





Small Intestinal Bacterial Overgrowth (SIBO) Interpretive Guide



This Interpretive Guide is divided into 2 sections: An in-depth review of SIBO pathophysiology, symptoms and treatment, followed by interpretive considerations of several test scenarios.

SIBO Pathophysiology and Symptoms

Small intestinal bacterial overgrowth (SIBO) is an increase in the number of bacteria and/or the presence of atypical microbiota in the small intestine.¹⁻³ Gram-positive flora might be present due to failure of the gastric acid barrier, whereas the presence of colonic bacteria may be due to failure of intestinal clearance and small intestinal anatomical alterations.⁴ The bacteria in SIBO are mainly colonic type bacteria, and it is hypothesized that it is the retrograde bacterial migration from the large intestine into the small intestine that leads to symptoms. These organisms produce gases, including hydrogen (H₂), methane (CH₄), and hydrogen sulfide (H₂S). The bacteria commonly found in SIBO include *Escherichia coli, Enterococcus* spp., *Klebsiella pneumonia,* and *Proteus mirabilis*.⁵ The common methane-producing organisms include archaea, such as *Methanobrevibacter smithii*, as well as bacteria, including certain *Clostridium* and *Bacteroides* species.⁶

There are many natural defense mechanisms against SIBO. These include, but are not limited to:4.7

- Antegrade peristalsis and the migrating motor complex (MMC)
- Bacteriostatic action of gastric acid, pancreatic enzymes, and bile; bile is an important suppressor of methanogenesis
- Intestinal mucus layer (traps bacteria)
- Ileocecal valve inhibits retrograde translocation of bacteria from the colon to the small intestine
- Immune system, specifically sIgA, prevents bacterial proliferation.

SIBO symptoms are non-specific, including abdominal pain/distention, flatulence, nausea, dyspepsia, constipation, and diarrhea.^{1,2,8} Post-prandial bloating is a common SIBO symptom due to the bacteria fermenting carbohydrates that produces gas, distension, and bloating.⁹

The mechanisms by which diarrhea may occur include bacterial de-conjugation of bile salts, enterotoxic effects of bacterial metabolites, increased small intestinal permeability, decreased vitamin B12, and low grade inflammation resulting from immune activation in the small intestinal mucosa. Immune activation involves an increased number of intraepithelial lymphocytes, mast cells, and enterochromaffin cells. The mediators of the host immune response trigger the enteric nervous system, which can alter GI motility and visceral hypersensitivity.⁴ Additionally, lipopolysaccharide (LPS), a gram-negative bacterial endotoxin, can accelerate intestinal transit.⁹

Intestinal Methanogen Overgrowth, or IMO, occurs when methane-producing organisms are present throughout the digestive tract - not just the small intestine. Methane (CH₄) production has been associated with the pathogenesis of common clinical conditions, such as obesity, irritable bowel syndrome (IBS), and constipation.¹⁰ Methane gas itself may slow intestinal transit,¹¹ and patients with CH₄-predominant overgrowth have been found to be five times more likely to have constipation compared to individuals with H₂-predominant overgrowth.¹² Moreover, the severity of constipation has been found to directly correlate with the CH₄ level.¹³

Associated Conditions

Conditions in which a high prevalence of overgrowth are commonly observed include, but are not limited to:^{2,8,14}

- Functional GI disorders (such as irritable bowel syndrome and gastroparesis)
- Hypothyroidism¹⁵
- · Neuromuscular diseases (such as restless leg syndrome)
- Inflammatory bowel disease (IBD)
- Pancreatic disease
- Celiac disease
- Liver disease
- Diabetes
- Fibromyalgia^{4,16}
- Rosacea
- Parkinson's disease
- Obesity
- Interstitial cystitis¹⁷

