

# Diagnosis and Treatment of Small Intestinal Bacterial Overgrowth

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## **ABSTRACT**

*Small intestinal bacterial overgrowth (SIBO) is a clinical condition, in which excess amounts of bacteria are found in small intestine. SIBO occurred when normal homeostatic mechanism which control enteric bacteria population disrupted. Elderly patients are more vulnerable to SIBO which can be caused by two conditions, which are gastric acid reduction and disproportionately drugs consumption which then caused hypomotility. There are several methods to diagnose SIBO, but diagnose often begin with suspicion and history of risk factors of SIBO. There are two most frequent tests in SIBO diagnostic, which are bacterial culture examination and breath test. Treatments of SIBO are: (1) Treatment of underlying disease and improvement of medical condition; (2) Eradication of excess bacterial growth; (3) Resolve nutritional deficiencies which related to SIBO.*

**Keywords:** *small intestinal bacterial growth, diagnosis, treatment*

## **ABSTRAK**

*Small intestinal bacterial overgrowth (SIBO) atau pertumbuhan bakteri berlebihan di usus halus adalah suatu kondisi klinik di mana terdapat bakteri dalam jumlah yang berlebihan di usus halus. SIBO terjadi ketika mekanisme homeostatis normal yang mengontrol populasi bakteri enterik terganggu. Pasien berusia lanjut lebih rentan mengalami SIBO yang dapat disebabkan oleh dua keadaan, yaitu pengurangan asam lambung, dan konsumsi obat-obat secara tidak proporsional yang kemudian menyebabkan hipomotilitas. Ada beberapa cara untuk menegakkan diagnosis SIBO, namun diagnosis sering dimulai dengan kecurigaan dan riwayat faktor risiko SIBO. Terdapat dua macam pemeriksaan yang paling sering dilakukan dalam penegakan diagnosis SIBO, yaitu pemeriksaan kultur bakteri dan breath test. Tatalaksana SIBO anatara lain: (1) Pengobatan penyakit dasar dan perbaikan kondisi; (2) eradikasi pertumbuhan bakteri yang berlebihan; (3) mengatasi defisiensi nutrisi yang berkaitan dengan SIBO.*

**Kata kunci:** *small intestinal bacterial growth, diagnosis, tatalaksana*

## INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a clinical condition, in which excess amount of bacteria are found in small intestine.<sup>1</sup> Pathogenesis of this disease still not fully understood yet. At first, this disease only occurred in small numbers of patients, however it was estimated to occurred in more patients. Patients with SIBO have various clinical manifestations, from mild symptoms to severe symptoms like severe diarrhea, weight loss, and malabsorption.<sup>1</sup> Several tests are already available for diagnosis of SIBO, although optimal regiment treatment still difficult to explained.

Nowadays, there is growing interest in SIBO researches. Currently, research showed that SIBO is important factor in pathophysiology mechanism of irritable bowel syndrome (IBS), with prevalence 38% to 48% in IBS patients.<sup>7</sup> SIBO is a clinical condition which caused by abnormal numbers of bacteria in small intestine, with different predisposing factors, like motility disorders and disruption in gastric acid barrier.<sup>7</sup>

Patients with SIBO often manifests as chronic diarrhea, weight loss, malabsorption, nutritional deficiencies, and osteoporosis.<sup>1</sup> Most frequent misconception is SIBO only affects small numbers of patients, which are patients with anatomical abnormality in upper gastrointestinal tract or patients with motility disorder.<sup>1</sup> However, SIBO proven to be occur in wider population than previously estimated, which proven through various diagnostic tests which increase the clinical capabilities in SIBO diagnosis.<sup>4</sup>

## DEFINITION OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

SIBO defined as a clinical condition when bacteria population in small intestine found to be more  $10^5$ - $10^6$  organism/mL.<sup>1,2</sup> In normal condition, it found less than  $10^3$  organisme/mL on upper region of small intestine which mostly are gram positive organisms.<sup>2,3</sup> Beside the absolute ammount of organism, type of microbial flora decide manifestation of signs and clinical symptoms of SIBO.<sup>1</sup> Characteristic things about SIBO are the excess aerob and anaerob bacteria which colonized small intestine, which an area where bacteria population is plentiful.<sup>4</sup> Bacteria which known spesifically as SIBO especially are colon type bacteria and therefore consist mostly of gram negative aerob bacteria and anaerob bacteria which feremented carbohidrate to gas.<sup>4</sup> Bacteria which usually found as SIBO are *Escherichia coli*, *Enterococcus spp*, *klebsiella pneumonia*, *Proteus mirabils*, and others.<sup>4</sup> Hypothesis which proposed

about SIBO are expansion of bacteria from colon to small intestine which causing symptoms like fullness sensation, uncomfertable feeling in stomach and alteration in stool consistency.<sup>4</sup>

