Bacterial Overgrowth in Short Bowel Syndrome and Intestinal Failure

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Disclosures

- **I have no financial disclosures relevant to this presentation**

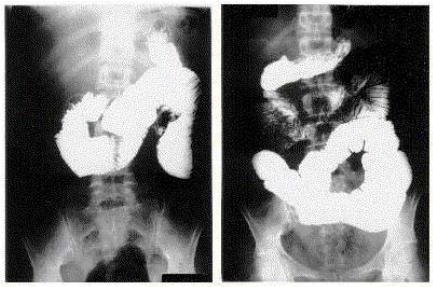
Learning Objectives

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

Case

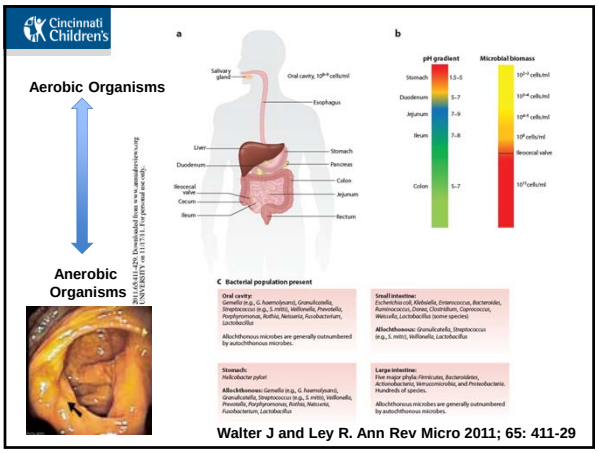
- **11 months old former 30 weeks GA**
- **Home PN and gastrostomy feeds**
  - History of small bowel resection leaving him with approximately 30% of estimated bowel length
  - ICV resected and Jejunum anastomosed to mid-ascending colon
- **New onset intermittent abdominal distention and gagging**
-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

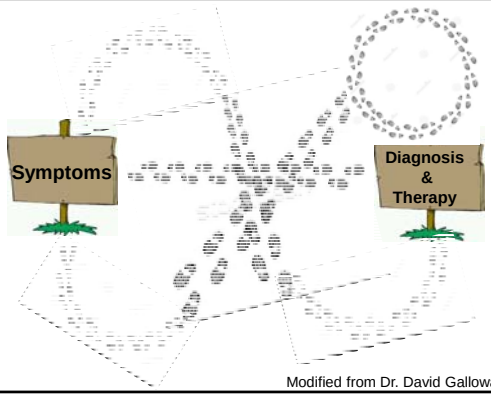


Walter J and Ley R. Ann Rev Micro 2011; 65: 411-29

Symptoms of SBBO

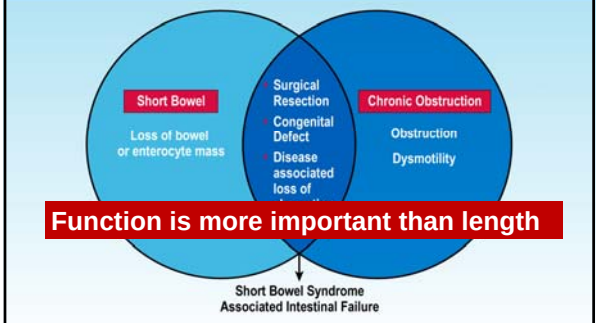
- Abdominal pain or distention
- Foul flatulence
- Interferes with digestive enzymes
- Intolerance to previously acceptable foods
- Hematochezia
- Altered mental status
- Unexplained metabolic acidosis
- Unexplained worsening of liver injury tests

Bacterial Overgrowth



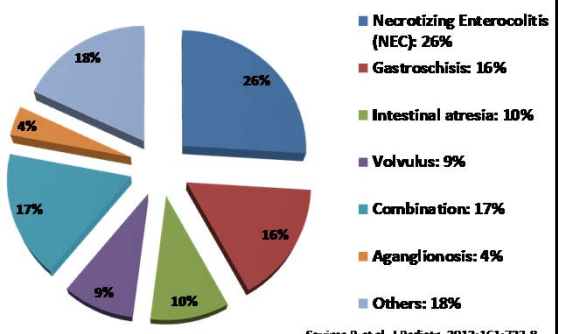
Modified from Dr. David Galloway

Intestinal failure



O'Keefe SJ et al. *Clin Gastroenterol Hepatol*. 2006;4:6-10.

