Small intestinal bacterial overgrowth in patients with irritable bowel syndrome

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Small intestinal bacterial overgrowth (SIBO)
- A disorder of excessive bacterial growth in the small intestine
- Abnormally large numbers of bacteria at least 10^5 bacteria per ml of fluid

Irritable bowel syndrome (IBS)
- Functional bowel disorder
  - abdominal pain
  - bowel habit changes
- Three major subtype of IBS
  - Diarrhea-predominant (IBS-D)
  - Constipation-predominant (IBS-C)
  - IBS with alternating stool pattern (IBS-A)

Gut bacteria
- The microflora of the stomach and proximal small bowel are predominantly gram-positive and aerobic bacteria (10^3-10^4 cfu/mL)
- Gram-negative > gram-positive in distal ileum

Test of SIBO
- Indirect tests
  - Hydrogen breath test
  - 14C-xylose breath test
- Direct tests
  - Bacterial cultures of small intestinal aspirate
  - Positive culture = total growth ≥ 10^5 cfu/mL intestinal fluid

Indirect test of SIBO
  - Glucose hydrogen breath test and 14C-xylose breath test have been considered as fairly reliable tools
- Corazza et al. (1993) and Riordan et al.(1996)
  - Lactulose breath test is low sensitivity and specificity in comparison with culture of small bowel aspirate
In direct test of SIBO (cont.)

- Pimentel et al. (2000, 2003)
  - Small intestinal bacterial overgrowth diagnosed by means of lactulose hydrogen breath test (LHBT) in 78–84% of IBS patients
- Pimentel et al. (2002)
  - IBS patients with positive LHBT were found to have altered small bowel motility

Aims of study

- To determine the prevalence of SIBO in a large sample of IBS patients using culture of small bowel aspirate.
- To evaluate whether bacterial overgrowth in patients could be related to small bowel motility characteristics, and to the symptom profile of the patients.

Subjects

- Patients with a clinical diagnosis of IBS, based on the ROME II criteria
- 162 patients divided into subgroups based on their predominant bowel habit
  - 49 patients with diarrhea predominant IBS (IBS-D)
  - 37 patients with constipation predominant IBS (IBS-C)
  - 76 patients with alternating type IBS (IBS-A)

Materials and Methods

- 42 healthy volunteers without any history of gastrointestinal symptoms
- No antibiotics within two weeks before the study
- No medications known to affect the gastrointestinal tract within 48 hours of the study
Study design

- Jejunal cultures
- Manometry
- Hydrogen breath tests

Jejunal cultures

- The samples were cultured for aerobic and anaerobic bacteria on blood agar plates with 4% defibrinated horse blood in aerobic and anaerobic atmosphere of 10%CO$_2$ and N$_2$.
- Selective cultivation of gram-negative strains was performed on Drigalski agar under aerobic conditions.
- Yeast fungus was cultured on Sabouraud’s agar.

Jejunal cultures (cont.)

- Culture verified SIBO was defined as $\geq 10^5$ cfu/mL.
- For explorative analyses we also looked at lower “cut-off levels”, $\geq$ 95th percentile in our healthy volunteers.

manometry

![Figure 1. Schematic picture of the manometric catheter with eight pressure recording ports. Three ports in the antrum (A1-3), three in the descending duodenum (D1-3), one close to the ligament of Treitz (T), and one in the proximal jejunum (J).](image)

Data analysis

- Characteristics of MMC phase III
- MMC cycle
- Motility index
- Postprandial motor pattern
- Presence of enteric dysmotility.
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Hydrogen breath test

- GMI exhaled H₂ monitor

Criteria to indicate SIBO

- >15 ppm increase in H₂ 15-120 minutes after ingestion of glucose in at least two breath samples
- Two distinct H₂ peaks (>20 ppm increase) 15-180 minutes after ingestion of lactulose

Statistical analysis

- Comparisons within the IBS group
  - Paired and unpaired non-parametric analysis
- The number of positive tests on small bowel culture, LHBT and GHBT
  - Chi-squared test
- Changes in H₂ over time during the LHBT
  - Repeated measures analysis of variance (ANOVA)
- p ≤ 0.05 significant

