

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome**Irritable bowel syndrome and small intestinal bacterial overgrowth: Meaningful association or unnecessary hype**

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Abstract

Irritable bowel syndrome (IBS) is a common condition characterized by abdominal pain or discomfort, bloating, and altered stool form and passage. Small intestinal bacterial overgrowth (SIBO) is a condition in which there is overgrowth of bacteria in small bowel in excess of 10^5 colony forming units per milliliter on culture of the upper gut aspirate. Frequency of SIBO varied from 4%-78% among patients with IBS and from 1%-40% among controls. Higher frequency in some studies might be due to fallacious criteria [post-lactulose breath-hydrogen rise 20 PPM above basal within 90 min (early-peak)]. Glucose hydrogen breath test (GHBT) has a low sensitivity to diagnose SIBO. Hence, studies based on GHBT might have underestimated frequency of SIBO. Therefore, it is important to analyze these studies carefully to evaluate whether the reported association between IBS and SIBO is over or under-projected. This review evaluates studies on association between SIBO and IBS, discordance between different studies, their strength and weakness including methodological issues and evidence on therapeutic manipulation of gut flora on symptoms of IBS.

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Key words: Glucose hydrogen breath test; Lactulose hydrogen breath test; Functional bowel disease; Dysbiosis; Gut flora

Core tip: Irritable bowel syndrome (IBS) has been conventionally thought to be a disorder without an organic basis. However, recently data are emerging to show that it may have organic basis at least in a subset of patients. Though several studies reported an association between small intestinal bacterial overgrowth (SIBO) and IBS, the frequency of SIBO reported to vary between 4% and 78%. The current review suggests that the association between SIBO and IBS is definite, but the studies reporting high prevalence of SIBO in IBS over-estimated its frequency due to use of fallacious diagnostic methods. Better test to diagnose SIBO in patients with IBS is highly needed.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common condition characterized by abdominal pain or discomfort, bloating, associated with altered stool form (such as diarrhea, constipation) and passage. World-wide, 4%-30% of subjects suffer from IBS^[1-7]. Small intestinal bacterial overgrowth (SIBO), which has been conventionally described in patients with anatomical abnormalities in the gut such

Table 1 Summary of prevalence of small intestinal bacterial overgrowth in irritable bowel syndrome by different diagnostic methods *n* (%)

Ref.	Type of the study	Frequency of SIBO in cases	Frequency of SIBO in controls	Methane producers in cases	Methane producers in controls	Method for diagnosis
Park <i>et al</i> ^[86]	Prospective (Case-control)	34/76 (44.7)	16/40 (40)	19/76 (25)	10/40 (25)	LHBT
Scarpellini <i>et al</i> ^[88]	Prospective (Case-control)	28/43 (65)	4/56 (7)	4/43 (9.3)	0	LHBT
Carrara <i>et al</i> ^[14]	Prospective	55/127 (43)	NCG	ND	ND	LHBT
Mann and Limoges-Gonzales ^[87]	Prospective	89/258 (34.5)	NCG	ND	ND	LHBT
Nucera <i>et al</i> ^[89]	Prospective	64/98 (65)	NCG	ND	ND	LHBT
Pimentel <i>et al</i> ^[17]	Prospective	157/202 (78)	NCG	ND	ND	LHBT
Sachdeva <i>et al</i> ^[18]	Prospective (Case-control)	14/59 (23.7)	1/37 (2.7)	5/59 (8.5)	9/37 (24.3)	GHBT
Reddymasu <i>et al</i> ^[90]	Prospective	35/98 (36)	NCG	Data NA	ND	GHBT
Lombardo <i>et al</i> ^[91]	Prospective (Case-control)	49/200 (24.5)	3/50 (6)	ND	ND	GHBT
Ford <i>et al</i> ^[74]	Meta-analysis	595/1921 (31)	NCG	ND	ND	GHBT
Parodi <i>et al</i> ^[92]	Prospective (Case-control)	21/130 (16.1)	3/70 (4.2)	34/130 (26)	Data NA	GHBT
Rana <i>et al</i> ^[93]	Prospective (Case-control)	25/225 (11.1)	1/100 (1)	ND	ND	GHBT
Majewski <i>et al</i> ^[94]	Prospective (Case-control)	93/204 (46)	NCG	27/204 (13.2)	ND	GHBT
Cuoco and Salvangnini ^[75]	Retrospective	44/96 (45.8)	NCG	ND	ND	GHBT
Lupascu <i>et al</i> ^[95]	Prospective (Case-control)	20/65 (31)	4/102 (4)	ND	ND	GHBT
Ghoshal <i>et al</i> ^[16]	Prospective (Case-control)	11/129 (8.5)	1/51(2)	ND	ND	GHBT
Posserud <i>et al</i> ^[12]	Prospective (Case-control)	6/162 (4)	1/26 (4)	ND	ND	Hydrogen breath test and culture of small bowel aspirate

