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Pediatric small intestine bacterial overgrowth in low-income countries

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Small intestine bacterial overgrowth (SIBO) occurs when colonic quantities of commensal bacteria are present in the small bowel. SIBO is associated with conditions of disrupted gastrointestinal (GI) motility leading to stasis of luminal contents. Recent data show that SIBO is also found in children living in unsanitary conditions who do not have access to clean water. SIBO leads to impaired micronutrient absorption and increased GI permeability, both of which may contribute to growth stunting in children. SIBO also disrupts mucosal immunity and has been implicated in oral vaccination underperformance and the development of celiac disease. SIBO in the setting of the impoverished human habitats may be an under-recognized cause of pediatric morbidity and mortality in the developing world.

Revisiting SIBO in developing-world children

The human GI tract is a complex organ system that is unique for its interactions between the epithelial cells that line the gut, the immune cells that infiltrate the mucosa, and the microbes in its lumen that comprise the microbiota (see Glossary). The microbiota is a dynamic entity that begins in the oral cavity with approximately 200 species of bacteria [1]. Descending through the GI tract, the quantity and diversity of bacteria increase, with 10^2–10^3 colony-forming units (CFU)/ml in the upper small intestine, 10^8 CFU/ml in the ileum, and as many as 10^{11} CFU/ml comprising up to 500 species in the colon [1,2]. Work has been done recently to better understand the effect of these bacteria on local and systemic immunity, nutrient absorption, and downstream effects of microbe metabolism in the gut. The focus of much of this research has weighed heavily toward the composition of the microbiota rather than the quantity. In light of new insights into the interactions of the gut flora with their host, it may be time to reinvestigate the effects of excess endogenous flora in the small bowel, especially as it relates to the health of children in the developing world.

SIBO is defined as greater than 10^5 CFU/ml of bacterial growth in upper small intestine luminal fluid. SIBO was thought to be a secondary condition resulting from abnormalities in gut structure and function that lead to stasis of intestinal contents. However, recent studies indicate that SIBO can occur in impoverished living conditions even without a structural gut abnormality [3–5]. Although the evidence remains limited to a scarce number of associative studies, SIBO in this setting has been implicated in nutrient malabsorption [6,7], decreased efficacy of oral vaccination [8], and increased intestinal translocation [9,10] and has been linked to celiac disease that is unresponsive to dietary change [11]. The effects of SIBO in developing-world youth may therefore be both subclinical and pervasive and deserve further investigation.

The dilemma of diagnosis in the pediatric research setting

The gold standard for SIBO diagnosis is culture of a jejunal aspirate obtained via endoscopy plated on both aerobic and anaerobic media. Greater than 10^5 CFU/ml of aspirate is considered diagnostic of SIBO. However, as endoscopy is invasive and not ethical for research purposes, hydrogen breath testing has been used as a noninvasive means of diagnosis. A fasting subject is given a standard quantity of

Glossary

Aboral flow: movement of gastrointestinal contents toward the rectum.
Celiac disease: an autoimmune disorder occurring in genetically predisposed persons that is precipitated by the ingestion of gluten and causes intestinal mucosal damage and inflammation. Systemic symptoms may also be present.
Commensal flora: microorganisms present in specific niches of the human body, interacting in a fashion commensal to the host.
Dysbiosis: alterations in the microbiota, usually associated with disease or clinical symptoms.
Hydrogen breath test: a means of detecting small intestinal overgrowth by detecting increased fermentation of a carbohydrate substrate (glucose or lactulose) by luminal bacteria, as measured by hydrogen exhaled in breath.
Lactulose:mannitol (L:M) ratio test: a means of detecting increased intestinal permeability by comparing the urinary excretion of two carbohydrates, one that does not permeate a healthy gut (lactulose) and one that does (mannitol). A high ratio indicates increased intestinal permeability and/or decreased absorption.
Microbiota: the species composition of the microbial population of a particular niche.
Migrating motor complex: a recurrent, cyclic motility pattern in the stomach and small intestine that maintains aboral flow of luminal contents during the interdigestive phase.
Small intestine bacterial overgrowth (SIBO): defined as greater than 10^5 CFU/ml of bacterial growth from small intestine luminal contents, usually representing an increase in small bowel flora over physiological levels.
Zonula occludens: tight junctions formed by the fusion of integral proteins of the lateral cell membranes of adjacent epithelial cells, limiting transepithelial permeability.

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glucose or lactulose, which enteric commensals ferment producing hydrogen that is absorbed and transported to the lungs, where it is exhaled. The protocol for conducting and interpreting hydrogen breath tests in children is not standardized. The 2009 Rome Consensus Conference on Breath Testing recommended glucose over lactulose for SIBO diagnosis, citing several trials in which glucose had better diagnostic accuracy [12]. The consensus paper also recommended using a cut-off of increased breath hydrogen by $\geq$12 ppm over patient baseline within the 2–3-h test window for diagnosis of SIBO [12]. However, these recommendations are based on studies of adults and thus generalization to children is questionable.

