

# Small Intestinal Bacterial Overgrowth (SIBO): Result of Altered Defensive Mechanism in Gastrointestinal – A Review

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## ABSTRACT

Small intestinal bacterial overgrowth (SIBO) is a condition that is characterized by an increased number of bacteria in the small intestine or an existence of bacteria type that generally should not be in the small intestine. In SIBO, the number of bacteria found in culture was more than  $10^5$  CFU (Colony-Forming unit) per ml. The fundamental problem in which SIBO occurred was the disruption in defensive mechanisms to prevent bacteria from overgrowing, including gastric acid juice, intestine motility, competent immune function, and intact anatomy. Disruption of this defensive mechanism will lead to SIBO, which furthermore will result in not only mild complications, such as abdominal complaints, but also severe complications, such as maldigestion/malabsorption, nutrient deficiency, or even systemic infection and acidosis. The manifestations of SIBO were often unclear so that it is hard to distinguish with other diseases, which much lead to misdiagnosis or underdiagnosis. Diagnosis of SIBO should be conducted very meticulously regarding underlying diseases that resulted in gastrointestinal defensive mechanism disturbance and malassimilation syndrome. Additional examinations for SIBO currently were jejunal aspiration and breath test, but both of them had their limitations in sensitivity and specificity. Therapeutical management consisted of treating the underlying diseases, eradicating bacteria with the antibiotic, particularly rifaximin, and improving nutritional deficiency.

**Keywords:** small intestinal bacterial overgrowth (SIBO), management, bacterial overgrowth, breath test, rifaximin

## ABSTRAK

Small intestinal bacterial overgrowth (SIBO) merupakan suatu kondisi yang ditandai dengan peningkatan jumlah bakteri pada usus halus ataupun keberadaan dari bakteri yang seharusnya tidak berada di dalam usus halus. Pada SIBO, jumlah bakteri yang ditemukan pada kultur lebih dari  $10^5$  colony-forming unit (CFU) per ml. Masalah dasar dimana terjadinya SIBO antara lain gangguan dalam sistem pertahanan dalam mencegah bakteri tumbuh berlebih antara lain cairan asam lambung, motilitas usus, fungsi imun yang kompeten, dan anatomi yang intak. Gangguan dalam mekanisme pertahanan akan menyebabkan terjadinya SIBO dimana lebih lanjut akan mengakibatkan tidak hanya gangguan ringan, seperti keluhan pada perut, tetapi juga gangguan berat, seperti maldigesti/malabsorpsi, defisiensi nutrient, sampai infeksi sistemik maupun asidosis. Manifestasi dari SIBO sering kali tidak jelas sehingga sulit untuk dibedakan dengan penyakit lain yang mengakibatkan

*terjadinya misdiagnosis atau underdiagnosis. Diagnosis dari SIBO sangat perlu dilakukan dengan teliti terkait penyakit-penyakit dasar yang menyebabkan gangguan mekansime pertahanan dan adanya sindrom malasimilasi. Pemeriksaan penunjang untuk SIBO saat ini adalah aspirasi jejunum dan tes nafas, tetapi keduanya memiliki keterbatasan dalam sensitivitas dan spesifitas. Manajemen terapi terdiri atas 3 hal penting, atasi penyakit yang mendasari, eradikasi bakteri dengan antibiotik, khususnya rifaximin, dan perbaiki defisiensi nutrisi.*

**Kata kunci:** *small intestinal bacterial overgrowth (SIBO), manajemen, bacterial overgrowth, tes nafas, rifaximin*

## INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a condition that is characterized by an increased number of bacteria in the small intestine or alteration of some type of bacteria that generally should not be in the small intestine. SIBO is characterized by an increased number of bacteria that are found in culture with an amount of  $10^5$  CFU (Colony-Forming units) per ml. However, there was a literature that doubted this number because the number of bacteria in the small intestine typically should not exceed  $10^3$  CFU/ml, which meant this number could be offered as another threshold of SIBO.<sup>1,2</sup> SIBO has been associated with some problematic conditions that affect the quality of life, such as malabsorption/maldigestion in the elderly and post large bowel surgery patients.<sup>3,4</sup> The underlying mechanism of SIBO until recently is still very complicated. Yet, the most crucial factor that leads to SIBO is the disruption of a homeostatic mechanism that prevents bacterial overgrowth.<sup>1,5</sup>