## RISK FACTORS OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

SIBO can develop in vatiuous population with risk factors. Several risk factors in the development of SIBO are: (1) Structural/anatomic: small intestine diverticulosis; small intestine strictur (radiation, medication, Crohn's disease); surgically created blind loops; ileiocecal valve resection; fistula between proximal and distal area of intestine; gastric resection; (2) Motility disorder: gastroparesis; small intestine dismotility; celiac disease; chronic intestine pseudo-obstruction; (3) Irritable bowel syndrome: in a study by Pimental et al, it was found that 78% of 202 patients who meet Rome I criteria for IBS diagnosis have abnormalities in lactulose breath test results which supported SIBO diagnosis. Extended gastric emptying, motility disorder, migrating motor complex disorder, which all of them happened in IBS become predisposition of SIBO<sup>1</sup>; (4) Metabolic disease: long and uncontrolled diabetes mellitus can impair gastrointestinal nervous system which then cause gastrointestinal motility disorder. Diabetic gastroparesis and neuropatic intestinal motility are related to SIBO. Current researches shown that SIBO found in 43% diabetic patients with chronic diarrhea, and 75% of them have significant improvement after treatment with antibiotic<sup>1</sup>; (5) Elderly patients: Mitsui et al with glucose breath test found that 33% elderly patients with disability have SIBO; (6) Disfunction of organ systems: cirrhosis; kidney failure; pancreatitis; imunodeficiency conditions; Crohn's disease; Celiac disease; malnutrition; (7) Medication: recurrent use of antibiotics; gastric acid suppression; (8) Chronic diarrhea.<sup>1-4</sup>

## PATHOGENESIS OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

SIBO occurred when normal homeostatic mechanism which control enteric bacteria population disrupted. Two most common processes which become predisposition of excess bacteria growth in small intestine are: decrease or loss of gastric acid secretion and small intestinal dismotility. Disorder in intestinal immune function and instestinal anatomic abnormality

also increase the possibility of SIBO. Then, SIBO will trigger an inflammatory response in intestinal mucosa, which in turn will trigger exacerbation of clinical symptoms of SIBO. Although often unobserved, excess growth of bacteria in intestine can cause microscopical inflammation in mucosa. Analysis of small intestine biopsy in elderly patients with SIBO showed dull intestinal villi, thinning of intestinal mucosa and crypts, and increase in the intraepithelial lymphocytes, which all of them can back to normal with administering antibiotic.<sup>1,4</sup>

### Gastric Acid

Gastric acid suppress bacterial growth, thus limiting numbers of bacteria in upper region of small intestine.<sup>1,4,7</sup> Loss of gastric acid (hypochlorhydria) is SIBO risk factor, and can occur after *Helicobacter pylori* colonization, or as consequence of aging process. Excess bacterial growth can cause false positive result in *H. pylori* diagnosis with urea-based test which shows presence of urease-positive bacteria strain. Inhibition to gastric acid secretion is through histamine type 2 receptor antagonist (H2RAs) or proton pump inhibitor can cause SIBO, although some studies still showed controversial results.<sup>1</sup>

Treatment with H2RA which caused SIBO in 18 patients are measured by bile acid breath test and jejunal aspiration. In a prospective study, 47 outpatients which treated with omeprazole 20 mg/day or cimetidine 800 mg/day shown that excess bacterial growth can be found on 53% which treated with omeprazole, compared to 17% which treated with cimetidine ( $p < 0.5$ ). Twenty patients which treated with omeprazole for 4 weeks experienced significant increase in number of bacteria in duodenum, compared baseline population which measured with endoscopic aspiration.<sup>4</sup>

