Small Intestinal Bacterial Overgrowth in Patients With Cirrhosis

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Small intestinal bacterial overgrowth (SIBO) is defined by increased density and/or abnormal composition of microbiota in the small bowel. SIBO is often encountered in patients with cirrhosis as a result of impaired intestinal motility and delayed transit time, both of which are exacerbated by more severe liver disease. Additional risk factors for SIBO commonly encountered in cirrhotic patients include coexisting diabetes, autonomic neuropathy, and/or alcoholic use. Diagnosis of SIBO is performed by breath testing or jejunal aspiration, the gold standard. In cirrhotic patients, the presence of SIBO can lead to profound clinical consequences. Increased intestinal permeability in these patients predisposes to bacterial translocation into the systemic circulation. As a result, SIBO is implicated as a significant risk factor in the pathogenesis of both spontaneous bacterial peritonitis and hepatic encephalopathy in cirrhotics. Antibiotics, especially rifaximin, are the best studied and most effective treatment options for SIBO. However, prokinetics, probiotics, nonselective beta-blockers, and treatment of underlying liver-related pathophysiology with transjugular intrahepatic portosystemic shunt placement or liver transplantation are also being investigated. This review will discuss the risk factors, diagnosis, manifestations in cirrhosis, and treatment options of SIBO. (J CLIN EXP HEPATOL 2019;9:257–267)

The bacterial environment of the gastrointestinal (GI) tract has long been investigated for its role in health maintenance and relationship to various disease states. In healthy hosts, microorganisms are present throughout the GI tract and are essential for gut barrier function, digestive support, and immune homeostasis. Small intestinal bacterial overgrowth (SIBO) is a pathology of gut microbiota dysregulation. SIBO is characterized by the presence of excessive density and/or abnormal composition of microbiota in the small bowel.¹ While SIBO has traditionally been considered a malabsorptive disorder associated with gut dysmotility, it has more recently been

associated with many clinical conditions, including cirrhosis.

The association between SIBO and cirrhosis was first reported in 1957, when increased *Streptococcus faecalis* was found in the small intestine of cirrhotic patients compared with normal subjects.² Since then, investigators have sought to characterize the prevalence and impact of SIBO in patients with cirrhosis. In some studies, SIBO has been identified in as many as two-thirds of patients with cirrhosis.^{3,4} Despite the high prevalence of gut flora derangement in cirrhotic patients, the role of SIBO in the pathogenesis of cirrhosis and its complications remains uncertain. In this review, we examine the relationship between SIBO and cirrhosis and what is known about its clinical, prognostic, and therapeutic implications.

Keywords: bacterial translocation, cirrhosis, liver disease, small intestinal bacterial overgrowth

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Abbreviations: CFUs: Colony-Forming Units; CP: Child-Pugh Score; ⁵¹Cr-EDTA: ⁵¹Cr-Ethylendiaminetetraacetic Acid; FODMAPS: Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols; GI: Gastrointestinal; HBV: Hepatitis B Virus; HE: Hepatic Encephalopathy; IBS: Irritable Bowel Syndrome; MHE: Minimal Hepatic Encephalopathy; mL: Milliliter; MMC: Migrating Motor Complex; OCTT: Orocecal Transit Time; PH: Portal Hypertension; PPI: Proton Pump Inhibitor; ppm: Parts Per Million; SBP: Spontaneous Bacterial Peritonitis; SBRT: Small Bowel Residence Time; SBTT: Small Bowel Transit Time; SIBO: Small Intestinal Bacterial Overgrowth; TIPS: Transjugular Intrahepatic Portosystemic Shunt

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PATHOGENESIS OF SIBO

A discussion of SIBO requires an understanding of the gut microbiota and the mechanisms regulating them. Along the GI tract, the concentration of bacteria increases from the mouth to the site of highest bacterial proliferation in the large intestine. In the small intestine of healthy individuals, there are estimated to be approximately 10³–10⁴ colony-forming units per milliliter (CFUs/mL) of bacteria.⁵ Although an individual's diet and environment can influence the composition, the gut microbiota of the duodenum and jejunum are primarily gram-positive aerobic bacteria with sparse anaerobes. The ileum has an increased

density of bacteria and contains a higher concentration of anaerobes, likely refluxing from the strictly anaerobic environment of the colon.⁶

SIBO develops when a disturbance occurs which increases the number of small bowel bacteria or alters the population of its microbiota. SIBO secondary to adjacent stomach and colon pathologies has been well described. Gastric acid plays an important role in the regulation of microbiota in the stomach, and diminished acid production (hypochlorhydria), as seen with proton pump inhibitor use and after gastric bypass, has been implicated in development of SIBO.⁷ The ileocecal valve has been investigated as a regulator of bacterial growth via defective relaxation or allowing reflux from the microbe-dense colon. Studies have found that patients with SIBO diagnosed by the breath test were more likely to have an incompetent ileocecal valve.⁸

