Small Intestinal Bacterial Overgrowth in Irritable Bowel Syndrome: Systematic Review and Meta-analysis

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Small Intestinal Bacterial Overgrowth in Irritable Bowel Syndrome: Systematic Review and Meta-analysis

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See related article, Spiegel B et al, on page 1944 in Gastroenterology.

BACKGROUND & AIMS: Small intestinal bacterial overgrowth (SIBO) has been proposed as an etiologic factor in irritable bowel syndrome (IBS), but evidence is conflicting. We conducted a systematic review and meta-analysis of the prevalence of SIBO in IBS. METHODS: MEDLINE and EMBASE were searched up to November 2008. Case series and case-control studies applying diagnostic tests for SIBO in unsellected adults meeting diagnostic criteria for IBS were eligible. Prevalence of a positive test for SIBO was extracted and pooled for all studies, and compared between cases and controls using an odds ratio and 95% confidence interval (CI). RESULTS: Twelve studies were identified containing 1921 subjects meeting criteria for IBS. Pooled prevalence of a positive lactulose or glucose hydrogen breath test was 54% (95% CI, 32%–76%) and 31% (95% CI, 14%–50%), respectively, with statistically significant heterogeneity between study results. Prevalence of a positive jejunal aspirate and culture was 4% (95% CI, 2%–9%). The pooled odds ratio for any positive test for SIBO in cases compared with healthy asymptomatic controls was 3.45 (95% CI, 0.9–12.7) or 4.7 (95% CI, 1.7–12.95), depending on the criteria used to define a positive test, with statistically significant heterogeneity for both. CONCLUSIONS: Prevalence of SIBO in individuals meeting diagnostic criteria for IBS was highest with breath testing. The prevalence in cases with IBS compared with controls varied according to criteria used to define a positive test. The role of testing for SIBO in individuals with suspected IBS remains unclear.

Irritable bowel syndrome (IBS) is a chronic relapsing and remitting disorder of the gastrointestinal (GI) tract. The condition is characterized by abdominal pain or discomfort in association with an alteration in bowel habit.1 The exact cause of IBS remains unknown, although the prevailing hypothesis is that there are abnormalities in the brain–gut axis. Proposed central mechanisms include abnormalities of pain processing,2,3 somatization,4 and maladaptive coping.5 Potential peripheral causes include abnormal motility,6,7 dysregulated intestinal immunity,8 low-grade inflammation and altered GI permeability after enteric infection,9,10 and imbalances in intestinal flora.11

Bloating is reported by up to 80% of IBS sufferers,12,13 and often is exacerbated by food.14 Although data are conflicting, some studies report increased intestinal gas on abdominal radiograph in IBS,15,16 particularly in the small intestine.16 Increased hydrogen production after the administration of fermentable substrate has been shown in IBS subjects compared with healthy controls,17 and total excretion of hydrogen also may be increased in IBS.18 It has been proposed that the unifying explanation for increased hydrogen production, and therefore symptoms such as bloating in a proportion of individuals assumed to have IBS, is colonization of the proximal small bowel by fermenting bacteria, as occurs in small intestinal bacterial overgrowth (SIBO).

There is some evidence to support this hypothesis. A group of researchers in the United States showed a prevalence of presumed SIBO in individuals with symptoms suggestive of IBS of almost 80%, using lactulose hydrogen breath testing.19 After treatment of presumed SIBO with antibiotics in a proportion of these individuals, symptoms including abdominal pain, bloating, and diarrhea improved. These findings led the same group of researchers to conduct a randomized controlled trial of rifaximin, a nonabsorbable antibiotic, in subjects with IBS.20 This led to a significant improvement in global IBS symptoms and a reduction in bloating scores after completion of therapy, compared with individuals who received placebo.

However, a recent large study from the United States that also used lactulose hydrogen breath testing to diagnose SIBO did not replicate these findings.21 In addition, direct aspiration and culture of jejunal secretions is considered the gold standard for the diagnosis of SIBO, but only one study has used this approach to date.22 This failed to show a significant difference in the prevalence of SIBO in cases meeting diagnostic criteria for IBS compared with healthy asymptomatic controls from the general population. Therefore, there is controversy surrounding the proposed etiologic role of SIBO in IBS. We performed a systematic review and meta-analysis in an attempt to examine this issue in more detail.

Methods

Search Strategy and Study Selection

A search of the medical literature was conducted using MEDLINE (January 1950 to November 2008) and EMBASE (January 1980 to November 2008). Studies on irritable bowel syndrome were identified with the terms irritable bowel syndrome and functional diseases, colon (both as Medical Subject Headings and free text terms), and IBS and functional adj5 bowel (as free

Abbreviations used in this paper: CI, confidence interval; GI, gastrointestinal; IBS, irritable bowel syndrome; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth.

