PROSPECTS
IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences, 22(2), 65-70
https://prospects.wum.edu.pl/

Review Article

SMALL INTESTINAL BACTERIAL OVERGROWTH – CURRENT, NOVEL AND POSSIBLE FUTURE METHODS OF TREATMENT AND DIAGNOSIS

Mateusz Sobczyk*[1], Mikołaj Porzak[1], Daria Żuraw[2], Alicja Sodolska[3], Paulina Oleksa[4], Kacper Jasiński[1]

[1] *Stefan Kardynał Wyszyński Province Specialist Hospital, al. Kraśnicka 100, 20-718 Lublin, Poland*

[2] *Central Clinical Hospital, University Clinical Center of Warsaw Medical University, ul. Banacha 1A, 02-097 Warsaw, Poland*

[3] *Lubimed - Family Medicine Center Lublin, ul. Woronieckiego 11, 20-492 Lublin, Poland*

[4] *Independent Public Clinical Hospital No. 4 in Lublin, ul. Doktora Kazimierza Jaczewskiego 8, 20-954 Lublin, Poland*

* Correspondence, e-mail: m.sobczyk1777@gmail.com

Received: 24.03.2024 / Accepted: 06.05.2024 / Published: 17.06.2024

ABSTRACT

Small intestinal bacterial overgrowth (SIBO) is a prevalent issue, frequently overlooked in clinical practice. Its prevalence is unknown because SIBO requires diagnostic testing, however, in most studies, SIBO has been detected anywhere from <2% to 22% of healthy controls. Breath tests, which detect the presence of hydrogen in exhaled air, are the most used diagnostic method. However, their low sensitivity and specificity indicate the need for research into new more accurate methods. The standard treatment is antibiotic therapy with rifaximin. After antibiotic therapy, there is a risk of recurrence and the emergence of multidrug-resistant bacterial strains. Recurrence ratio after antibiotic therapy have been documented in 12.6% of patients after 3 months, 27.5% after 6 months and 43.7% after 9 months. There are promising results from studies on the use of probiotics and herbal preparations in treatment, but these studies have been conducted on relatively small groups of patients. This indicates the need for multicentre randomised trials with large numbers of patients to develop effective methods for the diagnosis and treatment of SIBO.

KEYWORDS: SIBO, Irritable Bowel Syndrome, Rifaximin, Probiotics, Intestinal Microbiota.

1. Introduction

Small intestinal bacterial overgrowth (SIBO) is a common but insufficiently recognised disease. Its prevalence is unknown because SIBO requires diagnostic testing, however, in most studies, SIBO has been detected anywhere from <2% to 22% of healthy controls, depending on country, or region and criteria used [1–3]. Despite its prevalence, it remains underdiagnosed due to the invasive nature of diagnostic testing. Much of the controversy surrounding the diagnosis of SIBO is due to the wide range of clinical manifestations and overlap with other gastrointestinal diseases, especially irritable bowel syndrome (IBS) as the most cited example. Predisposing factors include the use of proton pump inhibitors, opioids, gastric bypass, colectomy and gastrointestinal peristalsis [4,5]. Peristalsis disorders can be caused by systemic diseases such as diabetes mellitus, Parkinson's disease, cystic fibrosis, systemic sclerosis, spondyloarthropathy, chronic pancreatitis, ulcerative colitis, Crohn's disease, metabolic-associated fatty liver disease (MAFLD), primary biliary cholangitis [6,7]. Another important risk factor is the status after gastrointestinal surgery, colectomy being a proven risk factor for SIBO. Patients with colectomy show a significantly higher incidence of SIBO and greater severity of gastrointestinal symptoms [8]. Clinical signs of SIBO include stomach pain, abdominal bloating, gases, diarrhoea and malabsorption. Flatulence and diarrhoea are common symptoms, but do not determine a positive diagnosis.

Small intestinal aspirate/culture with a growth rate of $\geq 10^3$ CFU/mL is generally accepted as the "best diagnostic method", unfortunately the disadvantage of this method is its invasiveness [9]. The glucose or lactulose breath test is a non-invasive but indirect method that needs further standardisation for the diagnosis of SIBO. Treatment, standardly consisting of antibiotic therapy, aims to alleviate symptoms by eradicating bacteria in the small intestine. A limited number of clinical studies have shown the efficacy of systemic antibiotics (norfloxacin and

metronidazole). Many authors have demonstrated in their studies that rifaximin, a non-systemic antibiotic not absorbed from the gastrointestinal tract, is effective against SIBO and well tolerated by patients [10–12].