Normal motility in the small bowel may be the single most important protective factor against the development of SIBO. Intestinal motility is facilitated by migrating motor complexes (MMCs), waves of electrical activity that trigger peristaltic waves and transport contents through the intestine. When there are abnormalities in these interdigestive motor complexes, resulting stasis of intestinal contents allows for bacterial colonization and overgrowth.⁹

RISK FACTORS FOR THE DEVELOPMENT OF SIBO IN CIRRHOSIS

There are many factors that place cirrhotic patients at high risk for developing SIBO (Figure 1). Intestinal dysmotility is common in patients with cirrhosis and is a major risk factor for SIBO in this population (Table 1). Chesta et al investigated the association between proximal small bowel motility and bacterial overgrowth in cirrhotic patients.¹⁰ Measuring intestinal motor complexes using manometry, they found that the duration of motor cycles was significantly prolonged in patients with cirrhosis compared with healthy controls (166 ± 19 min vs. 81 ± 14 min; $P < 0.02$). The slower motor cycles resulted primarily from increased quiescence during phase 2 of the motor cycle, normally composed of increased action potentials and contractility in healthy individuals.

Additionally, intestinal motility is impacted by the severity of liver disease. In one study, small bowel motility was assessed using perfused endoscopic catheters with transducers. Investigators found that abnormalities of MMC were more frequently encountered in Child-Pugh class C patients compared with Child-Pugh class A patients.¹¹ Abnormal clusters of contractions were not seen in any Child-Pugh class A patients but were present in 77% of Child-Pugh class C patients. Another study

Figure 1 The relationship among cirrhosis, SIBO, and systemic effects. SIBO, Small Intestinal Bacterial Overgrowth; TJ, Tight Junction; TIPS, Transjugular Intrahepatic Portosystemic Shunt.

Table 1 Studies on Intestinal Motility and Transit Time in Patients With Cirrhosis.

Dysmotility measurement studied	Study authors, [Reference] year	Patient population, n (Child-Pugh A/B/C; portal hypertension)	Comparison group, n (Child-Pugh A/B/C; portal hypertension)	Measurement of motility/transit	Findings
Intestinal motility	Chesta et al, 1993 ¹⁰	Cirrhosis, 16 (3/6/7; 14)	Healthy controls, 8	Manometry	Cirrhotics had phase 2 MMC abnormalities; motility dysfunction did not correlate with SIBO
	Madrid et al, 1997 ¹¹	Cirrhosis, 33 (8/12/13; N/A)	None	Manometry	MMC abnormalities increased from CP class A to C
	Chang et al, 1998 ⁴⁶	Cirrhosis with previous SBP, 20 (CP 10.5; N/A)	Cirrhosis without previous SBP, 20 (CP 8.1; N/A)	Manometry	Less and slower MMC activity in the SBP group; SBP group with higher SIBO
	Gunnarsdottir et al, 2003 ¹²	Cirrhosis, 24 (8/16/0; 12)	Healthy controls, 32	Manometry	PH group with more motor abnormalities; SIBO only in PH group
Intestinal transit time	Van Thiel et al, 1994 ⁴⁷	Cirrhosis being evaluated for transplant, 30 (N/A)	None	OCTT with lactulose	OCTT was slower in patients with more severe encephalopathy
	Galati et al, 1997 ¹⁷	Cirrhosis, 10 (N/A; 10)	Healthy controls, 10	OCTT with lactulose and scintigraphy	OCTT was slower compared with controls only when measured by scintigraphy
	Chen et al, 2000 ²⁰	HBV-related cirrhosis, 23 (10/5/8; 15)	Healthy controls, 45; HBV carriers, 45; chronic Hepatitis B, 26	OCTT with lactulose	OCTT was slower in cirrhotics; OCTT worse with ascites, not with PH or CP score
	Sadik et al, 2003 ²⁶	Cirrhotics with portal hypertension and esophageal varices, 16 (8/3/rest N/A; 16)	Healthy controls, 83	SBRT with radiopaque markers	SBRT was longer in male cirrhotics, and this was associated with SIBO
	Kalaitzakis et al, 2009 ¹³	Cirrhosis, 42 (24/15/3; 27)	Healthy controls, 83	SBRT with radiopaque markers	SBRT was longer in patients with cirrhosis
	Nagasako et al, 2009 ¹⁴	Nonalcoholic cirrhosis, 32 (13/19/0; 19)	Healthy controls, 21	OCTT with lactulose	OCTT was slower in CP class B, 42% of CP class B developed encephalopathy
	Gupta et al, 2010 ⁴⁹	Cirrhosis, 102 (48/42/12; 88)	None	OCTT with lactulose	OCTT was slower in patients with HE; HE higher with SIBO
	Chander et al, 2013 ¹⁵	Decompensated cirrhosis, 10 (1/5/4; 10)	Compensated cirrhosis, 10 (9/1/0; 0)	SBTT with wireless motility capsule	Decompensated cirrhotics and higher CP score had longer SBTT

