# REVIEW

## Questioning the Bacterial Overgrowth Hypothesis of Irritable Bowel Syndrome: An Epidemiologic and Evolutionary Perspective

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This article has an accompanying continuing medical education activity on page e59. Learning Objectives—At the end of this activity, the learner will appreciate the recent evidence linking small bowel bacterial overgrowth to irritable bowel syndrome and recognize the inconsistent data regarding the relationship between bacterial overgrowth and irritable bowel syndrome.

**Although studies indicate that small intestinal bacterial overgrowth (SIBO) is prevalent in irritable bowel syndrome (IBS), it remains unclear whether SIBO causes IBS. This review presents an epidemiologic and evolutionary inquiry that questions the bacterial overgrowth hypothesis of IBS, as follows. (1) Although the hypothesis may be biologically plausible, there is also a strong rationale for competing hypotheses; it is unlikely that SIBO is the predominant cause of IBS in all comers, because competing explanations are sensible and defensible. Moreover, data indicate that the test used to promulgate the SIBO hypothesis — the lactulose hydrogen breath test — may not have measured SIBO in the first place. (2) We do not have evidence of SIBO being absent before IBS symptoms, and present after IBS emerges. (3) There is not a dose-response relationship between small intestinal microbiota and IBS symptoms. (4) The relationship between SIBO and IBS is highly inconsistent among studies. (5) Many effective IBS therapies do not address SIBO at all, yet have a more favorable "number needed to treat" than antibiotics. (6) IBS does not behave like a traditional infectious disease, suggesting that microbes may not principally cause the syndrome. (7) Other factors may confound the relationship between SIBO and IBS, including proton pump inhibitors. (8) Whereas the brain-gut hypothesis is evolutionary sensible, the bacterial hypothesis is harder to defend from an evolutionary perspective. The article concludes that bacteria may contribute to some IBS symptoms, but that bacteria cannot be the only explanation, and a causal link between SIBO and IBS is not secure.**

*Keywords:* Irritable Bowel Syndrome; Small Intestinal Bacterial Overgrowth; Epidemiology.

The potential role for small intestinal bacterial overgrowth (SIBO) in irritable bowel syndrome (IBS) was popularized nearly 10 years ago after a strong association was reported between IBS and abnormal lactulose hydrogen breath tests (LHBT).[1] This association was described by Pimentel and colleagues, who found that 84% of IBS patients had SIBO.[2] Moreover, the investigators reported that patients with IBS were over 26 times more likely to harbor SIBO versus controls — a striking difference.[2] Several groups pursued the SIBO-IBS link in subsequent research;[3–11] some found similar results, whereas others were unable to establish an association. Figure 1 presents studies that measured LHBT results in IBS versus controls, all using the same SIBO definition of a hydrogen rise >20 ppm within 180 minutes. Meta-analysis of these studies revealed marked statistical heterogeneity,[12] suggesting that it is premature to accept a firm etiologic link between SIBO and IBS. Moreover, despite a decade of investigation evaluating the relationship between SIBO and IBS, it remains unclear whether SIBO *causes* IBS, or is instead a bystander of something else altogether. Some recent data challenge whether SIBO is present in IBS to begin with.[13]

However, some proponents of the bacterial hypothesis contend that the diagnosis of IBS itself should be questioned in any patient not found to have SIBO by diagnostic testing, or in those failing to respond to antibiotic therapy.[14] It has been further suggested that IBS patients failing to respond to antibiotics probably harbor some other, undiagnosed condition.[15] This causal explanation implies that the very definition of IBS is a response to antibiotics, such that failure to respond to gut-directed antibiotics indicates absence of IBS. In other words, antibiotic response is the *sina qua non* of IBS.

This review presents an epidemiologic and evolutionary perspective to assess the bacterial hypothesis of IBS. The review draws upon a wealth of old and new data that question the

***Abbreviations used in this paper:*** **cfu, colony forming units; HBT, hydrogen breath test; IBS, irritable bowel syndrome; LHBT, lactulose hydrogen breath test; NNT, number-needed-to-treat; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event Trial; TLR, Toll-like receptor.**


