SMALL BOWEL BACTERIAL OVERGROWTH: IS TESTING NECESSARY?

JAY J. MAMEL MD
INFLUENCES OF MICROBIOTA

- Metabolic / nutritional / energy utilization
  - vitamin synthesis
  - SCFA as energy source – role in obesity
- Innate immune regulation
  - dampening of inflammatory response
- Adaptive immune regulation
  - induction of immunosuppressive T-cells (Tregs)
- Epithelial development & survival
  - stimulation of proliferation, angiogenesis, epithelial restitution
  - cytoprotective effects of PRR signaling
- Competitive exclusion of pathogens
METABOLIC ACTIVITY OF INTESTINAL MICROFLORA

- Polysaccharide-fermenting bacteria
- Succinate- or lactate-utilizing bacteria
- Saccharolytic bacteria
- Absorbed or excreted by the host
- Butyrate
- Propionate
- Acetate
- CO₂, H₂
- CO₂-fixing acetogenic bacteria
- CH₄
- Methane-producing bacteria
COMPOSITION & DISTRIBUTION OF FLORA IN HUMAN G.I. TRACT

- **Major bacteria present**
  - Esophagus: Lactobacilli (≤10³ CFU/ml)
  - Stomach, Duodenum, Jejunum: Enterococci, Lactobacilli (10²-10⁹ CFU/ml)
  - Ileum, Colon, Large intestine: Enterobacteria, Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Clostridia, Lactobacilli (10⁴-10¹² CFU/ml)

- **Anus**
SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

- Upper intestinal tract relatively sterile environment
  - Normal peristalsis
  - Antibacterial action of gastric acid
- Define as > $10^5$ CFU / ml
- No validated diagnostic test
ETIOLOGY SIBO

- Anatomic
  - abdominal surgery
  - small bowel diverticula
- Disordered peristalsis
  - scleroderma
- Loss of I-C valve
- reflux of colonic bacteria

- Achlorhydria
  - vagotomy
  - atrophic gastritis
  - PPI usage?
- Advancing age
- Chronic pancreatitis
- Radiation enteritis
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>Vitamin deficiency</td>
</tr>
<tr>
<td>Bloating</td>
<td>B-12, A, D, E, K</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Fat &amp; carbohydrate malabsorption</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Hypoproteinemia or hypoalbuminemia</td>
</tr>
<tr>
<td>Weakness</td>
<td>Iron deficiency</td>
</tr>
</tbody>
</table>
MORPHOLOGIC & METABOLIC CONSEQUENCES OF SIBO

- Deconjugation of bile acids in proximal small bowel
- Subtle changes in light microscopy & enzyme content
- Mucosal changes secondary to cobalamin deficiency (anaerobes)
- Vitamin K & folate
- Loss of activity of brush border disaccharides
- Altered permeability
- D-lactic acidosis & encephalopathy from Gm(+) anaerobes
- Pneumatosis intestinalis
NUTRITIONAL CONSEQUENCES OF SIBO

- Severe malnutrition rare, rare hypoproteinemia
- Fat malabsorption: steatorrhea
- CHO malabsorption: osmotic diarrhea
- Vit B-12 deficiency common
- Levels of Vit. K and folate normal / increased
- Combination of SIBO & short-bowel can be devastating
IMMUNOLOGIC EFFECTS OF SIBO

- Increased IgA-2, IgM & IL-6
- No change in TNF alpha or IF gamma
- Increased lamina propria IgA plasma cell counts
- Unaltered lamina propria B- & T cell counts
- Increase levels of IgA anti-gliadin ab
- Defective complement activation & circulating IgG-3
BACTERIAL TRANSLOCATION & SEPSIS IN SIBO

- Passage of viable bacteria to extra-intestinal sites
- Key issue in intestinal failure
- Presumed promotion by increased intestinal permeability & impaired host defense
- Trans-cellular transport supported experimentally
- Translocation varies depending on flora: Pseudomonas, E. coli, Klebsiella, Proteus
- Gut derived sepsis associated with severe catabolic state
- Varying immuno-modulatory effect of flora on mucosa
BRAIN-GUT-ENTERIC MICROBIOTA AXIS
OVERVIEW