In a healthy condition, a normal flora in the gastrointestinal tract has a significant role in maintaining the function of this system. Normal flora will protect the digestive tract from pathogenic bacteria, perform a metabolic and trophic function, and provide nutrition (short-chain fatty acid). Then, the body itself has other defense mechanisms to prevent the colonization of bacteria in the gastrointestinal tract, including gastric acid and proteolytic enzyme, decent anatomical function, peristaltic movement of the intestine, and a competent immune system.<sup>6</sup> Disruption in this defense system will lead to bacterial colonization and proliferation excessively. As an example, a fistula between colon and small intestine will prompt coliform bacteria to migrate into the small intestine or in chronic PPI users, the amount of gastric acid will be significantly reduced.<sup>4</sup>

The problem associated with SIBO is this condition often occurs after some medical interventions such as small intestine surgery, chronic gastric acid suppressor user, and administration of drugs that decrease motility of intestine, like narcotics. Additionally, SIBO could also emerge secondarily because of systemic diseases

such as diabetes mellitus, cirrhosis hepatic, scleroderma, and chronic kidney disease.<sup>5</sup> The next problem is the symptoms are quite not specific, so it often leads to misdiagnose or underdiagnose, yet significantly influences the quality of life of the patient with bloating, diarrhea, weight loss, and nutrition deficiency.<sup>1,3</sup>

Because SIBO is often associated with many diseases and has a significant influence on the quality of life, so in this literature, SIBO is going to be discussed comprehensively.

## EPIDEMIOLOGY

First, for prevalence in SIBO until recently still cannot be defined for sure. Some studies showed that the prevalence of SIBO in healthy patients is 2.5–22%.<sup>5</sup> SIBO patients usually do not have a symptom or do have the symptoms but not significantly so that SIBO is usually underdiagnosed. Besides, SIBO often occurs with other diseases such as IBS or celiac disease that make SIBO not diagnosed promptly, and the prevalence of SIBO often varies depending on the conducted examination.<sup>4,5,7</sup>

In an examination with hydrogen breath tests on patients with gastrointestinal symptoms, there is 56% of patients positively diagnosed with SIBO while in a study that was conducted in 2003, there was a prevalence of 66% in the patients with celiac disease.<sup>8,9</sup> In another study with different celiac disease patients, prevalence numbers were resulted differently according to applied examination, including jejunal aspiration and breath test, which found as many as 11% and 23%, respectively.<sup>10</sup> Recently, a meta-analysis study showed that the prevalence of SIBO in the IBS population was 38% dan odds of SIBO were increased almost fivefold compared to healthy individuals.<sup>11</sup>

## PATHOPHYSIOLOGY

In the gastrointestinal tract, some mechanisms prevent bacterial overgrowth in intestines such as gastric juice, intestine motility, the competent immune system in the digestive tract, and intact anatomy.