CP, Child-Pugh Score; HBV, Hepatitis B Virus; HE, Hepatic Encephalopathy; MMC, Migrating Motor Complex; OCTT, Orocecal Transit Time; PH, Portal Hypertension; SBP, Spontaneous Bacterial Peritonitis; SBRT, Small Bowel Residence Time; SBTT, Small Bowel Transit Time; SIBO, Small Intestinal Bacterial Overgrowth.

observed the relationship between portal hypertension in cirrhotics and motility abnormalities.¹² Intestinal manometry was compared between patients with cirrhosis and portal hypertension and those with liver cirrhosis alone, with the same number of Child-Pugh class A and B patients in each group. MMCs were significantly longer in cirrhotics with portal hypertension compared with those without portal hypertension (125 ± 11 min vs. 83 ± 7 min; $P < 0.05$) and had more propagation abnormalities. Additionally, SIBO was observed in 33% of patients in the portal hypertension group but none of the patients with liver cirrhosis alone.

As a result of the impaired motility found in patients with cirrhosis, there is delayed small intestinal transit time that can predispose patients to development of SIBO.¹³ Intestinal transit time is measured in various ways. Orocecal transit time (OCTT) is commonly used and can be measured by recording exhaled hydrogen via breath testing after ingestion of lactulose. Using this method, OCTT was found to be slower in patients with more severe cirrhosis.¹⁴ The finding of intestinal transit time prolonging with increasing severity of liver disease was corroborated in another study using wireless motility capsule.¹⁵ There was a significant correlation between

small bowel transit time and Child-Pugh class. Patients with decompensated cirrhosis had significantly longer small bowel transit delays as compared with patients with compensated cirrhosis (6.17 h vs. 3.56 h; $P = 0.036$).

While severity of cirrhosis may be a risk factor for SIBO, this relationship has not been well studied. One likely contributor is the presence of portal hypertension in advanced cirrhosis. When portal hypertension was induced in mouse models, intestinal transit was delayed compared with healthy controls.¹⁶ This same effect has been evaluated in cirrhotic patients with portal hypertension. OCTT measured using radionuclide scintigraphy was significantly prolonged in cirrhotic patients with portal hypertension compared with healthy controls (127 ± 10.5 min vs. $80 \text{ mins} \pm 9.5$; $P < 0.003$).¹⁷ Pande et al used glucose-hydrogen breath testing to test for SIBO in patients with varying severity of cirrhosis.¹⁸ SIBO was present in 20% of patients with compensated cirrhosis compared with 61% of patients with decompensated cirrhosis ($P = 0.019$) and in 20% of Child-Pugh class A compared with 73% of Child-Pugh class C. SIBO has also been found to be more frequent in patients with ascites as OCTT is slower in patients with ascites, and it is possible that this may be yet another contributor to intestinal stasis.^{18–20}

Many liver patients also have concurrent diabetes and autonomic neuropathy.²¹ Abnormalities in intestinal motor complexes which may predispose to SIBO have been described in diabetics.²² Autonomic dysfunction was found in 48% of patients with liver disease in one study using standard cardiovascular tests, and autonomic dysfunction was more pronounced in patients with more severe liver disease.²³ Another study corroborated these findings as autonomic dysfunction was found significantly more in those with Child-Pugh class B or C compared with Child-Pugh class A (71.8% vs. 39.7%; $P < 0.0006$).²⁴

Another potential risk factor for SIBO in some patients with cirrhosis is increased alcohol use. Alcohol can be directly toxic to smooth muscle, and chronic alcoholism is associated with both myopathies and neuropathies. Jejunal aspirates of chronic alcoholics have been studied and

found to have a higher number of microorganisms compared with healthy controls.²⁵ Another study found that more than 30% of patients with alcoholic cirrhosis had SIBO by breath test compared with 0% in healthy subjects.¹⁹ While the direct effect of alcohol on smooth muscle may explain this association, patients with alcoholic cirrhosis have also been found to have increased risk of delayed small bowel transit.²⁶ However, patients with alcoholic liver disease have similar motility dysfunction compared with patients with nonalcoholic liver disease.¹⁰

DIAGNOSIS

Patients with SIBO may have nonspecific signs and symptoms, such as abdominal discomfort and diarrhea, or they may be asymptomatic (Table 2). In a retrospective study, patients with positive breath test for SIBO had similar prevalence of symptoms compared with those with a negative test.²⁷ As a result, reliance on symptoms alone cannot be used to assist in diagnosis of SIBO. Currently, the most common methods of diagnosing SIBO are cultures of small bowel aspirates and breath testing. However, both tests have significant limitations that should be considered (Table 3).