2. Materials and Methods

A review of the literature from 2013-2023 on small intestine bacterial overgrowth was performed using databases search conducted on PubMed and Google Scholar platforms. The paper reviews 51 scientific journal articles. The following keywords were used in search: SIBO, Irritable bowel syndrome, intestinal microbiota, probiotics, rifaximine. Exclusion criteria: studies conducted on animals, studies including children, studies incompatible with the purpose of the review.

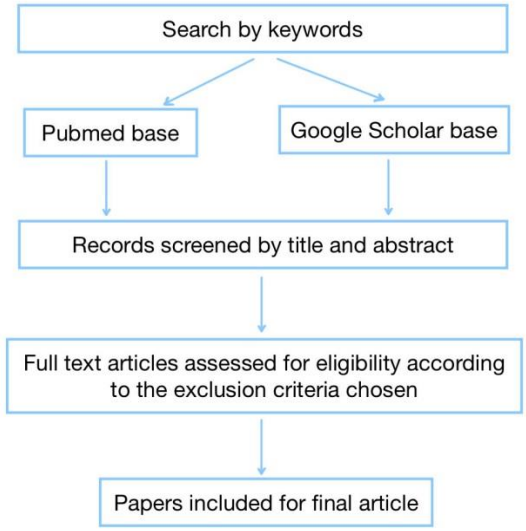

Fig 1. Search and selection of articles methodology.

3. Purpose of the work

The aim of this paper is to provide an overview of the latest diagnostic methods, pharmacological and non-pharmacological treatments for SIBO and research into therapies that may be applicable in the future.

4. Diagnostic methods used to diagnose Small Intestinal Bacterial Overgrowth

The main pathomechanism of SIBO is an increase in the number of bacteria that do not constitute the physiological microbiome of the small intestine. A better understanding of the small intestinal microbiome has proven to be key to understanding SIBO, as it helps clinicians determine the validity of any diagnostic method used to screen for the condition. In recent years, knowledge of the gut microbial flora has expanded significantly [13]. The human intestines are inhabited by 10^{14} bacterial cells [14]. The commensal microbiota protects the host from colonisation by opportunistic pathogens and can participate in food metabolism and energy production to provide essential nutrients and degrade compounds on which digestive enzymes do not act [15]. The small intestine microbiome consists mainly of Gram-positive and aerobic bacteria, while the large intestine contains mainly Gram-negative and anaerobic bacteria. The main types of bacteria found in the intestines are *Bacteroidetes* and *Firmicutes*, while *Actinobacteria*, *Fusobacteria*, *Verrucomicrobia* and *Cyanobacteria* are also present, albeit in smaller proportions [16].

4.1. Breath tests

Standard diagnostic tests recommended by scientific societies are breath tests: glucose hydrogen or lactulose hydrogen. Respiratory test criteria recommend a diagnosis of SIBO as an increase in exhaled hydrogen gas of at least 20 parts per million (ppm) above baseline within 90 minutes of oral ingestion of 75 g of glucose or 10 g of lactulose [17,18]. Only bacterial cells are capable of producing hydrogen, as opposed to human cells [19]. The presence of hydrogen in exhaled air indicates its production in the intestines by the bacteria residing there, followed by its absorption into the bloodstream and excretion through the respiratory system. For the test result to be reliable, prior to the breath test it is recommended that patients avoid antibiotics for 4 weeks and avoid stimulants and laxatives for at least 1 week. The day before the breath test, fermentable foods (e.g. complex carbohydrates) should be avoided. In addition, they should remain fasting for 8-12 hours. According to a systematic review by Khoshini et al. [20], the sensitivity of the lactulose test ranged from 31% to 68% and the specificity from 44% to 100%, while the sensitivity of the glucose breath test ranged from 20% to 93% and the specificity from 30% to 86% compared with small bowel aspirate cultures. This suggests the need to develop tests with better sensitivity and specificity to improve diagnosis.

4.2. Small intestine aspirate and culture

Small bowel aspirate and culture is often considered the gold standard for the diagnosis of SIBO. Small bowel aspirate collection involves inserting the endoscope into the upper gastrointestinal tract with deep intubation of the duodenum, while minimising aspiration of contents from the oropharynx, oesophagus and stomach to eliminate aspirate collection from outside the duodenum. However, standardisation of techniques for aseptic collection and culture of small bowel specimens are lacking [21].