### Gastric Juice

Gastric acid has been known to kill and reduce numbers of ingested bacteria, so the number of bacteria that is going to the intestine is significantly decreased. Then, in gaster, there are also proteolytic enzymes that help to kill bacteria and mucous layer to detain the bacteria. However, in hypochlorhydria or achlorhydria case, gastric acid is significantly reduced. Therefore, some bacteria could pass through the stomach. Those cases are often found in *H.pylori* infection, elderly patients, and chronic gastric acid suppressor users.<sup>12,13</sup>

### Intestine Motility

Motility in the gastrointestinal tract always moves antegrade so that bacteria could not easily attach in the intestine to colonize. Disturbance in motility could lead to ineffective swept of bacteria from proximal intestine to colon, which will allow developing into SIBO. Motility disorder is often found in some metabolic diseases such as diabetes mellitus, cirrhosis hepatic (through retrograde pressure from proximal duodenum), celiac disease, and chronic kidney disease by neuropathy of autonomic nerve.<sup>4,14,15</sup>

### Altered Immune Function

Patients with SIBO usually have immunity alteration in intestine mucous that has been shown by an increased concentration of immunoglobulin A (IgA). Additionally, some immunodeficiency disease such as AIDS and IgA deficiency usually has complications, which one of them is SIBO.<sup>5,16</sup>

### Anatomy Alteration

Some anatomy alteration could lead to SIBO are consisted of obstruction and stagnation, a sequel from previous surgery, and short bowel syndrome. Blockage and stagnation, either by stricture, adhesion, diverticula, or tumor, are associated with becoming SIBO. Previously conducted surgery like afferent loop syndrome following gastric surgery, Roux-en-Y, bariatric bypass surgery could lead to SIBO and often accompanied by metabolic disorder because of less

optimal food clearance and secretion. Short bowel syndrome could lead to SIBO because an absence ileocaecal valve will yield the migration of coliform bacteria to the intestine and also more undigested food, which is a relevant material to be fermented by bacteria in the intestine.<sup>5,17</sup>

Some causes and diseases that lead to abruption of this preventing bacterial overgrowth function are shown in Table 1.

In detail, this process starts when bacteria, particularly coliform bacteria, growth in excessive numbers than generally in the intestine, will yield to maldigestion and deficiency of carbohydrates such as lactose, sucrose, and sorbitol. Then, some of the carbohydrate fermentations will form formations of a short-chain fatty acid, propionate acid, and butyric acid. Although these formations are useful in the colon as a nutrition supplier, in the intestine, these fatty acids will abrupt absorption of nutrients and impair motility by peptide YY, neurotensin, and GLP-1, which aggravate the SIBO itself.<sup>18</sup> These bacteria will also produce some toxic components (peptidoglycans, D-lactate, and serum amyloid A. Fermentation of either carbohydrate or fatty acid, together with the produced toxic components, will lead to an inflammation process to mucous. This inflammation will become mucosal damage in the brush border, which will cause permeability disorder in the intestine and probably will lead to protein-losing enteropathy.<sup>19</sup> This permeability disorder will result in a nutrient deficiency.

Then, these bacteria will deconjugate with a bile salt, which will interfere absorption of fat and generate a deficiency of vitamin that solubles in fat. These bacteria will also use protein intraluminal that will result in deficiency protein and produce ammoniac excessively.<sup>5,20</sup>

This inflammation process not only affects the function of the gastrointestinal tract but also affect anatomically. Microscopically, there is some alteration in lamina propia and atrophy of intestinal villous. However, macroscopically, there might be ulcer or erosion in the mucous layer of the intestine. Then, these anatomical changes will magnify the symptom of SIBO.<sup>21</sup>

**Table 1. Some disorders that result in defense abruption to bacterial overgrowth<sup>4,7</sup>**

Defense disruption	Cause
Gastric achlorhydria	Chronic PPI use, chronic atrophic gastritis
Small bowel dysmotility	<i>helicobacter pylori</i> infection, gastric resection Gastroparesis, diabetic gastroenteropathy, scleroderma, IBS, Celiac Disease, chronic narcotics use, Chronic Intestinal Pseudo-Obstruction, neuropathy associated renal failure, hypothyroidism, amyloidosis, muscular dystrophy, motility suppressing drugs, Cirrhosis, end-stage renal disease.
Anatomical abnormality	Small intestine diverticula, stricture, surgical blind loop, Resection of Ileocaecal valve, Fistula, Gastric resection, Chron's Disease
Immune dysfunction	AIDS, IgA deficiency, immunodeficiency status
miscellaneous	Chronic pancreatitis, malnutrition, elderly, cystic fibrosis, intestinal failure