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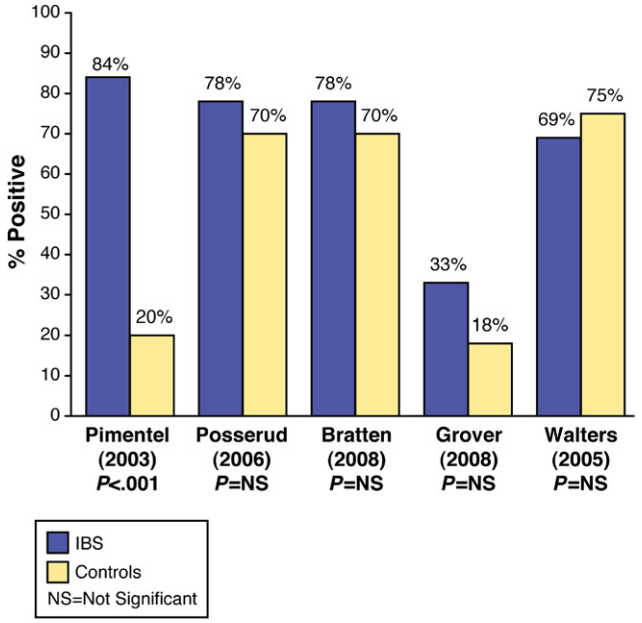


**Figure 1.** Studies evaluating the prevalence of SIBO between patients with IBS vs controls, using lactulose hydrogen breath testing among all studies, and defining a positive study as hydrogen rises >20 parts per million by 180 minutes.

bacterial hypothesis, and presents the data within an epidemiologic framework. Epidemiologically, there are several criteria to link a risk factor to a disease,[16] including: (1) biological plausibility; (2) temporal relationship; (3) dose-response effect; (4) consistency among studies; (5) removal of the causal factor removes disease; (6) treatments that address the purported causal mechanisms are more effective than therapies solely addressing competing mechanisms; and (7) lack of confounders undermining the relationship between risk factor and disease. The sections below review each criterion as it applies to the SIBO-IBS link. Following this epidemiologic discussion, the article evaluates how well the SIBO hypothesis sustains inquiry from an evolutionary perspective.

## Is the Bacterial Hypothesis Biologically Plausible?

In order to conclude that a risk factor causes a disease, there should be *biological plausibility* for the relationship. In the case of SIBO and IBS, this remains a possibility, as summarized in previous reviews.[17,18] However, it is important to revisit the original evidence that SIBO is common in IBS, because that observation was used to promulgate the bacterial hypothesis. Thus, we should begin by reviewing how to define SIBO in the first place, and acknowledge the difficulties in confirming presence versus absence of SIBO in IBS.

The traditional gold standard for SIBO is to culture jejunal aspirate. Whereas the jejunum normally has no more than $10^3$ colony forming units (cfu) of colonic-type bacteria in health, the concentration traditionally exceeds $10^5$ in SIBO (although this threshold has been criticized for being too high[18,19]). However, jejunal aspirates may not reach areas that matter. Because colonic bacterial migration begins distally, early forms of SIBO are undetectable by jejunal aspirate. Moreover, most luminal bacteria remain unidentifiable by traditional culture-based methods.

Hydrogen breath testing (HBT) is an alternative approach to diagnosing SIBO, and was the test used to promote the bacterial hypothesis of IBS. HBT involves oral administration of a carbohydrate, such as lactulose or glucose, which ferments upon exposure to colonic-type bacteria. This yields hydrogen gas that is detectable in expired air. Because hydrogen gas is not endogenously produced in the absence of bacteria, the presence of any hydrogen in expired air implies carbohydrate fermentation by colonic-type bacteria. In health, hydrogen production does not typically rise before 90 minutes following carbohydrate ingestion. An earlier rise connotes proximal migration of colonic-type bacteria into the small bowel. Similarly, a >20 ppm rise by 180 minutes is also thought to indicate SIBO.[2,20] LHBT is the most common breath test in the IBS literature.[12,19,21] Because lactulose is not absorbed, it remains available for fermentation in the distal small bowel. In contrast, glucose is absorbed proximally, so it is less sensitive for distal SIBO, but more specific for proximal SIBO.

