Participating in the Webinar

Listen using your computer audio. A headset is recommended but not required.

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.

ACG will submit MOC points on the first of each month. Please allow 3-5 business days for your MOC credit to appear on your ABIM account.

MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 2: Chronic Abdominal Pain and Bloating
Brian E. Lacy, MD, PhD, FACG
April 2, 2020 at Noon EDT

Week 3: Update on Managing Your Pregnant IBD Patient
Sunanda V. Kane, MD, MSPH, FACG
April 9, 2020 at Noon EDT

Visit gi.org/ACGVGR to Register

Disclosures:

Presenter:
William D. Chey, MD, FACG
Consultant: Salix/Valeant
Grant/Research Support: Commonwealth Diagnostics International, Salix/Valeant

Moderator:
Brooks D. Cash, MD, FACG
Consultant: Allergan, Salix, Takeda, QOL Medical
Speakers Bureau: Allergan, Salix, Takeda, QOL Medical

Small Intestinal Bacterial Overgrowth: Fact or Fiction

William D. Chey, MD
Professor of Medicine
Michigan Medicine
Twitter: @umfoodoc
**Small Intestinal Bacterial Overgrowth:**

- **Definition of Small Intestinal Bacterial Overgrowth (SIBO):**
  - Clinical syndrome of GI symptoms caused by the presence of excessive numbers of bacteria within the small intestine.
  - Widely accepted definition is $>10^5$ CFU/ml from the proximal jejunum.
  - Lower cut-off ($>10^3$ CFU/ml) appropriate for duodenal aspirates.
  - Current definition of SIBO focuses on quantity but important issue may be types of bacteria and their metabolic consequences.

- **Wide array of effects:**
  - Direct injury, changes in function/sensation, gut immunology, permeability, and loss of brush border enzymes.
  - Clinical manifestations from asymptomatic to frank malabsorption.

**Factors Which Protect Against SIBO**

**Disorders Commonly Associated with SIBO**

- Gastric acid suppression drugs
- Atrophic gastritis
- Vegetarian
- Celiac disease
- Crohn’s disease
- IBD
- Celiac disease
- Small bowel tics
- IC valve resection
- Bariatric surgery
- JI bypass
- Surgical blind loop
Testing for SIBO

Small bowel Aspiration & Culture: An Imperfect Gold Standard...

**Pros**
- Can be performed at time of endoscopy
- Direct assessment for SIBO
- Allows identification of potential organism +/- antibiotic sensitivity

**Cons**
- Cost
- Invasive (EGD)
- Time/Labor commitment
- Risk of sampling error
- Accuracy of culturing
- Potential for missing distal small bowel bacterial overgrowth

Breath Testing for SIBO

Saad RJ, Chey WD. Clin Gastroenterol Hepatol. 2014 Dec;12(12):1964-72

Saad & Chey. Gastroenterol 2007;133:1763

American College of Gastroenterology
Breath Testing for SIBO: Preparation

• **Before:**
  • Avoid antibiotics for 4 weeks
  • Avoid promotility agents & laxatives for 1 week.
  • Day before test, avoid fermentable foods (e.g., complex carbohydrates) and patient should fast for 8–12

• **During the breath test,**
  • Avoid smoking & minimize physical exertion

SIBO Breath Test Protocols: Rome & North American Consensus*

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Dose</th>
<th>Abnormal Rise in $H_2$ (90 minutes)</th>
<th>Abnormal Rise in $CH_4$ (90 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>10 grams</td>
<td>&gt;20 ppm</td>
<td>&gt;10 ppm</td>
</tr>
<tr>
<td>Glucose</td>
<td>50-75 grams</td>
<td>&gt;12-20 ppm</td>
<td>&gt;10 ppm</td>
</tr>
</tbody>
</table>

*Authors acknowledge that data to justify their suggested abnormal thresholds is poor*

Recent studies which performed glucose* or lactulose** breath testing and scintigraphy found that 65-85% of positive breath tests were falsely positive for SIBO.