SIBO: Small intestinal bacterial overgrowth; IBS: Irritable bowel syndrome; LHBT: Lactulose hydrogen breath test; GHBT: Glucose hydrogen breath test; NCG: No control group; ND: Not done; NA: Not available; *n*: Number of cases and controls.

as ileo-transverse anastomosis, stricture, fistula, slow motility and reduced gut defence, is also characterized by abdominal pain or discomfort, bloating, flatulence and loose motion^[8-10]. Recently, it has been realized that SIBO may occur in the absence of apparent anatomical abnormalities^[11]. These patients, however, may be wrongly diagnosed as IBS.

Small intestinal bacterial overgrowth is currently defined as presence of bacteria in excess of 10⁵ colony forming units per milliliter on culture of the upper gut aspirate^[12,13]. Since this is an invasive test, several non-invasive methods including lactulose and glucose hydrogen breath tests (LHBT and GHBT) have been popularly used to diagnose SIBO^[14-18]. This condition is being increasingly recognized among patients with IBS. In different studies, frequency of SIBO among patients presenting with IBS varied from 4% to 78% (Table 1), more so among patients with diarrhea-predominant IBS^[12,14,18,19]. Not only quantitative increase (SIBO) but qualitative change in the gut bacteria (dysbiosis) has been reported among patients with IBS^[20]. These studies led to a paradigm shift in understanding pathogenesis of IBS and have led to increasing debate on therapeutic manipulation of gut microbiota to treat this enigmatic chronic disorder using antibiotics, probiotics and lately fecal transplantation^[21-23]. However, it is important to recognize the wide-variability in frequency of SIBO among patients with IBS in different studies; such wide-variability in frequency may suggest that it is important to analyze these studies carefully to evaluate whether the reported association between IBS and SIBO is over or under-projected in some of the earlier studies?

We hereby review the studies on association between SIBO and IBS, discordance between different studies, their strength and weakness including methodological

issues and evidence on therapeutic manipulation of gut flora on symptoms of IBS.

REVIEW OF STUDIES ON SIBO IN IBS

Table 1 summarizes the results from studies on SIBO among patients with IBS. As can be noted from this table, the frequency of SIBO among patients with IBS varied from 4% to 78% and that among controls from 1% and 40%. In most studies, frequency of SIBO among patients with IBS was higher than that among controls. Therefore, it can be concluded that SIBO is associated with IBS. But it is important to critically evaluate the reasons for such a wide variability in frequency of SIBO in different studies.

CRITICAL EVALUATION OF STUDIES ON SIBO IN IBS: REASONS FOR DISCORDANCE

Could IBS phenotype determine frequency of SIBO?

IBS is a heterogeneous condition. The sub-types may be diarrhea or constipation-predominant or may be alternating. Patients with diarrhea-predominant IBS more often have organic cause including SIBO than other sub-types of IBS. In a study on 129 patients with non-diarrheal IBS, 73 with chronic non-specific diarrhea including diarrhea-predominant IBS, and 51 healthy controls, frequency of SIBO using GHBT was 11 (8.5%), 16 (22%) and 1 (2%), respectively^[16]. Similar findings were reported in other studies as well^[18,24]. Diarrheal IBS, therefore, should be particularly evaluated for SIBO than other types of IBS. Moreover, studies which included larger proportion of patients with diarrhea-predominant

IBS are likely to show higher frequency of SIBO.

