The Small Intestinal Bacterial Overgrowth-Irritable Bowel Syndrome Hypothesis: Implications for Treatment

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INTRODUCTION

Traditionally, small intestinal bacterial overgrowth (SIBO) has been characterized by symptoms of diarrhea, bloating, and sometimes signs of malabsorption. It has been defined as $>10^5$ cfu/ml of bacteria in aspirates obtained from the small intestine (1). This condition has typically been diagnosed in patients with readily identifiable alterations in small bowel function which predispose patients to SIBO (e.g. resected ileocecal valve, small intestinal hypomotility and possibly hypochlorhydria). Recently however, this clinical paradigm has been challenged by new theories about the etiology of irritable bowel syndrome (IBS) and has lead to renewed scrutiny of the tests employed to diagnose this condition and controversy concerning the use of antibiotics to treat IBS for suspected SIBO.

The proposal that SIBO accounts for the symptoms of IBS (2;3) is a novel and interesting hypothesis, given the rapidly growing evidence that luminal bacteria have previously unrecognized actions on multiple intestinal functions (4). While it has long been recognized that increased numbers of luminal bacteria in the small intestine disrupt digestion and absorption, it is now clear that they have other important actions, such as immune activation (4;5). Immune-mediated cytokines could have multiple actions including altered epithelial secretion, exaggerated nociceptive signaling, and abnormal motility(4). Together these changes could lead to symptoms which meet the criteria for IBS. It has also been proposed that this mechanism could account for overlap syndromes, such as fibromyalgia (6).

The publication of Pimentel and colleagues in 2000 (7) played a pivotal role in establishing the concept that SIBO is a major pathogenic mechanism underlying IBS. Two major tenets emerged from this study: 1) based on the results of the lactulose hydrogen breath test (LHBT), the large majority of patients with IBS have SIBO, and 2) when SIBO is eradicated with antibiotics based on the findings of a post-antibiotic LHBT, a large proportion of patients with IBS have symptom improvement. Although major concerns about the validity of these tenets have been raised in subsequent studies and reviews (8-
15), there has been a rapidly growing acceptance of the use of the antibiotics, such as rifaximin, to treat IBS in the United States (16) and elsewhere. This paper rigorously examines the validity of the LHBT for diagnosing SIBO in IBS, the supporting evidence that SIBO underlies IBS, and explores the findings from clinical trials examining the effects of antibiotics on IBS.

LHBT FOR DIAGNOSING SIBO IN IBS
Small Intestinal Bacterial flora in health and disease

Under normal conditions, the small intestine is a relatively sterile environment and at the ileocecal valve there is an abrupt rise in bacterial counts (Figure 1) (1;8). The proximal small intestine is populated with relatively small numbers of gram positive aerobes with the addition of anaerobes in the ileum (1). Using standard culture techniques, counts in the ileum range from $10^2$-$10^3$ and increase to $10^{10}$-$10^{12}$ in the cecum with a predominance of anaerobes. Overgrowth of bacteria in the small intestine is traditionally defined by counts $> 10^5$ colony forming units (cfu)/ml, based on the correlation of symptoms and counts obtained from aspirates from the proximal small intestine. However, it has been suggested this definition may be not be sufficiently precise because these cultures can contain largely gram positives from the upper respiratory flora and these have not been correlated with symptoms of SIBO (1). Hence, a more precise definition appears to be $>10^5$ cfu/ml of “colonic type” bacteria (i.e. gram negatives, strict anaerobes and enterococci) which have been correlated with symptoms of SIBO and possess known pathogenic mechanisms which could result in the symptoms of SIBO. Ultimately, the most precise definitions may rely on emerging molecular techniques with greater accuracy in identifying bacterial species which are difficult to culture (5;17).

Lactulose Hydrogen Breath Test (LHBT)

According to the proponents of the SIBO-IBS hypothesis, the overgrowth of bacteria is largely confined to the distal small intestine (3). As shown in Figure 2, this could explain why the standard diagnostic test using jejunal aspirates fails to detect overgrowth in this patient group (3). Similarly, the glucose hydrogen breath test also would be inaccurate because this sugar is absorbed in the more proximal small intestine (3). In contrast, lactulose is a non-absorbable carbohydrate, allowing it to reach the site of potential overgrowth in the small intestine even if it is in the distal portion of the small intestine.