• Bidirectional gut-brain interactions modulate motility, blood flow, secretion, intestinal permeability, mucosal immune activity & visceral sensations
• Intestinal microbiota has an important role in this interaction
• Brain-gut signaling can effect host-bacterial interactions in the GI tract
• Direct communication between epithelial cells & enteric bacteria
• Vagal afferent nerve signaling connects CNS with enteric microbiota - enterochromaffin cells
BIDIRECTIONAL GUT-BRAIN-MICROBE INTERACTIONS

- Direct and indirect modulation of enteric microbiota by the CNS
- GI motility, secretion, permeability
- Mucosal immune function
- Enteric microbiota
- Visceral stimuli perception: Emotion
- Modulation of nervous system function by enteric microbiota
- ANS
- HPA axis
- Viscerosensory mechanism
ENTEROCHROMAFFIN CELLS AS BIDIRECTIONAL SIGNAL TRANSDUCERS BETWEEN HOST & ENTERIC MICROBIOTA
ENDOCRINE CELL-MEDIATED SIGNALING FROM ENTERIC MICROBIOTA TO HOST
INTERFACE BETWEEN ENTERIC MICROBIOTA, IMMUNE CELLS IN LAMINA PROPRIA & ANS
TREATMENT OF SIBO: HISTORICAL PERSPECTIVE

- Tetracycline (minocycline / doxycycline, only 60%)
- Amoxicillin-clavulanic acid (Augmentin)
- Cephalexin (Keflex) + metronidazole (Flagyl)
- Colistin + metronidazole (Flagyl)
- Trimethoprin / sulfamethoxazole (Bactrim)
- Rifaximin (Xifaxin)
PREBIOTICS & SYNBIOTIQUIS IN SIBO

- Nondigestible, fermentable foods that alter gut flora
- Synbiotics = probiotic + prebiotic
- Stimulate preferred commensal flora & altered pH
- Inulin-type fructans beta 2-1 bonds
- Found in edible fruits & vegetables: wheat, onion, chicory, garlic, leeks, artichoke & bananas
- Produce lactic acid & SCFA in colon
PROBIOTICS IN SIBO: POTENTIAL MECHANISMS

- Competition with pathogens producing bacteriocins
- Inhibition of bacterial translocation
- Enhanced mucosal barrier function
- Signaling between luminal bacterial intestinal epithelium & immune system
- Limited studies & conflicting findings
- Well tolerated
- Cases of endocarditis, fungemia, bacteremia & diarrhea reported
### MICROORGANISMS USED AS PROBIOTIC AGENTS

<table>
<thead>
<tr>
<th>Lactobacillus sp</th>
<th>Bifidobacterium sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>acidophilus</td>
<td>adolescentis</td>
</tr>
<tr>
<td>bulgarious</td>
<td>bifium</td>
</tr>
<tr>
<td>casei (rhamnosus)</td>
<td>breve</td>
</tr>
<tr>
<td>johnsonn</td>
<td>infantis</td>
</tr>
<tr>
<td>lactis</td>
<td>lactis</td>
</tr>
<tr>
<td>plantarum</td>
<td>longum</td>
</tr>
<tr>
<td>reuteri</td>
<td></td>
</tr>
</tbody>
</table>
MICROORGANISMS USED AS PROBIOTIC AGENTS: OTHERS

- Bacillus cereus
- Enterococcus faecalis
- E. coli Nissel 1917
- S. boulardii
- S. cerevisiae
- S. thermophilus
78% (157/202) of IBS patients were positive for SIBO on lactulose breath testing.

47 patients retested after antibiotic Rx.

25/47 had eradication of SIBO.

