial composition varies across body regions and even within body regions, as well as between individuals. Thus, although it has been established that each anatomical region of the body has its own unique microbial composition, they all appear to function uniformly with respect to intermicrobial metabolism.

Assessing changes in the distribution of microbiota across different regions (compartments) of the intestine is becoming increasingly important. A classic example is SIBO. These microbiota changes are accompanied by excessive growth and altered microbiota composition, combined with diarrhea and malnutrition. SIBO develops in conjunction with impaired intestinal motility and leaky gut syndrome (LIS).

The diagnosis of SIBO is based on three criteria: (a) the presence of increased intestinal contents (volume), (b) demonstrated increased bacterial concentrations, and (c) a positive response to antibiotic and/or probiotic therapy. SIBO is diagnosed using a hydrogen or carbon dioxide breath test. Appendix 2 describes the SIBO diagnostic method. Hydrogen (H2) contained in exhaled air at rest is primarily produced by the metabolism of the intestinal microbiota. Anaerobic bacteria primarily metabolize sugar molecules (carbohydrates) through an enzymatic reaction (fermentation), which also produces Short-Chain Fatty Acids (SCFAs), carbon dioxide, and hydrogen. Of the SCFAs, butyrate (butyric acid) has attracted particular attention.

The H2 concentration measured in exhaled air reflects the number of bacteria and their metabolic activity in the intestine. The time it takes for the hydrogen concentration to rise during a breath test indicates the region of the intestine where fermentation processes are occurring. All of this is implemented in the Hydrogen Breath Test (HBT), the simplest method for diagnosing microbiota disorders. HBT requires further refinement and validation. The presented diagnostic option belongs to a large group of exhaled breath tests that detect approximately 1,000 so-called Volatile Organic Compounds (VOCs). Some of these are metabolites of the gut microbiota and are actively being studied for various diseases.

There are Five Main Areas of Research on the Gut Microbiome

- Using microbiome signatures as biomarkers for disease detection;
- Using enterotypes to classify people based on disease risk and drug pharmacokinetics;
- Using antibacterial, anti-inflammatory, and other small molecules produced by microbiome community members for therapeutic purposes;
- Developing new microbiome strains for T-cell stimulation, antimicrobial factors, and drug delivery;
- Developing biomarkers of the virome or other microbiome representatives for therapeutic or diagnostic purposes. A dedicated international group, the Microbiome Therapeutics Innovation Group, has been established. Since 2017, microbiome therapy has been actively discussed at the regulatory level in the United States, primarily with an emphasis on the safety of fecal microbiota transplantation.

Characteristics of the Small Intestinal Microbiota

The intestinal microbiota of the small intestine is predominantly represented by bacteria of the phyla Bacteroidetes and Firmicutes, with lesser contributions from Actinobacteria, Fusobacteria, Verrucomicrobia, Proteobacteria, and Cyanobacteria [1-3]. The microbial landscape in different sections of the small intestine (duodenum, jejunum, and ileum) differs in the proportion of microbial representatives, primarily belonging to the phylum Firmicutes. This is due to the fact that the conditions for the existence of microbial cells change as one moves from the proximal to the distal intestine. Thus, the composition of the microbiota of the duodenum and proximal jejunum is represented predominantly by gram-positive aerobic bacteria. Their excessive proliferation is suppressed by the aggressive environment of the upper Gastrointestinal Tract (GIT):

- bactericidal activity of primary bile acids
- activity of digestive enzymes and hydrochloric acid
- propulsive peristalsis
- low acid-base balance (pH)

In the distal jejunum and ileum, the activity of inhibitory factors weakens, which creates more favorable conditions for bacterial proliferation - in the duodenum their number is 10-103 colony-forming units per milliliter (CFU/ml), in the jejunum - 104-107 CFU/ml, in the ileum - 103-107 CFU/ml. Microbial antigens (lipopolysaccharides, lipid A, peptideglycans, flagella, bacterial DNA or RNA) sensitize Paneth cells, which in response express broad-spectrum antimicrobial peptides, for example, cathelicidin, defensins, phospholipase A2, C-type lectin and others [3]. Sensitization of Paneth cells, which belong to the innate immunity, indirectly activates the local adaptive (acquired) immune response. This is manifested by the synthesis of IgA immunoglobulins by plasma cells and the differentiation of CD4+ lymphocytes into T-helper lymphocytes type 17 (Th17). This results in local immune-mediated clearance of excess bacteria in the distal small intestine without the development of a systemic inflammatory response [3, 4].