Results

Cultures

- ≥10⁵ cfu/mL
- ≥10⁴ cfu/mL
Cultures

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Responded</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-A</td>
<td>5 x 10^8 E. coli</td>
<td>5 x 10^8 E. coli</td>
<td>Yes</td>
</tr>
<tr>
<td>IBS-C</td>
<td>10^8 mixed O. rose</td>
<td>10^8 E. coli</td>
<td>No</td>
</tr>
<tr>
<td>5 x 10^8 Clostridium</td>
<td>10^8 E. coli</td>
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<td></td>
</tr>
<tr>
<td>IBS-D</td>
<td>5 x 10^7 E. coli</td>
<td>5 x 10^7 E. coli</td>
<td>Yes</td>
</tr>
<tr>
<td>NS</td>
<td>5 x 10^7 K. oxyt</td>
<td>5 x 10^7 K. oxyt</td>
<td>No</td>
</tr>
<tr>
<td>10^8 E. coli</td>
<td>10^8 E. coli</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IBS-C</td>
<td>10^8 E. coli</td>
<td>10^8 E. coli</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Breath tests

- **Glucose hydrogen breath tests (GHBT)**
  - 54 IBS patients: only one positive test
  - 20 controls: no

- **Lactulose hydrogen breath tests (LHBT)**
  - 46 IBS patients: 7 patients positive test (15%)
  - 21 controls: 4 controls positive test (20%)

Small bowel motility

- Conventional manometric evaluation discovered enteric dysmotility in 86% of the patients with culture positive SIBO compared with 39% of the patients without SIBO (P=0.02)

- Patients with SIBO (n=7) tended to have fewer phase III compared with patients without SIBO (n=74) (0.6 [0.1-1.8] vs. 1.2 [0.4] / 3 h, P=0.08)
Small bowel motility (cont.)
- No differences on
  - phase III duration
  - propagation velocity
  - MMC cycle length
  - motility index

Predominant bowel habit and effects of treatment
- Small intestinal bacterial overgrowth did not correlate with IBS subtype based on the predominant bowel habit

Discussion

The best of knowledge
- First study evaluating growth of bacteria in the small bowel in a large sample of patients with IBS

Culture
- Using a definition of $\geq 10^5$ cfu/mL of colonic bacteria is not sufficient to detect SIBO
  - As sampling is restricted to one location in the proximal small bowel, missing more distal overgrowth

Culture (cont.)
- False negative culture
  - Water-perfused manometry could result in a dilution and a lower count of bacteria.
  - Aspirates were not immediately incubated
Hydrogen breath test

- GHBT → FAIL
- Previous studies using the GHBT and 14C-xylose test have failed to show a high prevalence of abnormal tests in IBS (Parisi et al, 2003 and Walters et al, 2005)

Hydrogen breath test (cont.)

- LHBT
- Results from the LHBT, using the double peak definition, with 15% positive tests in patients
- Walters et al (2005) positive LHBT in 10% of IBS patients
- Abnormal LHBT with single peak H2 within 90 or 180 minutes

Antibiotic

- About half of the patients with SIBO in our study reported symptom improvement after antibiotic treatment
- Sample was too small to perform a randomized placebo-controlled evaluation

Motility

- The patients with culture verified SIBO had fewer phase III
- They did not perform a formal correlation analysis between the amount of bacteria and the degree of abnormality of the MMC
- Duration of recordings were relatively short (as for practical reasons)

Motility (cont.)

- The importance of mildly elevated small bowel bacteria seen in IBS is unclear
- There is a possibility that this is just an epiphenomenon due to altered motility
- No significant differences in the motility parameters before and after treatment

Future studies

- After treatment with antibiotic
- Better characterize these bacterial alterations in IBS, including possible correlations to symptoms
- Looking at both systemic and local inflammatory activity together with an evaluation of the presence of post-inflammatory IBS

Sample was too small to perform a randomized placebo-controlled evaluation
Conclusion

- Mildly elevated counts of small bowel bacteria seem to be more common in IBS.
- However, they do not support a strong association between IBS and small intestinal bacterial overgrowth according to standard definition.