48% of eradicated group no longer met IBS criteria.
RIFAXIMIN FOR IBS

- Percent

- Weekly IBS Sx
- Weekly bloating Sx
- Daily IBD Abd pain

- Rifaximin
- Placebo
OVERALL IMPROVEMENT OF GLOBAL IBS SYMPTOMS WITH RIFAXIMIN DURING 10 WEEKS OF F/U

Patients with adequate relief (%)

- **Rifaximin**
- **Placebo**

14 Day double-blind treatment phase

10 week F/U No study medication

WEEK

P=0.001
• 40% IBS were found to have SIBO by jejunal cultures

• Similar proportions if (+) LHBT & GHBT vs. controls

• Did not confirm a strong association between IBS & SIBO
BREATH TEST [H] ARE ABNORMAL WHEN:

• **A:** [H] > 20 ppm over baseline

• **B:** Sustained rise [H] > 10 ppm over baseline

• **C:** [CH3] > 15 ppm over baseline

• **D:** Rise [H] > 20 ppm over baseline or [CH3] > 15 ppm
BREATH TESTING

- Standard substrate: glucose, sucrose, fructose, lactose, lactulose, xylose
- Measure breath hydrogen & methane gas chromatograph every 30 min for 2-3 hrs.
  - Baseline [H] > 25 ppm
  - Baseline [CH3] > 7 ppm
  - Rise of > 20 ppm above baseline
- Variations in sensitivity & specificity
## TESTS FOR SIBO

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Simplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunal culture</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Poor</td>
</tr>
<tr>
<td>Urinary indican</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Jejunal bile acids</td>
<td>Fair</td>
<td>Excellent</td>
<td>Poor</td>
</tr>
<tr>
<td>14C-bile acid BT</td>
<td>Fair</td>
<td>Poor</td>
<td>Excellent</td>
</tr>
<tr>
<td>14C-xylose BT</td>
<td>Good</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td>Fasting H2 BT</td>
<td>Poor</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Lactulose H2 BT</td>
<td>Poor</td>
<td>Fair</td>
<td>Excellent</td>
</tr>
<tr>
<td>Glucose H2 BT</td>
<td>Fair</td>
<td>Fair</td>
<td>Excellent</td>
</tr>
</tbody>
</table>
FACTORS INFLUENCING BREATH TESTING

- Antibiotics
- Laxatives diarrhea / antidiarrheals
- Bread, pasta, fiber
- Cigarette smoking
- Exercise
- Sleep
- Oral flora (Rx chlorhexidine mouthwash)
- Acid suppression PPI (?)
LACTULOSE BREATH TEST

- Lactulose non-absorbable disaccharide galactose & fructose
- Cleaved by bacteria in proximal colon into hydrogen
- Bacterial overgrowth: early hydrogen peak observed after 60-90 min
- Lactulose accelerates transit
- Double peak in breath [H]: 1st small bowel, 2nd colonic
- Sensitivity: 68-84%, Specificity: 44-68%
GLUCOSE BREATH TESTING

- Normally entirely absorbed in proximal jejunum
- SIBO; glucose metabolized by flora into CO2 & H2
- If breath [H] elevate likely SIBO
- If breath [H] negative, may be missing distal SIBO
- Sensitivity 62%; Specificity 83%
METHANE BREATH TESTING

- Produced by methanogenic, anaerobic bacteria *Methanobrevibacter smithii*
- Shunting H2 into methane producing negative rise in breath hydrogen
- Animal model studies:
  - exogenous methane slows transit
  - augments non-propagating contractions
- Associated with constipation.
PPI THERAPY DOES NOT PREDISPOSE TO SIBO  RATUAPLI ET AL., 2012

- IBS patients are more likely than controls to receive PPI
- PPI therapy may promote SIBO by eliminating gastric acid
- 1,191 patients (70% female), 48% on PPI therapy
- GHBT did not differ significantly between PPI users & non-users
CLEVELAND CLINIC BREATH TEST
VOLUME 2009-2011

Number of Procedures

<table>
<thead>
<tr>
<th>Year</th>
<th>Glucose</th>
<th>Lactose</th>
<th>Fructose</th>
<th>H. pylori</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>400</td>
<td>150</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2010</td>
<td>250</td>
<td>100</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>2011</td>
<td>200</td>
<td>80</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