## CLINICAL MANIFESTATION

Symptoms of SIBO manifestation depend on how severe the disease itself and the underlying conditions. In most cases, SIBO is asymptomatic or shows complaints that similar to IBS, including bloating, flatulence, abdominal discomfort, explosive diarrhea, and abdominal pain.<sup>6</sup> In more severe cases, the symptoms are sometimes accompanied by malabsorption, malnutrition, weight loss, steatorrhea, edema, and other symptoms that are associated with micronutrient deficiency. These are primarily encountered in elderly patients because SIBO, until recently, is considered as the leading cause of unexplained diarrhea and maldigestion in elderly patients.<sup>20</sup> The symptoms of SIBO are indeed unspecific, so that it is hard to distinguish SIBO with other diseases like intolerance and IBS. Therefore, SIBO is often misdiagnosed or underdiagnosed.<sup>4</sup>

Micronutrient deficiencies vary in many forms. Anemia in SIBO could be microcytic because of a lack of iron either due to gastrointestinal bleeding or due to chronic illness. However, anemia could also be macrocytic because of a lack of vitamin B12 due to the overgrowth of anaerobic bacteria. Vitamin V12 also results in not only polyneuropathy but also other neuropathy complications such as ataxia, speech disorder, and mental status disorder. Lack of vitamin D could result in hypocalcemia so that prompt other disorder such as tetany or bone mineral disease.<sup>5</sup>

Other severe complications that could happen yet quite rare are D-lactic acidosis, systemic infection, and worsen liver disease. D-lactic acidosis is a disorder due to the involvement of *Lactobacillus*-type bacteria in SIBO, particularly in a patient with short bowel syndrome.<sup>5</sup> This type of acidosis could also be prompted in SIBO through alcohol and acetaldehyde production that result in alcoholic liver disease.<sup>22</sup> Bacterial translocation is a combination process of SIBO, increased intestine permeability, and immunity alteration so that bacteria could translocate to peritoneum and portal system. Bacterial translocation into the portal system and peritoneum has a more significant opportunity to lead to systemic sepsis. This condition is often found in patients with liver diseases. Then, in patients with liver disease as cirrhosis hepatic, SIBO will magnify the state of patients because of encephalopathy hepatic, which will be improved with oral antibiotic administration.<sup>23</sup>

## MANAGEMENT

### Diagnosis

Diagnosis of SIBO is a difficult one because physical and laboratory examinations are not specific, while SIBO patients often come with symptoms and complications that are also not specific. For SIBO diagnosis, probably need to consider it is SIBO if there are abdominal complaints that are by with weight loss or malassimilation syndrome, especially on special occasions such as elderly, systemic diseases, history of gastrointestinal surgical, and other cases that affected defense mechanism.

Until recently, no examination has been considered as a gold standard to establish the diagnosis of SIBO. However, there are two additional diagnosis examinations, which are still controversial, to diagnose SIBO, including direct tests by bacterial culture through jejunal aspiration and indirect test through carbohydrate breath tests.<sup>7</sup> Bacterial culture from jejunal aspiration is viewed as an invasive procedure, yet specifically in diagnosis SIBO. For carbohydrate breath tests, it is a feasible and easy test, but there is still no proper standardization.<sup>24</sup>

