Bacterial Overgrowth: 
Getting the Bugs Out

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Bacterial Flora of the Gut

• Up to a million trillion ($10^{15}$) bacteria in gut  
  – Only $10^{14}$ human cells in average body  
  – ~500 distinct species identified in colon  
  – Only ~1/3 of bacteria can be cultured  
• Relatively stable populations  
  – Selection of resident bacteria by gut immune system  
• Traditionally viewed as commensals: no great benefit, no great harm
Bacterial Flora of the Gut

- Most bacteria are located in colon
- Bacterial flora in proximal small bowel is relatively sparse (<10^5 bacteria per mL)
- Density of bacteria in distal small bowel is higher (<10^8/mL), but still several orders of magnitude less than in colon
- Low density of bacteria in small intestine facilitates digestion


Effects of Bacterial Overgrowth

- Deconjugation of bile acids
  - Allows absorption of bile acid throughout gut
  - Reduces bile acid concentration below critical micellar concentration \(\rightarrow\) fat malabsorption
- Carbohydrate fermentation
  - Reduces carbohydrate absorption
  - Produces gas
- Interferes with vitamin B\(_{12}\) absorption
- Mucosal injury
Physiological Suppression of Bacterial Overgrowth

- Very low pH in stomach
- Secretory IgA
- Defensins/other Paneth cell products
- Gastric and small bowel motility
  - Migrating motor complex during fasting
- Ileoceleval valve

Settings in which Bacterial Overgrowth is Seen

- Hypochlorhydria due to gastritis or drugs
- IgA deficiency/immunodeficiency states
- Small bowel dysmotility, gastroparesis
  - Diabetes
  - Scleroderma
  - Pseudo-obstruction
- Structural problems
  - Blind loops/postoperative changes
  - Diverticula/strictures/gastrocolic fistulas
Clinical Predictors of SIBO

- 675 patients at Mayo Clinic who had duodenal aspirate for quantitative culture
  - 8% were positive
- Factors associated with (+) culture
  - Older age
  - Steatorrhea
  - Narcotic use
  - IBD, small bowel diverticula, pancreatitis


Old Presentations of Bacterial Overgrowth

- Malabsorption syndrome
  - Diarrhea/steatorrhea
  - Malnutrition
  - Vitamin deficiency states
    - Macrocytic anemia
    - Neuropathy
    - Tetany/osteomalacia
    - Night blindness/dermatitis
- Tropical sprue
New Presentations of Bacterial Overgrowth

- Chronic watery diarrhea
- Irritable bowel syndrome
  - A work in progress
  - Prevalence ranges from 5-80% of IBS patients in different studies (? test artifact)
  - “Chicken vs. egg” (treatment effects)
  - ? More distal location of excess bacterial flora
  - ? Relation to post-infectious state

Improvement in IBS Symptoms 1-10 weeks after completing 10 days of therapy with rifaximin or placebo

\[ N=44 \text{ (P), } 43 \text{ (R)} \]
\[ P=0.02 \]

New Presentations of Bacterial Overgrowth

• Other gut disorders\(^1\)
  – ? Inflammatory bowel disease
  – ? Unspecified sprue
  – ? Colorectal cancer
• Extraintestinal disease
  – ? Nonalcoholic fatty liver disease\(^2\)
  – Rosacea

\(^1\)DuPont AW, DuPont HL. *Nat Rev Gastroenterol Hepatol* 2011;8:523-531.

Diagnosis

• Direct tests
  – Quantitative culture of luminal aspirate
• Indirect tests
  – Products of bacterial metabolism
    • Short chain fatty acid concentration in aspirate
    • Urinary metabolite (4-hydroxyphenylacetic acid)
  – Absorption of exogenous substrate
    • D-xylose tolerance test (serum or urine)
    • Schilling test
Diagnosis

• Indirect tests
  – Bile acid deconjugation
    • Endogenous bile acid: unconjugated serum bile acid
    • Exogenous bile acid conjugated to marker
      – Ursodeoxycholic acid—p-aminobenzoic acid
      – Cholic acid—p-aminobenzoic acid
  – Breath tests