### Gastrointestinal Dismotility

Several research shown that abnormality in migrating motor complex can be SIBO predisposition. During fasting, migrating motor complex arise every 90–120 minute to moving the food digestion residual in gastrointestinal system. Gastroparesis is a chronic disorder in form of gastric emptying disorder, which could arise because of long uncontrolled diabetes, connective tissue disorder, previous viral infections, and ischemia. Impaired intestinal peristalsis can cause SIBO because of food stasis and bacteria in gastrointestinal upper region.<sup>1</sup>

Small intestine motility disorder can also become SIBO predisposition, because the bacteria was not effectively removed from proximal intestine into colon. Patients with cirrhosis and portal hypertension (compared with patients without portal hypertension) have retrograde pressure wave in proximal duodenum, grouped contraction, and abnormality of migrating motor complex which increase the SIBO prevalence. Patients with chronic renal impairment have neuropathic-like motor abnormality in small intestine and have tendency to cause SIBO. Neuropathic process as chronic pseudo-obstruction intestinal (CIP), and myopathic process, such as scleroderma and polymyositis have tendencies to relate with SIBO. In the small group of patients with systemic sclerosis with over 105 CFU/ $\mu$ L by duodenal aspiration, 7 out of 8 patients have positive results in lactulose breath test.<sup>1</sup>

### Gastrointestinal Structural Abnormality

Gastrointestinal structural abnormality is an ideal environment for bacteria colonization and SIBO development. Gastrointestinal surgery which formed blind loop (Billroth II or Roux-en Y anastomosis procedure) is a predisposition bacterial static and SIBO development because of motility disorder and ineffective gastrointestinal clearance. Patients who undergone jejunioileal bypass, end-to-side enteroenteric anastomosis, or Koch distal ileal pouch forming procedure also risked to develop SIBO.<sup>1</sup>

Small intestine diverticulosis also happened in almost 1% – 6% population based on autopsy and various radiography research. This disorder commonly incidental, asymptomatic, and small sized. However, large duodenum or jejunum diverticulosis can trigger SIBO development. Small intestine stricture which can form after surgery or after radiation procedure in Crohn's disease can trigger SIBO development.<sup>1</sup> Ileocecal valve resection also increase the risk of SIBO development because enabled retrograde motion of bacteria from colon into small intestine. A research with Crohn's patients showed that ileocecal valve resection significantly increase SIBO prevalence from 18% to 30%.<sup>1</sup>

### Immune Function

Patients with immunodeficiency because of antibody response abnormality or T cell response have susceptibility to SIBO. Patients with SIBO compared to patients with normal jejunal aspiration have tendencies to have immunity disorder in intestinal

mucous, which proved with increased concentration of luminal immunoglobulin A (IgA) and number of plasma IgA cell in lamina propria. Patients with cellular and humoral immunodeficiency not predisposed to SIBO development because they have normal intestinal microflora.<sup>1</sup>

### PREVALENCE OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Prevalence of SIBO and its correlation with several disorders are not known yet, because of difficulty in research and definition. The difficulty in determine the true prevalence of SIBO is because of correlation of SIBO with several disease and many symptoms often overlapping between them. Characteristic thing about SIBO is presence of excessive amounts of aerobic bacteria. Several patients often did not come to physician to be treated so that SIBO often undiagnosed. Small intestinal bacterial overgrowth could be asymptomatic or appear with unspecific clinical symptoms. Furthermore, prevalence of SIBO depend on characteristic of the study population and diagnostic methods used to diagnose SIBO. If breath test used as diagnostic method, prevalence will varied depend on the nature and dosage of the substrate being used.<sup>4</sup>

In healthy people, SIBO found in 0-12,5% with glucose breath test, 20-22% with lactose breath test, dan 0-35% with <sup>14</sup>C D-xylose breath test. Elderly patient are more vulnerable to SIBO which can be caused by two conditions, which are gastric acid reduction and disproportionately drugs consumption which then caused hypomotility.<sup>4</sup> Prevalence of SIBO in IBS patients varied from 30% to 85% according the source being used. Prevalence of SIBO in hepatic cirrhosis is around 50%, whereas in celiac disease prevalence of SIBO in several studies is around 50%. Prevalence of SIBO in asymptomatic obese patients is around 17%.<sup>4</sup>