### Direct Test

Examination with bacterial culture as a method to diagnose SIBO needs standardization because, until recently, there has not been established yet. The aspirate sample is collected from the liquid in the proximal jejunum, but some studies recommended to collect samples from upper duodenal because it is more practical and feasible.<sup>12,24</sup> Diagnosis of SIBO is established if the bacterial colony from the culture is as many as  $>10^5$  CFU/mL.<sup>25</sup> If the bacterial colony is less than  $10^5$  CFU/mL, SIBO should be considered in case there are species of coliform bacteria.<sup>26</sup> A study in 2008 recommended that coliform bacterial in proximal jejunal that is found more than  $10^3$  CFU/mL should be fundamental to diagnose SIBO.<sup>2</sup> The limitations of this examination, including contamination from upper gastrointestinal bacteria, unable to reach the distal small intestine, and the difference in place and time of aspiration, will yield many results. Therefore, it sometimes needs multiple sample aspirations. Then, not all types of bacteria could be cultured easily, particularly anaerobic bacteria.<sup>20,24,26,27</sup>

## Indirect Test

A breath test is a non-invasive examination that can be done at a relatively lower price. The hydrogen breath test will depend on hydrogen production from bacterial carbohydrate fermentation in the colon. Most of the produced gas will enter into blood vessels and end at the lungs, where it will be excreted.<sup>7,28</sup> The mechanism of this hydrogen production becomes the basis of the hydrogen breath test examination. The test itself is started by consuming carbohydrates (glucose, lactose, and xylose) orally. Then, the end-expiratory breath will be measured every 15 minutes in 3 hours. Lactulose is the most common carbohydrate to be used in this hydrogen breath test. Because the human body does not break down lactulose so that naturally lactulose will stay in its form through from small intestine to colon and will be fermented by coliform bacteria.<sup>20,28</sup> This examination will be positive if there is both an escalation of hydrogen level > 20 ppm and a double peak in breath hydrogen expiration graph. This double peak is caused by increased gas production from lactulose fermentation by flora in small bowel and colon.<sup>7,20</sup> If there is no double peak, but there is an early escalation in breath hydrogen test after lactulose consumption (< 90 minutes), that may mean there is bacterial overgrowth.<sup>20</sup> False-positive is often found in the case of carbohydrate malabsorption, digestion by oral bacterial, while false-negative can be seen in a patient with prior antibiotic exposure.<sup>7</sup>

## Therapeutic Trial

Because of the limitation of both jejunal aspiration test and breath test to diagnose SIBO due to lack of sensitivity, specificity, and availability in some countries for both tests, some clinicians approached using therapeutic trials with the empirical antibiotic or rifaximin. However, this method still has not been standardized. Then, if the patients do not respond with the therapeutic trial, it does not mean that the diagnosis of SIBO has been excluded.<sup>5,13,29</sup>

## Therapy

The therapy principal in SIBO problems emphasizes on three things, which are 1) treat the underlying disease, 2) eradicate bacterial overgrowth, and 3) improve malnutrition and deficiency that follow SIBO.<sup>27</sup> Treat the underlying condition could be conducted in many forms, as dietary change, surgical treatment, or medication treatment. Dietary change can be applied in patients with celiac disease cofounded

with SIBO, whereas a strict regimen will result in a better improvement. Additionally, in most of the patients sometimes need to be given a lactose-free diet while increasing energy needs from fat by administering medium-chain triacylglycerol oils.<sup>5</sup> Surgical should be performed if there is an anatomical alteration that prompts SIBO, such as diverticulosis, fistula, stricture, adhesion, or obstruction.<sup>4</sup> In a case of motility disorder of gastrointestinal tracts, like narcotics user or gastroparesis patients, should be administered with prokinetic agents to increase motility or even octreotide. Yet, long term benefit has been proven less effective.<sup>30</sup> In patients with long term PPI use as in GERD patients, dose adjustment is needed as minimum as possible to maintain free of GERD symptoms because this adjustment could be beneficial to improve overgrowth symptoms.