Risk Factors

Decreased intestinal motility is a key factor in the development of SIBO and its recurrence. Out of all the diseases and disorders associated with SIBO, 90% of cases involve either small intestinal motility disorders and/or chronic pancreatitis.⁷ The migrating motor complex (MMC) describes the waves of electromechanical activity that sweep through the intestines in regular cycles between meals. The MMC triggers waves that move non-digestible substances through the gastrointestinal tract from the stomach distally to the terminal ileum.^{8,9} In addition, the MMC is responsible for moving bacteria from the small intestine to the large intestine, as well as inhibiting the migration of colonic bacteria into the terminal ileum.¹⁸ Any disorder that impairs MMC function can be a risk factor for SIBO. Gastroenteritis that leads to post-infectious IBS-D is thought to be a risk factor for SIBO. Campylobacter jejuni, Salmonella, E. coli, and Shigella produce cytolethal distending toxin (CDT), and the host can produce an autoimmune response that damages the pacemaker cells for the MMC, resulting in decreased MMC activity.¹⁹

Other key SIBO risk factors include conditions that result in immunocompromise, decreased bacteriostatic digestive secretions (HCl, pancreatic enzymes, bile acids), and ileocecal valve dysfunction.⁷

Complications of SIBO

Because SIBO is not consistently characterized by the same species, different symptoms or complications may result, depending on the organisms that are present and their specific function in the GI tract.¹ SIBO can result in damage to the small intestinal mucosa leading to malabsorption and intestinal permeability. Microscopic inflammatory changes in the lamina propria and villous atrophy are common.⁷ Destruction of the intestinal mucosa can result in reduced disaccharidase function and increased intraluminal bacterial carbohydrate degradation, causing SIBO symptoms.²⁰ The bacteria themselves can consume nutrients, leading to micronutrient deficiencies, and deconjugate bile acids, leading to fat and fat-soluble vitamin malabsorption. Bacteria can produce toxic substances resulting in increased serum endotoxin, stimulating inflammatory cytokine production.⁷ SIBO complications include:^{1,7,20}

- Weight loss
- Steatorrhea



- Vitamin/mineral deficiency
 - » Fat-soluble vitamins (A,D,E,K)
 - » Vitamin B12
 - » Iron
- Hypoproteinemia/hypoalbuminemia
- Bile acid deficiency
- Anemia
- Osteoporosis
- Neuropathies

Treatment Considerations

Antibiotics are commonly used to treat SIBO, and studies show normalized breath tests as well as symptomatic relief.⁴ The underlying causes of SIBO must be treated properly. Otherwise, the likelihood of SIBO recurrence is very high, even after antibiotic therapy.⁸ In general, clinical management of the SIBO patient involves antibiotics^{8,21-23} and/or natural antimicrobial agents,¹⁷ promotility/prokinetic agents,²⁴⁻²⁶ nutrient supplementation for depleted nutrients and/ or for brush border healing,^{20,27} dietary interventions, meal spacing,²⁷ and treatment of comorbid conditions.²⁶

Treat the Overgrowth

Antibiotics

- Rifaximin is a non-absorbable antibiotic that has been FDA-approved for IBS-D, traveler's diarrhea, and hepatic encephalopathy.⁸ It has been extensively studied in functional bowel disorders.⁸ It is efficacious against Grampositive and Gram-negative aerobic and anaerobic bacteria.⁴ It can target common SIBO organisms including *E. coli, Klebsiella* spp., *Enterobacter spp.*, and *E. faecalis*. In addition to its direct antibiotic effects, rifaximin may also modulate the host inflammatory response with its anti-inflammatory effect.²⁸ It is best used for hydrogen-predominant SIBO.²⁷
- While rifaximin can be used as an individual agent in patients with methane positive breath-testing, an additional agent may be a more effective treatment in instances of constipation-predominant symptomology or when both H₂ and CH₄ are present.²¹ Rifaximin plus neomycin, both non-absorbable antibiotics, have been described as an effective treatment for constipation-predominant cases.²²
- A variety of other antibiotics have been studied for SIBO with varying efficacy. These include metronidazole, ciprofloxacin, norfloxacin, amoxicillin-clavulanic acid, cefoxitin, and doxycycline.²⁰

