Bacterial Overgrowth in Short Bowel Syndrome and Intestinal Failure

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Disclosures

• I have no financial disclosures relevant to this presentation

Learning Objectives

• Define small bowel bacterial overgrowth
• Discuss risk factors
• Review symptoms and differential diagnosis
• Review diagnostic challenges and therapeutic options
• Future directions
Case

- 11 months old former 30 weeks GA
- Home PN and gastrostomy feeds
  - History of small bowel resection leaving him with approximately 30% of estimated bowel length
  - ICV resected and Jejunum anastomosed to mid-ascending colon
- New onset intermittent abdominal distention and gagging
- Increased stool output
- Weight loss documented

UGI with SBFT

Small Bowel Bacterial Overgrowth

- Defined as
  - colonization of small bowel with colon derived bacteria usually in the order of
  - $>10^5$ cfu/ml of aspirate
Symptoms of SBBO

- Abdominal pain or distention
- Foul flatulence
- Interferes with digestive enzymes
- Intolerance to previously acceptable foods
- Hematochezia
- Altered mental status
- Unexplained metabolic acidosis
- Unexplained worsening of liver injury tests
Function is more important than length

PIFCon (n=272)

Risk Factors

- Dysmotility
- Anatomical disturbances in the bowel, including
  - Resection of ileo-cecal valve
  - Fistulae
  - Diverticula and blind loops created after surgery
- Gastroenteritis induced alterations to the small intestine
**Risk Factors**

- Lack of enteral nutrition
  - Absence of lumenal sweep
  - Alteration of pH

- Use of certain medications:
  - proton pump inhibitors
  - H2 blockers
  - Antibiotics
  - Probiotics

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**Epidemiology**

- Very common in patients with risk factors:
- 50% in children with short bowel syndrome from NEC
- Diagnosis of SBBO was not related to bowel length or degree of enteral tolerance in these children
- However, the colon was in continuity with the residual small bowel at the time of the diagnosis.
- Ileocecal valve was absent in 60%


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**Epidemiology**

- Gutierrez et al. confirmed high prevalence of SBBO
- SBBO was present in 75% of 57 of these children with risk factors
- Patients receiving parenteral nutrition were more likely to develop SBBO compared to those without it (70% vs. 35%)

Diagnosis

• Bacterial overgrowth can be diagnosed by:
  • Demonstrating elevated numbers of bacteria in duodenojejunal aspirate or bacteria densely adherent to the mucosal surface of duodenojejunal biopsy specimens obtained during upper endoscopy > 10^5 bacteria/ml

• Disadvantages
  • Invasive
  • Bacterial Contamination


Diagnosis

• Abnormal breath hydrogen excretion with the use of glucose substrate:
  • Breath tests are considered abnormal (positive)
    – If there was an increasing curve of hydrogen or methane by >15-20 parts per million (ppm) above baseline within 90 minutes
    – If baseline breath hydrogen or methane >20 ppm

Ostrander CR et al., JPGN 1983; 2(3):525-33

Breath hydrogen tests

• Why is glucose the preferred substrate?
  – Monosaccharide
  – Rapidly and completely absorbed in the small bowel
  – Under physiological circumstances, does not reach the colon

Breath hydrogen tests

• Advantages
  – Noninvasive and easy procedure for the collection of expired air
  – Cheap

• Disadvantages
  – Rapid transition in short bowel syndrome
  – Dependent on the subject
  – Time (duration of 2 hours)

Diagnosis

• Elevated plasma partial difference-lactate concentration
  – Lactic acidosis

Consequences
• Gram positive anaerobes
  – Clostridium species
  – Eubacterium
  – Lactobacillus
  – Propionobacterium acnes
  – Peptostreptococci
  – Enterococcus

Consequences
• Carbohydrate and protein deprivation
• Diarrhea from carbohydrate malabsorption
• Deconjugation of bile acids by luminal bacteria leads to:
  – Fat malabsorption including deficiencies in fat-soluble vitamins
  – Steatorrhea
• Megaloblastic, macrocytic anemia
  – Utilization of vitamin B12 by luminal bacteria

Bacterial overgrowth
• Malabsorption of nutrients and fluids
  – Dehydration
  – Poor growth
• In children
  – Inadequate for normal growth and development

Ramadori K et al. J. Infect Dis 1984;150:213-8
SBBO increased the odds for BSI > 7 fold (p=0.009)
Calprotectin levels were higher in those with SBBO (p<0.05)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of BSI in PN</th>
<th>Number of BSI in non-PN</th>
<th>SBBO increased odds of BSI if PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>10</td>
<td>1</td>
<td>3.9</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>5</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>3</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>1</td>
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</tr>
<tr>
<td>Bacteroides</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Methanobrevibacter</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
</tbody>
</table>
| *Not that organism listed for single final value.