The LHBT exploits the fact that the only source of H$_2$ gas production in the body is the fermentation of carbohydrate substrate (1) and this can be monitored by measuring H$_2$ ppm in expired breath because it readily diffuses from the lumen into the circulation (Figure 1). In the normal setting, repeated measurements of breath H$_2$ ppm remain low as the lactulose transits through the relatively sterile environment of the small intestine until it reaches the high numbers of bacteria within the cecum. This leads to a rapid rise in H$_2$ gas as a result of bacterial fermentation of the sugar. When these colonic bacteria migrate proximally into the small intestine, as proposed to occur in IBS, the timing of the rise in H$_2$ should be altered. More recently, measurements of expired methane (CH$_4$) gas following lactulose ingestion in studies of IBS patients have been reported, because this gas has been implicated in constipation - predominant IBS (see below, Unresolved Links in the SIBO-IBS Hypothesis).

Three different criteria have been employed in clinical trials to define an abnormal LHBT in patients with IBS (Figure 2). In Pimentel’s original study (7), they used the traditional double peak criteria. The initial peak is thought to result from fermentation of the initial bolus of lactulose in the region of SIBO and the second peak resulting from the arrival of the residual lactulose in the cecum (1). In subsequent studies, Pimentel and others rejected these criteria, accepting either a rise in H$_2$ before 90 min (>20 ppm in some studies) and/or an absolute rise from baseline of 20 ppm by 180 min (Figure 2).

Recently, a Canadian (13), Swedish (15), and United States (18) study have examined the validity of these criteria by examining LHBT in IBS patients and healthy controls (Figure 3). In Pimentel’s original study in 2000, they reported 78% of IBS patients have SIBO based on the double peak criteria. In contrast, none of the recent studies were able to detect levels above 17% and these proportions did not differ from healthy controls (Figure 3). Subsequent studies by Pimental et al. (19), applying the criteria of a rise of H$_2$ by 90 min or an absolute rise in H$_2$ > 20 ppm by 180 min, again reported high numbers of
IBS patients with SIBO (~ 80%). When these criteria were applied in the three subsequent studies (Figure 3), a high proportion of IBS patients with “positive tests” were also found, however, no differences were found between IBS patients and healthy controls.

Closer scrutiny of the origins of the criteria for diagnosing SIBO with the LHBT suggests that these have been a source of controversy since the test’s inception (1;10). The association between an early rise in H2 levels following lactulose ingestion and small intestinal bacterial overgrowth was first observed by Levitt and colleagues (20) and over time the LHBT became recognized as a non-invasive means of diagnosing SIBO. However, subsequent studies designed to test the validity of the original “double H2 peak” criteria (see Figure 2) compared results in culture positive patients predisposed to SIBO and found a disappointing low sensitivity (17% - 68%) and specificity (44- 70%)(21;22). Proposed explanations for these poor results included fermentation by oral and gastric flora, and the effects of transit time (1).

The influence of transit time is an important consideration, particularly for the more recent “single peak” criteria proposed by Pimental and colleagues, i.e. H2 rise by 20 min or >20 ppm by 180 min (Figure 2). In fact, the LHBT was first proposed as a means of diagnosing orocecal transit time (23) using the sharp rise in H2 levels as an indication that the lactulose had reached the fermenting anaerobes in the cecum (Figure 1). This association was confirmed in healthy controls by intubating the distal ileum and aspirating PEG which was co-ingested with the lactulose. In each case the PEG was aspirated before the rise in H2, reflecting the lag time to reach the cecum. These studies showed that in healthy controls the transit time was dose-dependent and there was a wide range in times, ranging from 25 min to 118 minutes, with a mean of 72 min. A number of reviews (1;10) have drawn attention to the fact that several studies show up to 50% of asymptomatic individuals have a rise in H2 by 90 min. These findings highlight the concern that single H2 peaks simply reflect transit to the cecum, as opposed to resulting from fermentation by colonic bacteria in the small intestine. These concerns were further supported by studies which combined lactulose with Tc99, enabling the tracer to be temporally aligned with the H2 levels, to determine if increases occur before or after reaching the cecum (21). In patients predisposed to SIBO, the initial rise in H2 was preceded by the arrival of Tc99 in the cecum in 22% of cases and a cecal source for double peaks was suggested in 50% of patients. Twenty four hour calorimetric studies also indirectly suggest that H2 gas in IBS patients originates from colonic bacteria. They have shown increased rates of H2 excretion in unselected cases of IBS and that a reduction of gas excretion occurs following elimination diets including fiber reduction(24). They have also shown two groups exist, one with high H2 excretion and another which did not differ from controls(25). This latter group did not respond to an exclusion diet and the LHBT did not differentiate between the two IBS groups (i.e. high and low H2 excreters). The implication being that some IBS patients have greater numbers of gas forming bacteria in the colon and fiber reduction decreases fermentation. Thus, based on the available evidence, it seems highly unlikely that single peak criteria for an abnormal LHBT can discriminate between IBS and healthy controls, because these values fall within the range of normal transit times to the cecal flora.