Natural Agents

 In addition to pharmaceutical agents, limited evidence suggests a possible role for natural anti-microbial agents such as berberine, allicin (a component of garlic), oregano oil, and/or neem. One study showed that herbal therapies are at least as effective as rifaximin for SIBO resolution confirmed by lactulose breath test. The herbal products used in this study were a combination of Dysbiocide and FC Cidal (Biotics Research Laboratories) or Candibactin-AR and Candibactin-BR (Metagenics, Inc.).¹⁷

Elemental Diet

- Elemental formulas are medical foods that provide nutrition that is absorbed in the proximal small intestine, thus limiting the delivery to the bacteria residing in the distal small intestine.
- This diet may be an alternative to antibiotics in patients with allergies to antibiotics or who cannot tolerate antibiotics.⁸

Provide Nutritional Support

Numerous nutritional consequences have been associated with SIBO including: weight loss, fat soluble vitamin deficiency, vitamin B12 deficiency, iron deficiency, hypoproteinemia, and low serum bile acids.²⁰ Any patient with such secondary consequences may warrant nutraceutical support until SIBO has been addressed.

Dietary adjustments to support the management of bacterial overgrowth are also commonly utilized in SIBO. Because no dietary approach has been found to be uniformly effective for the management of symptoms, ongoing dietary modifications, based on patient feedback, is imperative. Common dietary SIBO interventions include the Specific Carbohydrate Diet (SCD), Low FODMAPs, SIBO Specific Diet (a combination of low FODMAPs and SCD designed by Allison Siebecker, ND), SIBO Bi-Phasic Diet (designed by Australian clinician Nirala Jacobi, ND), a liquid elemental diet, GAPS Diet, the Cedars-Sinai Medical Center's Low Fermentation/SIBO Diet (Mark Pimentel, MD), and the Fast Tract Diet (designed by Norman Robillard, PhD).

Probiotics may be beneficial, but further studies are needed to determine the dose and strain.²⁰ Prebiotics, often added to probiotic supplements, are fermentable foods for bacteria and can encourage overgrowth; these should be avoided during treatment. Other supplements used by functional medicine key opinion leaders include hydrochloric acid, digestive enzymes, and brush border healing supplements, including mucilaginous herbs (licorice, slippery elm, aloe vera, marshmallow), colostrum, L-glutamine, zinc carnosine, vitamins A and D, curcumin, resveratrol, glutathione, and N-acetylcysteine.²⁷

Correct the Underlying Cause

While it may not always be possible, depending on the condition, treatment should include strategies to minimize any risk factors or comorbid conditions for SIBO. Patients with impaired GI motility that affects the migrating motor complex (MMC), or anatomical abnormalities of the digestive tract, are particularly susceptible to SIBO.^{1,2}

Optimal functioning of the MMC may be supported in the following ways:

- Meal spacing every 4 5 hours and an overnight fast. The MMC is active during fasting states and is stopped by feedings.²⁷
- Use of prokinetic/promotility agents:
 - » Pharmaceutical agents include low-dose erythromycin,²⁴ low-dose naltrexone (LDN),²⁵ and others. Erythromycin is a motilin agonist and can increase the frequency of phase III of the MMC.²⁴ LDN is an opioid antagonist and can stimulate peristalsis and increase transit.²⁹
 - » Natural agents include the botanical product Iberogast, ginger, and others.²⁶ Iberogast consists of 9 herbs and, when compared with the prokinetics metoclopramide and cisapride, there was comparable effectiveness in the treatment of dyspepsia.^{30,31} Ginger increases motility during phase III of the MMC.³²

Retesting

In a patient treated for SIBO, many variables affect the decision of when to retest, including the patient's underlying condition and its severity, and the length and type of treatment. The North American consensus group suggests that breath tests may be performed shortly after cessation of antibiotic therapy to confirm eradication.¹³