The excess bacterial load in the small intestine, which determines the development of SIBO, is formed predominantly by gram-negative aerobes and anaerobes, among which Escherichia, Enterococcus spp., Klebsiella, and Proteus are most often identified [5]. Compared to healthy volunteers, the small intestinal aspirate of such patients showed an increased abundance of Proteobacteria (by 4.31 times), a decreased proportion of Firmicutes (by 1.64 times), and a decrease in microbial α-diversity. In addition, a direct relationship was found between the abundance of the Enterobacteriaceae family (class Gammaproteobacteria) and the severity of bloating, as well as between an increase in the number of representatives of the Aeromonadaceae family and the frequency of urgent urges to defecate [6]. Methanogenic archaea, such as Methanosphaera stadtmaniae and Methanobrevibacter smithii, may be the only microorganisms that form an excessive microbial abundance [7].

Pathogenetic Mechanisms that Determine the Development of SIBO

The pathogenetic mechanisms that determine the development of SIBO are based on changes in metabolic and immunological processes in the small intestine:

- active breakdown of carbohydrates results in the formation of excess bacterial metabolic products (e.g., H2, CH4, H2S, CO2), which cause the development of visceral hypersensitivity, bloating, and diarrhea (the resulting hydrogen sulfide additionally has a direct damaging effect on enterocytes and also stimulates a proinflammatory response by activating the nuclear transcription factor NFkB [8,9].
- the amount of methane produced increases (especially with excessive growth of methanogenic archaea, which most authors consider to be the main methane producers), which leads to a slowdown in colonic motility and leads to the development of bloating and constipation symptoms
- low-grade inflammation is maintained by secondary bile acids (mainly lithochoic acid) and by-products of fatty acid metabolism, which leads to increased permeability of the mucoepithelial barrier of the small intestine [10, 8, 11].
- secondary disaccharidase deficiency occurs when the brush border of enterocytes is damaged, which leads to maldigestion of oligosaccharides and subsequent malabsorption of monosaccharides [12].
- microbial breakdown of amino acids and low molecular weight proteins in the small intestine increases, leading to the development of malabsorption [12].
- decreased absorption of fats and fat-soluble vitamins due to excessive deconjugation of bile salts, which also leads to symptoms of malabsorption [13].
- increased competition between the human body and the small

intestinal microbiota for vitamins B1, B2, B3, B5, and B12 (due to an increase in the number of bacteria that utilize these vitamins) [14, 15, 16].
- increased production of toxic metabolites synthesized by bacteria (ammonia, D-lactate, and bacterial peptide glycans [12].
- impaired permeability of the epithelial barrier and increased bacterial translocation [17].
- increased intensity of the local and systemic immune response due to an increased pool of proinflammatory cytokines (IL-1a, IL-1b, IL-6, and tumor necrosis factor alpha TNF-α) [18, 19].

The above mechanisms lead to clinical manifestations of the disease and also worsen the course of chronic non-communicable diseases. For example, by increasing the pro-inflammatory immune response, SIBO aggravates the clinical course and worsens the short-term prognosis in patients with rosacea, liver cirrhosis, chronic heart failure and bronchial asthma [17-23].