**UNRESOLVED LINKS IN THE SIBO-IBS HYPOTHESIS**

Why would IBS patients be predisposed to develop SIBO? A missing link in the SIBO - IBS hypothesis is the mechanism which predisposes IBS patients to SIBO. Most conditions known to predispose patients to SIBO, such as small bowel dilatation, mechanical factors, terminal ileal resection, and diverticuli are not associated with IBS, but hypomotility cannot be excluded. One study examined small bowel motility in IBS patients with positive LHBTs and found that the duration and frequency of the MMC was significantly reduced in these patients (26). Moreover, 50% of IBS patients lacked an MMC during the recording interval. While potentially important, there are major limitations to this study. This was a retrospective study where patients were referred because of an abnormal LHBT (defined by the double peak criteria), not because they had IBS. Most important, however, was the absence of a comparable control group. The controls were obtained from a different center which used a different catheter (solid state) and recorded for differing lengths in the small intestine and for a longer time period. Other studies of IBS patients have reported widely variable results (27;28); (29); (30-32) and the LHBT status was not assessed. The discrepancy between these studies may reflect differences in techniques and the wide variability in motility patterns observed in healthy controls (32). In a more recent study which
combined manometry with jejunal aspirates in IBS patients, the very small number of patients (4%) with a positive aspirate (> 10^5 cfu/ml) had a reduced number of MMCs compared to those with normal aspirates (96%). It is unknown how IBS patients with an abnormal LHBT correlated with controls in this study but the frequency of MMCs in the aspirate-negative group approximated the control group used in the Pimentel study (26). The relationship between small bowel motility and IBS is further complicated by the possibility that the IBS group could be contaminated by small numbers of patients suffering from mild chronic intestinal pseudo-obstruction, given that IBS patients are largely identified by symptom criteria. Taken together, the technical differences and lack of adequate controls suggest further studies are needed to clarify this issue.

Can SIBO account for symptoms in IBS patients with both constipation and diarrhea?

Another pathogenic uncertainty is the explanation as to how SIBO could result in diarrhea in some IBS patients and constipation in others. Pimentel and colleagues suggest that the production of methane (CH₄) gas in the constipation group provides the explanation (16). All CH₄ gas is a metabolic product of intestinal bacteria and methanogenic bacteria reside in the colon under normal conditions (33). CH₄ production is estimated to occur in 36-50% of healthy subjects (34;35). In IBS studies, an association between constipation predominant IBS and CH₄ production (abnormal test defined as a rise in CH₄ following lactulose ingestion within 90 min or >20 ppm during 180 min measurement(19)) has been well documented (36), but its causal relationship is not clear. On one hand, animal studies have shown that CH₄ gas can reduce antroduodenal motility in vivo, yet exaggerate contractile responses in vitro (37). In addition, in a retrospective review of a small number of IBS cases who underwent LHBT and antroduodenal motility testing, CH₄ producing patients had an increased motility index compared to H₂ producing patients (37). Based on these findings, it was suggested that CH₄ production could result in non-propogating contractions in the small intestine leading to constipation. While these data are intriguing, there are a number of inherent biases in the human studies and plausible alternate explanations, including the effects of methane production on colonic motility (33;38). The finding that patients with diarrhea due to other conditions such as Crohn’s or Ulcerative colitis (33;34) have a very low prevalence of CH₄ excretion may suggest that diarrhea simply precludes the proliferation of methogens in the colon (33). This notion is supported by the finding that colon cleansing (34) and low fiber diets dramatically lower CH₄ excretion. The proposed relationship is further complicated by a recent study which found the prevalence of CH₄ producers is not different between IBS patients and healthy controls (18), raising further questions about the validity of breath testing in IBS. Taken together, these studies suggest that more rigorous studies of methane production in IBS and the effects of CH₄ on small and large bowel motility are needed.