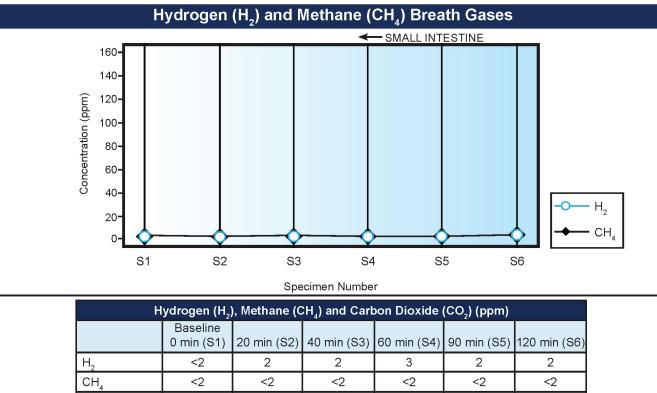
Genova's SIBO Breath Test

Genova's SIBO Profiles are non-invasive breath tests which capture exhaled hydrogen (H_2) and methane (CH_4) gases, following patient ingestion of a lactulose solution, to evaluate bacterial overgrowth of the small intestine (SIBO). Expected values for both H_2 and CH_4 are based on the 2017 North American breath testing consensus group recommendations.¹³

Genova offers both a 2-hour and a 3-hour test. Lactulose's normal transit from mouth to large intestine is approximately 90 minutes.^{33,34} In patients with slower transit times, a 3-hour test should be considered. Currently, there is no standard recommendation in the literature on the optimal time frame for SIBO breath testing. Genova's evaluation for hydrogen and methane are based on the same criteria for both the 2-hour and 3-hour tests.

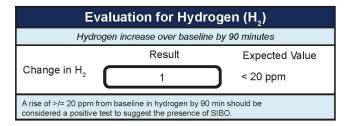
Combined values of $H_2 + CH_4$ are provided on each report. However, the North American breath testing consensus group does not offer guidelines for interpreting combined values of $H_2 + CH_4$. They are provided for clinicians who are familiar with this result reporting and who wish to continue utilizing this data.

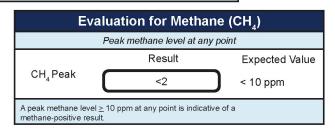
NEGATIVE HYDROGEN, NEGATIVE METHANE:



$H_2 + CH_4$	NR	NR	NR	NR	NR	NR	
CO ₂ **	1	1	1	1	1	1	
	Actual Collection Times						
Actual Time	8:10	8:30	8:50	9:10	9:40	10:10	
Actual Interval	0 min	20 min	40 min	60 min	90 min	120 min	

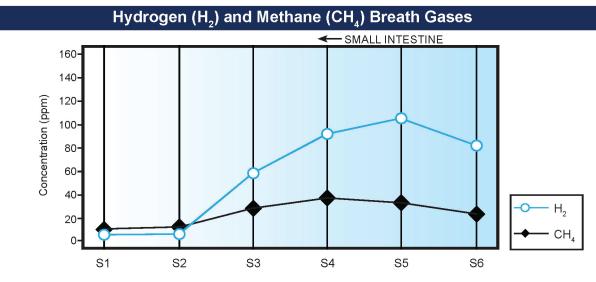
**CO₂ is measured for quality assurance. ✓ indicates the CO₂ level is acceptable. X indicates room air contamination exceeding acceptable limits.





- Negative for SIBO;¹³ clinicians may use this as confirmation of eradication after a round of antibiotics.
- In a symptomatic patient, with a high pre-test probability, false negatives should be considered. Certain bacteria use hydrogen (H₂) in metabolism, forming hydrogen sulfide (H₂S), which is not measured on breath testing.³⁵ Hydrogen sulfide gas has a "rotten egg" odor.
- It is also important to ensure proper sample collection if suspicious of a false negative.
- If a patient has slow transit or constipation, lactulose may take longer to travel the length of the small intestine. A 3-hour test may be considered in this case.