Risk factors for the development of SIBO include conditions that disrupt the physiological elimination of excess bacteria in the small intestine and/or create favorable conditions for their proliferation. These include:
- impaired motility of the small and large intestine [24-28].
- disruption of the anatomical integrity of the intestine after surgery [29].
- ileocecal valve dysfunction [30].
- hypochlorhydria in the stomach [31,32].
- inflammation in the small and large intestine [24].
- immunodeficiency (including congenital, acquired, and selective IgA immunodeficiency [12, 33].
- decreased pool of primary bile acids [34]
- maldigestion or malabsorption of various etiologies [28, 35, 36].

The Most Controversial Positions

Causal Relationship between SIBO and Steatosis. Some studies show an association between SIBO and steatosis, particularly in patients with obesity or metabolic syndrome. However, meta-analyses and large cohorts do not support a consistent link with fibrosis progression or NASH2.

The Role of Endotoxins (LPS) in the Pathogenesis of MAFLD. Although LPS-induced TLR4 activation and liver inflammation are actively discussed, clinical data on LPS concentrations and their correlation with steatosis severity remain controversial.

Diagnosis of SIBO. The use of breath tests (glucose, lactulose) is controversial due to low sensitivity and specificity. This complicates the reproducibility of results and the interpretation of the association with liver pathologies. Effect of diet (eg, Mediterranean) in SIBO + MAFLD Although the Mediterranean diet is beneficial for steatosis, it may worsen SIBO symptoms (bloating, pain) due to its high FODMAP content, which reduces adherence to therapy.

Least studied/promising areas:
- The small intestinal microbiome in SIBO and steatosis. Most studies focus on the fecal microbiome. The small intestinal microbiota remains a "black box" due to difficulties in sampling and analysis.
- SIBO types (methane-producing, hydrogen-producing) and their impact on the liver. Different types of bacterial overgrowth may have different effects on intestinal permeability, LPS production, and inflammation, but this is largely unexplored.
- The role of microbial metabolites (e.g., ethanol, TMAO, SCFA). Some metabolites (e.g., endogenous ethanol from E. coli) may exacerbate steatosis, but clinical data are fragmentary.
- Gut-liver axis dynamics during interventions. The effects of antibiotics, probiotics, FMT, or diet on the microbiota and liver are being studied, but the long-term effects and mechanisms remain unclear. The importance of differentiating between SIBO variants is already being emphasized. Differentiating SIBO subtypes. Different gas types reflect the activity of different microbial populations:
- Hydrogen – a product of carbohydrate fermentation by bacteria; associated with diarrhea.
- Methane – synthesized by archaea (Methanobrevibacter smithii) from hydrogen; slows motility, associated with constipation.
- Hydrogen sulfide (H2S) – produced by sulfate-reducing bacteria (Desulfovibrio, Fusobacterium); can cause inflammation, disrupt barrier function, and modulate neurotransmitter pathways.

Specifics of SIBO Coding

Coding according to the International Statistical Classification of Diseases and Related Health Problems.

According to ICD-10 (possible variant): K63.8 Other specified bowel diseases.

Classification of the disease or condition (group of diseases or conditions). There is no generally accepted classification system for SIBO. Some authors separately distinguish SIBO detected by a breath test with a hydrogen analyzer ("hydrogen" SIBO) or methane ("methanogenic" SIBO) in exhaled air, which implies an overgrowth of hydrogen-producing or methanogenic microorganisms [37]. However, this classification is conditional.

Achievements in the Assessment of the Methanogenic Variant of SIBO

The inflammatory effect of methane is associated with its ability to reduce oxidative stress and modulate inflammatory signaling pathways, including the suppression of proinflammatory cytokine production and NF-κB activation. Research shows that methane acts as a gaseous mediator, similar to nitric oxide or hydrogen sulfide, and has a protective effect on tissues during inflammatory processes.

Methane in Exhaled Breath

Clinical Significance.
- Elevated methane levels are associated with decreased intestinal motility, chronic constipation, and bloating.
- Diagnosis: Breath tests are used to detect small intestinal bacterial overgrowth (SIBO) and assess the microbiota.
- Normal vs. abnormal: Low levels (up to 5 ppm) are considered physiological, while persistent increases above 10 ppm require clinical interpretation.