Proponents of the SIBO hypothesis interpret the HBT data to mean that abnormal fermentation must occur in IBS, and that breath testing has utility for diagnosing IBS.[19,21] However, compelling new data undermine this assertion, and indicate that the LHBT may not test for SIBO at all, but is instead a surrogate of intestinal transit time and colonic bacteria. In an innovative study from Canada, Yu and colleagues combined LHBT and technetium scintigraphy to evaluate orocecal transit time versus LHBT results.[13] IBS patients ingested a test meal with technetium and lactulose, and the investigators measured the location of the meal with scintigraphy and breath testing. Sixty-three percent of IBS patients had an abnormal LHBT at 180 minutes. However, in most every case of a positive LHBT (88%), the technetium arrived in the cecum *before* the LHBT became abnormal. In other words, abnormal small bowel transit likely explained the positive LHBT — not SIBO. This study is important, because it demonstrates that the test used to develop the SIBO hypothesis may not have measured SIBO in the first place, but simply reflected that orocecal transit is abnormal in many IBS patients.

There are other data to support this hypothesis. Posserud and colleagues performed jejunal aspirates in 126 Swedish patients with Rome III IBS, and measured LHBT results in a subset of 80 patients.[22] The investigators tracked the relationship between these biomarkers and IBS symptoms. They found that only 3% of IBS subjects met the traditional $\geq 10^5$ cfu/mL criterion for SIBO, and 9% met the less stringent $\geq 10^3$ criterion. Patients with a 90-minute LHBT rise were more likely to have severe diarrhea and loose stools. In contrast, small bowel bacterial concentrations did not correlate with IBS symptoms at all. This is important, because a rapid peak on breath testing could simply result from rapid motility, not SIBO. Similarly, neither Grover et al[6] nor Sandhu et al[9] could find any relationship between LHBT results and symptom patterns in IBS. These clinical data corroborate the imaging data from Yu et al,[13] suggesting convergent validity from different investigators in different countries.

In short, the LHBT data may indicate that dysmotility underlies IBS. This is not surprising, as previous data reveal that IBS symptoms partly arise from abnormal motility.[23,24] Moreover, therapies that address motility improve IBS symptoms.

For example, alosetron,[25–27] linaclotide,[28] lubiprostone,[29–31] and tegaserod[32–36] all affect motility to some degree, and all have high quality randomized controlled trials supporting their efficacy in IBS.[37] In short, it is hard to debate that dysmotility underlies, at least in part, *some* IBS symptoms, although its impact on global outcomes like quality of life remains debatable.[38] The bottom line is that abnormal LHBT results probably reflect underlying dysmotility in IBS — not necessarily SIBO.

However, there is no debate that dysmotility can cause SIBO. Perhaps the most powerful example is scleroderma, where hypomotility and stagnation lead to SIBO, with attendant defecatory symptoms and bloating.[39] Nobody has yet claimed that SIBO causes scleroderma — it must be the other way around. Nonetheless, antibiotic therapy is effective in improving the gastrointestinal distress of scleroderma. *The fact that antibiotics help scleroderma does not indicate that SIBO causes scleroderma*; it simply reflects that SIBO is a disruptive and highly symptomatic consequence of scleroderma, and that treating SIBO can help scleroderma symptoms, but certainly does not cure the underlying disease.

Could the same be true in IBS? Might it simply be that IBS is associated with dysmotility (now proven[13,23,24]), and that dysmotility can lead to SIBO (also well established[40])? Just as SIBO does not cause scleroderma, one could argue that SIBO does not cause IBS. If that were true, then treating SIBO might very well improve some IBS symptoms, just as it does with scleroderma, but would not treat the disease directly at all. That is, treating SIBO in IBS would not target the underlying, fundamental mechanisms of symptom expression, but would instead target a troublesome epiphenomenon, such as bloating. This is an important point: the observation that antibiotics help some IBS patients[41] is not necessarily evidence that SIBO *causes* IBS, any more than the benefits of antibiotics in scleroderma do not prove that SIBO causes scleroderma. This argument does not imply that antibiotics have no role in IBS (discussed further, below) — it simply means we should be cautious about claiming that SIBO *causes* IBS.

Future research should evaluate whether altering motility can, in and of itself, improve HBT results, or even SIBO, without the use of antibiotics at all; it might be that effectively treating dysmotility will clear SIBO, when present, and that antibiotics are unnecessary. It is also clear that we need a better gold standard for SIBO than the LHBT, a test that appears to measure intestinal transit,[13,22] not SIBO. Without a gold standard, we must reason in circular perpetuity about the pathogenic role of SIBO in IBS, because we cannot reliably confirm whether pathogenic SIBO occurs in IBS. Like an Escher print, it is hard to tell where the reasoning begins and ends, and whether a fallacy occurred along the way.