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Results

The search strategy identified 9517 potentially relevant citations (Figure 1). Of these, 17 appeared to be relevant to the study question and were retrieved for further evaluation. Five were ineligible for various reasons, leaving 12 studies containing 2247 subjects, 1921 (85.5%) of whom met diagnostic criteria for IBS, 19,21,22,31–39 Six were case-control studies, 21,22,32,33,37,38 using either healthy members of the general population or healthy relatives as controls. Only one of the case-control studies stated specifically that assessors interpreting the results of diagnostic tests for SIBO were blinded to the symptom status of the subjects.23 Detailed study characteristics, including the criteria used in each study to define the presence of SIBO, are provided in Table 2. Six of the studies excluded individuals who had used

Data Synthesis and Statistical Analysis

The proportion of individuals meeting diagnostic criteria for IBS with a positive test for SIBO was combined for both case series and case-control studies, subgrouped according to the test used, to give a pooled prevalence in all individuals meeting diagnostic criteria for IBS. In addition, for case-control studies data were pooled for both cases and controls, and the prevalence of a positive test for SIBO, regardless of the type of test used, was compared between the 2 groups with an odds ratio and 95% confidence interval (CI). We planned to conduct sensitivity analyses according to geographic region, study setting (primary care, secondary care, tertiary care), diagnostic criteria used to define IBS, and, for case-control studies, according to whether the assessors were blinded to the symptom status of the subject to examine whether this had any effect on the prevalence or odds of SIBO and to explore reasons for any heterogeneity observed.

Data were pooled using a random effects model26 to give more conservative estimates. StatsDirect version 2.4.4 (StatsDirect, Ltd, Cheshire, England) was used to generate Forest plots of pooled prevalences and pooled odds ratios with 95% CIs. We assessed for evidence of heterogeneity using the I² statistic,28 and for publication bias by applying the Egger test to funnel plots.30