SIBO associated with unsanitary living conditions

To date, only three studies have been conducted in children in low-income countries to investigate the prevalence of SIBO and its association with sanitation (Table 1). While one must be cognizant of publication bias with such a small body of literature, the results of these studies are persuasive. Periera *et al.* first investigated SIBO in developing-world children in a cohort of 340 children under the age of 5 years in rural Burma (Myanmar) [5]. The prevalence of SIBO (as diagnosed by hydrogen breath testing) was 12.5% in the first year of life, increased to 27.8% by the end of the second year, and remained in the 20–30% range through age 5 years. No control group was used nor comparisons made with breath tests in other populations [5]. Dos Reis and colleagues expanded on these findings in a study where 50 asymptomatic children aged 5–11 years living in an urban slum in Brazil were compared with a matched control group of 50 children who lived in the same city but had the financial resources to seek health care at a private clinic [4]. The prevalence of SIBO in the slum-dwelling children was 37.5%, whereas only 2.1% of the control group had the condition. This study suggested that the development of SIBO was related to socioeconomic status and resulting sanitation [4]. Mello *et al.* substantiated these results in another Brazilian cohort of 6–10-year-old children [3]. Eighty-five children living in an urban slum were compared with 43 private-school children. The slum children had a SIBO prevalence of 30.9%, while the controls had a 2.4% prevalence [3]. In a subgroup of 20 SIBO-positive subjects, a 14-day course of trimethoprim–sulfamethoxazole and metronidazole had a 95% reversal rate in positive SIBO lactulose breath tests, with a threefold reduction in hydrogen production tested 1 month after treatment [13]. Only results of breath tests were assessed and thus the effect on the clinical features of SIBO was not investigated. Despite the small sample size and noncontrolled design, these results supported the notion that SIBO was both present and treatable with generic, relatively inexpensive, and widely available antibiotics. Relapse in SIBO after treatment is common but was not assessed by this study [13].

Together, these three studies suggest that the improper sanitation that accompanies poverty predisposes children to SIBO. However, no mechanistic explanation for why these children develop SIBO has been offered. Furthermore, with two of the studies in similar populations (Brazilian children) and different breath hydrogen testing protocols utilized in each study, the causative relationship between living in a resource-poor setting and development of SIBO remains speculative.

Possible mechanism of SIBO development in the setting of unsanitary living conditions

SIBO has long been understood in the developed world as a condition that arises in the setting of altered GI motility. SIBO is most commonly associated with anatomic abnormalities of the GI tract that lead to GI stasis and subsequent overgrowth of commensal bacteria. Such disorders include blind-loop anatomy, intestinal stricture, and small bowel diverticulosis [1]. Motility disorders leading to delayed intestinal transit times also lead to stagnation of luminal contents and overgrowth. SIBO due to decreased aboral flow of luminal contents has been described in systemic scleroderma and diabetes mellitus [14–16]. In the developed world SIBO has been shown to be reversible with improved gut motility using octreotide, a somatostatin analog that stimulates aboral flow [16].

It is our hypothesis that the mechanism of SIBO development in the setting of unsanitary living conditions stems from repeated exposure to abnormal levels of lipopolysaccharide (LPS) via contaminated soil and drinking water, which abrogates the migrating motor complex leading to luminal stasis. The migrating motor complex consists of waves of electrical activity that originate in the stomach and sweep through the intestine during the interdigestive period, maintaining aboral flow of luminal contents. In animal models, *Escherichia coli*-derived LPS has been shown to decrease both the frequency and strength of small intestinal contractions and to eliminate the migrating motor complex [17,18]. In a germ-free mouse model, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* effected an increase in the migrating motor complex, while *Micrococcus luteus* and *E. coli* had inhibitory effects [19,20]. In female patients with late radiation enteropathy, a diminished migrating motor complex was associated with overgrowth of Gram-negative bacilli in the small intestine [21]. The implication of these studies is that constant exposure to Gram-negative bacillus-derived LPS can lead to a diminished migrating motor complex and stasis of luminal contents during the interdigestive period. This stasis then leads to overgrowth of colonic-type flora in the small intestine.

Recent studies have shown that children living in low-income settings have increased exposure to enteropathogenic Gram-negative bacteria compared with controls, creating a setting for the development of SIBO. Bangladeshi infants living in an urban slum had a high enteropathogen burden (i.e., three to five enteropathogens identified in non-diarrheal stool at any one time) that was evident as early as the first month of life [22]. By contrast, children of mid-to-high socioeconomic status in the USA had a frequency of enteropathogens of less than one. This difference in enteropathogenic exposure continued throughout the first year of life, demonstrating the intensity of fecal–oral contamination very early in life [22]. Through observation of infant–caregiver pairs in rural Zimbabwe, common sources of fecal–oral contamination were found to include food, the infant's hands, toys, utensils, the mother's hands,