PIFCon (n=272)



Squires R et al. J Pediatr. 2012;161:723-8

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**

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%

Cole et al J Pediatr. 2010; 156: 941–947.e1.

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%)

Gutierrez IM et al. J Pediatr Surg 2012;47:1150-4.

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

Kaufman S, Loseke CA et al. J. Peds.1997; 131: 356-361

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

Cole CR, Rising R & Lifshitz F. Arch Pediatr Adolesc Med. 1999; 153:1098-102
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

Sieczkowska et al. J Pediatr Gastroenterol Nutr. 2015 Jul 20. [Epub ahead of print]

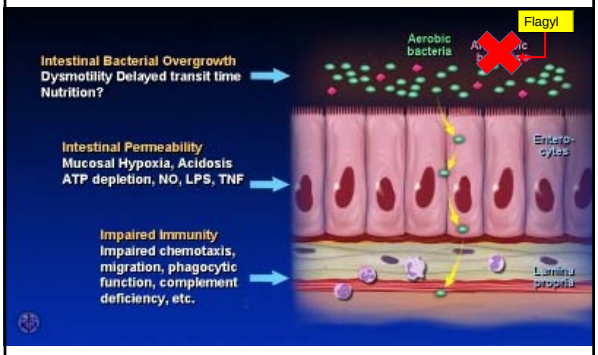
Breath hydrogen tests

- **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 malabsoprtion**
- **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

Ramotar K et al. J. Infect Dis 1984;150:213-8
Brandt LJ et al. Ann Intern Med 1977;87:546-51

Bacterial overgrowth

- **Malabsorption of nutrients and fluids**
  - **Dehydration**
  - **Poor growth**
- **In children**
  - **Inadequate for normal growth and development**

Milewski PJ et al. BMJ 1980; 280:1356-7
O'Keefe SJ et al Clin. Gastroenterol. Hep. 2006;4: 6-10

Cincinnati Children's

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

The Rate of Bloodstream Infection Is High in Infants with Short Bowel Syndrome: Relationship with Small Bowel Bacterial Overgrowth, Enteral Feeding, and Inflammatory and Immune Responses

Conrad R. Cole, MD, MPH, MSc, Juliana C. Frem, MD, Brian Schmotzer, MS, Andrew T. Gewirtz, PhD, Jonathan B. Meddings, MD, Benjamin D. Gold, MD, and Thomas R. Ziegler, MD

Results BSI incidence was high (80%), and SBBO was common (50%). SBBO increased the odds for BSI (>7-fold; $P = .009$). Calprotectin levels were higher in children with SBS and SBBO versus those without SBBO and healthy control subjects ($P < .05$). Serum TNF-α, was elevated at baseline versus controls. Serum TNF-α and interleukin-1 β, -6, and -8 levels diminished with increased enteral nutrition. Anti-flagellin and anti-lipopolysaccharide immunoglobulin G levels in children with SBS were lower versus control subjects and rose over time.

SBBO increased the odds for BSI > 7 fold (p=0.009)
Calprotectin levels were higher in those with SBBO (p<0.05

Organisms	Number of BSIs (n = 20) (% of total BSI)	BSI caused by microorganism (% of children)
Gram-positive		
Enterococcus faecalis	5 (25%)	4 (40%)
Coagulase-negative Staphylococci	3 (15%)	3 (30%)
Leuconostoc spp.	1 (5%)	1 (10%)
Gram-negative		
Klebsiella pneumoniae	7 (35%)	4 (40%)
Mixed infections*	4 (20%)	3 (30%)

*More than 1 organism isolated from single blood culture.

J Peds 2010; 156: 941-947

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)**

Kaufman S, Loseke CA et al. J. Peds.1997; 131: 356-361

Biomarkers

Original Communication

aspen

Increased Anti-Flagellin and Anti-Lipopolysaccharide Immunoglobulins in Pediatric Intestinal Failure: Associations With Fever and Central Line–Associated Bloodstream Infections

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DOI: 10.1177/0148607114537073
jpen.sagepub.com
hosted at
online.sagepub.com
SAGE

David P. Galloway, MD[1]; Misty L. Troutt, MS[1]; Samuel A. Kocoshis, MD[1]; Andrew T. Gewirtz, PhD[2]; Thomas R. Ziegler, MD[3]; and Conrad R. Cole, MD, MPH[1]