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![Figure 1. Flow diagram of assessment of studies identified in the systematic review.](image-url)
Table 2. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Country and setting</th>
<th>Prior antibiotic use allowed</th>
<th>Diagnostic tests applied for SIBO</th>
<th>Criteria used to define SIBO</th>
<th>Sample size</th>
<th>Number of subjects meeting diagnostic criteria for IBS</th>
<th>Number of subjects with IBS with a positive test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimentel et al, 1999</td>
<td>Case series</td>
<td>United States, tertiary care</td>
<td>Not stated</td>
<td>Lactulose hydrogen breath test</td>
<td>2 distinct peaks of hydrogen production, hydrogen production &lt;90 min after lactulose ingestion, or an increase in hydrogen concentration of &gt;20 ppm over baseline</td>
<td>202</td>
<td>202</td>
<td>157 (78)</td>
</tr>
<tr>
<td>Nucera et al, 2005</td>
<td>Case series</td>
<td>Italy, tertiary care</td>
<td>None within prior 2 months</td>
<td>Lactulose hydrogen breath test</td>
<td>2 distinct peaks of hydrogen production &gt;10 ppm above baseline, or hydrogen production &lt;90 min after lactulose ingestion</td>
<td>98</td>
<td>98</td>
<td>64 (65)</td>
</tr>
<tr>
<td>Madrid et al, 2007</td>
<td>Case series</td>
<td>Chile, tertiary care</td>
<td>Not stated</td>
<td>Lactulose hydrogen breath test</td>
<td>An increase in hydrogen concentration of &gt;20 ppm over baseline</td>
<td>225</td>
<td>225</td>
<td>172 (76)</td>
</tr>
<tr>
<td>Parodi et al, 2007</td>
<td>Case-control</td>
<td>Italy, unclear</td>
<td>Not stated</td>
<td>Lactulose hydrogen breath test</td>
<td>Not specified</td>
<td>162</td>
<td>132</td>
<td>66 (50)</td>
</tr>
<tr>
<td>Bratten et al, 2008</td>
<td>Case-control</td>
<td>United States, tertiary care</td>
<td>None within prior 1 month</td>
<td>Lactulose hydrogen breath test</td>
<td>2 distinct peaks of hydrogen production &gt;12 ppm above basal value with decrease of ≥5 ppm before second peak, an increase in hydrogen concentration &lt;90 min after lactulose ingestion, or an increase in hydrogen concentration of &gt;20 ppm over baseline</td>
<td>214(^a)</td>
<td>180</td>
<td>121 (67) or 25 (14)(^b)</td>
</tr>
<tr>
<td>Carrara et al, 2008</td>
<td>Case series</td>
<td>Italy, secondary care</td>
<td>None within prior 2 weeks</td>
<td>Lactulose hydrogen breath test</td>
<td>An increase in hydrogen concentration of &gt;20 ppm over baseline &lt;90 min after lactulose ingestion</td>
<td>127</td>
<td>127</td>
<td>55 (43)</td>
</tr>
<tr>
<td>Lupascu et al, 2005</td>
<td>Case-control</td>
<td>Italy, tertiary care</td>
<td>None within prior 2 months</td>
<td>Glucose hydrogen breath test</td>
<td>An increase in hydrogen concentration of &gt;20 ppm over baseline</td>
<td>167</td>
<td>65</td>
<td>20 (31)</td>
</tr>
<tr>
<td>McCallum et al, 2005</td>
<td>Case series</td>
<td>United States, tertiary care</td>
<td>Not stated</td>
<td>Glucose hydrogen breath test</td>
<td>An increase in hydrogen or methane production resulting in an absolute value &gt;20 ppm</td>
<td>143</td>
<td>143</td>
<td>55 (38.5)</td>
</tr>
<tr>
<td>Majewski and McCallum, 2007</td>
<td>Case series</td>
<td>United States, tertiary care</td>
<td>Not stated</td>
<td>Glucose hydrogen breath test</td>
<td>Peak of hydrogen or methane production of &gt;20 ppm (if baseline &lt;10 ppm, or &gt;12 ppm (if baseline &gt;10 ppm)</td>
<td>204</td>
<td>204</td>
<td>93 (46)</td>
</tr>
<tr>
<td>Rana et al, 2008</td>
<td>Case-control</td>
<td>India, secondary care</td>
<td>None within prior 1 month</td>
<td>Glucose hydrogen breath test</td>
<td>An increase in hydrogen concentration of ≥12 ppm above baseline</td>
<td>325</td>
<td>225</td>
<td>25 (11)</td>
</tr>
</tbody>
</table>
antibiotics within the past 2 weeks to 2 months.\textsuperscript{21,22,31,36,38} Despite the fact that many of the studies used more than one criteria to define a positive test result, only 2 studies reported the prevalence according to the different criteria separately.\textsuperscript{21,22} One study that used lactulose hydrogen breath testing reported that the prevalence was highest when an increase in breath hydrogen concentration within 90 minutes of lactulose ingestion was used to define SIBO, and lowest when a dual peak of breath hydrogen production was used.\textsuperscript{21} Another study examining the yield of jejunal aspirate and culture in suspected IBS reported the lowest prevalence when 10\textsuperscript{5} or more colony-forming units of colonic bacteria per milliliter was used to define a positive test, and the highest prevalence when a bacterial count, including noncolonic bacteria, was that in the 95th or higher centile of the count in healthy controls was used.\textsuperscript{22} We conducted sensitivity analyses with the data from these 2 studies included according to the criteria used to define a positive test that gave either the highest or lowest prevalence of SIBO. Because of the small number of studies identified it was not possible to conduct the majority of our a priori sensitivity analyses, with the exception of the prevalence of a positive test for SIBO in suspected IBS according to the diagnostic test used.

Prevalence of a Positive Lactulose Hydrogen Breath Test in Subjects Meeting Diagnostic Criteria for Irritable Bowel Syndrome

Six studies reported prevalence of a positive lactulose hydrogen breath test in 964 subjects.\textsuperscript{19,21,31,34,36,37} Five studies used the Rome II criteria to define IBS,\textsuperscript{21,31,34,36,37} whereas the sixth study used the Rome I criteria.\textsuperscript{19} Three of the studies were conducted in Italy,\textsuperscript{31,36,37} 2 in the United States,\textsuperscript{19,21} and 1 in Chile.\textsuperscript{34} If the criteria that gave the lowest prevalence of SIBO in the study by Bratten et al\textsuperscript{21} were used then the prevalence in individual studies ranged from 14% to 78%, with a pooled prevalence in subjects meeting diagnostic criteria for IBS of 54% (95% CI, 32%–76%) (Figure 2). If the criteria that gave the highest prevalence of a positive test for SIBO in the Bratten et al\textsuperscript{21} study were used then the prevalence in individual studies ranged from 43% to 78%, with a pooled prevalence of 64% (95% CI, 52%–75%). There was statistically significant heterogeneity detected between study

![Figure 2. Prevalence of a positive lactulose hydrogen breath test in subjects meeting diagnostic criteria for IBS.](image-url)
Prevalence of a Positive Glucose Hydrogen Breath Test in Subjects Meeting Diagnostic Criteria for Irritable Bowel Syndrome

Four studies reported on the prevalence of a positive glucose hydrogen breath test in 637 subjects meeting Rome II criteria for IBS. The studies were conducted in India, Italy, and the United States. The prevalence of a positive glucose hydrogen breath test in individual studies varied between 11% and 46%, with a pooled prevalence of 31% (95% CI, 26%–41%). Again, there was statistically significant heterogeneity detected between study results ($I^2 = 96$%; $P < .001$).