Bloating is a frequent symptom reported by patients with IBS. Frequency of bloating has been reported to vary from 26% to 83% in studies on IBS from Asia^[3,25]. The pathogenesis of bloating may be related to increased amount of gas in the gut, its abnormal distribution and increased visceral perception in response to distension of the gut^[26,27]. Patients with SIBO may have increased amount of gas inside the gut, hence, it is logical to believe that IBS patients with marked bloating are expected to have SIBO^[16]. However, there are limited data on this issue. Several studies showed that both fasting as well as post-substrate (*e.g.*, glucose, lactulose) breath hydrogen is higher among patients with IBS than controls^[16,28]. Probiotics and antibiotics, which are known to reduce gas inside the gut, are known to relieve abdominal bloating among patients with IBS^[17,29,30]. It has been reported that successful treatment with antibiotics causes the hydrogen breath test to revert to normal^[17]. Hence, patients with IBS with marked bloating and flatulence should be particularly evaluated for SIBO. More studies, however, are needed on this issue.

Could technique used to diagnose SIBO determine its frequency?

Several techniques have been used to diagnose SIBO; these include LHBT, GHBT, ¹⁴C xylose breath test, and quantitative culture of jejunal aspirate^[12,15,31,32]. Principle of hydrogen breath tests is summarized in Figure 1. Dietary carbohydrates, unabsorbed in the small intestine, produce hydrogen in the large intestine by bacterial fermentation^[33]. In patients with SIBO, the bacteria ferment these carbohydrates in the small bowel itself producing hydrogen, which gets absorbed and is exhaled in the breath^[33].

Hydrogen breath test involves giving patients a load of carbohydrate (usually in the form of glucose and lactulose) and measuring expired hydrogen concentrations over a period of time. Diagnosis of SIBO using hydrogen breath test is based on the physiological principle that in patients with SIBO, glucose would be fermented by bacteria in the small bowel resulting in production of hydrogen gas that is absorbed and exhaled in expired air (Figure 1, A1)^[31,33]. In contrast, lactulose, which is a non-absorbable disaccharide, will produce an early peak due to fermentation in small bowel (typically within 90-min) or double peak (first due to small bowel fermentation and second from colon), if SIBO is present (Figure 1, B2 and B3)^[33]. There are several limitations in hydrogen breath test for diagnosis of SIBO. There may be similarities in the pattern of gas production in patients with SIBO and subjects with rapid intestinal transit, thus making distinction difficult^[34]. An early peak is often false positive in people with fast gut transit time. For example, in a study from India, median oro-cecal transit time was 65 min (range 40-110 min) in healthy subjects^[35]. In another study from Taiwan, mean oro-cecal transit time was 85 min^[36]. This has also been substantiated in

Western population recently by simultaneously using LHBT and radio-nuclide method to assess gut transit^[37-39]. Double peak criteria for diagnosis of SIBO using LHBT is quite insensitive^[15,33]. Sensitivity of GHBT to diagnose SIBO is 44% considering quantitative culture of upper gut aspirate as gold standard^[15]. Hence, it is expected that the authors who used an early peak criteria in LHBT would get a high frequency of SIBO among patients with IBS as well as controls. In contrast, those who would use either GHBT or double peak criterion in LHBT would get a low frequency of SIBO both in patients with IBS and controls. It is worth noting from the Table 1 that the frequency of SIBO among patients with IBS and controls on LHBT (early peak criteria) varied from 34.5% to 78% and 7%-40%, respectively; in contrast, the frequency on GHBT varied from 8.5%-46% and 2%-18%, respectively.