Although the underlying disease or disorder that leads to SIBO has been treated, it still mandatory to eradicate overgrowing bacteria by administering antibiotics. The main target of antibiotic administration not only to eliminate bacteria but also tend to reduce the number of bacteria, particularly normal flora of gut.<sup>13</sup> Ideally, antibiotic therapy is given selectively to the overgrowth bacteria of each patient based on bacterial sensitivity test against some antibiotics.<sup>31</sup> Nevertheless, this approach is quite tricky because this examination is less sensitive and specific. This problem leads to the therapy approach by administering broad-spectrum antibiotics. However, it is essential to remember that long term administration could lead to diarrhea, the development of *C. difficile*, antibiotic resistance, and cost issue.<sup>5</sup>

Rifaximin is an antibiotic that has been shown effective in treating SIBO. Rifaximin has been shown to eradicate SIBO up to 80% effectively.<sup>32</sup> Rifaximin is a semi-synthetic form of rifampicin group with low systemic absorption, yet good activity on eradicating bacteria in the gastrointestinal tract. Rifaximin is a chosen antibiotic to deal with the SIBO case because this antibiotic covers all kinds of bacteria.<sup>33</sup> A recent meta-analysis study showed that rifaximin had been succeeded in eradicating bacteria 70.8%, even with improved symptoms of 67.7%. The study also showed that dosage is another critical factor that had been associated with increasing eradication rates.<sup>34</sup> The current recommended dosage for rifaximin in SIBO is 800 mg. However, rifaximin 600 mg, 1200 mg, and 1600 mg were also effective enough to eradicate. The duration of administration that is currently recommended is seven days.<sup>35,36</sup> Additional therapies such as prebiotic or probiotic are still controversial

because data about them are still limited and yielded different and contradicting results even though most studies showed that probiotic provides symptoms relief but not the prevention of SIBO. Therefore, more studies are needed for a further recommendation.<sup>37–39</sup>

Nutritional deficiency improvement is another fundamental part of additional therapy that as important as those two before. Nutritional improvement could be made by administrating vitamin replacement, particularly fat-soluble vitamins and other micronutrient deficiencies. In a case that has been accompanied by severe mucosal damage, it will probably need a more extended period of nutritional correction although eradication of bacterial overgrowth has been achieved.<sup>13</sup>

### PROGNOSIS AND COMPLICATION

The prognosis of SIBO varies depending on the severity of the underlying disease that prompts SIBO, as the most severe problem of SIBO is an intestinal failure.<sup>40</sup> Additionally, most of the antibiotic therapy in SIBO is still followed with a recurrence that is shown by a relapse of symptoms, so that they need another review and therapy regimen. Rifaximin has also been reported resistant and recurrence, as shown in a study that found recurrence cases of SIBO that have been treated with rifaximin after nine months are as many as 35/80 patients (44%). Recurrence will be found much more in elderly patients, a history of appendectomy, chronic PPI therapy.<sup>41</sup>

### CONCLUSION

SIBO is a condition, which consisted of increased abnormal numbers of bacteria or alteration of the bacterial type in the intestine. SIBO is associated with some diseases that affected protection to bacterial overgrowths, such as intestine motility, gastric acid, competent immune system, and free of anatomy alteration. The symptoms that occur in SIBO vary from mild (bloating) to severe, for example, decreased body weight and nutritional deficiency. Until recently, establishing a diagnosis still becomes a primary focus to develop because of limitations in sensitivity and specificity. The therapy approach is attempted in 3 principals, resolve underlying disease, eradicate bacterial overgrowth, and restore nutritional deficiency.