Finally, we should consider whether colonic bacteria contribute to IBS symptoms, and if antibiotics reduce bloating by affecting the colonic reservoir — not by altering small intestinal colonies. In fact, calorimetric studies indicate that hydrogen gas in IBS arises from colonic bacteria — not small intestinal bacteria.[42] Moreover, elimination diets may work in IBS by altering colonic bacteria, as indicated by reductions in hydrogen excretion in IBS patients following dietary intervention.[42,43] As further suggested by Yu[13] and Vanner,[44] future therapies might aim to alter colonic flora using approaches other than antibiotics, such as pre- or probiotics.

## Are Competing Hypotheses Less Biologically Plausible Than SIBO?

Let us assume for now that the LHBT is extremely accurate, that SIBO truly occurs in most every IBS patient,[2] and that SIBO is a plausible explanation for IBS symptoms.[17,18] Still, in order for a risk factor to be the *predominant cause* of a disease, we should expect that competing hypotheses are *less* biologically plausible, suggesting that the hypothesized risk factor is primary, and alternative risks are of secondary importance.

It remains difficult to imagine how the soldier who develops intense abdominal pain and diarrhea in the fits of active combat[45–47] has been simultaneously stricken by SIBO, or how the student with diarrhea, pain, "butterflies," and nausea in advance of a final examination[48] has coincidentally burgeoned her intestinal microbiota. It is also hard to explain how SIBO comports with the finding that IBS patients have greater activation of their anterior cingulate cortex and hypothalamus in response to stress,[49] or have thinner gray matter density in widespread areas of the brain versus controls.[50] These clinical scenarios and scientific discoveries do not invalidate bacteria as a contributor to IBS symptoms, but suggest that bacteria alone may not be the predominant explanation. There are other competing hypotheses with a strong biological rationale, such as the biopsychosocial, visceral sensitivity, postinflammatory, and neurohormonal models;[49,51–56] the bacterial theory may not fully explain these models. Moreover, all of these theories might be simultaneously true — that is, they are not mutually exclusive. Like the adage of the 3 blind men and the elephant,[57] we may all be encircling the same beast, but just not yet know it. Adopting 1 predominant theory at the expense of others (no matter what the theory) does not comport with our modern understanding of IBS.

## Is There a Temporal Relationship Between SIBO and IBS?

In addition to biological plausibility, there should be a *temporal relationship* between the exposure and disease, such that the exposure consistently precedes the disease. This is hard to determine for SIBO in IBS, because there are no data evaluating objective measures of SIBO before versus after the onset of IBS symptoms. In contrast, there are extensive data evaluating presence of IBS symptoms before versus after other exposures, such as acute gastroenteritis[58] or psychological trauma.[59] However, we do not have data evaluating HBT, fecal flora, or jejunal aspirates before versus after the onset of IBS symptoms, compared with non-IBS controls.

## Is There a Dose-Response Effect Between SIBO and IBS?

Beyond the temporal relationship, there should be a *dose-response effect*, or biological gradient, such that larger amounts of the preceding risk factor correlate with a higher likelihood or increased severity of illness. This, too, remains unproven between SIBO and IBS. In fact, small intestinal bacterial counts do not correlate with illness severity. For example, Posserud and colleagues measured jejunal aspirates in patients

with IBS, and found no difference in IBS symptoms between those with $\geq 10^5$ versus $<10^5$ cfu/mL.[22] Because this threshold has been criticized as too high,[18,19] the investigators also conducted analyses using the $10^3$ cfu/mL threshold, and once again found no relationship between microbiota concentration and symptoms. Similarly, Grover and colleagues could not demonstrate a relationship between HBT results and IBS symptoms, including bloating.[6] Moreover, presence versus absence of HBT positivity does not predict response to antibiotic treatment in IBS.[60,61] Yet, if SIBO were a cause of IBS in most patients, then we would expect that higher amounts of the causal agent would yield a higher likelihood of IBS, or an increased severity of IBS symptoms. In contrast to the lack of dose-response data between SIBO and IBS, data indicate that other purported risk factors for IBS, such as psychological trauma, reliably predict developing IBS in a dose-response manner.[59,62–65]