Culture and quantification of bacteria from a jejunal aspirate is traditionally considered the gold standard test for diagnosing SIBO.²⁸ This is an invasive test, requiring endoscopy with sedation to access the small bowel for culture. Additionally, this testing method carries a risk of contamination from oropharyngeal flora during endoscopy or improper laboratory handling for aerobic and anaerobic culture. Furthermore, jejunal aspiration is notably difficult, given the limited reach of a standard endoscope, often leading to aspiration of the distal duodenum instead. Even if the endoscope is successfully passed to the jejunum, there is a potential that bacterial overgrowth may be missed, given patchy distribution or more distal location.²⁹

Traditionally, the cutoff level of bacterial concentration used for diagnosing SIBO has been greater than or equal to 10^5 CFUs/mL. However, this value has not been well

Table 2 When to Suspect and Test for SIBO in Patients With Cirrhosis.

When to Suspect SIBO		When to Test for SIBO
Risk factors + signs/symptoms		
<ul style="list-style-type: none"> • Intestinal dysmotility • Severe cirrhosis • Portal hypertension • Diabetes/Autonomic neuropathy • Alcohol use 	<ul style="list-style-type: none"> • Bloating/flatulence • Pain/cramping • Diarrhea • Macrocytic anemia/B12 deficiency • Fecal fat 	<ul style="list-style-type: none"> • For symptomatic patients with predisposing conditions, SIBO should be considered in the differential • Once other causes of similar symptoms are ruled out, empiric antibiotics vs. breath testing for SIBO should be considered • If there is symptom response with antibiotics and recurrence of symptoms, then breath testing for SIBO is indicated • If breath testing is negative and there is continued suspicion for SIBO, jejunal aspiration may be indicated

SIBO, Small Intestinal Bacterial Overgrowth.

Table 3 Pros and cons of breath testing and small bowel aspirate for diagnosis of SIBO.

Test for SIBO	Pros	Cons
Breath testing	<ul style="list-style-type: none"> • Noninvasive and inexpensive 	<ul style="list-style-type: none"> • Inconsistent glucose or lactulose dosing recommendations • Inconsistent hydrogen or methane thresholds for a positive test • May be ineffective in cirrhosis • Results are altered by recent antibiotics, laxatives/promotility drugs, carbohydrates/dairy products, smoking, exercise • May underdiagnose in methane-producers
Small bowel aspirate	<ul style="list-style-type: none"> • Gold Standard is jejunal aspirate 	<ul style="list-style-type: none"> • Invasive and costly to perform endoscopy • Inconsistent bacterial colony count thresholds for a positive test • Risk of contamination from oropharyngeal flora • May aspirate too proximal or distal • May miss SIBO if patchy distribution

SIBO, Small Intestinal Bacterial Overgrowth.

validated, and more recently, this cutoff threshold has been challenged. A recent systematic review found that jejunal concentrations of greater than or equal to 10^5 CFUs/mL were only validated in patients with stagnant loop situations, conditions associated with the highest risk of SIBO.³⁰ Based on the data in this review, a recent North American consensus group concluded that current small bowel culture techniques were not sufficient for the assessment of SIBO, but, if used, a threshold of greater than 10^3 CFUs/mL should be used for diagnosis of SIBO.³¹

Owing to the aforementioned concerns about jejunal aspirate use, breath testing is commonly used for diagnosis of SIBO. Breath testing is a simple, inexpensive, and noninvasive method of SIBO detection. The principle underlying breath testing is that gut microbes will change or increase the concentration of hydrogen and methane produced in the intestine via fermentation of ingested carbohydrates.³² While glucose is normally entirely absorbed in the small bowel, it is instead fermented in the setting of SIBO, releasing hydrogen and methane to be absorbed into the bloodstream. Lactulose is normally not absorbed and undergoes fermentation in the colon but will instead be processed and absorbed earlier in SIBO. As these absorbed gases are exhaled, their production can be measured with a breath analyzer.