Fifteen percent of people may have methanogenic flora in the gut^[34,40]. *Methanobrevibacter smithii*, *Methanobrevibacter stadmanae* and possibly some of the coliform bacteria are methanogens^[41]. In these subjects, only hydrogen breath tests may not diagnose SIBO, estimation of methane is also needed (Figure 1). Table 1 shows that 8.5%-26% of IBS patients and 0%-25% of controls exhaled methane in their breath. Therefore, SIBO could not have been diagnosed if methane was not estimated in them. As summarized in Table 1, in a large proportion of studies, methane was not estimated, which could have resulted in underestimation of frequency of SIBO in these studies. Excessive methane production is associated with constipation^[42]. Hence, methane estimation in breath, which is not available in several commercially available hydrogen breath test machines, is particularly important in patients with constipation-predominant IBS. Some individuals may have slow transit through the small intestine making prolonged testing up to five hours necessary and many individuals may not like to undergo such prolonged testing^[43,44]. However, a shorter period of testing for them may miss the diagnosis of SIBO.

The jejunal aspirate culture has traditionally been used as the gold standard to diagnose SIBO (Figure 2)^[15,45]. However, the limitations of this test include invasiveness and the challenges posed by attempting to culture all strains and species^[46]. In fact, use of air during endoscopy can lead to a false negative result as anaerobes do not grow once these are exposed to oxygen present in the air^[13]. Also, a large proportion of bacteria are not cultured^[47,48]. In contrast, single lumen catheter passed through the nose or through the biopsy channel of endoscope, may lead to contamination by oropharyngeal flora giving false positive result^[13]. Therefore, we designed a double-lumen catheter to prevent such oro-pharyngeal contamination (Figure 2)^[13]. Studies on SIBO among patients with IBS using quantitative culture of small bowel aspirate are scanty (Table 1). A study by Posserud *et al.*^[12] reported a frequency of SIBO of 4% among patients with IBS. Considering the result of other studies using GHBT, which has sensitivity of 44%