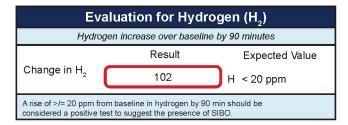
POSITIVE HYDROGEN AND METHANE:

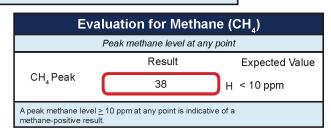


Specimen Number

Hydrogen (H ₂), Methane (CH ₄) and Carbon Dioxide (CO ₂) (ppm)							
	Baseline 0 min (S1)	20 min (S2)	40 min (S3)	60 min (S4)	90 min (S5)	120 min (S6)	
H ₂	4	7	59	97	106	76	
CH4	10	12	28	38	35	26	
H ₂ + CH ₄	14	19	87	135	141	102	
CO ₂ **	1	1	~	1	>	1	
		Actual	Collection T	imes			
Actual Time	9:55	10:17	10:39	11:00	11:30	12:00	
Actual Interval	0 min	22 min	44 min	65 min	95 min	125 min	
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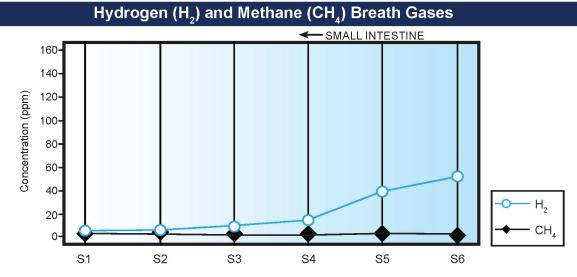
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- A rise of $H_2 \ge 20$ ppm over baseline by 90 minutes is positive for SIBO.¹³
- A peak level of CH4 ≥10 ppm at any point is a methane-positive result.¹³
- When both H₂ and CH₄ are present, treatment may require more than one antimicrobial agent.³⁶ Patients who
 received a combination of rifaximin and neomycin showed a higher rate of methane eradication on breath testing
 compared to patients who received either rifaximin or neomycin alone. There was also a better clinical response
 with the combination therapy.¹⁰

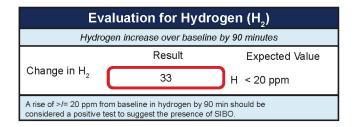
POSITIVE HYDROGEN, NEGATIVE METHANE:

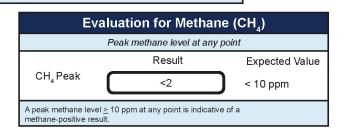


Specimen Number

Hydrogen (H ₂), Methane (CH ₄) and Carbon Dioxide (CO ₂) (ppm)						
	Baseline 0 min (S1)	20 min (S2)	40 min (S3)	60 min (S4)	90 min (S5)	120 min (S6)
H ₂	5	4	5	13	38	51
CH4	<2	<2	<2	<2	<2	<2
$H_2 + CH_4$	NR	NR	NR	NR	NR	NR
CO ₂ **	1	 Image: A set of the set of the	1	1	1	 Image: A set of the set of the
		Actual	Collection T	ïmes		
Actual Time	7:00	7:20	7:41	8:00	8:30	9:00
Actual Interval	0 min	20 min	41 min	60 min	90 min	120 min
**CO ₂ is measured	for quality assura	nce. 🗸 indicates th	e CO ₂ level is acce	ptable. X indicates	s room air contami	nation exceeding

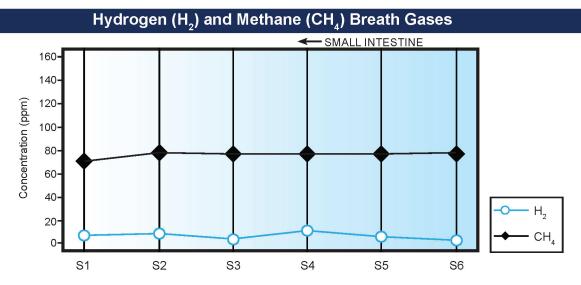
acceptable limits





- Hydrogen increase by ≥20 ppm over baseline by 90 minutes is a positive SIBO test.¹³
- In symptomatic patients with slower transit times, an elevated H₂ beyond 90 minutes may be positive for SIBO. If the lactulose has not had sufficient time to reach the junction of the small and large intestine by 90 minutes, a distal SIBO may be missed. There is no absolute way of knowing a patient's exact transit time; it can only be estimated.