Currently under investigation there are tests involving oral capsules that can measure *in vivo* hydrogen and carbon dioxide after ingestion of a carbohydrate meal [22]. Capsule technologies that can sample bacteria from the small intestine (small intestinal capsule detection system) are also emerging, and these technologies can provide a more direct and accurate assessment of SIBO [23]. The use of capsule technologies requires clinical studies on the sensitivity and specificity of the results. In the future they may provide a better alternative to current techniques for measuring hydrogen in the breath.

5. Treatment strategies for Small Intestinal Bacterial Overgrowth

The standard treatment for SIBO is antibiotic therapy. As alternative methods, researchers point to dietary treatment, the use of probiotics, faecal microbiota transplant, prokinetics and the use of herbal medicine

[24,25]. Stool transplantation and the use of probiotics according to the recommendations of scientific societies are not applicable for the treatment of SIBO, their potential use is currently in the research phase.

5.1. Antibiotics

The current standard of treatment for SIBO is antibiotic therapy. The aim of antibiotic therapy is not to completely eradicate the intestinal bacterial flora, but to modulate it [2]. Most studies on SIBO treatment have evaluated the efficacy of amoxicillin with clavulanic acid, ciprofloxacin, doxycycline, metronidazole, neomycin, norfloxacin, tetracycline, cotrimoxazole, or rifaximin [25]. There are limited data comparing the efficacy of different antibiotics. In addition, there are frequent recurrences of SIBO symptoms after antibiotic therapy, which have been documented in 12.6% of patients after 3 months, 27.5% after 6 months and 43.7% after 9 months [26,27]. The antibiotic of choice for the treatment of SIBO is rifaximin, which is a non-absorbable oral antibiotic first introduced in Italy in 1987 and in the United States in 2004 [28]. Rifaximin has a good safety profile and is not absorbed from the gastrointestinal tract, so it only acts locally on bacteria within the intestine. Furthermore, it dissolves well in bile, has a broad spectrum of antimicrobial activity against aerobic and anaerobic, Gram-positive and Gram-negative bacteria, and its side effects are comparable to placebo [29]. It seems particularly beneficial that, according to studies, rifaximin acts as an eubiotic in the lumen of the gastrointestinal tract, meaning that it protects the intestinal microbiota and increases the number of desired bacterial strains of the *Lactobacillus* and *Bifidobacterium* genera [30]. Additionally, it improves the function of the intestinal barrier, reduces bacterial translocation and reduces inflammation [30]. According to the meta-analysis by Gatta et al. the overall SIBO eradication rate after rifaximin therapy was more than 72% [10].

5.2. Probiotics

Probiotics, including bacteria and yeast, are live microorganisms that have demonstrated beneficial effects on human health [31]. In SIBO, the beneficial effect of probiotics is mainly due to their ability to modulate the composition of the intestinal microbiota and protect the gut from colonisation by pathogens. Probiotics produce substances that fight pathogenic bacteria and show adhesion to the intestinal walls, which prevents pathogenic bacteria from adhering [2,32]. In addition, probiotics compete with other bacteria for nutrients. In a clinical study conducted by Skrzydło-Radomańska et al. [33] in patients with irritable bowel syndrome, supplementation with *Bifidobacterium lactis* BI040 significantly reduced the frequency and intensity of abdominal pain compared with the placebo group; additionally, probiotic supplementation had a positive effect on stool consistency. The results indicate a high efficacy of probiotic use in IBS which may indicate a beneficial effect in SIBO, however, this requires multicentre randomised trials.

A meta-analysis by Zhong et al. [34] examined existing studies of probiotics in SIBO and found that probiotics appear to reduce hydrogen production with an odds ratio of 1.61 (CI = 1.19-2.17), but the studies were conducted on a small number of patients and were of poor quality. However, SIBO-associated conditions were mixed, and although there may have been some improvement in some symptoms such as abdominal pain, probiotic therapy had no effect on stool frequency. In contrast, another case-control study found that probiotics could cause SIBO and D-lactic acidosis leading to gas and bloating, and that probiotic withdrawal combined with antibiotic therapy led to resolution of symptoms [35].

5.3. Faecal Microbiota Transplant

Faecal microbiota transplantation (FMT) is a method of direct alteration of the intestinal microbiota, involving the administration of faecal content into the duodenum from donor to recipient in order to normalise the composition of the bacterial flora and obtain therapeutic benefits [36]. FMT is used as standard for the treatment of recurrent *Clostridium difficile* infections, and there is also intensive research into its use in many other diseases [36,37]. Data on the use of FMT for the treatment of SIBO are limited, however, there are some publications suggesting a risk of SIBO in FMT recipients. In case report the authors describe severe constipation in a subject who underwent FMT for a *C. difficile* infection. It was later determined that the recipient acquired the phenotypes of constipation and a methane-positive breath test from the FMT donor [38]. In another study, researchers screened donor patients for SIBO based on a lactulose breath test [39], although a positive breath test did not exclude the donation of faecal material. People with *C. difficile* receiving stool from donors with a positive lactulose breath test showed more gastrointestinal symptoms after FMT, although this did not reach statistical significance [39]. In 2019, the FDA issued warnings regarding multidrug-resistant organisms transmitted to recipients during FMT [40]. This indicates the need for diagnosis of abnormal gut flora in transplant material including diagnosis of SIBO.