### CLINICAL MANIFESTATIONS OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Although the clinical symptoms of SIBO can be known clearly, there are several studies which aim to determine typical clinical symptoms of SIBO. Clinical symptoms of SIBO normally covered by clinical symptoms of the underlying diseases, such as scleroderma. Clinical manifestations of SIBO are depend on severity of the disease. In Billroth II subjects, when the number of coliform  $\geq 1 \times 10^5$  cfu/mL patient will experience significant malabsorption

as well as the typical symptom of bloating, but it is unclear whether these symptoms are caused by surgery, amount of intestine bacteria, or because of another consequences. But now, it was believed that most patients with SIBO not experienced clinical malnutrition due to malabsorption. In this case, unspecific clinical symptoms include distension, flatulence, and diarrhea. Only several rare conditions such as jejunoileal bypass operation or short bowel syndrome which caused vitamin and mineral deficiencies, including fat-soluble vitamins such as vitamin A, vitamin D, vitamin B12 and iron.

Recent researches showed that SIBO correlated to IBS and excess bacterial growth is part of IBS pathogenesis.<sup>7,8</sup> SIBO is also reported have clinical manifestation rosacea, which is a clinical condition in skin face.<sup>4</sup> D-Lactic acidosis is a severe complication of short bowel syndrome (with intact colon). This condition is caused by excess growth of *Lactobacillus*. This condition can be accompanied by neurological abnormalities like confusion, cerebellar ataxia, speech disorder, memory loss, and consciousness impairment.<sup>4</sup>

**Table 1. Steps of SIBO Identification in patient**

	Test type
Physical examination	Non-specific findings: abdomen distension, small intestinal succession splash (Taylor et al, 1991), connective tissue related to previous surgery, severe cases which can caused latent tetany, polyneuropathy, dan skin manifestation (rosacea)
Laboratory test	Anemia, low level of vitamin B12, malnutrition clinical signs (limfopenia, low level of serum pre-albumin dan transferrin, increased level of serum folic dan vitamin K (produced by bacteria)
Direct examination	Quantitative culture of luminal contents
Indirect examination Other diagnostic tests radiology/colonoscopy	Breath test: <sup>14</sup> C d-xylose, hydrogen Urine tests, Serum tests Barium test, CT enterography to determine mechanical cause of small intestinal bacterial overgrowth

### DIAGNOSIS OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

There are several methods to diagnose SIBO, but diagnose often begin with suspicion and history of risk factors of SIBO. Many sources recommend aspiration and direct culture of jejunum as gold standard although limitation on diagnostic biopsy tools often make SIBO undiagnosed. There is not diagnostic test to diagnose SIBO, although SIBO has been known as a clinical entity. Physical examination and laboratory test can be used, although the results often not specific. Gold

standard test to diagnose SIBO is quantitative culture from jejunal aspirate, with result  $> 1 \times 10^5$  CFU/mL liquid. However, this value is not validated yet and currently it was thought to be more accurate if the value  $> 1 \times 10^3$  based on systematic review.

There are two most common methods in SIBO diagnosis, which are bacteria culture test and breath test.<sup>4</sup> In breath test, specifically hydrogen breath test can be done. Non-invasive breath test shown sensitivity 60-90%, and specificity 85%, although validations with culture are still limited.<sup>4</sup> Stool test also can be used to determine whether steatorrhea presents or not. Furthermore, small intestine barium radiography and CT enterography can be used to identify mechanical predisposition factors of intestinal stasis.

### **Direct Test of Small Intestinal Bacterial Overgrowth (SIBO)**

Most accepted test to diagnose SIBO is quantitative culture of intestinal contents, with value  $> 1 \times 10^5$  CFU/mL which traditionally perceived as not normal. However, recent evidences support argument that this value is too much and only represent SIBO in surgery patients. Based on normal human small intestine culture, definition of SIBO is number of bacteria  $> 10^3$  CFU/mL. Appropriate culture technique is still not well determined. Sterile catheter which through upper gastrointestinal endoscopy is a specimen collection tool that is free from contamination of saliva and other secretion fluids. Culture technique on aspirate samples also varied. Test samples often place in non-selective media. The main concern in culture method is the difficulty to access distal region of small intestine. This test required relatively expensive cost and quite risky, because endoscopy and fluoroscopy are needed to place aspiration catheter. Limitation of jejunal aspirate are only small portion of small intestine bacteria that can be culture because of there are 400 to 500 bacteria species in intestine, and most of these bacteria is not routinely cultured, also orofaringeal flora contamination can be happened during specimen collection. Beside that, bacterial growth can be excessive.