Clinical Presentation of SIBO

Characteristic features of the clinical picture of SIBO include complaints of bloating, as well as abdominal pain and diarrhea (in some cases, symptoms of constipation may be observed due to an abundance of methanogenic microorganisms in the small intestine) [7]. It is not possible to estimate the prevalence of these symptoms or identify a predominant one [11].

There is evidence that approximately one-third of patients do not present the above-mentioned complaints, but may experience symptoms of complications characteristic of SIBO. These

include manifestations of malabsorption—steatorrhea, weight loss, and weakness—as well as neurological disorders caused by a deficiency of B vitamins and symptoms associated with hypovitaminosis of the fat-soluble vitamins A, D3, and E (vitamin K deficiency is generally not observed in SIBO) [38, 13, 39, 40]. Other clinical manifestations of an impaired local and systemic immune response in SIBO include frequent exacerbations of chronic non-infectious diseases or a less favorable course of these diseases, which is largely associated with increased levels of proinflammatory cytokines in the bloodstream in SIBO [41].

Potential and Limitations of SIBO Diagnosis

Traditional Diagnostic Criteria: SIBO is diagnosed based on clinical, anamnestic, and instrumental data.

Complaints and Anamnesis

Characteristic complaints of patients with SIBO are described in Section 1.6 "Clinical Picture." When interviewing the patient, it is important to pay attention to the patient's medical history to identify possible risk factors for the development of SIBO (see Sections 1.2 "Etiology and Pathogenesis of the Disease"). The degree of bacterial colonization in the small intestine does not correlate with disease activity and symptom severity, making it difficult to diagnose SIBO based solely on clinical and laboratory data.

Physical Examination

An objective examination of patients with SIBO most often reveals moderate abdominal pain in the periumbilical region upon palpation, a pronounced tympanic sound upon abdominal percussion, and chaotic intestinal peristalsis upon auscultation. With the development of hypovitaminosis of fat-soluble vitamins and B vitamins (most commonly, vitamin B12 (cyanocobalamin) deficiency), patients with SIBO may experience corresponding changes in the skin, nails, hair, tongue, and neurological disorders [13, 39, 42, 43].

Laboratory Diagnostic Tests

Specific abnormalities in routine blood and stool laboratory tests are not characteristic of SIBO. Nonspecific changes in these parameters are observed with SIBO-induced malabsorption, but in most cases they are minor.

Patients with SIBO who have laboratory data supporting hyperchromic macrocytic anemia are recommended to have blood vitamin B12 (cyanocobalamin) levels and/or serum folate levels tested to diagnose SIBO-associated cyanocobalamin deficiency [13,40]. Fecal calprotectin testing is not recommended for diagnosing SIBO in patients with suspected SIBO [44, 45]. Some clinical studies demonstrate a significant increase in calprotectin levels in patients with systemic sclerosis and Crohn's disease in patients with SIBO [44, 45]. There is no convincing evidence to support testing fecal calprotectin levels in all patients with suspected SIBO.

Instrumental diagnostic tests. Specific diagnostic tests for SIBO include small intestinal aspirate culture and breath tests [46, 47]. Both methods have their advantages and disadvantages.

Small intestinal aspirate culture with colony counting is recommended for patients with suspected SIBO to verify the disease [46], but molecular diagnostic methods are preferred.

Level of recommendation: A (level of evidence: 1). Historically, it was assumed that the small intestinal microbial population was considered overgrown if ≥1×105 CFU/mL of aspirate was detected. However, this concept was based on early studies in patients with blind loop syndrome and did not take into account the microbial landscape of patients with intact small intestine. Subsequent systematic reviews demonstrated the low validity of this criterion, so currently, the threshold for overgrowth for SIBO is considered to be ≥1×103 CFU/mL of mucosal surface aspirate. [46]. Despite its shortcomings, a number of publications recognize the culture method as the "gold standard" for verifying SIBO [10, 48].