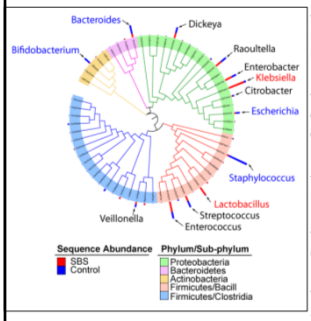
- Neither plasma anti-FLiC nor anti-LPS IgA or IgG levels distinguished CLABSI from non-bacterial febrile episodes
- Anti-FLiC and anti-LPS IgA (p=0.02) in addition to anti-FLiC and anti-LPS IgG (p=0.01) were significantly elevated at baseline among IF subjects on prophylaxis for small bowel bacterial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



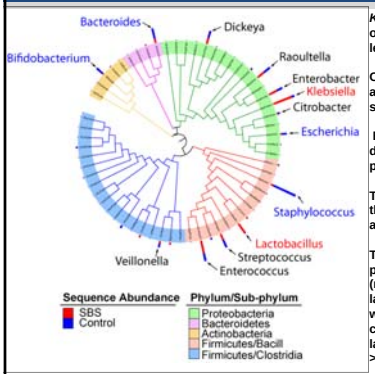
• Collaboration with Drs. Frank and Pace at Univ. of Colorado, Boulder

• 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).**

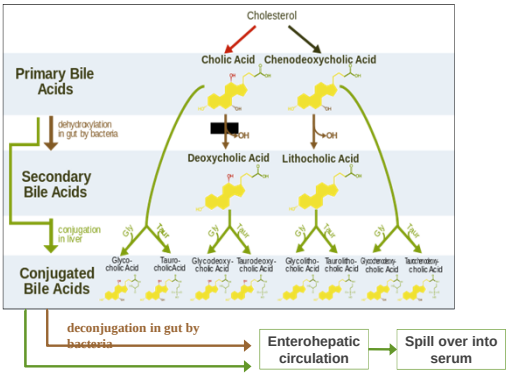
Other genera, such as *Enterococcus* and *Lactobacillus* also enriched in the stool of infants with SBS.

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 [a], D.L. Harrison [b], J.M. Gilbert [b] and G.M. Mupthy [c]

[a] Clinical Mass Spectrometry Laboratory, Department of Gastroenterology and Nutrition, Children's Hospital Medical Center, Cincinnati, Ohio (USA), [b] Clinical Mass Spectrometry Section, Clinical Research Centre, Harrow, Middlesex, HA1 3UJ (UK) and [c] Gastroenterology Unit, Department of Medicine, Guy's Hospital and Medical School, London (UK)

(Received August 27th, 1984; revision July 23rd, 1985)

- Identified **deoxycholic acid** as potential marker for small bowel bacterial overgrowth

SBBO and Unconjugated bile acids

Digestive Diseases and Sciences, Vol. 45, No. 2 (February 2000), pp. 407–414

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

TONATIUH MELGAREJO, PhD, DAVID 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. TANGERMAN, A. VAN SCHAIK, E. W. VAN DER HOEK* & J. H. M. VAN TONGEREN Department of Medicine, Division of Gastroenterology, University Hospital Nijmegen, Nijmegen and *Department of Medicine, Carolus Hospital, Den Bosch, The Netherlands

Received 21 October 1988 and in revised form 10 March 1989

- 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)

Treatment

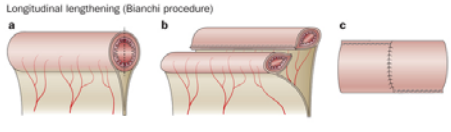
- **Little good data on treatment regimens in SBS**
  - **Medications**
    - **Metronidazole**
    - **Ciprofloxicin**
    - **Amoxicillin**
    - **Augmentin**
    - **Rifaximin**
    - **Nitazoxanide(Alinia)**
  - **? Probiotics or prebiotics**
  - **Dietary**
    - **Low carbohydrate formula**
    - **Hydrolyzed formula**

Cole CR et al , J Pediatr 2010;156: 941-7
Cole and Ziegler. Curr Gastroenterol Rep. 2007; 9:456-62

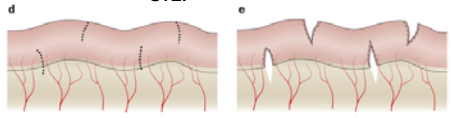
Treatment

- **Little good data on treatment regimens in SBS**
  - **Surgery**

Bianchi Procedure



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

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Thank you!!!

Conrad.Cole@cchmc.org