### CONFLICT OF INTEREST

The authors stated there is no conflict of interest

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### REFERENCES

1. Chu H, Fox M, Zheng X, Deng Y, Long Y, Huang Z, et al. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome: clinical characteristics, psychological factors, and peripheral cytokines. *Gastroenterol Res Pract* 2016;2016:3230859.
2. Khoshini R, Dai S, Lezcano S, Pimentel M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Dig Dis Sci* 2008;53:1443-54.
3. Deng L, Liu Y, Zzang D, Li Y, Xu L. Prevalence and treatment of small intestinal bacterial overgrowth in postoperative patients with colorectal cancer. *Mol Clin Oncol* 2016;4:883-7.
4. Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol* 2007;3:112-22.
5. Bures J, Cyrany J, Kohoutova D, Förstl M, Rejchrt S, Kvetina J, et al. Small intestinal bacterial overgrowth syndrome Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol* 2010;16:2978-90.
6. Gasbarrini A, Lauritano EC, Gabrielli M, Scarpellini E, Lupascu A, Ojetti V, et al. Small intestinal bacterial overgrowth: diagnosis and treatment. *Dig Dis* 2007;25:237-40.
7. Sachdev AH, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. *Ther Adv Chronic Dis* 2013;4:223-31.
8. Martins CP, Chaves CHA, Castro MGB de, Gomes IC, Passos M do CF. Prevalence of small intestine bacterial overgrowth in patients with gastrointestinal symptoms. *Arq Gastroenterol* 2017;54:91-5.
9. Tursi A, Brandimarte G, Giorgetti GM. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. *Am J Gastroenterol* 2003;98:839-43.
10. Losurdo G, Marra A, Shahini E, Girardi B, Giorgio F, Amoroso A, et al. Small intestinal bacterial overgrowth and celiac disease: a systematic review with pooled-data analysis. *Neurogastroenterol Motil* 2017;29:x.
11. Chen B, Kim JJW, Zhang Y, Du L, Dai N. Prevalence and predictors of small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis. *J Gastroenterol* 2018;53:807-18.
12. Franco DL, Disbrow MB, Kahn A, Koepke LM, Harris LA, Harrison ME, 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;2015:971582.
13. Podolsky DK, Camilleri M, Fritz JG, Kalloo AN, Shanahan F, Wang TC. *Yamada's Textbook of Gastroenterology*. Yamada's Textbook of Gastroenterology. Chicester: John Wiley & Sons, Ltd.; 2015.
14. Gunnarsdottir SA, Sadik R, Shev S, Simrén M, Sjövall H, Stotzer PO, et al. Small intestinal motility disturbances and bacterial overgrowth in patients with liver cirrhosis and portal hypertension. *Am J Gastroenterol* 2003;98:1362-70.