5.4. Diet treatment

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, the so-called low FODMAP diet, which is also used in IBS, deprives bacteria of their source of energy necessary for proliferation and reduces bacterial fermentation, as evidenced by low levels of hydrogen in breath tests [41]. The use of elemental diets, which contain pre-digested nutrients, is not recommended in SIBO despite some promising study reports [2,13,42]. According to some studies, soluble fiber supplementation can lessen symptoms of IBS and SIBO [43]. Targeted probiotic therapy can also increase the effectiveness of antibiotic treatment and improve bowel regularity. Optimal dietary patterns therefore play a key role in the treatment of SIBO.

A number of other studies have evaluated diet in the treatment of SIBO, but these studies have been of low methodological quality, which means that their results cannot be implemented into clinical practice [43]. Therefore, there is still insufficient scientific evidence to support a specific type of diet for the treatment of SIBO. There is need for further research into the effectiveness of dietary treatment of SIBO.

5.5. Prokinetics

As a potential alternative treatment for SIBO, some authors also mention the use of prokinetic drugs, especially in co-morbidities with gut motility disorders [45]. Conversely, drugs that may slow motility, such as opiates, should be

avoided. Studies on the use of prokinetics in the treatment of SIBO are limited and have been conducted on a small group of patients [25]. In a small study by Madrid et al. of 12 cirrhotic patients given cisapride, a reduction in the incidence of SIBO was observed on the basis of hydrogen breath tests [46]. A small, prospective study involving five scleroderma patients with documented SIBO treated with octreotide 50 mg subcutaneously for 3 weeks showed normalisation of SIBO respiratory tests and a reduction in symptoms of nausea, vomiting, flatulence and abdominal pain [47]. The promising results of the described studies indicate the need for trials with prokinetics on more patients.

5.6. Herbal medicine in treatment of SIBO

An increasing number of patients are interested in using complementary and alternative therapies to improve gastrointestinal health. Research into the use of herbal medicines in the treatment of SIBO may be promising. Promising in the treatment of SIBO is the use of natural substances of plant origin with bactericidal properties. Oil of oregano (*Origanum vulgare*) is a well-documented botanical that directly kills or strongly inhibits the growth of intestinal microbes [44]. Oil of oregano has other beneficial properties, such as inducing apoptosis in human colon cancer cells [45]. Berberine and thyme extracts are also well known for their broad antimicrobial activity.

Wormwood (*Artemisia absinthium*) has substantial antimicrobial and anti-inflammatory properties that may be important to the pathogenesis of SIBO and has been used to successfully induce remission of Crohn's Disease [46,47]. *Equisetum arvense L.* has been shown to have a broad spectrum of very potent antimicrobial activity against various intestinal microorganisms, including *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella enteritidis* and the fungi *Aspergillus niger* and *Candida albicans* [48].

A study by Chedid et al. [46] showed that 46% of patients normalised their lactulose breath test result after herbal therapy. There was no statistical difference between antimicrobial herbs (46%) and rifaximin (34%) (P=0.24). SIBO tends to recur, and frequent antibiotic use can have long-term adverse effects on the gut microbiome and be costly; therefore, herbal therapy may be a reasonable treatment option for patients with SIBO, especially those with a history of recurrent SIBO. In the study described, the adverse effect profile of herbs compared to rifaximin was not statistically different with P = 0.22. However, the incidence of adverse effects in the rifaximin group was 9%. Adverse effects of antibiotic therapy included diarrhoea associated with *Clostridium difficile* and other diarrhoea unrelated to *C. difficile*. Only 1 case of diarrhoea unrelated to *C. difficile* (1%) was observed in the herbal preparation group (37 patients). In addition to the lower risk of side effects, the significantly lower cost of therapy with herbal preparations is also important. A limitation of this study was its retrospective nature and the heterogeneity and multiplicity of herbs used, plus the diet was not controlled. However, the promising results need to be confirmed in multicentre randomized clinical trials.