• Esophagogastroduodenoscopy is recommended in patients with suspected SIBO to aspirate the contents of the proximal small intestine for subsequent culture analysis [48]. In rare cases, esophagogastroduodenoscopy in patients with SIBO may reveal nonspecific endoscopic findings in the duodenum, including edema and decreased vascularity. Morphological changes in small intestinal biopsies in these patients are also nonspecific and may include intraepithelial lymphocytosis, increased neutrophil and eosinophil counts, and significant villus flattening [49].

The main recommendation in the series is to perform a hydrogen breath test with a carbohydrate load in patients suspected of having SIBO to diagnose the disease [48, 46, 47, 50,54]. The concentration of hydrogen or methane in the air is determined in parts per million (ppm) using a gas chromatograph or a specialized gas analyzer equipped with electrochemical and/or infrared sensors. Air samples are collected sequentially, starting from baseline (on an empty stomach, immediately before ingestion of a carbohydrate substrate) at 15-minute intervals. An increase in metabolite levels in the first 90 minutes reflects the enzymatic activity of the microbiota in the small intestine, and after 90 minutes, in the large intestine [50-52].

To reduce the variability of recorded data when collecting exhaled air, the patient should take a deep breath, hold it for 15 seconds, then slowly exhale approximately 50% of the inhaled volume into the atmosphere. Only then should the sample be exhaled into the gas analyzer or a bag (bag) for collecting exhaled air samples. This procedure reduces the impact of functional "dead" space (approximately 150–200 ml) and measures a portion of alveolar air that best reflects the concentration of the gas metabolites being studied in venous blood [47, 53]. Some gas analyzers are capable of automatically determining the concentration of gas metabolites exclusively in the alveolar portion of exhaled air and allow for continuous exhalation.

Unlike small intestinal aspirate culture, breath testing is an inexpensive, noninvasive, simple, and widely available method for detecting SIBO. However, the following disadvantages exist:

- the content of hydrogen and/or methane in exhaled air is directly influenced by the composition of the small intestinal microbiota: methanogenic archaea utilize H2 to reduce CO2 to CH4, while sulfate-reducing bacteria utilize H2 to form H2S [48, 47].
- it is difficult to assess the composition of the microbiota that causes microbial overgrowth. Data are presented on a positive correlation between the levels of representatives of the Gammaproteobacteria class and the Enterobacteriaceae family, the area under the curve for H2 during the first 90 minutes of the lactulose breath test**, and the severity of bloating in SIBO [6].
- air analyzers capable of simultaneously assessing the concentration of hydrogen and methane are often more cost-effective;

- in patients with accelerated or slowed small intestinal motility, the probability of a false-positive or false-negative result is high [54].

Compared to the culture method, the sensitivity of the dextrose breath test** varies from 20 to 93%, and the specificity – from 30 to 86%. For the lactulose breath test**, these figures are 31-68% and 44-100%, respectively [50]. Preparatory measures are recommended for patients suspected of having SIBO before performing a breath test to increase the diagnostic value of the test results [51-53]. The main preparatory measures are aimed at eliminating factors that affect small intestinal peristalsis and the number of microorganisms in its lumen at the time of the test. This allows for a more accurate and natural analysis of the concentration of microbial metabolites in exhaled air in response to a carbohydrate load [51-53].

Before Performing a Breath Test, It Is Necessary To:

- 4 weeks
- before: avoid taking systemic antibacterial drugs (including intravenous administration), intestinal antimicrobials, and probiotics (antidiarrheal microorganisms);
- 2 weeks before: avoid endoscopic or surgical interventions that require colon preparation with laxatives;
- 1 week prior: stop taking medications for functional gastrointestinal disorders (including gastrointestinal motility stimulants, laxatives, antidiarrheals, intestinal anti-inflammatory and antimicrobial drugs, and other antidiarrheal drugs). If it is not possible to stop taking them for the recommended period, it is permissible to stop taking them 48 hours before the test;
- 24 hours prior: exclude alcohol and foods rich in low-absorbable carbohydrates and plant fiber from your diet (e.g., vegetables, fruits, cereals, grains)
- 8-12 hours prior: fast (drinking water is acceptable);
- on the day of the test: quit smoking (due to an increase in hydrogen concentration in exhaled air immediately after smoking);
- 2 hours prior: avoid intense physical activity (the resulting hyperventilation reduces the concentration of hydrogen in exhaled air);
- Immediately before performing the breath test, the oral cavity must be thoroughly sanitized (to avoid a false increase in the amount of hydrogen due to the activity of the oral microbiota).
- It is recommended to use dextrose or lactulose as a carbohydrate load in patients with suspected SIBO for the breath test [48, 46, 50, 52].
- The level of evidence for the recommendations is B (the level of certainty of evidence is 2).
- Comments: Recommended doses of carbohydrate loading substrates, their comparative characteristics, advantages and disadvantages, as well as criteria for interpreting the results are presented in Table 2 [48, 46, 50, 52]. Some authors verify a positive result only in the presence of two peaks of H2 increase - in the interval up to 90 minutes (small intestine) and after 90 minutes (large intestine).

Table 1 – Features of breathing tests. Substrate	Substrate Amount and Test Duration	Positive Result Criteria Increase threshold from zero)	Characteristics and Notes
Dextrose	50 or 75 g dextrose** and 250 ml water, orally, single dose	≥20 ppm H2 (≥15 ppm H2 for 50 mg dextrose**) ≥10 ppm CH4	A negative test excludes proximal but not distal bacterial overgrowth Difficult to use in patients with diabetes
Lactulose	10 g lactulose** orally, single dose (can be taken with a small amount of water)	May accelerate motility, giving False negative result May cause bloating or diarrhea Interpretation is difficult if a single peak increase is detected in the first 90 minutes	

It is recommended to perform a breath test assessing both hydrogen and methane levels in patients suspected of having SIBO to increase the diagnostic value of the breath test results [8, 11, 48, 47, 52, 55].

High methane levels in exhaled air interfere with the accurate interpretation of the increase in hydrogen concentration during a breath test. A retrospective analysis of 14,043 exhaled breath samples from patients with SIBO in response to 10 g of lactulose** showed low hydrogen concentrations in samples with high methane levels ($p<0.0001$). Moreover, a diagnostically significant increase in hydrogen concentration (≥20 ppm) in serial air samples in patients with SIBO was detected significantly less frequently in subjects with a methane-positive breath test result (23.1% vs. 55.7%; odds ratio (OR) = 0.20; 95% CI = 0.18-0.22, $p<0.0001$) [56]. This is due to the fact that most methanogenic archaea in the small intestine utilize H2 to produce CH4, which potentially affects H2 level measurements [8, 11, 47].

Furthermore, the methane breath test allows for the detection of excessive growth of methanogenic microbiota, which is relevant in the presence of constipation symptoms in patients suspected of having SIBO [11, 48, 52].

Treatment Including Drug and Non-Drug Therapies

Antibacterial therapy is the preferred tactic for eradicating small intestinal bacterial overgrowth. Studies evaluating the efficacy of systemic antibacterial agents and enteric antimicrobials for SIBO vary in the sample size, diagnostic methods, dosage, and duration of treatment. Treatment effectiveness is determined by the clinical presentation [1, 50, 51].

We draw attention to the following:

Empirical treatment with systemic antibacterial agents and enteric antimicrobials is not recommended for patients suspected of having SIBO until the diagnosis is confirmed [1]. Empirical use of systemic antibacterial agents and enteric antimicrobials in patients suspected of having small intestinal bacterial overgrowth (SIBO) without confirming the diagnosis is not justified, as it exposes them to an unjustified risk of developing antibiotic resistance, antibiotic-associated diarrhea, and C. difficile-associated disease [1].