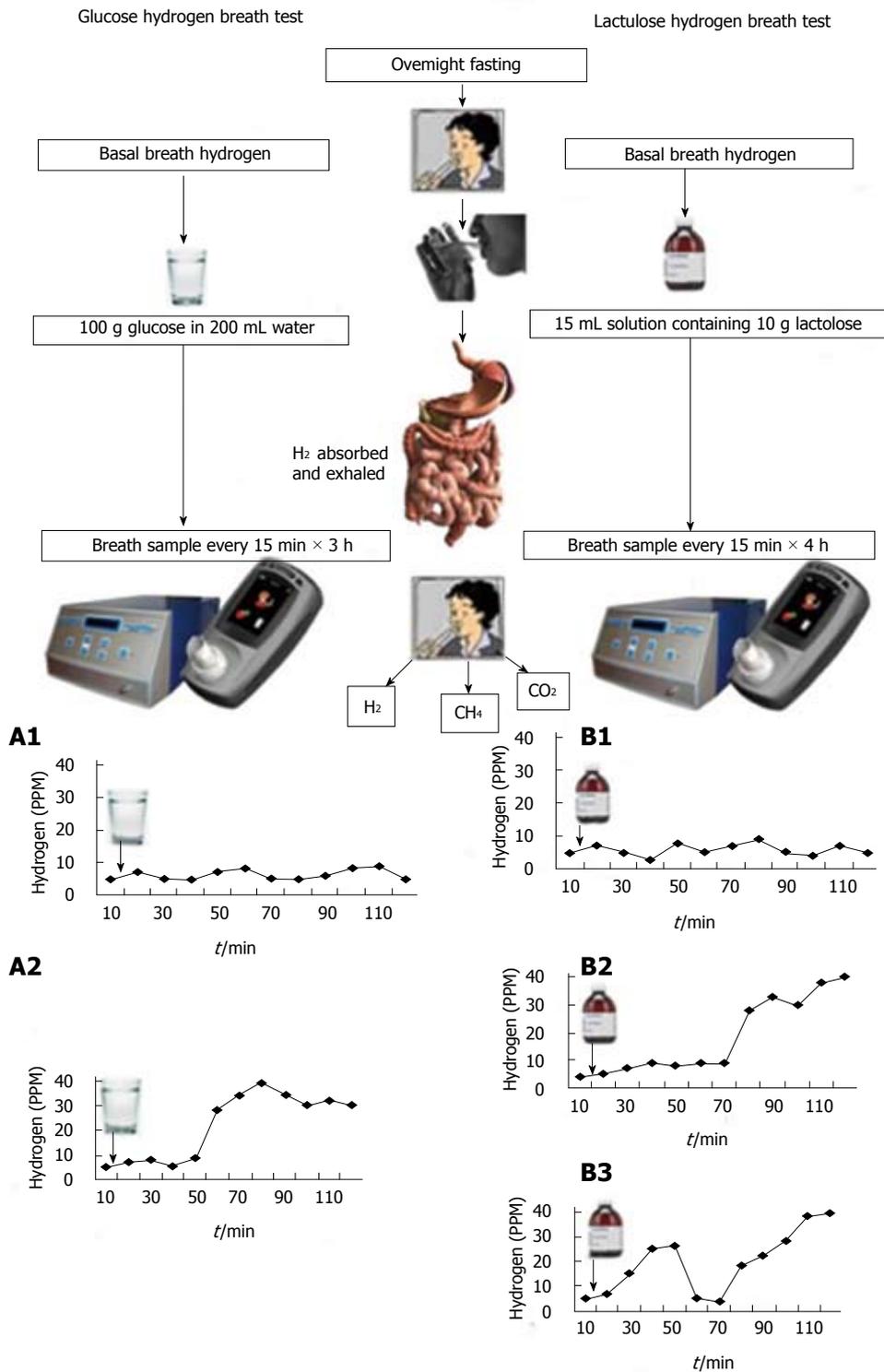


Figure 1 Outline of principle of method and interpretation of glucose and lactulose hydrogen breath tests. On the left panel, method and result of glucose hydrogen breath test (GHBT) is shown. A1: GHBT is negative for SIBO as there is no peak in hydrogen production; A2: GHBT shows presence of SIBO. On the right panel, method and result of lactulose hydrogen breath test (LHBT) is shown. B1: LHBT is negative for SIBO as there is no peak in hydrogen production; B2: LHBT shows an early peak (within 90 min of lactulose ingestion); B3: LHBT shows double peaks in hydrogen, the earlier one from small bowel due to SIBO and the later one from the colon. Please note that Quintron machine of the left gives values of hydrogen, methane and CO₂ (for correction) and the Bedfont machine of right side estimates hydrogen only. It is also important to note that in the graphs hydrogen breath test do not show methane levels. SIBO: Small intestinal bacterial overgrowth; GHBT: Glucose hydrogen breath test; LHBT: Lactulose hydrogen breath Test; PPM: Parts per million.

to diagnose SIBO considering upper gut aspirate as gold standard, the former study appears to have falsely underestimated the frequency of SIBO among patients with

IBS^[15]. More studies are needed on this issue.

¹³C and ¹⁴C based tests have also been developed based on the bacterial metabolism of D-xylose (Figure