Box 1. - the LHBT does not discriminate between IBS patients and health controls
  - further studies are needed to determine if CH₄ production causes hypomotility in IBS patients or is simply a physiological marker of constipation

Does SIBO account for IBS overlap syndromes?

IBS is known to overlap with a number of other poorly understood chronic conditions, including fibromyalgia. Recently, it has been suggested that SIBO may also be a unifying hypothesis between these conditions (6) given that very high numbers of patients in both groups had an abnormal LHBT and that patients had a symptomatic response to antibiotic treatment (6;10). However, the findings in these studies are undermined by the absence of a proper control group confirming that the LHBT can accurately discriminate between these patients and healthy controls (see also discussion of LHBT above).

CLINICAL TRIALS USING ANTIBIOTICS TO TREAT IBS

Results of Clinical Trials

The symptom response of patients with IBS to antibiotics has been examined in three relatively small, prospective placebo-controlled studies (Table I) (19;39;40). Several Important differences in study design need to be taken into account when comparing these results. In particular, the entry criteria...
in the study by Sharara and colleagues (gas and flatulence; ~ 60% met Rome II on retrospective analysis) differed significantly from the others (Rome I). In addition, the most recent study by Pimentel and colleagues (39) analyzed the data using a complex statistical mixed model which creates a blending of symptom responses over the entire period rather than a conventional single endpoint (12). Each of these three studies reports a significant, albeit modest reduction, in either global symptom or composite symptom scores (mean range = 15-24% over placebo) although the placebo responses were low (range = 11 – 21%), particularly for IBS studies. These findings are only applicable to the time periods studied (7 days – 10 weeks).

A number of other studies (7;41-45) are often referenced in support of these prospective studies. Although all report symptom reduction with antibiotics, the interpretation of their findings is seriously limited by their study design. These studies lack a placebo group, are retrospective, and/or do not examine a clearly defined group of IBS patients.

Several studies have examined specific symptoms which underlie the improvement in global symptom scores following antibiotic treatment (24;39;40;45). Two of these studies (40;45) recruited patients with gas–bloat syndrome rather than IBS, but many of these patients met the criteria for IBS. All of these studies found that a reduction in bloating and/or related symptoms correlated with global symptom reduction (Table 2). In the two larger studies (39;40), logistic regression of the individual symptoms showed a correlation with bloating, but not with other IBS symptoms. Two of these studies (40;45) also showed a correlation with these specific symptoms and changes in H2 excretion following antibiotic treatment. In the one study (24) where fecal anaerobes were cultured, both antibiotics and fiber reduction resulted in a significant reduction in bacterial counts. Although larger studies are required to confirm these observations, these data do suggest that the major benefit of antibiotics in IBS results from a decrease in gas forming bacteria. It is unclear whether they reside in the colon as opposed to the small intestine.

Does symptom improvement correlate with normalization of the LHBT?

The hypothesis that SIBO accounts for the symptoms of IBS is based on the LHBT, but the correlation between the normalization of the LHBT following antibiotics and symptom improvement has become less clear (Table 3). In the study by Pimentel at al 2003 (19), only 20% of the LHBTs normalized following antibiotics and although symptom reduction correlated best with this group, there was a much larger number of patients who had a significant reduction in symptoms scores compared to placebo who did not normalize their LHBT. Moreover, in the subsequent 2006 study by this same group, although LHBTs were performed these data were not reported (results removed in the review process, M. Pimentel, personal communication). The post-hoc analysis of rifaximin responders by Sharara and colleagues (see Table 3) showing a correlation between decreased bloating and a reduction in H2 at 180 min may be supportive, but could also simply reflect a reduction in gas forming bacteria in the colon, given the 180 min time interval (see LHBT above).

Could antibiotics be detrimental in IBS?

Although the favourable short term safety profile of newer non-absorbable antibiotics, such as rifaximin (46), may make the use of antibiotics in IBS more attractive, enthusiasm should be tempered by several considerations. There are no long term studies with antibiotics in IBS and less is known about the safety of these antibiotics long term. IBS is a common disorder with recognized high placebo response rate and studies show the effects of antibiotics on measurable outcomes are short lived. Hence there is significant potential for committing large numbers of patients to antibiotics.