## Is There Consistency Among Studies Linking SIBO and IBS?

In order to claim causality between a risk factor and disease, there should be a *consistent association* among studies. For example, there are no credible studies concluding that smoking protects against lung cancer. Smoking *causes* lung cancer, so that is why study after study shows just that. In the case of SIBO and IBS, Figure 1 reveals that the relationship is inconsistent. Because of this inconsistency, Ford and colleagues performed a meta-analysis to calculate the pooled prevalence of SIBO across 12 studies.[12] Using LHBT as a diagnostic surrogate, the authors found that 54% of IBS patients met SIBO criteria. However, the difference between IBS and controls was not statistically significant. In addition, there was evidence of a publication bias, meaning that small, negative studies were missing from the literature. In short, the data were inconsistent among published studies, suggesting that it is premature to draw a causal link between SIBO and IBS. Moreover, there are studies revealing a negative relationship between IBS and SIBO,[10] at least when compared with other organic conditions known to be associated with SIBO, such as cirrhosis, abdominal surgery, and diabetes.

## Does Removing SIBO Remove the Disease?

Fifth, if a risk factor is *completely* etiologic, then removal of that factor should remove the disease. Indeed, if the right antibiotic is chosen in a patient with pneumonia, for example, then complete cure of the pneumonia is likely; same thing with traveler's diarrhea, or cellulitis, or septic arthritis, and so forth. In the case of SIBO and IBS, we have compelling data that symptoms improve in a subset of IBS patients who receive gut-directed antibiotic therapy instead of placebo.[41] However, the effect size is modest and on par with other nonantibiotic therapies for IBS (Table 1). Moreover, few speak of antibiotics *curing* IBS; complete symptom abrogation from antibiotics is unusual, suggesting that the cause-and-effect relationship is imperfect. Furthermore, improvement of IBS symptoms with antibiotics does not necessarily imply that SIBO causes IBS, because it remains plausible that IBS causes SIBO, and treating SIBO transiently might not address the root cause of IBS. Instead, treating SIBO may target an epiphenomenon of a more fundamental process that will persist long after the antibiotic effect wanes, leading to indefinite repeated courses for some. Finally, the results of preantibiotic HBT do not reliably predict treatment response in patients with suspected SIBO.[60] Thus, it remains unclear if the benefit of antibiotics is from clearing SIBO, in contrast to some other, as yet unknown, mechanism. Again, this does not invalidate antibiotics as a reasonable therapy for some patients with IBS symptoms; indeed, I use antibiotics in selected patients, such as those with persistent bloating, fullness, or distention despite other failed attempts at management, including assistance from an IBS-trained dietician. However, these data undermine the argument that SIBO is the principal cause of IBS in most patients, in contrast to being 1 of several mechanisms that underlie IBS.

**Table 1.** Comparing NNT of Available Pharmacotherapies for IBS

| IBS treatment | NNT vs placebo[a] | References |
|---|---|---|
| Alosetron | 8 | 25–27,67 |
| Antidepressants | 4 | 66 |
| Antispasmodics | 5 | 68 |
| Fiber | 11 | 68 |
| Linaclotide[b] | 8 | 28[b] |
| Lubiprostone | 12 | 29–31 |
| "Placebo without deception"[c] | 4 | 69 |
| Peppermint oil | 2.5 | 68 |
| Rifaximin | 11 | 41 |
| Tegaserod | 10 | 32–36 |

NOTE. If SIBO were the predominant cause of IBS, and if gut-directed antibiotics cleared SIBO, then we should expect antibiotic therapy to have a large effect size in treating IBS — and certainly larger than therapies that do not address SIBO at all. The data indicate that for every 11 patients treated with rifaximin instead of placebo, there is 1 additional symptomatic benefit. This NNT is on par or higher than other competing therapies, suggesting that other mechanisms must underlie IBS — not merely SIBO.

[a]Lower NNT is more desirable. Comparisons based on a binary outcome measure in randomized controlled trials.

[b]Linaclotide data unpublished at the time of writing — data based on company press release. NNT based on using Food and Drug Administration–endorsed interim end point.