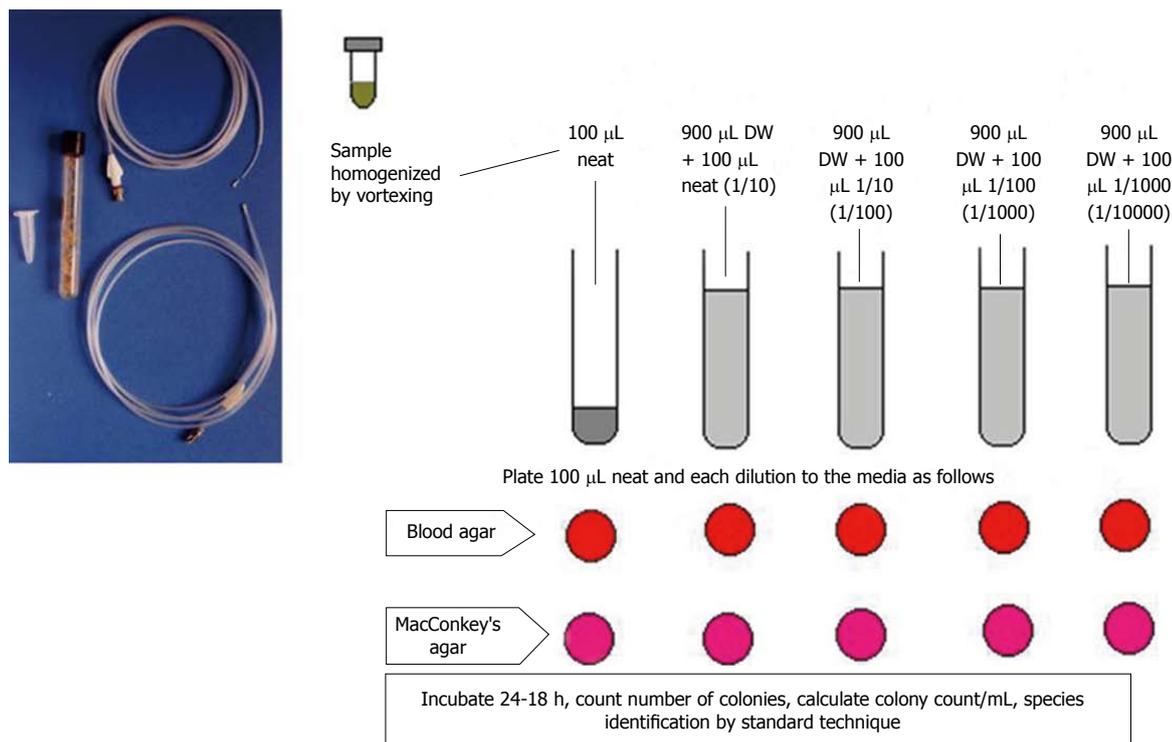


Figure 2 Outline of method of culturing bacteria from the upper gut aspirate and counting the colonies by serial dilution technique. DW: Distilled water.

3)^[32]. Bacterial de-conjugation of bile acids containing ¹³C and ¹⁴C can also be used to diagnose SIBO^[49]. The glycocholic acid breath test involves the administration of the bile acid ¹⁴C glycocholic acid, and the detection of ¹⁴CO₂, which would be elevated in SIBO (Figure 3)^[50,51].

MECHANISM OF IBS SYMPTOMS IN PATIENTS WITH SIBO

Bacteria in gut lumen play important role in modulating multiple intestinal functions. Quantitative change in luminal bacteria in the small intestine (SIBO) disrupts digestion and absorption. Gut bacteria are also important for immune activation^[52]. Immune mediated cytokines could have multiple actions including altered epithelial secretion, exaggerated nociceptive signalling and abnormal motility^[52,53]. Together, these changes may lead to IBS like symptoms. It has also been proposed that this mechanism could account for overlap syndromes, such as fibromyalgia^[54,55]. There has been renewed interest in gut flora recently, as there are recent developments on relationship between gut flora and intestinal function, pathogenesis of various diseases and potential value of probiotics, and other means of modifying gut flora as therapeutic modalities.

In patients with SIBO, bacteria ferment ingested carbohydrates in the small intestine causing increased gas production^[15]. Accumulation of this gas in the intestine results in bloating and flatulence^[56,57]. Excessive luminal distension may even cause abdominal pain or discomfort^[57]. 15% of the population produces methane in-

stead of hydrogen gas^[13,34]. Evidence suggest that excessive methane produced by overgrowth of methanogenic flora causes constipation^[42]. Reduction in breath methane by therapeutic manipulation of gut flora improves constipation^[58].