Prevalence of a Positive Sucrose Hydrogen Breath Test in Subjects Meeting Diagnostic Criteria for Irritable Bowel Syndrome

Only one study conducted in the United States used sucrose hydrogen breath testing in 158 subjects with Rome II IBS. The prevalence of a positive test in subjects meeting diagnostic criteria for IBS was 33% (95% CI, 26%–41%).

Prevalence of Positive Jejunal Aspirate and Culture in Subjects Meeting Diagnostic Criteria for Irritable Bowel Syndrome

A Swedish study used jejunal aspirate and culture to detect possible SIBO in 162 individuals with Rome II IBS. The prevalence of a positive test was only 4% (95% CI, 2%–9%) when $10^5$ or more colony-forming units of colonic bacteria per milliliter were used to define SIBO. When a lower bacterial count, including noncolonic bacteria, of the 95th or higher centile of the count in healthy controls was used the prevalence was 43% (95% CI, 35.5%–51%).

Prevalence of Small Intestinal Bacterial Overgrowth in Subjects Meeting Diagnostic Criteria for Irritable Bowel Syndrome Compared With Healthy Controls

There were 6 case-control studies, containing 1248 subjects, 922 (74%) of whom met diagnostic criteria for IBS. All 6 studies used the Rome II criteria to define IBS. Two studies used lactulose hydrogen breath testing, 2 studies used glucose hydrogen breath testing, and 1 study used sucrose hydrogen breath testing. Only one study used jejunal aspirate and culture. Controls were members of the general population in 5 studies, and healthy first-degree relatives in the sixth study. If the criteria that gave the lowest prevalence of a positive test in the Bratten et al and Posserud et al studies were used there were 195 (21%) of 922 subjects meeting Rome II criteria for IBS testing positive for SIBO, compared with 23 (7%) of 326 healthy controls without symptoms suggestive of IBS. The odds of a positive test for SIBO in individuals meeting diagnostic criteria for IBS compared with controls was 3.45 (95% CI, 0.9–12.7) ($I^2 = 84$%; $P < .001$), but no evidence of funnel plot symmetry (Egger test, $P = .32$). If the criteria that gave the highest prevalence of a positive test in the Bratten et al and Posserud et al studies were used there were 354 (38%) of 922 subjects meeting Rome II criteria for IBS testing positive for SIBO, compared with 40 (12%) of 326 healthy controls without symptoms suggestive of IBS. The odds of a positive test for SIBO in individuals meeting diagnostic criteria for IBS compared with controls was 4.7 (95% CI, 1.7–12.95) ($I^2 = 78$%; $P = .003$), and evidence of funnel plot asymmetry (Egger test, $P = .04$).

Effect of Proton Pump Inhibitor Use on the Prevalence of Small Intestinal Bacterial Overgrowth in Subjects Meeting Diagnostic Criteria for Irritable Bowel Syndrome

Three studies containing 445 subjects with symptoms suggestive of IBS reported data on PPI use. Two studies stated that they had excluded those individuals who had used PPIs within the past 2 months, and only 1 study stated that it had not controlled for PPI use. In the remaining studies this issue was unclear. There were 70 (33%) of 212 individuals with a positive test for SIBO who were prescribed a PPI, compared with 69 (30%) of 233 individuals testing negative. The odds ratio for PPI use in those with a positive test for SIBO was 1.4 (95% CI, 0.9–2.1).

Figure 3. Odds of a positive test for SIBO in subjects meeting diagnostic criteria for IBS compared with healthy controls using criteria that gave the lowest prevalence of a positive test.