[c]"Placebo without deception" involves giving a placebo and actively informing the patient that it is an inactive agent. Patients were informed that they received "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes." Compared with no treatment, this approach was highly effective in a well-documented randomized controlled trial.[69]

## Is There a Large Effect Size of Treating SIBO in IBS?

Therapies that target the purported causal mechanism should be more effective than therapies that target competing mechanisms. If SIBO causes IBS, then we should expect antibiotic therapy to have a large effect size in treating IBS — and certainly a larger effect than other therapies. The recent Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) studies provide a benchmark to test this theory.[41] In a pair of large, well-designed, phase III registration trials, patients with mild-to-moderate, nonconstipating IBS were randomized to either the minimally absorbed antibiotic rifaximin (550 mg, thrice daily for 2 weeks) or placebo. More patients in

the rifaximin group achieved adequate relief of IBS symptoms during the 4-week period after treatment versus those receiving placebo (40.7% vs 31.7%, $P < .001$); treated patients also had a higher response rate for bloating (40.2% vs 30.3%, $P < .001$). Of note, the investigators did not test patients for SIBO in advance of treatment; there were no exclusion criteria based on HBT or other screening tests. Although the rationale for empiric treatment was not described by the authors, one surmises that current tests are not accurate enough to direct use of antibiotics, again raising the circular argument previously described. Nonetheless, the treatment worked in this study, leading the authors to conclude that "rifaximin is affecting an underlying cause of IBS."

Although rifaximin was superior to placebo, the TARGET data translate into a number-needed-to-treat (NNT) of 11. That is, for every 11 patients treated with rifaximin, instead of placebo, there was 1 additional response. How does that NNT compare with other IBS treatments? Table 1 places the data into perspective. The NNT for antidepressants,[66] antispasmodics,[68] alosetron,[25–27] fiber,[68] and even peppermint oil[68] are all equal to or more favorable than the NNT of rifaximin. In the absence of head-to-head trials, we cannot yet conclude that rifaximin is superior to other therapies listed in Table 1.

We should also consider the data from nonpharmacological interventions in IBS. There have been at least 15 trials measuring the impact of nonpharmacological therapies, including a range of educational interventions, physician-patient relationship interventions, relaxation training regimens, and psychological therapies.[37,66] There is a large, consistent, and statically significant effect size of these interventions.[37,66,70] One study even found that IBS patients improve with placebo versus no treatment at all — and the patients were literally *informed* that they were receiving a placebo.[69] This "placebo without deception" had an NNT of only 4. These nonpharmacological IBS studies are relevant, because they distinguish IBS from other conditions where a biological cause-and-effect relationship is secure, such as pneumonia. Patients with community-acquired pneumonia are unlikely to derive large benefits from psychotherapy, hypnosis, relaxation training, or "pneumonia class" (akin to the "IBS class" of Ringstrom et al[71]). Instead, patients with pneumonia benefit most from the right antibiotic given at the right time in the right way. The observation that IBS patients consistently benefit from nonpharmacological therapies distinguishes it from a condition like pneumonia and suggests that a cause-and-effect link remains elusive.

## Is There a Lack of Confounding Between SIBO and IBS?

The SIBO hypothesis does not appear to unify competing hypotheses of IBS and does not meet all epidemiologic criteria for causality. In light of these facts, we should question whether SIBO causes IBS, or whether it is a bystander or epiphenomenon of something else.[12] The lack of consistency in the data linking SIBO to IBS suggests that some other factor may be operating in the background. Although the inconsistent results could be a consequence of varying study methodologies, different local SIBO prevalence, or disparate definitions of IBS, it may also simply reflect the presence of another factor for SIBO that travels along with IBS but is not, in fact, intrinsic to IBS at all.

For example, we previously hypothesized that the SIBO-IBS link may be confounded by the use of proton pump inhibitors (PPIs).[72] IBS patients are more likely than controls to receive PPI therapy, and data indicate that PPI therapy may promote SIBO by eliminating gastric acid.[73–78] Moreover, most studies linking SIBO to IBS have not adjusted their results for the use of PPI therapy, including the TARGET study.[41] It is notable that the most common side effects of PPIs include abdominal pain, bloating, flatulence, constipation, and diarrhea — symptoms that overlap with IBS.[77] Recently, an Italian group reported nearly twice the incidence of SIBO among patients using PPIs compared with IBS patients (50% vs 24.5%).[76] Moreover, Compare et al. performed a prospective study in patients with reflux disease receiving PPI therapy, and found that 43% developed de novo bloating after 8 weeks of therapy.[77] Six months later, nearly 20% of PPI users met Rome III criteria for IBS — none had IBS starting therapy. Data also indicate that, among patients with HBT positivity receiving rifaximin, regrowth of SIBO is predicted by concurrent PPI therapy.[79] Thus, not only might PPIs lead to SIBO in some patients with IBS, but the recurrence of SIBO following rifaximin might be accelerated in the setting of PPIs. In other words, so long as the risk factor for SIBO is present, the condition may recur despite temporary removal with antibiotics. It might make sense to stop PPIs, where possible, before considering antibiotics. In contrast to these various studies, Law and Pimentel reported that PPI therapy did not predict LHBT results in IBS patients,[80] and others have found a positive, yet nonsignificant relationship between PPI exposure and SIBO.[9,81,82]