Bacteria in the intestine may produce toxic by-products after fermentation, which may damage the inner lining of the small intestine and colon^[59]. A study on small bowel biopsies in patients with SIBO revealed thinning of the mucosa and crypts and increased intra-epithelial lymphocytes^[60]. This may cause osmotic load in the intestine resulting into diarrhea. Studies have revealed that patients with IBS having SIBO more often have diarrhea-predominant disease^[11,12,14,18,19]. Bacteria also de-conjugates bile salts present in the intestine. These de-conjugated bile salts can stimulate colonic water secretion causing diarrhea. Thereafter, free bile acids, which are toxic to the intestinal mucosa may cause mucosal inflammation and release of pro-inflammatory cytokines^[61,62]. SIBO is known to be associated with increased IL-8 levels (pro-inflammatory cytokine)^[63].

Pathophysiology of IBS includes altered motility, visceral hypersensitivity and abnormal brain-gut interaction. Bacteria affect the sensori-motor functions of the gut^[64]. Bacterial chemotactic peptides, such as formyl-methionyl-leucyl-phenylalanine, stimulate the enteric nervous system and afferent nerves, while endotoxins (lipopolysaccharides) may affect gut motility^[65]. Bacteria in the small intestine in patients with SIBO produce short-chain fatty acids (SCFA) such as butyrate, acetate, and propionate. Colonic motility is increased due to acidification by SCFA^[66,67]. In contrast, SCFA causes reduction in motil-

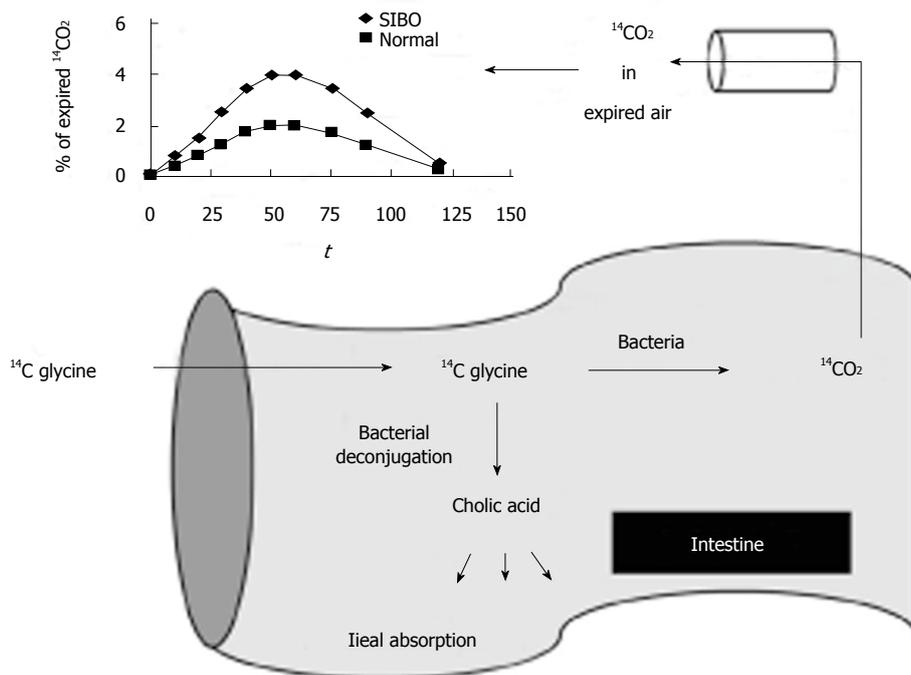


Figure 3 Bile acid breath test involves the administration of the bile acid ¹⁴C glycocholic acid, and the detection of ¹⁴CO₂, which would be elevated in small intestinal bacterial overgrowth.

ity of proximal intestine due to release of peptide YY, neurotensin and glucagon-like peptide-1 in the ileum^[68]. Therefore, alteration in gut flora may cause altered motility and predispose to IBS like symptoms.