6. Limitations of the study

A limitation of our study was the review of the literature within the PubMed and Google Scholar databases. Literature from databases such as Cochrane, Embase and Medline were not included in the review.

7. Conclusions

Due to increasingly better diagnostic methods and physicians' wider knowledge of diagnosis and treatment, the number of SIBO diagnoses is likely to increase in the coming years. The current therapeutic standard based on antibiotic therapy is effective and safe in the treatment of SIBO, but due to the high frequency of recurrence and the increasing number of multidrug-resistant strains, it is necessary to search for alternative and effective treatment methods. New treatment alternatives to antibiotic therapy are essential for the effective treatment of patients. Dietary treatment, the use of probiotics and the use of herbal medicines appear to be particularly beneficial. However, for their common use, clinical confirmation of their efficacy through multicentre randomised trials is necessary. For diagnostic methods, it is advisable to improve low-invasive diagnostic methods in order to increase the comfort of patients undergoing examination and reduce diagnostic costs. Capsule-based techniques seem particularly promising, but multicentre studies are needed to determine their efficacy and safety.

Author Contributions: Conceptualization, M.S., M.P.; methodology, M.S., D.Ż., A.S., K.J.; validation, M.S., M.P.; investigation, M.S.; resources, M.S., P.O., A.S., M.P. K.J.; writing—review and editing, D.Ż., P.O., K.J, A.S.; visualization, M.S.; supervision, M.S., M.P., A.S.; project administration, M.S.;. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Grace, E.; Shaw, C.; Whelan, K.; Andreyev, H.J.N. Review article: small intestinal bacterial overgrowth – prevalence, clinical features, current and developing diagnostic tests, and treatment. *Aliment. Pharmacol. Ther.* **2013**, *38*, 674–688. DOI: 10.1111/APT.12456
2. Skrzydło-Radomańska, B.; Cukrowska, B. How to Recognize and Treat Small Intestinal Bacterial Overgrowth? *J. Clin. Med.* **2022**, *11(20)*, 6017. DOI: 10.3390/JCM11206017
3. Krajicek, E.J.; Hansel, S.L. Small Intestinal Bacterial Overgrowth: A Primary Care Review. *Mayo Clin. Proc.* **2016**, *91*, 1828–1833. DOI: 10.1016/J.MAYOCP.2016.07.025
4. Rao, S.S.C.; Bhagatwala, J. Small Intestinal Bacterial Overgrowth: Clinical Features and Therapeutic Management. *Clin. Trans. Gastroenterol.* **2019**, *10*, e00078. DOI: 10.14309/CTG.0000000000000078
5. Jacobs, C.; Coss Adame, E.; Attaluri, A.; Valestin, J.; Rao, S.S.C. Dysmotility and proton pump inhibitor use

are independent risk factors for small intestinal bacterial and/or fungal overgrowth. *Aliment. Pharmacol. Ther.* **2013**, *37*, 1103–1111. DOI: 10.1111/apt.12304

6. Efremova, I.; Maslennikov, R.; Poluektova, E.; Vasilieva, E.; Zharikov, Y.; et al. Epidemiology of small intestinal bacterial overgrowth. *World J. Gastroenterol.* **2023**, *29*, 3400-3421. DOI: 10.3748/WJG.V29.I22.3400

7. Gudan, A.; Jamioł-Milc, D.; Hawryłkowicz, V.; Skonieczna-Żydecka, K.; Stachowska, E. The Prevalence of Small Intestinal Bacterial Overgrowth in Patients with Non-Alcoholic Liver Diseases: NAFLD, NASH, Fibrosis, Cirrhosis-A Systematic Review, Meta-Analysis and Meta-Regression. *Nutrients* **2022**, 1*4(24)*, Art. No: 5261. DOI: 10.3390/NU14245261

8. Rao, S.S.C.; Tan, G.; Abdulla, H.; Yu, S.; Larion, S.; et al. Does colectomy predispose to small intestinal bacterial (SIBO) and fungal overgrowth (SIFO)? *Clin. Transl. Gastroenterol.* **2018**, *9*, Art. No: 146. DOI: 10.1038/S41424-018-0011-X

9. Tansel, A.; Levinthal, D.J. Understanding Our Tests: Hydrogen-Methane Breath Testing to Diagnose Small Intestinal Bacterial Overgrowth. *Clin. Transl. Gastroenterol.* **2023**, *14*, Art. No: e00567. DOI: 10.14309/CTG.0000000000000567

10. Gatta, L.; Scarpignato, C.; McCallum, R.W.; Lombardo, L.; Pimentel, M.; et al. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. *Aliment. Pharmacol. Ther.* **2017**, *45,* 604-616. DOI: 10.1111/APT.13928