### **Indirect Test of Small Intestinal Bacterial Overgrowth (SIBO)**

Nowadays, breath test is commonly used as alternative test to direct aspiration test because of this test is relatively non-invasive and not expensive. Most commonly used breath test is  $^{14}\text{C}$  d-xylose breath test depend on intestinal bacteria to release absorbed  $^{14}\text{C}$

$\text{CO}_2$  which then eliminated through breath which can be counted. Radioactive  $^{14}\text{C}$  or stable isotop  $^{13}\text{C}$  can be used to mark 1 g xylose. According to King and Toskes,  $^{14}\text{C}$  d-xylose test sensitivity ranged between 14,3% to 95%, and specificity between 40% to 94%. However this test not routinely used because of not widely available and replaced by hydrogen breath test which considered more accurate. Beside that, disorder that related to gastric emptying can give false negative result, while very fast gastric emptying can give false positive which caused by early exposure to test substrate in colon.<sup>4</sup>

Hydrogen breath test based on consideration that carbohydrate fermentation by intestinal flora, especially anaerob bacteria in colon which is the only one hydrogen source in the body. When bacteria in colon colonized in small intestine as SIBO, carbohydrate fermentation in small intestine produced premature hydrogen gas in large amount. The  $\text{H}_2$  which produced by this way diffused to systemic circulation and excreted from lungs in expired air. Hydrogen breath test done 12 hours after low fiber food consumption in 1 day period. Patient then asked to exhale breath to a tube that connected into a bag and baseline  $\text{H}_2$  value obtained before substrate intake that will be fermented. Then, carbohydrate substrate (glucose, lactulose, dan xylose) given orally and end sequential expired breath done after 15 minutes in 3 hours period. Because of relatively cheap and easy procedure, hydrogen breath test is the most commonly used test to diagnose SIBO, and lactose hydrogen breath test is the most commonly used hydrogen test. Increased hydrogen level after lactulose consumption first reported by Bond and Levitt.<sup>4</sup> In this case, intestinal flora fermented lactulose, produced hydrogen and or methane. After 10 gram lactulose administration, breath samples taken with 15 minutes interval 15 menit in 3 hours period.<sup>4</sup>

Criteria for positive breath test is still problematic and not well validated. However, the most commonly used technique to determine increased hydrogen more than 20 ppm and double peak in hydrogen breath expiration graphic.<sup>1</sup> First peak value caused by gas that produced by intestinal bacteria which undergo excess growth in small intestine. The second cause is cecal flora activity. Almost all researchers assume that increased  $\text{H}_2$  level happened 90 minutes after lactulose enter the gastrointestinal system. This breath test become chosen test modality to screening and treatment monitoring.<sup>1</sup>

Other tests that useful to diagnose SIBO is

radiological examination which useful to identified causative factors like jejenum divertikulosis. Biopsy in SIBO patients is not effective to diagnose SIBO because of wounds in mucous and atrophy of villi only happend in patients with severe SIBO. Urinary choly p-aminobenzoic acid (choly-PABA) and indicant also can be used to diagnose of SIBO.<sup>4</sup>

### TREATMENT OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Treatment of SIBO is quite complex and individualized. According to Quigley and Abu Shanub, three main components in treatment of SIBO: (1) Treatment of underlying disease and improvement of medical condition; (2) Eradication of excess bacterial growth; (3) Resolve nutritional deficiencies which related to SIBO.<sup>4</sup>

It is important to determine and treat the causes, symptoms and complications related to SIBO. If the cause is anatomical abnormality which potential to excess bacterial overgrowth, such as adhesion, intestinal obstruction, or strictur, then the treatment of SIBO is to fix the anatomical abnormality. Beside that, treatment of bacterial overgrowth including elimination of drugs that reduce intestinal motility or drugs that reduce gastric acidity. According to Vanderhoof et al, diet plan also have significant role in SIBO treatment. In many patients, it is important to eliminate lactose from dietary plan, to reduce other simple sugar molecules, to increase calory from fat, and to give medium chain triglycerol (MCT). In cases of decreased motility, such as chronic pseudo-obstruction, method to increase motility which used in United States are prokinetic drugs administration, such as metoclopramid and eritromisin. However while this method that used in Europe also by prucalopride administration, although this method have not been fully investigated as SIBO treatment. In condition where PPI is the cause of SIBO, lifestyle modification can bes used as gastroesophageal reflux disease (GERD) treatment or with reduce drugs that suppress stomach acid into the lowest dose or shortest duration may be useful in reduce SIBO symptoms.<sup>4</sup> Despite efforts to treat the main causes SIBO has been done as mentioned before, but most patients still need antibiotics. Antibiotic administration must be done selectively in accordance to strain that caused SIBO.