EVIDENCE FROM STUDIES ON THERAPEUTIC MANIPULATION OF GUT FLORA IN IBS

Gut flora of IBS patients is different from that of healthy subjects, resulting in more gas production due to bacterial fermentation^[69-71]. Evidence suggest that therapeutic manipulation of gut flora either with antibiotics or probiotics may lead to relief in symptoms of IBS^[72,73]. Several meta-analysis have reported the presence of SIBO in a subset of IBS patients^[14,17,74]. Recent studies have revealed that treatment of SIBO relieves symptoms of IBS^[17,75]. In a study, eradication of SIBO by open label antibiotic treatment resolved symptoms of IBS to the extent of Rome I criteria turning negative in 48% of patients^[17]. SIBO is more often found in diarrheal IBS than other subtypes^[16]. Treatment of patients with diarrhea-predominant IBS with antibiotics, which is the primary treatment of SIBO, may lead to relief in symptoms including bloating, abdominal pain and loose stools. Rifaximin, a non-absorbable broad spectrum antibiotic, has been widely used for treatment of SIBO^[76]. In a phase 3, double-blind, placebo-controlled trial on IBS patients without constipation, treatment with rifaximin provided significant relief in bloating, abdominal pain, and loose or watery stools as compared to placebo^[77].

Methane produced by methanogenic flora is shown

to cause slow transit constipation, which is associated with IBS^[78]. Recently, rifaximin is found to reduce methane gas and improve gut transit^[58]. A combination of rifaximin and neomycin is more effective in treating methane-producing IBS patients as compared to treatment with neomycin and rifaximin as single agents (87% vs 33% and 28%, respectively)^[79].

Some studies support the use of probiotics to be as effective as antibiotics in relieving IBS related symptoms^[80,81]. A study showed that treatment with probiotics was effective in reducing symptoms of abdominal pain, bowel frequency, urgency and distension in patients with chronic diarrhea^[82]. Lactobacilli are less gas producing than other bacteria^[70]. Therefore, administration of Lactobacilli in patients with IBS was associated with reduced gas-related symptoms^[83]. In a single blinded randomized control trial, IBS patients randomized to receive *Lactobacillus acidophilus*, *Lactobacillus helveticus*, and Bifidobacterium showed significant improvement in pain and bloating as compared to those who received placebo^[84]. Another study showed *Bacillus subtilis* and *Streptococcus faecium* to be effective in reducing abdominal pain as compared to placebo in patients with diarrhea or alternating type of IBS^[85]. However, more studies are needed to know the best strains of probiotic bacteria, their dose and duration for treatment of patient with IBS.

CONCLUSION

Association between IBS and SIBO is definite. In fact, controversy exists whether patients presenting with IBS but found to have SIBO on further testing should be diagnosed as IBS or should be considered as SIBO as

symptoms of IBS and SIBO are similar. However, in the current diagnostic algorithm of Rome Foundation, IBS is diagnosed by symptom-based criteria. Exclusion of SIBO by appropriate testing is not essential before diagnosing IBS. In future iteration on IBS diagnostic algorithm by Rome Foundation, it may be important that consideration is given to exclude SIBO before a diagnosis of IBS is made, at least in a subset of patients with higher probability of SIBO. However, as evident from the review of the existing data, we conclude that whereas in some studies, the frequency of SIBO was over-estimated, in others it was under-estimated. Studies that used an early-peak criteria on LHBT showed higher frequency of SIBO than those that used other methods to diagnose. In the context of recent studies that showed that early-peak criteria on LHBT is often false positive, it is likely that all these studies over-estimated frequency of SIBO and therefore, created an un-necessary hype^[14,17,86,87]. GHBT has a low sensitivity to diagnose SIBO^[15]. Therefore, studies based on GHBT might have under-estimated frequency of SIBO. Though jejunal aspirate culture is considered as gold standard for diagnosis of SIBO, this has limitations. Most importantly, this is invasive and hence, not acceptable to the patients. Therefore, there is urgent need to know the clinical predictors for considering diagnosis of SIBO in patients presenting as IBS and better diagnostic techniques to confirm this.

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