B. infantis 15924 may cause false positive LBT for methane but not hydrogen***

---


---

American College of Gastroenterology
Emerging Tests for SIBO

- Orocecal scintigraphy with simultaneous breath testing
- Hydrogen sulfite measurement in breath
- Molecular testing of small bowel aspirate
- Novel capsule based diagnostics for volatile organic compounds, gases, or bacteria

Banik et al. J. Breath Res. 10 (2016) 026010

Gas Sensing Capsule Technology


ACG Clinical Guideline
Diagnosis of SIBO

1. We suggest the use of breath testing (glucose or lactulose hydrogen) for the diagnosis of SIBO in patients with IBS (conditional recommendation, very low level of evidence).

2. We suggest using glucose or lactulose hydrogen breath tests for the diagnosis of SIBO in symptomatic patients with suspected motility disorders (conditional recommendation, very low level of evidence).

3. We suggest testing for SIBO using glucose or lactulose hydrogen breath tests in symptomatic patients (abdominal pain, gas, bloating, and/or diarrhea) with previous luminal abdominal surgery (conditional recommendation, very low level of evidence).

Pimentel et al. Am J Gastroenterol 2020;115:165-78
What do we know about methane?

- Methanogens are archaea
  - prokaryotic organisms distinct from bacteria & eukaryotes
- Methanobrevibacter smithii is the key methanogen responsible for breath methane production in humans
- Methane is associated with slowing of gut transit
- A meta-analysis found that methane is associated with chronic constipation (OR 3.51, 95% CI 2.00-6.16)
- Very limited treatment data:
  - Rifaximin 550 mg tid and Neomycin 500 mg bid x 14 days recommended
  - Lovastatin?

Pimentel et al. Am J Gastroenterol 2020;115:165-78

Treatment of SIBO

ACG Clinical Guideline
Diagnosis of SIBO

We suggest the use of antibiotics in symptomatic patients with SIBO to eradicate overgrowth and resolve symptoms
(conditional recommendation, low level of evidence)

Pimentel et al. Am J Gastroenterol 2020;115:165-78
Antibiotic Regimens for SIBO

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Recommended dose</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin</td>
<td>550 mg t.d.</td>
<td>61%–78%</td>
</tr>
<tr>
<td>Thiocionato</td>
<td>85 mg b.i.d.</td>
<td>50%</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td>43%–100%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>250 mg t.i.d.</td>
<td>43%–87%</td>
</tr>
<tr>
<td>Neomycin</td>
<td>500 mg b.i.d.</td>
<td>33%–50%</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400 mg t.i.d.</td>
<td>39%–100%</td>
</tr>
<tr>
<td>Teluracil</td>
<td>250 mg q.i.d.</td>
<td>87.5%</td>
</tr>
<tr>
<td>Thiocionato</td>
<td>500 mg/900 mg b.i.d.</td>
<td>95%</td>
</tr>
</tbody>
</table>

Most of the studies are small and methodologically flawed.

Lack of a gold standard for diagnosis presents problems.

Most treat to negative BT result but others to symptom relief.

Largest amount of data with rifaximin.

Pimentel et al. Am J Gastroenterol 2020;115:165-78

Efficacy of Antibiotics for SIBO

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of studies</th>
<th>Total number of subjects</th>
<th>Number with breath test normalization</th>
<th>For cost with breath test normalization</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin</td>
<td>13</td>
<td>281</td>
<td>107</td>
<td>35.4-51.0</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2</td>
<td>132</td>
<td>62</td>
<td>45.0-62.3</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>4</td>
<td>59</td>
<td>15</td>
<td>51.7-78.2</td>
<td></td>
</tr>
<tr>
<td>Teluracil</td>
<td>13</td>
<td>281</td>
<td>44</td>
<td>49.5-50.5</td>
<td></td>
</tr>
</tbody>
</table>

Breath Test Recurrence After Treatment with Rifaximin

- Positive LBT associated with pain, bloating, flatus, diarrhea


- 61 consecutive IBS pts

- Rifaximin 1.2 grams/day x 7 d

- 3 9

- 10

- 20

- 30

- 40

- 50

- 60

- 70

- 80

- 90

- 100
What about probiotics for SIBO?