Goal of treatment with antibiotic administration is to reduce not eliminate all normal flora in intestine, therefore to improve symptoms. According to Singh

and Toskes, ideally antibiotic selection can be based on bacterial sensitivity test to the antibiotics. However, antiobiotic administration should be based on culture test results in several subjects.<sup>4</sup> There is not yet a general consensus on selection, dose, and duration of antiobiotic treatment. Chosen broad spectrum antibiotic which covered enteric aerob and anaerob antibiotic listed in the table below, which covered ciprofloxacin, norfloxacin, amoxicillin/clavulanat, metronidazole, cephalixin, and newest antibiotic, rifaximin. According to Frissora and Cash, rifaximin start getting known because of its nonabsorbable characteristic, have less side effects, and only little evidence of bacterial resistance to this antibiotic. According to Vanderhoof et al, Yang et al, Rabenstein et al, dan Di S et al, rifaximin can be chosen antibiotic because of its clinical resistance less than other types of antibiotic.<sup>4</sup>

**Table 2. Antibiotics for Treatment of SIBO4**

Antibiotic choices for treatment of SIBO
Rifaximin
Ciprpfloracin
Norfloxacin
Amoxicillin/Clavulanate
Metronidazol + trimetophrim/sulfamethoxazole
Metronidazole + Cephalixin

Although management with antibiotic administration has been done, patients often require repeated antibiotic administrations and on some cases long term antibiotic use, such ad on extended small intestine divertikulosis. According to Lauritano et al, on some convensional cases, often repeated breath test needs to be done such as if abdominal pain, bloating, and flatulence symptoms back. According to Pimentel et al, there is no clinical study which determine duration of treatment or management of recurrence SIBO, and current recomendation only based on clinical experience despite the success of treatment with rifaximin is reported.<sup>4</sup>

### COMPLICATIONS OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Complications of SIBO is varied from mild complications, such as diarrhea and vitamin deficiencies, to severe ones, such as malabsorption and neuropathy caused by fat-soluble vitamins deficiencies. Nutrical complications of SIBO is caused by maldigestion and malabsorption of foods in intestine.<sup>1</sup> Malabsorption caused by microscopic structural damage in small intestine which reduce the absorptive ability of

microvilli. Fat malabsorption caused by deconjugation of bile salts by bacteria.<sup>1</sup> Deconjugated bile salts is more absorbable in jejunum than in ileum, resulted in impairment micelle formation, fat malabsorption and fat-soluble vitamins deficiencies (vitamin A, D, E, K).<sup>1</sup> But symptoms are rarely present, except on severe cases, such as xerophthalmia (vitamin A deficiency), osteomalacia and tetany caused by hypocalcemia (vitamin D deficiency), prothrombin time (PT) elongation (vitamin K deficiency), neuropathy, retinopathy, and T cell function disorder. Carbohydrate malabsorption caused by premature breaking of sugar molecule by bacteria in conjugation with decreased activity of disaccharide enzyme caused by intestine brush border damage.<sup>1</sup> Protein malabsorption caused by destruction process by bacteria, whereas enteropathy caused by protein loss due to intestine mucous damage.

Most common complication of SIBO is vitamin B12 deficiency. Patients with flora usus normal intestinal flora depend on gastric intrinsic factor which bind with B12 vitamin to allow the absorption process in ileum. SIBO patients with atrophic gastritis absorbs less vitamin B12 which bind to protein, compared with control. However, this condition can be improved with antibiotic administration. Level of folic acid can be normal, but more common to be elevated due to increased synthesis of folic acid by bacteria in small intestine.<sup>1</sup>

## CONCLUSION

SIBO defined as increasing number of bacteria in small intestine. Because of different etiologies of SIBO, often SIBO cases are misdiagnosed or underdiagnosed, since varied clinical manifestations and the treatment must be individualized with focus in the treatment of underlying disease.<sup>4</sup> When antibiotic become main treatment, main attention is on the understanding of SIBO mechanism in patient became important to prevent relapse.<sup>4</sup>

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