There are also indirect studies which imply that antibiotics could play a role in the pathogenesis of IBS. A study in a general practice setting found that prior antibiotic use strongly correlated with patients having the symptoms of IBS (47). It has also been shown that the use of antibiotics is related to increased reporting of functional bowel symptoms (48). In an animal model (49), the use of non-absorbable antibiotics was shown to induce low level colonic inflammation and visceral hypersensitivity. Clearly, further studies are needed to confirm these associations in humans, but given that antibiotics
suppress bacteria in the small and large bowel, these studies highlight the potential for antibiotic use to have detrimental effects, particularly with continuous or repeated courses.

Box 2.  - antibiotics result in a modest reduction in global symptoms that is short lived
  - bloating is the major symptom which is reduced by antibiotics
  - there is insufficient evidence to recommend antibiotics for the treatment of IBS at present

CONCLUSIONS AND FUTURE DIRECTIONS

The hypothesis that SIBO accounts for the symptoms of IBS has helped to focus on the role of bacteria in intestine and in particular their potential to modulate sensation and motility. Although this is an intriguing hypothesis which has stimulated significant work in this area this remains an unproven hypothesis. The inability of the LHBT to discriminate between IBS patients and healthy controls, together with the findings of available IBS studies examining antibiotic treatment, make it plausible that colonic, rather than small bowel bacteria, account for the findings of these studies. Proof of the SIBO-IBS hypothesis requires more definitive studies to resolve this issue, such as direct culture from the distal small bowel either with oral intubation or double balloon enteroscopy. Continued use of the LHBT to diagnose SIBO in IBS requires validation studies, such as combined Tc99 scanning with the LHBT to determine whether changes in H2 levels suggesting bacterial fermentation correlate with Tc99 in the small intestine or cecum. Given the absence of reasonable proof for the SIBO-IBS hypothesis at present and the concerns about antibiotic use, it is difficult to recommend antibiotic treatment for IBS at this time.

Despite the current lack of evidence, it remains possible that quantitative and/or qualitative differences in bacteria exist within the small intestine in patients suffering from the IBS. One study (15) examining bacterial aspirates in IBS patients failed to detect significant numbers of IBS patients with > 10^5 cfu/ml of colonic bacteria (4%) but when they defined a positive test as ≥ 5 X 10^3, they found a significant increase in IBS patients (43% IBS vs. 12% controls). Whether these findings are relevant to the expression of IBS however, is unclear. These findings did not correlate with small bowel manometry or with positive LHBT and glucose hydrogen breath tests. An emerging area of investigation which may also help to resolve the implications of such observations is the use of quantitative DNA fingerprinting of fecal bacteria. This techniques has the advantage of identifying large numbers of species, especially obligate anaerobes, which cannot be identified using traditional culture techniques (50). Using fecal samples, recent molecular studies suggest that quantitative alterations in the microbial biota exist in IBS patients (51;52). This may provide another approach to evaluate bacteria in the small intestine to determine if abnormal numbers or qualitative species differences exist in IBS patients.

Even if the SIBO – IBS hypothesis is ultimately rejected, findings from these studies will help to stimulate new treatments for IBS. For example, if the reduction in bloating due to antibiotics results from suppression of colonic bacteria, studies are needed to characterize the species involved and safe, long term treatment modalities explored (e.g. probiotics, see (5;53;54). The evidence that CH4 may inhibit motility is also intriguing, even if the methanogenic bacteria originate in the colon, and further basic and clinical studies are needed to explore the mechanism and possible treatments.

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The author has no competing interests.
Reference List


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FIGURE LEGENDS

Figure 1. Schematic drawing of the intestine showing the small and large bowel flora in healthy individuals and the response to lactulose ingestion. Lactulose is a non-absorbable sugar which is only hydrolyzed by colonic type bacteria. This fermentation produces H₂ gas in almost all individuals and changes in H₂ gas levels can be measured sequentially in expired gas to determine when this fermentation occurs.

Figure 2. Schematic drawing showing the overgrowth of colonic bacteria in the distal small intestine and the LHBT criteria used to detect this overgrowth. A. The lactulose reaches the bacterial overgrowth (SIBO, jagged lines) in the distal small intestine where it is fermented by the bacteria. Proponents of SIBO-IBS hypothesis propose that the glucose hydrogen breath test is not adequate because the sugar is absorbed before it reaches the distal small bowel (9). Similarly, small bowel aspirates are obtained in the proximal small bowel, therefore failing to detect the more distal overgrowth. B. Three different criteria have been proposed in clinical studies to detect SIBO in IBS patients.