15. Kurniawan AH, Suwandi BH, Kholili U. Diabetic gastroenteropathy: a complication of Diabetes Mellitus. *Acta Med Indones* 2019;51:263–71.
16. Riordan SM, McIver CJ, Wakefield D, Thomas MC, Duncombe VM, Bolin TD. Serum immunoglobulin and soluble IL-2 receptor levels in small intestinal overgrowth with indigenous gut flora. *Dig Dis Sci* 1999;44:939-44.
17. Machado JD-C, Campos CS, Lopes Dah Silva C, Marques Suen VM, Barbosa Nonino-Borges C, Dos Santos JE, et al. Intestinal bacterial overgrowth after roux-en-Y gastric bypass. *Obes Surg* 2008;18:139-43.
18. Ghoshal UC, Shukla R, Ghoshal U. Small intestinal bacterial overgrowth and irritable bowel syndrome: A bridge between functional organic dichotomy. *Gut Liver* 2017;11:196–208.
19. DiBaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. *Clin Gastroenterol Hepatol* 2006;4:11–20.
20. Fan X, Sellin JH. Review article: Small intestinal bacterial overgrowth, bile acid malabsorption and gluten intolerance as possible causes of chronic watery diarrhoea. *Aliment Pharmacol Ther* 2009;29:1067–77.
21. Hoog CM, Lindberg G, Sjoqvist U. Findings in patients with chronic intestinal dysmotility investigated by capsule endoscopy. *BMC Gastroenterol* 2007;7:29.
22. Spinucci G, Guidetti M, Lanzoni E, Pironi L. Endogenous ethanol production in a patient with chronic intestinal pseudo-obstruction and small intestinal bacterial overgrowth. *Eur J Gastroenterol Hepatol* 2006;18:799-802.
23. Almeida J, Galhenage S, Yu J, Kurtovic J, Riordan SM. Gut flora and bacterial translocation in chronic liver disease. *World J Gastroenterol* 2006;12:1493–502.
24. Iturrino J, Grover M. Small-intestinal bacterial overgrowth. In: Wallace MB, Aqel BA, Lindor KD, Devault KR. In book: *Practical Gastroenterology and Hepatology Board Review Toolkit*. New York: John Wiley and Sons 2016.p.285–90.
25. Chandra S, Dutta U, Noor MT, Taneja N, Kochhar R, Sharma M, et al. Endoscopic jejunal biopsy culture: A simple and effective method to study jejunal microflora. *Indian J Gastroenterol* 2010;29:226–30.
26. Corazza GR, Menozzi MG, Strocchi A, Rasciti L, Vaira D, Lecchini R, et al. The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. *Gastroenterology* 1990;98:302-9.
27. Quigley EMM, Abu-Shanab A. Small intestinal bacterial overgrowth. *Infect Dis Clin North Am* 2010;24:943-59.
28. Rana SV, Malik A. Hydrogen breath tests in gastrointestinal diseases. *Indian J Clin Biochem* 2014;29:398-405.
29. Krajicek EJ, Hansel SL. Small Intestinal Bacterial Overgrowth: A Primary Care Review. *Mayo Clin Proc* 2016;91:1828-33.
30. Krishnan B, Babu S, Walker J, Walker AB, Pappachan JM. Gastrointestinal complications of diabetes mellitus. *World J Diabetes* 2013;4:51-63.
31. Singh V V., Toskes PP. Small bowel bacterial overgrowth: Presentation, diagnosis, and treatment. *Curr Treat Options Gastroenterol* 2004;7:19-28.
32. Pimentel M. Review of rifaximin as treatment for SIBO and IBS. *Expert Opin Investig Drugs* 2009;18:349-58.
33. Ojetti V, Lauritano EC, Barbaro F, Migneco A, Ainora ME, Fontana L, et al. Rifaximin pharmacology and clinical implications. *Expert Opin Drug Metab Toxicol* 2009;5:675-82.
34. Gatta L, Scarpignato C, McCallum RW, Lombardo L, Pimentel M, D'Incà R, et al. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. *Aliment Pharmacol Ther* 2017;45:604-16.
35. Scarpellini E, Gabrielli M, Lauritano CE, Lupascu A, Merra G, Cammarota G, et al. High dosage rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2007;25:781-6.
36. Lauritano EC, Gabrielli M, Lupascu A, Santoliquido A, Nucera G, Scarpellini E, et al. Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2005;22:31-5.
37. Leventogiannis K, Gkolfakis P, Spithakis G, Tsatali A, Pistiki A, Sioulas A, et al. Effect of a Preparation of Four Probiotics on Symptoms of Patients with Irritable Bowel Syndrome: Association with Intestinal Bacterial Overgrowth. *Probiotics Antimicrob Proteins* 2019;11:627-34.
38. Chen WC, Quigley EMM. Probiotics, Prebiotics & synbiotics in small intestinal bacterial overgrowth: Opening up a new therapeutic horizon! *Indian J Med Res* 2014;140:582-4.
39. Zhong C, Qu C, Wang B, Liang S, Zeng B. Probiotics for Preventing and Treating Small Intestinal Bacterial Overgrowth. *J Clin Gastroenterol* 2017;51:300-11.
40. Ziegler TR, Cole CR. Small bowel bacterial overgrowth in adults: A potential contributor to intestinal failure. *Curr Gastroenterol Rep* 2007;9:463-7.
41. Lauritano EC, Gabrielli M, Scarpellini E, Lupascu A, Novi M, Sottili S, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. *Am J Gastroenterol* 2008;103:2031-5.