Breath testing is not without its own set of limitations. There is inconsistency in the recommended load of glucose and/or lactulose to be administered and the time required for detecting fermentation to sufficiently perform breath testing.³³ Debate also exists regarding the definition of a positive breath test for SIBO. A rise in hydrogen of greater than or equal to 20 parts per million (ppm) from baseline within 90 min is usually considered a positive test for SIBO. However, this definition may miss a large subset of the general population whose gut microbiota use hydrogen and produce excessive methane. A combination of hydrogen and methane testing was found to have improved specificity and sensitivity for detecting SIBO in subjects with excessive methane production.³⁴ Generally,

a cutoff value of greater than 10 ppm of methane is considered a positive test, but further studies are needed to further characterize subjects with excessive methane production.

Unfortunately, glucose breath hydrogen testing may be an ineffective means of diagnosing SIBO in patients with cirrhosis. Bauer et al compared the performance of breath testing versus jejunal aspirates in patients with cirrhosis.³⁵ Using the threshold of greater than or equal to 10^5 CFUs/mL on jejunal aspirates for the gold standard of SIBO diagnosis, they found that a 20-ppm increase in breath hydrogen concentration after administration of glucose to cirrhotic patients had only 41% sensitivity and 45% specificity for diagnosing SIBO. The authors suggest that this poor correlation between glucose breath hydrogen testing and jejunal aspirates in cirrhotics may be a function of intestinal dysmotility impeding carbohydrate absorption.

CLINICAL MANIFESTATIONS AND SYSTEMIC EFFECTS OF SIBO

Patients with SIBO will often present with nonspecific symptoms, such as abdominal discomfort, diarrhea, or bloating. Many of these symptoms are a result of SIBO's impact on small bowel function and disruption of the intestinal lining. Bacteria can have a direct toxic effect on the intestinal wall, which may lead to villous atrophy and inflammation.³⁶ These structural changes can decrease the mucosal absorptive surface area, contributing to malabsorption. Electron microscopy used to evaluate the jejunal mucosa in animals has also found that deconjugated bile salts produced by bacterial overgrowth can cause breakdown of the intestinal epithelium.³⁷

While bacterial overgrowth is associated with many complications in the intestine, SIBO can importantly lead to profound systemic effects on patients with cirrhosis. These clinical consequences are largely suspected to result from bacterial translocation or transmucosal

passage of bacteria across the intestine. Different mechanisms have been proposed, the most accepted being that bacterial translocation is passage of bacteria through the intestinal wall to mesenteric lymph nodes as a gateway to other sites. The phenomenon of bacterial translocation has been found to be increased in patients with advanced cirrhosis, with enteric organisms isolated from mesenteric lymph nodes in 30.8% of Child-Pugh class C patients in one study compared with 3.4% in class A and 8.1% in class B ($P < 0.05$).³⁸

Numerous studies have examined the intestinal permeability in cirrhotic patients to better understand the mechanisms by which bacterial translocation occurs. Nitric oxide, bacterial endotoxin, and tumor necrosis factor- α are among those compounds implicated in altering the intestinal permeability.^{39,40} Increased intestinal permeability may result from the aforementioned epithelial cell damage caused by SIBO but also likely involves an impairment of tight junctions. Tight junctions are a collection of proteins which form a seal between adjacent epithelial cells and allow selective permeability. The most common methods to evaluate tight junction function and intestinal integrity are to measure orally the administered test markers in the urine (i.e. polyethylene glycols or radiolabeled chelates (^{51}Cr -ethylenediaminetetraacetic acid [^{51}Cr -EDTA]) or presence of intraluminal substances (i.e. endotoxins) in systemic circulation. Miele et al studied patients with liver disease for intestinal permeability using ^{51}Cr -EDTA and expression of tight junction proteins.⁴¹ Patients with liver disease had decreased expression of ZO-1, an important tight junction protein and increased ^{51}Cr -EDTA urinary excretion when compared with healthy subjects. Another study performed duodenal biopsy in patients with cirrhosis and found that there was decreased expression of tight junction proteins occludin and claudin-1 as compared with healthy controls and that this expression was further diminished in decompensated cirrhotic patients compared with compensated cirrhotics.⁴² As a result of increased intestinal permeability, SIBO may place patients with cirrhosis at higher risk of feared complications of portal hypertension, such as spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (HE).