11. Franco, D.L.; Disbrow, M.B.; Kahn, A.; Koepke, L.M.; Harris, L.A.; et al. Duodenal Aspirates for Small Intestine Bacterial Overgrowth: Yield, PPIs, and Outcomes after Treatment at a Tertiary Academic Medical Center. *Gastroenterol. Res. Pract.* **2015**, *2015*, Art. ID: 971582. DOI: 10.1155/2015/971582

12. Guo, H.; Lu, S.; Zhang, J.; Chen, C.; Du, Y.; et al. Berberine and rifaximin effects on small intestinal bacterial overgrowth: Study protocol for an investigator-initiated, double-arm, open-label, randomized clinical trial (BRIEF-SIBO study). *Front. Pharmacol.* **2023**, *14,* Art. No: 1121435. DOI: 10.3389/FPHAR.2023.1121435/FULL

13. Achufusi, T.G.O.; Sharma, A.; Zamora, E.A.; Manocha, D. Small Intestinal Bacterial Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods. *Cureus* **2020**, *12(6)*, Art. No: e8860. DOI: 10.7759/CUREUS.8860

14. Wang, Z.; Li, F.; Liu, J.; Luo, Y.; Guo, H.; et al. Intestinal Microbiota - An Unmissable Bridge to Severe Acute Pancreatitis-Associated Acute Lung Injury. *Front. Immunol.* **2022**, *13*, Art. No: 913178. DOI: 10.3389/FIMMU.2022.913178

15. Dong, L.N.; Wang, M.; Guo, J.; Wang, J.P. Role of intestinal microbiota and metabolites in inflammatory bowel disease. *Chin. Med. J.* **2019**, *132*, 1610-1614. DOI: 10.1097/CM9.0000000000000290

16. Rezaie, A.; Buresi, M.; Lembo, A.; Lin, H.; McCallum, R.; et al. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. *Am. J. Gastroenterol.* **2017**, *112*, 775–784. DOI: 10.1038/AJG.2017.46

17. Paterson, W.; Camilleri, M.; Simren, M.; Boeckxstaens, G.; Vanner, S.J. Breath Testing Consensus Guidelines for SIBO: RES IPSA LOCQUITOR. *Am. J. Gastroenterol.* **2017**, *112*, 1888–1889. DOI: 10.1038/AJG.2017.233

18. Pimentel, M.; Saad, R.J.; Long, M.D.; Rao, S.S.C. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. *Am. J. Gastroenterol.* **2020**, *115*, 165–178. DOI: 10.14309/AJG.0000000000000501

19. Smith, N.W.; Shorten, P.R.; Altermann, E.H.; Roy, N.C.; McNabb, W.C. Hydrogen cross-feeders of the human gastrointestinal tract. *Gut Microbes* **2019**, *10*, 270-288. DOI: 10.1080/19490976.2018.1546522

20. Khoshini, R.; Dai, S.C.; Lezcano, S.; Pimentel, M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Dig. Dis. Sci.* **2008**, *53*, 1443–1454. DOI: 10.1007/S10620-007-0065-1/METRICS

21. Erdogan, A.; Rao, S.S.C.; Gulley, D.; Jacobs, C.; Lee, Y.Y.; et al. Small intestinal bacterial overgrowth: duodenal aspiration vs glucose breath test. *Neurogastroenterol. Motil.* **2015**, *27*, 481–489. DOI: 10.1111/NMO.12516

22. Kalantar-Zadeh, K.; Berean, K.J.; Ha, N.; Chrimes, A.F.; Xu, K.; et al. A human pilot trial of ingestible electronic capsules capable of sensing different gases in the gut. *Nat. Electron.* **2018**, *1,* 79–87. DOI: 10.1038/s41928-017-0004-x

23. Singh, S.; Allan, N.; Wahl, C.; Lee, S.N.; Chuang, E.; et al. Sa1717 – Development of a Swallowable Diganostic Capsule to Monitor Gastrointestinal Health. *Gastroenterology* **2019**, *156*, Art. No: S-376. DOI: 10.1016/S0016-5085(19)37784-4

24. Nickles, M.A.; Hasan, A.; Shakhbazova, A.; Wright, S.; Chambers, C.J.; et al. Alternative Treatment Approaches to Small Intestinal Bacterial Overgrowth: A Systematic Review. *J. Altern. Complement. Med.* **2021**, *27*, 108–119. DOI: 10.1089/ACM.2020.0275