Figure 3. Comparison of the proportion of IBS patients (grey box) and healthy controls (open box) having an abnormal LHBT based on three different criteria. A. The original Pimentel study (2000) used the double peak criteria and found a very high proportion of IBS patients had an abnormal test. Subsequent studies failed to reproduce these findings and found no
differences between IBS patients and healthy controls. Using the \( \text{H}_2 \) rise at 90 min (Sharara et al. = \( \text{H}_2 \) rise > 20 ppm) (B.) and the \( \text{H}_2 \) > 20 ppm by 180 min (C.) criteria, much higher proportions of IBS patients were found to have abnormal tests but, in contrast to the Pimentel study (2003), these did not differ from controls. Numbers in brackets represent the number of individuals studied in each group.

### Table 1 Summary of prospective, placebo-controlled studies of antibiotics for treating IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Entry criteria</th>
<th>Treatment</th>
<th>Outcome (% improved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimentel 2003</td>
<td>43</td>
<td>Rome I</td>
<td>Neomycin 500 mg bid</td>
<td>35% 11% p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>44 placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharara 2006</td>
<td>63</td>
<td>Gas/Flatulence 59% Rome II</td>
<td>Rifaximin 400 mg bid</td>
<td>29% 12% p=0.03</td>
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<tr>
<td></td>
<td>61 placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimentel 2006</td>
<td>55</td>
<td>Rome I</td>
<td>Rifaximin 400 mg tid</td>
<td>36% 21% p=0.026</td>
</tr>
<tr>
<td></td>
<td>56 placebo</td>
<td></td>
<td></td>
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### Table 2 Correlation of specific and global symptom improvement

<table>
<thead>
<tr>
<th>Study</th>
<th>Time points</th>
<th>Primary endpoint and symptom scoring</th>
<th>Improvement in primary endpoint</th>
<th>Specific symptoms correlating with primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dear 2005</td>
<td>last 7 d flagyl or fiber reduction</td>
<td>Composite score, 6 symptoms</td>
<td>38% vs. 33%</td>
<td>Bloating, Wind</td>
</tr>
<tr>
<td>Sharara 2006</td>
<td>10 d post rifaximin or placebo</td>
<td>Global improvement, 15 symptoms</td>
<td>29% vs 12%</td>
<td>Bloating</td>
</tr>
<tr>
<td>Pimentel 2006</td>
<td>10 week period post rifaximin or placebo</td>
<td>Global improvement, 4 symptoms</td>
<td>36% vs 21%</td>
<td>Bloating</td>
</tr>
<tr>
<td>Di Stephano 2000</td>
<td>10 d post rifaximin or placebo</td>
<td>Global improvement, 5 symptoms</td>
<td>44% vs 2%</td>
<td>Flatus, Abdominal girth</td>
</tr>
</tbody>
</table>
Table 3  Correlation of symptom response with normalization of the LHBT

<table>
<thead>
<tr>
<th>Study</th>
<th>LHBT</th>
<th>Normalization of LHBT</th>
<th>Correlation of Symptom Response with Normalization of LHBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimentel 2000</td>
<td>LHB T</td>
<td>25 yes 22 no</td>
<td>Strong correlation</td>
</tr>
<tr>
<td></td>
<td>47 antibiotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimentel 2003</td>
<td>LHB T</td>
<td>8 yes 32 no 42 no</td>
<td>Not accounted for by small number of responders</td>
</tr>
<tr>
<td></td>
<td>41 antibiotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>43 placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimentel 2006</td>
<td>LHB T</td>
<td>Not reported</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sharara 2006</td>
<td>LHB T</td>
<td>*All normal at baseline</td>
<td>No change in LHB T for rifaxmin group; **decreased bloating correlates with H2 reduction at 180 min</td>
</tr>
<tr>
<td></td>
<td>63 rifaximin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61 placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* abnormal defined as rise >20 ppm at 90 min, ** subgroup analysis of rifaximin responders only
Figure 1
**Figure 2**

A diagram showing the flow of glucose and lactulose through the jejunum and cecum, leading to the development of SIBO.

Graph B illustrates the increase in hydrogen (H₂) ppm over time. The black line shows a > 20 ppm H₂ rise by 180 min, the dark grey line represents a double peak, and the light grey line indicates a rise in H₂ before 90 min.
Figure 3