Patients with cirrhosis have an increased risk of bacterial infections including SBP. Animal model studies suggest that bacterial translocation to mesenteric lymph nodes could be involved in development of SBP. In cirrhotic rats, bacterial translocation was significantly more frequent in those with SBP compared with those without SBP, and the same bacterial strain was identified in the small bowel, mesenteric lymph nodes, and ascites in 87% of instances.⁴³ The association between the intestinal permeability and increased risk of SBP has also been observed in patients with cirrhosis. Scarpellini et al assessed the intestinal permeability by measuring urinary

and ascitic ^{51}Cr -EDTA and found the intestinal permeability to be significantly more frequent in cirrhotic patients compared with controls.⁴⁴ Additionally, impaired intestinal permeability was found in 75% of Child-Pugh C patients, and ^{51}Cr -EDTA was found in 100% of ascitic samples in patients with SBP compared with only 17% without SBP. Therefore, SIBO in patients with increased intestinal permeability would seemingly promote an increased risk of developing SBP. Indeed, incidence of SIBO diagnosed by glucose breath testing was found to be higher in cirrhotic patients with SBP compared with those without SBP (68.2% vs. 17.4%), possibly because the SBP group had impaired intestinal motility.^{45,46} In another study, SBP was found in 30.76% of cirrhotics with SIBO and ascites, significantly more than in those without SIBO.¹⁹ It is important to note that some commonly cited studies did not find a significant relationship between SIBO and SBP, likely because they only included 6 patients with SBP.^{3,18} Bauer et al found that of patients with ascites who developed SBP, 83% (5 of 6 patients) had SIBO, whereas only 65% of patients who did not develop SBP had SIBO.³ However, his finding did not reach the level of clinical significance owing to the small sample size.

Hepatic encephalopathy (HE) is a complication of liver disease defined by cognitive and psychomotor deficits that impair the quality of life. Ammonia and other nitrogenous substances produced by gut bacteria are have been implicated in the pathogenesis of HE. Intestinal dysmotility and delayed transit time, both well-established risk factors for SIBO, have been studied and shown to be associated with the development of HE. For example, Van Thiel et al found that OCTT was delayed in patients with HE.⁴⁷ Fewer studies have examined the direct relationship between SIBO and HE as patients with HE are often excluded from SIBO studies. However, one study of 34 patients with hepatitis C virus-related cirrhosis found that SIBO was significantly associated with increasing severity of HE, with 100% of patients with severe HE having SIBO diagnosed by lactulose breath testing.⁴⁸ Another study examined patients with cirrhosis and found that 38.6% of those with minimal hepatic encephalopathy (MHE) had SIBO and that SIBO was the only factor predictive of MHE in their multivariate analysis.⁴⁹ Lunia et al similarly found an association between SIBO and HE, as well as an increase in the prevalence of SIBO with higher grade HE.⁵⁰ They found SIBO in 16.13% of patients without HE, as compared with 48.28% in the MHE group and 46.67% in the early/grade 1 HE group ($P = 0.018$).

TREATMENT

Given the difficulty of diagnosing SIBO, treatment often consists of a trial of antibiotics based on symptoms with

Figure 2 Management algorithm for SIBO in patients with cirrhosis. FODMAPS: Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols. SIBO, Small Intestinal Bacterial Overgrowth.

monitoring for the response to therapy (Figure 2). This approach is usually only reserved for patients with classic risk factors and symptoms leading to high suspicion of SIBO, given the risks of antibiotics use (i.e. adverse reactions, *Clostridium difficile* infection, antibiotic resistance) and difficulty in monitoring for the complete treatment response. Numerous antibiotics have been used for the treatment of SIBO, with neomycin, metronidazole, and ciprofloxacin among those showing benefit.^{51,52}

However, rifaximin is the best studied antibiotic for SIBO treatment. Rifaximin is a poorly absorbed oral antibiotic, which allows for the local enteric antibacterial activity with minimal risk of systemic toxicity (Table 4). In trials studying rifaximin alone and measuring eradication of SIBO by breath testing, rifaximin at various doses had a 50–59.4% eradication rate and was efficacious in both hydrogen and methane producers.^{53–55} In one randomized controlled trial comparing rifaximin with placebo, 87.5% of patients randomized to the rifaximin group had eradication of SIBO versus 0% in the placebo group.⁵⁶ Another trial comparing rifaximin with placebo yielded 100% negative breath testing for SIBO after treatment.⁵⁷ Several studies have compared the efficacy of different doses of rifaximin.^{58,59} Lauritano et al found that rifaximin at 1200 mg/day was associated with the

highest rate of glucose breath test normalization rate, compared with 600 mg/day and 800 mg/day, without higher incidence of side effects.⁵⁸ A second study found higher SIBO eradication (80–82%) with 1600 mg/day compared with 1200 mg/day, suggesting an improvement with higher doses of rifaximin.⁵⁹