25. Ginnebaugh, B.; Chey, W.D.; Saad, R. Small Intestinal Bacterial Overgrowth: How to Diagnose and Treat (and Then Treat Again). *Gastroenterol Clin North Am.* **2020**, *49*, 571–587. DOI: 10.1016/J.GTC.2020.04.010

26. Quigley, E.M.M.; Murray, J.A.; Pimentel, M. AGA Clinical Practice Update on Small Intestinal Bacterial Overgrowth: Expert Review. *Gastroenterology* **2020**, *159*, 1526–1532. DOI: 10.1053/J.GASTRO.2020.06.090

27. Lauritano, E.C.; Gabrielli, M.; Scarpellini, E.; Lupascu, A.; Novi, M.; et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. *Am. J. Gastroenterol.* **2008**, *103*, 2031–2035. DOI: 10.1111/J.1572-0241.2008.02030.X

28. Shimura, S.; Ishimura, N.; Mikami, H.; Okimoto, E.; Uno, G.; et al. Small Intestinal Bacterial Overgrowth in Patients with Refractory Functional Gastrointestinal Disorders. *J. Neurogastroenterol. Motil.* **2016**, *22*, 60-68. DOI: 10.5056/JNM15116

29. Pimentel, M. Review of rifaximin as treatment for SIBO and IBS. *Expert Opin. Investig. Drugs* **2009**, *18*, 349–358. DOI: 10.1517/13543780902780175

30. Wang, J.; Zhang, L.; Hou, X. Efficacy of rifaximin in treating with small intestine bacterial overgrowth: a systematic review and meta-analysis. *Expert Rev. Gastroenterol. Hepatol.* **2021**, 15, 1385–1399. DOI: 10.1080/17474124.2021.2005579

31. Ponziani, F.R.; Zocco, M.A.; D'Aversa, F.; Pompili, M.; Gasbarrini, A. Eubiotic properties of rifaximin: Disruption of the traditional concepts in gut microbiota modulation. *World J. Gastroenterol.* **2017**, *23*, 4491-4499. DOI: 10.3748/WJG.V23.I25.4491

32. Kim, S.K.; Guevarra, R.B.; Kim, Y.T.; Kwon, J.; Kim, H.; et al. Role of Probiotics in Human Gut Microbiome-Associated Diseases. *J. Microbiol. Biotechnol.* **2019**, *29*, 1335–1340. DOI: 10.4014/JMB.1906.06064

33. Monteagudo-Mera, A.; Rastall, R.A.; Gibson, G.R.; Charalampopoulos, D.; Chatzifragkou, A. Adhesion mechanisms mediated by probiotics and prebiotics and their potential impact on human health. *Appl. Microbiol. Biotechnol.* **2019**, *103*, 6463–6472. DOI: 10.1007/S00253-019-09978-7

34. Skrzydło-Radomańska, B.; Prozorow-Król, B.; Kurzeja-Mirosław, A.; Cichoż-Lach, H.; Laskowska, K.; et al. The Efficacy and Safety of Single-Strain Probiotic Formulations Containing Bifidobacterium lactis or Bacillus coagulans in Adult Patients with Irritable Bowel Syndrome—A Randomized Double-Blind Placebo-Controlled Three-Arm Interventional Trial. *J. Clin. Med.* **2023**, *12*, Art. No: 4838. DOI: 10.3390/JCM12144838

35. Zhong, C.; Qu, C.; Wang, B.; Liang, S.; Zeng, B. Probiotics for Preventing and Treating Small Intestinal Bacterial Overgrowth: A Meta-Analysis and Systematic Review of Current Evidence. *J. Clin. Gastroenterol.* **2017**, *51*, 300–311. DOI: 10.1097/MCG.0000000000000814

36. Rao, S.S.C.; Rehman, A.; Yu, S.; Andino, N.M. Brain fogginess, gas and bloating: a link between SIBO, probiotics and metabolic acidosis. *Clin. Transl. Gastroenterol.* **2018**, *9(6)*, Art. No: 162. DOI: 10.1038/s41424-018-0030-7

37. Wang, J.W.; Kuo, C.H.; Kuo, F.C.; Wang, Y.K.; Hsu, W.H.; et al. Fecal microbiota transplantation: Review and update. *J. Formos. Med. Assoc.* **2019**, *118*, 23–31. DOI: 10.1016/J.JFMA.2018.08.011

38. Gupta, K.; Tappiti, M.; Nazir, A.M.; Koganti, B.; Memon, M.S.; et al. Fecal Microbiota Transplant in Recurrent Clostridium Difficile Infections: A Systematic Review. *Cureus* **2022**, *14(5)*, Art. No: e24754. DOI: 10.7759/CUREUS.24754