N= 830, 679, 647
USF MORSANI SMALL BOWEL BREATH TESTING N= 88
## GHBT POSITIVITY BETWEEN PPI USERS & NONUSERS

<table>
<thead>
<tr>
<th>Breath Test Criteria</th>
<th>PPI users (n=566)</th>
<th>PPI nonusers (n=625)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[H] &gt;20 n(%)</td>
<td>71(13)</td>
<td>87(14)</td>
<td>0.49</td>
</tr>
<tr>
<td>[H] &gt;10 n(%)</td>
<td>146(26)</td>
<td>149(24)</td>
<td>0.44</td>
</tr>
<tr>
<td>[CH3] &gt;15 n(%)</td>
<td>77(14)</td>
<td>72(12)</td>
<td>0.28</td>
</tr>
<tr>
<td>Either [H] or [CH3] &gt;15 n(%)</td>
<td>126(22)</td>
<td>131(21)</td>
<td>0.59</td>
</tr>
</tbody>
</table>
PROKINETIC THERAPY FOR SIBO

- Cisapride. erythromycin
- Somatostatin analog (octreotide) induced MMC
MANAGEMENT OF SIBO IN INTESTINAL FAILURE

- Surgical approaches: loops, taperings, lengthening, reversed segments, transplantation
- TPN - children with short-bowel & SIBO less likely to wean from PN
- Need additional fat-soluble vitamins, B-12 & certain minerals
ANTIMICROBIAL THERAPY FOR SIBO

- Amoxicillin-clavulanic acid (500 mg 3x daily)
- Ciprofloxacin (250 mg 2x daily)
- Chloramphenicol (250 mg 4x daily)
- Doxycycline (100 mg 2x daily)
- Metronidazole (250 mg 3x daily)
- Neomycin (500 mg 4x daily)
- Norfloxacin (800 mg/day)
- Tetracycline (250 mg 4x daily)
- Trimethoprim-sulfamethoxazole DS (2x daily)
- Rifaximin (1200 mg daily).
## USF Morsani Breath Testing Demographics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Mean Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>50</td>
</tr>
<tr>
<td>Females</td>
<td>55</td>
</tr>
</tbody>
</table>

Age range 26 - 87 years old
SYMPTOMS OF PATIENTS UNDERGOING BREATH TESTING

- Diarrhea
- Nausea
- Constipation
- Bloating

Percent

0 20 40 60 80 100

Percent
# POSITIVE LACTULOSE BREATH TESTS

(N=88)

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Positive Tests</td>
<td>51%</td>
</tr>
<tr>
<td>Hydrogen (+) SIBO</td>
<td>77%</td>
</tr>
<tr>
<td>Methane (+) SIBO</td>
<td>23%</td>
</tr>
<tr>
<td>Methane(+) / Hydrogen (-)</td>
<td>2%</td>
</tr>
</tbody>
</table>
BOWEL DYSFUNCTION IN METHANOGENIC PATIENTS

<table>
<thead>
<tr>
<th>Bowel dysfunction</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>27%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55%</td>
</tr>
</tbody>
</table>
TREATMENTS OFFERED FOR SIBO AT USF

N=116, (+) BT=47

- Rifaxamin
- Metronidazole
- Metronidazole + Cipro
- Amox / Amp
- Tetracycline
TREATMENT OUTCOMES FOR SIBO AT USF

53% improved / resolved
WHY IS TESTING FOR SIBO USEFUL?

- Allows identification of SIBO (+) patients who may need variation in treatment plans for complete clinical response
- Undocumented trials of antimicrobial therapy potentially exposes individuals to *C. difficile* associated infection
PREBIOTICS, PROBIOTICS, PROKINETICS

- Little or no data on their use in SIBO
- Limited options for prokinetics, no data
References:


Quigley E & Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics and probiotics. Gastroenterology 2008; 130: S78-90


Shanahan F. Gut microbes; from bugs to drugs. Am J Gastroent 105: 275-79.