When compared with other antibiotics, rifaximin therapy is associated with superior efficacy and a more favorable side effect profile.^{60,61} Lauritano et al (2009) found a higher SIBO eradication rate with rifaximin 1200 mg/day compared with metronidazole, a commonly used antibiotic for SIBO. In addition, there were numerous moderate and severe adverse events in metronidazole group leading to early study termination in some subjects. Rifaximin was also observed to be associated with improved eradication rates when combined with insoluble dietary fiber supplements (bran, guar gum).^{62,63} One important caveat is that methane-producing bacteria, such as *Methanobrevibacter smithii*, are often more resistant to antibiotics.⁶⁴ However, there are conflicting data regarding the benefit of adding neomycin to rifaximin for SIBO eradication in methane producers.⁶⁵ Unfortunately, treatment with antibiotics may only provide a temporary response if the underlying risk factors for SIBO are not corrected as treatment with antibiotics is associated

Table 4 Rifaximin Treatment for Small Intestinal Bacterial Overgrowth (SIBO).

Rifaximin vs. comparison	Study authors, [Reference] year	Patient population with SIBO, treatment, n	Comparison group, treatment, n	Measurement of SIBO, days after treatment until retest	Findings
Rifaximin alone	Esposito et al, 2007 ⁵³	IBS, 1200 mg/d × 7d, 32	None	Lactulose breath test, 7	Rifaximin had 59.4% eradication; ciprofloxacin treatment of those without eradication only eradicated additional 7% (1/13)
	Majewski et al, 2007 ⁵⁴	SIBO symptoms, 800 mg/d × 28d, 20	None	Glucose breath test, 7	50% eradication, 54.5% of hydrogen producers, 50% of methane producers
	Peralta et al, 2009 ⁵⁵	IBS, 1200 mg/d × 7d, 54	None	Lactulose breath test, 21	Rifaximin had 52% eradication
	Zhang et al, 2015 ⁶⁷	Cirrhosis, 600 mg/d × 7d, 17	None	Glucose breath test, 28	Rifaximin had 76% eradication and improvement in HE
Rifaximin vs. placebo	Biancone et al, 2000 ⁵⁷	Crohn's disease, 1200 mg/d × 7d, 7	Crohn's disease, placebo × 7d, 7	Glucose breath test, 14 and 30	Rifaximin with 100% eradication after 14d; 100% recurrence at 30d
	Parodi et al, 2008 ⁵⁶	Rosacea, 1200 mg/d × 10d, 32	Rosacea with SIBO, placebo × 10d, 20	Lactulose and glucose breath tests, 30	Rifaximin arm had significantly higher eradication (87.5%)
Rifaximin different doses	Lauritano et al, 2005 ⁵⁸	SIBO symptoms, 1200 mg/d × 7d, 30	SIBO symptoms, 800 mg/d × 7d, 30; 600 mg/d × 7d, 30	Glucose breath test, 30	1200 mg/d had highest eradication (60%), no difference between 800 mg/d and 600 mg/d
	Scarpellini et al, 2007 ⁵⁹	IBS, 1600 mg/d × 7d, 40	IBS, 1200 mg/d × 7d, 40	Glucose breath test, 30	1600 mg/d had higher eradication (80–82%)
Rifaximin vs. other antibiotics	Di Stefano et al, 2000 ⁶⁰	SIBO symptoms, 1200 mg/d × 7d, 10	SIBO symptoms, chlortetracycline 1000 mg/d × 7d, 11	Glucose breath test, 3	Rifaximin had higher eradication (70%)
	Lauritano et al, 2009 ⁶¹	IBS, 1200 mg/d × 10d, 71	SIBO symptoms, metronidazole 750 mg/d × 10d, 71	Glucose breath test, 30	Rifaximin had higher eradication (63.4%) and did not have moderate or severe adverse events
Rifaximin + additional agent	Cuoco et al, 2006 ⁷⁰	IBS, 1200 mg/d × 7d followed by probiotics × 21d, 23	None	Glucose breath test, 120 to 150	Rifaximin with probiotics had 82.6% eradication without adverse events
	D'Inca et al, 2007 ⁶⁰	Uncomplicated diverticular disease, 1200 mg/d × 14d with daily dietary fiber supplements, 12	Uncomplicated diverticular disease, placebo × 14d with fiber supplements, 10	Lactulose breath test, N/A	Rifaximin had a 83% eradication with fiber supplements
	Furnari et al, 2010 ⁶³	SIBO symptoms, 1200 mg/d × 10d with guar gum, 40	SIBO symptoms, 1200 mg/d × 10d, 37	Glucose breath test, 30	Rifaximin with guar gum had a 85% eradication rate compared to 62% without
	Pimentel et al, 2014 ⁶⁵	IBS methane producers, 1650 mg/d × 14d with neomycin, 15	IBS methane producers, neomycin × 14d with placebo, 16	Fasting breath test, 28	Addition of neomycin did not improve SIBO eradication but improved symptoms

d, Day; HE, Hepatic Encephalopathy; IBS, Irritable Bowel Syndrome; mg, Milligrams.