- Meta-analysis 14 studies/8 abstracts (10-480 pts each)
- Wide range of probiotics
- No decrease in prevalence of SIBO with probiotic vs. placebo (6 studies, RR = 0.63, 95% CI = 0.29-1.36)
- Eradication rate:
  - Probiotics alone = 53%
  - Probiotics & antibiotics = 86%
  - Probiotics vs. antibiotics (6 studies) = 38% vs. 18%, p = 0.091
  - Probiotic vs. placebo (2 trials) RR = 1.6, 95% CI = 1.19-2.17
- Recently reported cases of d-lactic acidosis, brain fog, SIBO attributed to probiotics

Rifaximin vs. Herbal Therapy for SIBO

- 104 patients with SIBO by LBT
- Offered open label rifaximin 400 mg tid or herbal therapy for 4 weeks

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rifaximin</th>
<th>Herbal Therapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>67</td>
<td>37</td>
<td>.61</td>
</tr>
<tr>
<td>Age (y), range</td>
<td>56.4 ± 18.8 (19-90)</td>
<td>61.5 ± 16.8 (16-70)</td>
<td>.22</td>
</tr>
<tr>
<td>Gender</td>
<td>48 (71%)</td>
<td>29 (78%)</td>
<td>.87</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (29%)</td>
<td>9 (22%)</td>
<td>.35</td>
</tr>
<tr>
<td>Response (%)</td>
<td>26 (15)</td>
<td>10 (8%)</td>
<td>.06</td>
</tr>
<tr>
<td>Response Rate (%)</td>
<td>34</td>
<td>46</td>
<td>.24</td>
</tr>
<tr>
<td>Adverse Events (%)</td>
<td>2.19</td>
<td>1.27</td>
<td>.83</td>
</tr>
</tbody>
</table>

Other Possible Treatments

- **Diet interventions**
  - Low FODMAP diet
  - Specific Carbohydrate diet
  - Elemental diet

- **Prokinetics**
  - Erythromycin
  - Prucalopride
  - Tegaserod
  - Pyrindostigmine

What is the evidence to support an association between SIBO and IBS?

Fecal Microbiota in IBS vs. Controls: A Systematic Review

- 24 studies from 22 articles included
- Results varied amongst the studies but IBS pts differed from controls
- α-Diversity decreased
- Cause & effect unproven

Small Intestine Microbiome Altered in Patients with GI Symptoms

- 126 pts with GI symptoms vs 38 HVs
- SB microbiome differed in pts vs. HVs
- 52% of pts had SIBO on aspirates
- 29% of pts vs. 3% of HVs had SB dysbiosis
- No correlation between SIBO & dysbiosis
- Metabolic pathways for simple sugars & fiber differed between pts and HVs
- High fiber diet in HVs was associated with SIBO on SB aspirate
- Diet changes lead to measurable changes SB microbiome and metabolome

SIBO & IBS: Meta-analysis
25 Case Control Studies, 3,192 IBS patients and 3,320 controls


IBS 31.0% (95% CI 29.4–32.6) vs. Controls 20.9% (95% CI 19.5–22.2), OR of 3.7 (95% CI 2.3–6.0, P<0.001)

IBS and SIBO: Cause or Effect?