The main recommendation from international publications is to prescribe Rifaximin as first-line therapy for patients with SIBO to eliminate small intestinal bacterial overgrowth [56]. Rifaximin is the most studied drug for the treatment of SIBO. Its advantages over systemic antibacterial agents include low gastrointestinal absorption (less than 0.4%), a low incidence of systemic side effects, and a low risk of developing bacterial strains resistant to systemic antibacterial agents and enteric antimicrobials. A systematic review and meta-analysis of 32 studies of rifaximin in SIBO showed its efficacy in 72.9% of patients (95% confidence interval (CI) 65.5–79.8).

However, the studies included in the meta-analysis were characterized by a wide range of doses (600–1600 mg per day) and treatment duration (5–28 days). Nevertheless, the meta-analysis showed a dose-dependent effect of rifaximin in the eradication of SIBO. The drug is characterized by good tolerability: adverse events such as weakness, headache, constipation, increased diarrhea, dizziness, sleep disturbance, nausea, skin rash, dry skin (characterized by subjects as mild), anaphylactic shock (1 case), and the development of C. difficile-associated disease (1 case) were observed in 4.6% of 815 subjects in 17 studies reporting them. Discontinuation of the drug due to adverse events (nausea without vomiting, headache, dry skin) was noted in only one study, in which 5 out of 120 patients (6% of subjects) discontinued the drug [56].

Rifaximin (400 mg 3 times a day for 7-14 days) is recommended for patients with SIBO to eliminate bacterial overgrowth in the small intestine [53, 56, 41].

Other antibiotics have also been prescribed in publications: Ciprofloxacin (500 mg 2 times a day for 5-10 days), metronidazole (250 mg 3 times a day for 10 days), and Norfloxacin (400 mg 2 times a day for 7-10 days). However, the level of evidence for the recommendations is no higher than C (questionable efficacy).

Additional comparisons of the effectiveness of SIBO treatment.

Table 2: Comparative Characteristics of Antibiotics for SIBO

Parameter	Rifaximin (1st line)	Ciprofloxacin	Metronidazole	Norfloxacin
Absorption	< 0.4% (local action)	High (systemic)	High (systemic)	Moderate (systemic)
Spectrum of action	Broad (aerobes, anaerobes, gram+/-)	Gram(-) bacteria	Anaerobes	Predominantly gram(-) aerobes
Level of evidence	2 (high)	2	2	2
Systemic side effects	Very rare (less than 4.6%)	Often (gastrointestinal tract, risk of tendonitis)	Often (metallic taste, disulfiram reaction)	Rarely (gastrointestinal tract, dizziness)
Risk of resistance	Low	High	Moderate	High
Typical dose	400 mg 3 t/day (7–14 days)	500 mg 2 t/day (5–10 days)	250 mg 3 t/day (10 days)	400 mg 2 t/day (7–10 days)
Main advantage	Safe and no impact on overall microbiota	Highly effective in Crohn's disease	Effective in cases of excess obligate anaerobes	Alternative in case of intolerance to other groups

Other antibiotics and doses are also prescribed in publications: Ciprofloxacin (500 mg twice daily for 5-10 days), metronidazole (250 mg three times daily for 10 days), and norfloxacin (400 mg twice daily for 7-10 days). However, the strength of these recommendations is no higher than C (questionable efficacy).

There is no specific prevention for SIBO. The criteria for disease recurrence and treatment failure remain unclear. Forty-four percent of patients with SIBO experience a relapse of symptoms within 9 months of treatment with systemic antibacterial agents [57]. A more in-depth study of the course of SIBO is needed when a clinical response is achieved or when conservative treatment is ineffective. General measures for the prevention of SIBO include promptly seeking medical attention.

The role of SIBO (small intestinal bacterial overgrowth) in the pathogenesis of symptoms of functional bowel disorders such as Irritable Bowel Syndrome (IBS) is controversial. A recent systematic review and meta-analysis concluded that SIBO is more common in patients with IBS than in controls; when using a breath test, the odds ratio for SIBO in IBS patients was 4.9, and up to 33.5% of IBS patients had SIBO [58-82].

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