Many other confounders could undermine the link between SIBO and IBS. For example, some patients with IBS demonstrate low-grade mucosal inflammation.[83] In addition, recent data indicate a "leaky gut" in IBS,[84] with upregulation of Toll-like receptor (TLR) 4 and 5.[85] These TLRs respond to bacterial cell wall components, and, when stimulated, amplify local innate immunity. According to this theory, IBS patients might have diminished mucosal barrier function from a number of reasons, including stress itself,[86] and colonic microbiota simply penetrate the permeable mucosa and activate TLR4 and TLR5. That is, the leaky gut is the primary problem in this model, and the microbiota are secondary, falling through the cracks in the mucosal defense — not the root cause of IBS. These mechanisms might also change the milieu to enhance growth of the mucosal biofilm. In this context, one could argue that abnormalities in mucosal inflammation and permeability drive IBS symptoms, and further argue that SIBO is a by-product of variations in mucosal physiology or mucosal-microbial interactions — not the other way around.

Other potential confounders include variations in antibiotic, probiotic, prebiotic, or other dietary ingestions in IBS patients versus controls.[87,88] Although large-scale epidemiology studies are lacking on this topic, it is possible that IBS patients consume these substances at a different rate from non-IBS controls — a consequence of variations in medical care and personal habits related to having IBS in the first place. These medical and lifestyle variations might alter the intestinal microbiome in IBS patients. Future research should evaluate whether these differences exist between IBS patients and controls.

In each of these cases, the conclusion might be that SIBO does not cause IBS, but is a by-product of a more fundamental

mechanism. Whether PPI exposure, inflammation, immune dysfunction, intestinal permeability, variations in consumption of antibiotics, probiotics, dietary variations, or a combination of all these factors, each raises a question about the primacy of bacteria in IBS. In short, given our current understanding of IBS, it is sensible to conclude that SIBO is but 1 underlying factor, and that other mechanisms appear likely; that is, IBS cannot have a one-size-fits-all solution, either pathophysiologically or clinically. The data indicate that we should remain flexible in our thinking, open to alternative explanations, and accepting that 1 predominant mechanism seems unlikely. Finally, it is possible for multiple mechanisms to be simultaneously true, with bacteria playing a role alongside other factors.

## SIBO and IBS: An Evolutionary Perspective

Finally, in order for an illness paradigm to be causal, it helps if the theory holds up under inquiry from an evolutionary perspective.[89] Diseases typically persist over millennia if they provide some unique survival advantage, either for the host or for the pathogen. For example, hemochromatosis likely protected against bubonic plague.[90] Sickle cell anemia protected against malaria. Hypercholesterolemia helped maintain vitamin D levels in sub-Saharan Africa and Northern Europe.[91] Even diabetes provided a survival advantage in extremely cold climates.[92]

Did IBS provide a survival advantage? In the context of the "brain-gut" theory of IBS, the model could explain how the visceral anxiety of IBS might trigger "gut feelings" in the midst of a threat, leading the host to either fight or flee.[93] Over thousands of generations, this small advantage could provide a survival benefit, and might even explain why soldiers develop gastrointestinal distress in the midst of extraordinarily stressful combat,[45–47,62,63] or why residents in Nicaragua developed long-standing gastrointestinal distress after exposure to the brutality of the Sandanista revolution.[64,65] For most modern patients, there are no physical threats in their immediate environment — no actual combat, or lions lurking in wait. But there are other threats, both perceived and real. Whereas the brain-gut mechanism of IBS may have been evolutionarily advantageous 10,000 years ago, it may no longer provide the same survival advantage, but persists nonetheless.