39. Chang, B.W.; Rezaie, A. Irritable Bowel Syndrome-Like Symptoms Following Fecal Microbiota Transplantation: A Possible Donor-Dependent Complication. *Am. J. Gastroenterol.* **2017**, *112*, 186–187. DOI: 10.1038/AJG.2016.472

40. Allegretti, J.R.; Kassam, Z.; Chan, W.W. Small Intestinal Bacterial Overgrowth: Should Screening Be Included in the Pre-fecal Microbiota Transplantation Evaluation? *Digest. Dis. Sci.* **2018**, *63*, 193–197. DOI: 10.1007/S10620-017-4864-8/METRICS

41. Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms | FDA. **2019**. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse (Accessed 21 Jan 2024)

42. Dionne, J.; Ford, A.C.; Yuan, Y.; Chey, W.D.; Lacy, B.E.; et al. A Systematic Review and Meta-Analysis Evaluating the Efficacy of a Gluten-Free Diet and a Low FODMAPs Diet in Treating Symptoms of Irritable Bowel Syndrome. *Am. J. Gastroenterol.* **2018**, *113*, 1290–1300. DOI: 10.1038/S41395-018-0195-4

43. Pimentel, M.; Constantino, T.; Kong, Y.; Bajwa, M.; Rezaei, A.; et al. A 14-day elemental diet is highly effective in normalizing the lactulose breath test. *Digest. Dis. Sci.* **2004**, *49*, 73–77. DOI: 10.1023/B:DDAS.0000011605.43979.E1

44. Wielgosz-Grochowska, J.P.; Domanski, N.; Drywień, M.E. Efficacy of an Irritable Bowel Syndrome Diet in the Treatment of Small Intestinal Bacterial Overgrowth: A Narrative Review. *Nutrients* **2022**, *14(16)*, Art. No: 3382. DOI: 10.3390/NU14163382

45. Ghosh, G.; Jesudian, A.B. Small Intestinal Bacterial Overgrowth in Patients with Cirrhosis. *J. Clin. Exp. Hepatol.* **2019**, *9*, 257–267. DOI: 10.1016/J.JCEH.2018.08.006

46. Madrid, A.M.; Hurtado, C.; Venegas, M.; Cumsille, F.; Defilippi, C. Long-Term treatment with cisapride and antibiotics in liver cirrhosis: effect on small intestinal motility, bacterial overgrowth, and liver function. *Am. J. Gastroenterol.* **2001**, *96*, 1251–1255. DOI: 10.1111/J.1572-0241.2001.03636.X

47. Soudah, H.C.; Hasler, W.L.; Owyang, C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. *N. Engl. J. Med.*, **1991**, *325*, 1461–1467. DOI: 10.1056/NEJM199111213252102

48. Cui, H.; Zhang, C.; Li, C.; Lin, L. Antibacterial mechanism of oregano essential oil. *Ind. Crops Prod.*, **2019**, *139*, Art. No: 111498. DOI: 10.1016/J.INDCROP.2019.111498

49. Athamneh, K.; Alneyadi, A.; Alsamri, H.; Alrashedi, A.; Palakott, A.; et al. *Origanum majorana* Essential Oil Triggers p38 MAPK-Mediated Protective Autophagy, Apoptosis, and Caspase-Dependent Cleavage of P70S6K in Colorectal Cancer Cells. *Biomolecules* **2020**, *10(3)*, Art. No: 412. DOI: 10.3390/BIOM10030412

50. Chedid, V.; Dhalla, S.; Clarke, J.O.; Roland, B.C.; Dunbar, K.B.; et al. Herbal Therapy Is Equivalent to Rifaximin for the Treatment of Small Intestinal Bacterial Overgrowth. *Glob. Adv. Health Med.* **2014**, *3*, 16-24. DOI: 10.7453/GAHMJ.2014.019

51. Szopa, A.; Pajor, J.; Klin, P.; Rzepiela, A.; Elansary, H.O.; et al. *Artemisia absinthium* L.—Importance in the History of Medicine, the Latest Advances in Phytochemistry and Therapeutical, Cosmetological and Culinary Uses. *Plants* **2020**, *9*, Art. No: 1063. DOI: 10.3390/PLANTS9091063

52. Al-Snafi, A.E. The pharmacology of *Equisetum arvense* - A review. *IOSR Journal Of Pharmacy* Www.Iosrphr.Org. **2017**, *7*, 31–42. www.iosrphr.org (Accessed 19 Jan 2024)