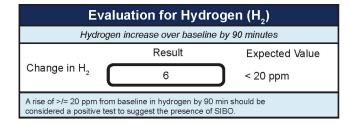
NEGATIVE HYDROGEN, POSITIVE METHANE:

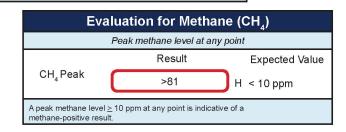


Specimen Number

Hydrogen (H ₂), Methane (CH ₄) and Carbon Dioxide (CO ₂) (ppm)								
	Baseline 0 min (S1)	20 min (S2)	40 min (S3)	60 min (S4)	90 min (S5)	120 min (S6)		
H ₂	4	6	4	10	9	7		
CH4	71	>81	>81	>81	>81	>81		
H ₂ + CH ₄	75	NR	NR	NR	NR	NR		
CO ₂ **	1	~	1	1	~	 Image: A second s		
	Actual Collection Times							
Actual Time	10:12	10:32	10:52	11:12	11:42	12:12		
Actual Interval	0 min	20 min	40 min	60 min	90 min	120 min		

**CO₂ is measured for quality assurance. ✓ indicates the CO₂ level is acceptable. X indicates room air contamination exceeding acceptable limits.

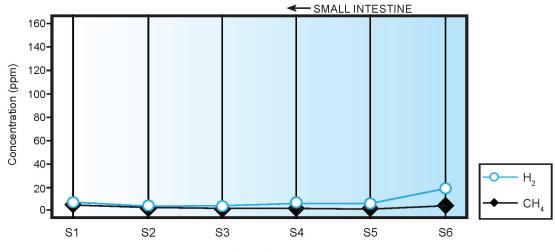




- Elevated methane ≥10 ppm anywhere on the test is a positive finding.¹³
- Treatment may require more than one antimicrobial agent in patients with a methane positive result.³⁶ Patients who received a combination of rifaximin and neomycin showed a higher rate of methane eradication on breath testing compared to patients who received either rifaximin or neomycin alone. There was also a better clinical response with the combination therapy.¹⁰



BORDERLINE METHANE:



Specimen Number

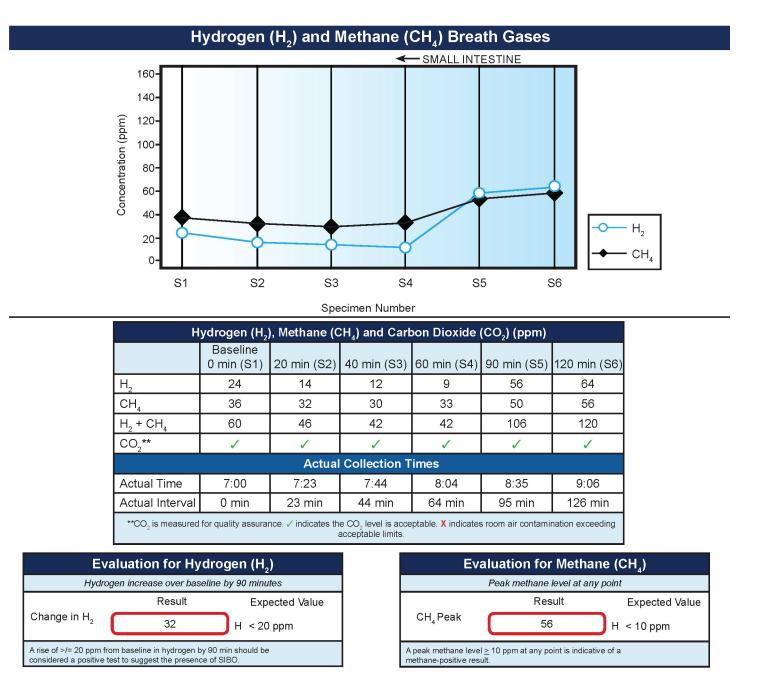
Hydrogen (H ₂), Methane (CH ₄) and Carbon Dioxide (CO ₂) (ppm)							
	Baseline 0 min (S1)	20 min (S2)	40 min (S3)	60 min (S4)	90 min (S5)	120 min (S6)	
H ₂	6	6	7	9	10	24	
CH4	5	4	4	5	5	8	
H ₂ + CH ₄	11	10	11	14	15	32	
CO ₂ **	>	~	1	1	>	1	
	Actual Collection Times						
Actual Time	8:00	8:20	8:40	9:00	9:30	10:00	
Actual Interval	0 min	20 min	40 min	60 min	90 min	120 min	
**CO ₂ is measured	for quality assura		e CO ₂ level is acce acceptable limits.	ptable. X indicates	s room air contami	nation exceeding	

Evaluation for Hydrogen (H_2)						
Hydrogen increase over baseline by 90 minutes						
	Result	Expected Value				
Change in H ₂	4	< 20 ppm				
	om baseline in hydrogen by 90 mi est to suggest the presence of SIE					

Evaluation for Methane (CH₄)						
Peak methane level at any point						
	Result	Expected Value				
CH₄ Peak	8	< 10 ppm				
A peak methane level ≥ 10 ppm at any point is indicative of a methane-positive result.						

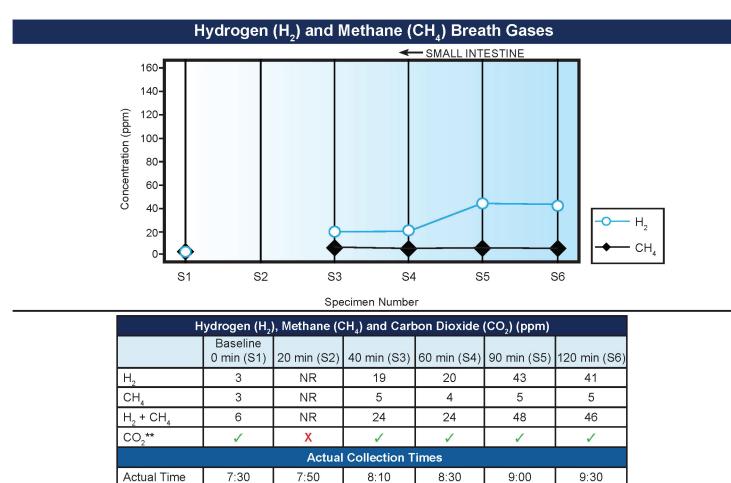
• Peer-reviewed literature suggests an association with certain clinical conditions and methanogen overgrowth at levels as low as 3 ppm. These conditions include chronic constipation, IBS-C, and obesity.¹⁰ Therefore, any CH₄ value between 3-9 ppm may indicate a need for treatment in symptomatic patients.³⁷⁻³⁹

ELEVATED BASELINE:



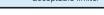
- Elevated baseline hydrogen can be seen in patients who did not adhere to fasting and pretest dietary guidelines. The clinical significance of elevated baseline H₂ levels in patients reporting adherence to fasting and dietary guidelines is not known.¹³
- Falsely elevated baseline findings may result from incomplete avoidance of high-fiber foods, residual fiber in the intestine due to delayed transit time, residual oropharyngeal (mouth and throat) bacteria, exposure to tobacco smoke, napping during collection, or not waiting a full hour after waking for the day.¹³
- Baseline elevation of methane is common and is clinically significant in symptomatic patients.⁴⁰