**Figure 2.** Public service announcement from the Maryland Department of Transportation. Surveys revealed that this image, more than any other in the Maryland "Street Smart" campaign, was effective in transmitting its message. The scene viscerally affects some viewers, who report a sense of nausea and abdominal discomfort upon contemplating the image. The artist taps into an evolutionary drive to feel literally sickened in the midst of a mortal threat — in this case, even a hypothetical threat. This example, albeit dramatic, highlights the obvious fact that the brain and gut are connected, and that we need not invoke bacterial overgrowth to explain gastrointestinal symptoms in the face of stress. It also illustrates how the brain-gut model of IBS makes evolutionary sense, because it might have provided a survival advantage over millennia by amplifying life-saving gut feelings in the face of actual threats. See text for further details. Image from Street Smart public safety campaign, Maryland Department of Transportation.

Consider the image in Figure 2, an emotionally charged illustration of a mother struck by a car while crossing the street with her infant. I recently found myself behind a city bus in Washington, DC, staring at this image affixed to the back panel of the bus. The image is a public service announcement, developed by the Maryland Department of Transportation, designed to dissuade text messaging and other distractions while driving. The details are engrossing. The scenario is horrifying. As a parent, and as a person, the image struck me both emotionally and physically; it rendered me feeling nauseous, with a deep, swollen, aching knot in the pit of my stomach. The artist tapped into an evolutionary drive to feel literally sickened in the midst of a mortal threat — in this case, even a hypothetical threat. And I don't even have IBS. This example, albeit dramatic, highlights the obvious fact that the brain and gut are connected, and that we need not invoke SIBO to explain gastrointestinal symptoms in the face of stress. It also illustrates how the brain-gut model makes evolutionary sense, because it might have provided a survival advantage over millennia by amplifying life-saving gut feelings in the face of actual threats.

With this background, it is reasonable to ask what evolutionary advantage the SIBO mechanism might afford. For most infectious diseases, the advantage is for the pathogen, not the host.[89] The goal of intestinal microbiotia is to survive, reproduce, and move from one host to the next — a model followed by pathogens for other infectious diseases. How would IBS help microbiota with these goals? Or, if IBS *is* SIBO, then we might ask if IBS behaves as other infectious diseases. Does IBS spread from person to person? Perhaps — there is a familial form of IBS.[94] Do we see the same DNA fingerprinting in fecal samples among family members with IBS? That could be studied. Does IBS spread through the fecal oral route? Is IBS less prevalent in hygienic populations? Epidemiologic data do not demonstrate such a relationship.[95] These questions, although seemingly fanciful or far-fetched, are legitimate to ask of a purportedly infectious disease, as suggested in a recent review.[18] If SIBO causes IBS — that is, if SIBO were the *predominant* mechanism of the IBS illness experience — then we might expect IBS to behave like other infectious diseases. If IBS does not behave like a microbial disease, but is nonetheless caused by microbiota, then it would mark a type of disorder that has not been described before. The evolutionary inquiry helps put this into perspective.

## Conclusion

Although bacteria probably contribute to some IBS symptoms, the relationship between bacteria and IBS is imperfect and, as of yet, not clearly causal. To recap, the following facts undermine the SIBO hypothesis of IBS:

(1) The test used to promulgate the SIBO hypothesis (LHBT) may not have measured SIBO in the first place.[13]

(2) Although the SIBO mechanism may be biologically plausible, there is also a strong rationale for competing mechanisms. Thus, it is unlikely that SIBO is the *predominant* cause of IBS in all comers, because competing explanations are sensible and defensible.

(3) We do not have evidence of SIBO being absent before the onset of IBS symptoms, and present after IBS emerges, especially compared with controls.
(4) A dose-response effect between intestinal microbiota and IBS symptoms is lacking, in contrast to other hypothesized risk factors for IBS, such as psychological trauma.
(5) The relationship between SIBO and IBS is inconsistent among studies.[12] In some studies, IBS is a negative predictor of SIBO compared with other organic diseases traditionally associated with overgrowth.[10]
(6) Therapies that do not address SIBO also work in IBS, suggesting that multiple mechanisms may underlie IBS — not merely SIBO. Many therapies have a more favorable "number-needed-to-treat" than antibiotics. Even "placebo without deception"[69] appears to have a larger effect size than antibiotics.
(7) IBS does not behave like an infectious disease, suggesting that microbes may not principally cause the syndrome, even if they play an important role in symptom propagation in some patients.
(8) Several factors may confound the relationship between SIBO and IBS, including PPI exposure,[72] underlying dysmotility inherent to IBS,[23,24] dysregulated immune function or inflammation in IBS,[83] or variations in diet among IBS versus non-IBS subjects.[87,88]

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*Conflicts of interest*

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