with a high recurrence rate.^{57,66} Furthermore, despite the elevated risk of SIBO in cirrhotics, the efficacy of antibiotics in this patient population is understudied. One small study included 17 cirrhotics with SIBO;

following treatment with low-dose 600 mg/day of rifaximin, 13 of 17 (76%) had negative breath testing.⁶⁷

Probiotic cocktails have been explored in various GI conditions because of their potential for competition

with intestinal pathogens, anti-inflammatory effect, and enhancement of the intestinal barrier function. As a result, probiotics have also been studied as a potential therapeutic agent in the treatment of SIBO, largely focused on reducing bacterial translocation. In animal models, *Lactobacillus plantarum* supplementation reduced bacterial translocation to mesenteric lymph nodes and liver tissue, but such findings have been inconsistent.⁶⁸ In patients with SIBO, *Lactobacillus fermentum* did not produce a significant difference in breath testing compared with placebo.⁶⁹ Nevertheless, while probiotics alone may have mixed results, one trial examining the use of probiotics in conjunction with rifaximin did find a benefit. Cuoco et al treated IBS patients with 1200 mg/day of rifaximin and probiotics (*Lactobacilli* and *Bifidobacteria* cocktail) and found an eradication rate of 83%, although there was no control arm.⁷⁰ Given the wide range of probiotics available, more studies are required to understand their role in treating SIBO and their potential benefit in cirrhotics.

The role of nonselective beta-blockers in SIBO treatment is also being explored. Because nonselective beta-blockers are associated with decreased intestinal transit time and lower risk of SBP, there is a hope that their use may reduce the intestinal permeability and bacterial translocation from SIBO.^{71,72} Reiberger et al investigated 50 patients with cirrhosis and esophageal varices who had evidence of intestinal permeability on a triple sugar test (sucrose, lactulose, mannitol test). They demonstrated that treatment with a nonselective beta-blocker reduced the intestinal permeability and markers of bacterial translocation.⁷³

Ultimately, correcting the underlying cause for development of SIBO has the potential to make the biggest therapeutic impact. When intestinal dysmotility is a concern, prokinetic drugs can be considered. Conversely, medications that may slow motility, such as opiates, should be avoided. Madrid et al found that cisapride, a prokinetic agent, improved the cyclic activity of the MCC, was associated with SIBO resolution at a rate similar to treatment with antibiotics, and was significantly more effective than placebo.⁷⁴ Similarly, octreotide has been used in patients with scleroderma to improve the intestinal motility.⁷⁵ As has been previously discussed, intestinal dysmotility is a common feature of cirrhosis. Therefore, treatment aimed at cirrhosis pathophysiology via transjugular intrahepatic portosystemic shunt (TIPS) insertion or liver transplantation may provide relief from SIBO through improvement in small bowel motility. TIPS has been associated with decreased intestinal permeability, but its effect on intestinal motility has not been studied.⁷⁶ Only one study has been conducted to assess the benefit of liver transplantation in improving motility.⁷⁷ Two patients who had abnormal MMC before liver transplantation were found to have normalized motility within 6 months of the pro-

cedure. Further investigation into TIPS and transplantation for treatment of SIBO in cirrhotic patients is required.

CONCLUSION

SIBO is a common finding in patients with cirrhosis, particularly in those with advanced liver disease and portal hypertension. Patients with cirrhosis have abnormalities in the intestinal motility which place them at higher risk for SIBO, and those with more advanced liver disease have more severe intestinal dysfunction. In addition to higher risk of SIBO, cirrhosis is associated with increased intestinal permeability. This combination can lead to severe clinical consequences such as SBP and HE through bacterial translocation. Antibiotics, especially rifaximin, are the mainstay of treatment. However, treating the underlying cause and risk factors for SIBO should also be a priority. There is some evidence that intestinal dysmotility improves after liver transplantation. More research is required to understand the impact of SIBO and bacterial translocation on cirrhotic patients as well as the optimal therapy for this condition in a vulnerable population.

AUTHOR CONTRIBUTIONS

All authors were involved in writing the manuscript and providing critical revision of the manuscript.

CONFLICTS OF INTEREST

The authors have none to declare.

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