Impact of SBBO on PN duration

- Small intestinal inflammation correlated with bacterial overgrowth (r = 0.69)
- Children with severe enteritis identified before weaning remained on the PN regimen for a longer period (36 +/- 15 months) compared to children with:
  - Mild enteritis (21 +/- 14 months)
  - No inflammation (13 +/- 11 months) (p < 0.02)


Biomarkers

- Neither plasma anti-FLIC nor anti-LPS IgA or IgG levels distinguished CLABSI from non-bacterial febrile episodes
- Anti-FLIC and anti-LPS IgA (p=0.02) in addition to anti-FLIC and anti-LPS IgG (p=0.01) were significantly elevated at baseline among IF subjects on prophylaxis for small bowel bacterial overgrowth
Fecal microbiome in SBS

- Stool from patients with SBS had a significantly greater abundance of the bacterial classes
  - Gammaproteobacteria and Bacilli.
- Stool from patients with SBS who experienced increased stool frequency tended to have
  - Increased abundance of Lactobacillus (P = .057)
  - Decreased abundance of Ruminococcus

Davidovics ZH et al. JPEN 2015 [Epub ahead of print]

Gut microbiome in infants with SBS (n=10) vs age-matched control infants (n=5)

- Collaboration with Drs. Frank and Pace at Univ. of Colorado, Boulder
- PCR amplicon libraries constructed by pan-bacterial PCR of stool DNA and sequenced using high-throughput Genome Sequencer FLX pyrosequencing platform.
- 24,860 sequence tags generated (1308/subject).
- To identify bacteria, rDNA sequences analyzed by BLAST.

Microbiome Data in Pediatric SBS

Klebsiella spp. most prominent (17% of sequences) from SBS infants; and less abundant in controls (p = 0.053).
Other genera, such as Enterococcus and Lactobacillus also enriched in the stool of infants with SBS.
Each branch of the tree shows a different genus, color-coded by the phylum.
The heights of the bars surrounding the tree are proportional to the abundances of sequences.
The colors of the bars denote the proportion of sequences from SBS (red) or controls (blue). Genera labeled in blue (e.g., Bacteroides) were >2-fold enriched in controls compared with SBS, while those labeled in red (e.g., Klebsiella) were >2-fold enriched in SBS cases.
Bile acids and bacteria

SBBO and Unconjugated bile acids

Serum unconjugated bile acids: qualitative and quantitative profiles in ileal resection and bacterial overgrowth

K.D.R. Setchell 1, D.L. Harrison 2, J.M. Gilbert 1 and G.M. Mapthye 4

1 Clinical Mass Spectrometry Laboratory, Department of Gastroenterology and Nutrition, Children’s Hospital Medical Center, Cincinnati, Ohio 45229, 2 Clinical Mass Spectrometry Section, Children’s Research Center, Harrow, Middlesex, HA1 3UJ (UK), and 4 Gastroenterology Unit, Department of Medicine, Guy’s Hospital and Medical School, London (UK)

(Received August 27th, 1984; revision July 21st, 1985)

• Identified deoxycholic acid as potential marker for small bowel bacterial overgrowth

SBBO and Unconjugated bile acids

Serum Unconjugated Bile Acids as a Test for Intestinal Bacterial Overgrowth in Dogs

TONATUIR MIHAGARO, PHD, JAYDE A. WILLIAMS, PHD, NANCY C. O’CONNELL, MS, and KENNETH D.R. SETCHELL, PHD

• Fraction of unconjugated bile acids increased 10-20 fold in dogs with overgrowth
SBBO and UBA

Unconjugated serum bile acids as a marker of small intestinal bacterial overgrowth

A. MASCLEE, A. TANGERMANN, A. VAN SCHAIK, E. W. VAN DER BOEK & J. H. M. VAN CONINXELLEN
Department of Medicine, Division of Gastroenterology, University Hospital Mijlweg, Nijmegen and *Department of Medicine, Cornaro Hospital, Den Bosch, The Netherlands

Received 21 October 1998 and in revised form 10 March 1999

- Compared serum UBA to the “gold standard” (aspirate)
- 10 adult subjects with culture proven SBBO; 16 controls
- Serum UBA elevated in subjects (6.4 vs. 0.9 μmol/l; p<0.005)

Little good data on treatment regimens in SBS

Medications
- Metronidazole
- Ciprofloxacin
- Amoxicillin
- Augmentin
- Rifaximin
- Nitazoxanide (Alinia)

- ? Probiotics or prebiotics

Dietary
- Low carbohydrate formula
- Hydrolyzed formula

Cole CR et al., J Pediatr 2010;156: 941-7

Surgery

Bianchi Procedure

Longitudinal lengthening (Bianchi procedure)

Serial transverse enteroplasty

STEP

Nature Reviews | Gastroenterology & Hepatology
Treatment

- Little good data on treatment regimens in SBS
  - Surgery

  Tapering

Conclusion

• All of the available methods to test for SBBO have inherent limitations and no 'gold-standard' diagnostic test for the condition exists
• Accurate diagnosis of SBBO requires identification of bacterial species growing inappropriately within the small intestine
• Symptom response to antibiotics

Future directions

• Identification of non invasive markers for SBBO
  - Calprotectin or other stool marker
  - Serum or Urine bile acids
  - Fecal microbiome
• Evaluate efficacy of therapy and antibacterial prophylaxis
Thank you!!!

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