- IBS patients have a higher likelihood of an abnormal aspirate or breath test than healthy volunteers
- SIBO can affect a number of factors which have been linked to the pathogenesis of IBS, causing or exacerbating IBS symptoms
- However, it is also possible that abnormalities in motility, gut immune function, microbiome, CHO metabolism which are intrinsic to IBS could increase the likelihood of SIBO
Empiric Rifaximin for Global Improvement in IBS: A meta-analysis of RCTs

<table>
<thead>
<tr>
<th>Measure Outcomes</th>
<th>Response Rates (%)</th>
<th>Weight</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharara</td>
<td>27.0</td>
<td>9</td>
<td>1.4%</td>
<td>18%</td>
</tr>
<tr>
<td>Pimental</td>
<td>32.5</td>
<td>9</td>
<td>1.6%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Lembo</td>
<td>52.3</td>
<td>44.2</td>
<td>8.1%</td>
<td>12.3</td>
</tr>
<tr>
<td>Target 1</td>
<td>40.8</td>
<td>31.2</td>
<td>34.9%</td>
<td>9.6</td>
</tr>
<tr>
<td>Target 2</td>
<td>40.6</td>
<td>32.2</td>
<td>36.8%</td>
<td>8.4</td>
</tr>
<tr>
<td>Overall</td>
<td>43.3</td>
<td>34.2</td>
<td>100%</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=5.26$, df=4, I$^2=24\%$, p=0.26


2,438 patients were treated and completed 2 weeks of rifaximin 550 mg in the open-label phase. 59% entered the double-blind phase after symptom recurrence. 328 patients randomized to placebo, 308 patients randomized to rifaximin 550 mg TID.

Median time to recurrence of symptoms was 10 weeks (range of 6-24 weeks).

TARGET 3: Study Design and Patient Disposition

2,438 patients entered open-label phase, 328 patients entered double-blind phase after symptom recurrence. 308 patients randomized to placebo, 328 patients randomized to rifaximin 550 mg TID.

Efficacy of First and Second Retreatments

LOCF Analysis

- Urgency and bloating improved significantly with both repeat treatments
- Abdominal pain and stool consistency improved significantly with first retreatment
- At time of recurrence, IBS-D symptoms were less severe compared to symptoms at onset of study

LOCF, last observation carried forward.

Responder defined as subjects responding to IBS-D related abdominal pain and stool consistency for ≥2 of 4 weeks.

Why should we bother with breath testing? Why not just treat with empiric antibiotics?

Summary
- The microbiome plays a critical role in normal development and function of the human GI tract.
- Gastric acid, pancreaticobiliary secretions, the MMC, gut immune system, permeability, and IC valve protect against the development of SIBO.
- SIBO presents a clinical spectrum of disease.
- Differences in the distribution & composition of gut bacteria make diagnosis difficult.
- All available tests have pros and cons.
- Changes in gut flora may lead to IBS symptoms.
- Antibiotics offer short term benefits to those with SIBO and a subset of IBS sufferers.

Key Concepts:
ACG SIBO Clinical Guideline 2020
1. Most common symptom is bloating.
2. Vitamin deficiencies are uncommon & usually seen with structural abnormality (eg surgery/blind loop). Folate may be elevated as bacteria produce folate.
3. Breath testing is useful for identifying SIBO noninvasively before antibiotic treatment.
4. >10³ CFU/mL is most suggestive of SIBO when using duodenal culture.
5. Methanobrevibacter smithii appears to be the key methanogen responsible for breath methane production and is associated with constipation.
6. Targeting methanogens may reduce methane production and improve constipation.
7. A proportion of subjects with IBS are found to have SIBO, based both on breath testing and on culture.
8. There is inconsistent data to support recommending specific probiotics in the treatment of SIBO.
9. There is currently no basis for fecal microbiota transplant in the treatment of SIBO.
10. A focus on prevention of SIBO is important to avoid the need for repeated courses of antibiotics. Treatment of the underlying cause represents the primary mode of prevention.
Six questions to start the discussion on IBS

gi.org/patients/ibs-screener/

Patients select treatment “currently using,” “have tried in the past” or “wish to discuss”

gi.org/patients/ibs-treatment-checklist/