Figure 4. Odds of a positive test for SIBO in subjects meeting diagnostic criteria for IBS compared with healthy controls using criteria that gave the highest prevalence of a positive test.
Discussion

This study has shown a prevalence of SIBO in subjects meeting diagnostic criteria for IBS of between 4% and 64%, depending on the type of test used and the criteria used to define a positive test result. However, there was significant heterogeneity when data from studies that used the same type of test were combined. In addition, when jejunal aspirate and culture was used, the current gold standard test for the detection of SIBO, with a cut-off level of 10³ or more colony-forming units of colonic bacteria per milliliter used to define the presence of SIBO, the prevalence of a positive test in individuals with symptoms suggestive of IBS was less than 4%. When the prevalence of a positive test for SIBO was compared between cases with symptoms suggestive of IBS and healthy asymptomatic controls, regardless of the test used, there was a 3- to 5-fold increase in the odds of a positive test result in individuals meeting diagnostic criteria for IBS, although this was not statistically significant when the criteria that gave the lowest prevalence of a positive test for SIBO in the studies by Bratten et al. and Posserud et al were used. In addition, there was significant heterogeneity between studies, and when data were pooled using the criteria that gave the highest prevalence of a positive test for SIBO, the funnel plot asymmetry suggested publication bias, or other small study effects. There remains, therefore, uncertainty concerning the utility of testing for SIBO in IBS.

Strengths of our study include the exhaustive literature search, rigorous statistical methods, and pooling of data to allow synthesis of all the available published evidence to allow us to examine the yield of testing for SIBO in IBS, as well as our extraction of data to estimate the effect of PPI use on the prevalence of a positive test result for SIBO. Weaknesses of the study, as with any systematic review and meta-analysis, arise from the available evidence. A majority of studies were based in tertiary care, which may limit the generalizability of the findings to subjects with symptoms suggestive of IBS in routine clinical practice. There were only very limited data reporting on the yield of jejunal aspirate and culture, the current gold standard for diagnosing SIBO. In addition, case-control studies are subject to spectrum bias because the study design often omits mild cases that are difficult to diagnose, and SIBO is itself controversial. There are some studies that have evaluated intestinal flora with methods such as hypnotherapy and cognitive behavioral therapy. Although SIBO could account for why some individuals with IBS experience an improvement in symptoms after a course of antibiotics, it would not explain why symptoms in IBS appear to improve with other nonpharmacologic treatments such as hypnotherapy and cognitive behavioral therapy. The benefit of antibiotics could arise as a result of the high placebo response rate of IBS to therapy in randomized controlled trials. There appeared to be an association between SIBO and IBS in many of the studies we identified, but this was not consistent and there remains the possibility of confounding by another factor. Recently, it has been proposed that the apparent association between SIBO and IBS may be caused by concurrent use of PPIs. This could arise because individuals reporting GI...
symptoms are likely to be prescribed PPIs empirically as a therapeutic measure. The resultant inhibition of gastric acid secretion then could render an individual more susceptible to bacterial colonization of the upper small intestine, and therefore SIBO. Unfortunately, only 3 of the studies we identified reported data concerning rates of PPI use in involved subjects, and although the proportion using PPIs, and the odds ratio for PPI use, were somewhat higher in those meeting diagnostic criteria for IBS with a positive breath test result than those without, the difference was not statistically significant. If PPI use is indeed causing an apparent increase in SIBO in individuals with IBS it may be that antibiotics, such as rifaximin, are treating this deleterious effect of PPI therapy successfully.

Unfortunately, the pooling of data from studies identified by this systematic review and meta-analysis do not allow us to resolve these unanswered questions. To address these uncertainties we need researchers in the future to either control for PPI use or exclude PPI users altogether from prevalence studies of SIBO in IBS. In addition, we require more data validating the current available tests for confirming the presence of SIBO before their utility in IBS can be determined. In summary, this systematic review and meta-analysis has shown conflicting evidence for the yield of tests for SIBO in individuals meeting diagnostic criteria for IBS compared with healthy individuals from the general population, with the prevalence varying according to the criteria used to define a positive test. Additional evidence examining this subject is required before the routine exclusion of SIBO in individuals with suspected IBS can be recommended in usual clinical practice.

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Reprint requests
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Conflicts of interest
The authors disclose the following: Nicholas Talley has received consultancy fees from Procter and Gamble, Lexicon Genetics, Inc, Astellas Pharma US, Inc, Pharma Frontiers, Ltd, Callisto Pharmaceuticals, AstraZeneca, Addex Pharma, Ferring Pharma, Salix, MGI Pharma, McNeil Consumer, Microbia, Dynogen, Conexus, Novartis, and Metabolic Pharmaceuticals, and has received research support from Novartis, Takeda, GlaxoSmithKline, Dynogen, and Tioga; Paul Moayyedi is the chair at McMaster University and is funded partly by an unrestricted donation by AstraZeneca, and has received consultant’s and speaker’s bureau fees from AstraZeneca, AxCan Pharma, Nycomed, and Johnson and Johnson. The remaining authors disclose no conflicts.

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