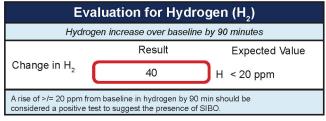
SAMPLE REJECTION:

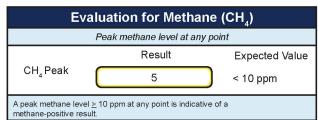


 Actual Interval
 0 min
 20 min
 40 min
 60 min
 90 min
 120 min

 **CO₂ is measured for quality assurance. ✓ indicates the CO₂ level is acceptable. X indicates room air contamination exceeding acceptable limits

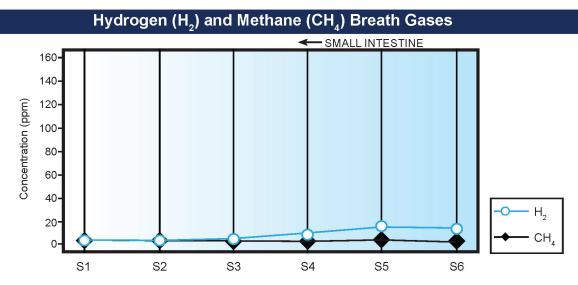






- Each sample is tested for carbon dioxide (CO₂) as a measure of quality assurance. The presence of CO₂ represents room air contamination. Contaminated samples will be rejected and not graphed. Instead, a red "x" is placed in the collection chart to denote sample rejection.
- Sample 1 must be be submitted and pass CO₂ quality assurance. If sample one is rejected, subsequent results will be invalid and the patient will need to retest.
- Three out of four specimens before 90 minutes must also pass CO₂.
- Even with one rejected sample, results can still be interpreted if the baseline is available.

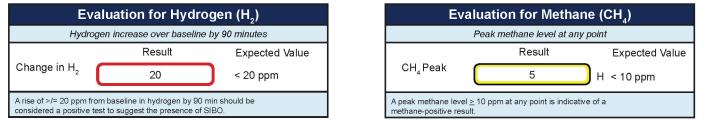
ALTERED COLLECTION SCHEDULE:



Specimen Number

Hydrogen (H ₂), Methane (CH ₄) and Carbon Dioxide (CO ₂) (ppm)							
	Baseline 0 min (S1)	20 min (S2)	40 min (S3)	60 min (S4)	90 min (S5)	120 min (S6)	
H ₂	3	3	4	9	23	22	
CH4	2	<2	<2	<2	5	3	
H ₂ + CH ₄	5	NR	NR	NR	28	25	
CO ₂ **	>	~	>	1	~	1	
Actual Collection Times							
Actual Time	9:37	10:00	10:21	10:42	11:14	11:45	
Actual Interval	0 min	23 min	44 min	65 min	97min	128 min	

**CO₂ is measured for quality assurance. ✓ indicates the CO₂ level is acceptable. X indicates room air contamination exceeding acceptable limits.



- It is important to take notice of the actual patient collection times and compare them with the recommended collection times.
- If the patient collection schedule ended earlier than the recommended collection schedule, then a distal SIBO may be missed.
- If a patient collection schedule ended later than the recommended collection schedule, then false positive hydrogen results may be reported. The hydrogen result is the difference between the baseline hydrogen (S1) and the highest finding among S2, S3, S4 or S5. The result does not take into account actual collection times. It is expected that the patient followed recommended collection times.
- In the example above, the patient's S5 sample for hydrogen was the highest finding among S2-S5. The highest finding of 23 minus the baseline finding of 3 results in a finding of 20 for hydrogen. A rise of H₂ \geq 20 ppm over baseline by 90 minutes is positive for SIBO.¹³ However, this sample was collected at 97 minutes versus the recommended 90 minutes. While a few minutes may not significantly alter interpretation, the test should be interpreted in light of this altered schedule and within the clinical context. Greater time discrepancies may result in a different interpretation of the test results.



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