Breath Tests

• Based on bacterial metabolism of isotopically-labeled conjugated bile acid to isotopically-labeled CO₂ or fermentation of carbohydrate to hydrogen or methane gas
• Very dependent on technical factors
  – Dose of substrate administered
  – Collection of expired air for analysis
  – Time-course
  – Interpretation of concentration vs. time graphs\textsuperscript{1}

\textsuperscript{1}Ghoshal UC. *J Neurogastroenterol Motil* 2011;17:312-317.
Breath Tests

- Additional technical factors
  - 10-20% of individuals do NOT have hydrogen-producing bacteria
    - Simultaneous measurement of methane excretion may compensate for this
  - Analysis of expired air depends on precise methods, fastidious technique; not always reproducible from laboratory to laboratory
  - Increase in concentration that is positive signal is arbitrary (10 or 20 ppm)

Substrates for Breath Tests

- **Glucose**
  - Absorbed rapidly in proximal jejunum
  - Little substrate available in distal small bowel even with large dose (25 g)

- **Xylose**
  - Less well absorbed than glucose
  - Tiny doses (1 g) absorbed in proximal intestine
  - Larger doses (25 g) distributed further down gut

GLUCOSE AND XYLOSE ONLY MEASURE PROXIMAL OVERGROWTH
Substrates for Breath Tests

• Lactulose
  – Poorly absorbed in small bowel
    • Exposed to entire length of small bowel
    • Most enters colon and exposed to bacteria there
  – Interpretation of H₂ concentration—time curve
    • “Double-peak”
    • “Early peak” (<4 hours from ingestion)
    • “High peak” (>50 ppm at any time)
  – Confounding due to rapid transit
    • Independent transit measure: scintigraphy

• Isotopically-labeled conjugated bile acid
  – Normally absorbed in terminal ileum
    • Exposed to entire length of gut
    • Little should get to colon if ileal function is normal
      (Effect of rapid transit/ileal dysfunction)
  – Should pick up distal small bowel bacterial overgrowth, but no “gold standard” to compare
  – Isotopically-labeled CO₂ (not H₂) is detected
Performance Characteristics of Breath Tests

• Highly variable
• Breath hydrogen vs. quantitative culture
  – Glucose
    • Sensitivity: 27-93%
    • Specificity: 30-86%
  – Lactulose
    • Sensitivity: 17-89%
    • Specificity: 44-100%

Performance Characteristics of Breath Tests

• Isotopically-labeled CO$_2$ vs. quantitative culture
  – D-xylose (1 g dose)
    • Sensitivity: 42-100%
    • Specificity: 59-100%
  – Isotopically-labeled conjugated bile acid
    • Sensitivity: 70%
    • Specificity: 90%
Recommendations for Diagnostic Testing

- For **proximal** small bowel overgrowth
  - Aspirate for quantitative culture
  - Isotopically-labeled 1 g d-xylose breath test
  - Glucose breath hydrogen test
- For **distal** small bowel overgrowth
  - Ideal test not devised
  - Isotopically-labeled bile acid breath test
  - ? Aspiration via double-balloon enteroscopy

Treatment

- Effective antibiotic therapy is key
- Few controlled studies
- Choose agents that kill gram-negative aerobic enteric flora and/or anaerobes
  - Trimethoprim-sulfamethoxazole
  - Amoxicillin
  - Fluoroquinolones
  - Tetracyclines
  - Metronidazole
**Rifaximin**

- Poorly absorbable antibiotic, rifaximin, has been much studied lately
- Currently FDA-approved for treatment of travelers’ diarrhea (200 mg TID X 3 days), hepatic encephalopathy (550 mg BID)
- Doses used in studies: 400-550 mg TID X 7-14 days, ? more is better\(^1\)
- Did better than chlortetracycline for relief of symptoms and breath hydrogen excretion\(^2\)

\(^1\)Saadi M, McCallum RW. *Ther Adv Chronic Dis* 2013;4:71-75.

**Treatment**

- Initial course of treatment → assess response
- Relapse likely because fundamental process (e.g., stasis, immune problem) not addressed by antibiotics, but time to relapse uncertain
- Rotation of antibiotics to avoid resistance advised, but unproven
- Continuous therapy should be avoided