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Pediatric Small Intestinal Bacterial Overgrowth in Low-Income Countries

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Abstract

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 GI motility leading to stasis of luminal contents. Recent data show that SIBO is also found in children living in unsanitary conditions that 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 habitat may be an under recognized cause of pediatric morbidity and mortality in the developing world.

Keywords

Small intestine bacterial overgrowth; commensal bacteria; environmental enteropathy; malnutrition; oral vaccine failure; celiac disease

Revisiting Small Intestine Bacterial Overgrowth in developing world children

The human gastrointestinal (GI) tract is a complex organ system that is unique for its interactions between the epithelial cells that line the gut, 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 comprised of up to 500 species in the colon[1, 2]. Much work has been done recently in order 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 work has weighed heavily

toward the composition of the microbiota, rather than the quantity. In light of new insights on the interactions of the gut flora with their host, it may be time to re-investigate the effects of excess endogenous flora in the small bowel, especially as it relates to the health of children in the developing world.

Small intestine bacterial overgrowth (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], 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, pervasive, and deserving of 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 non-invasive means of diagnosis. A fasting subject is given a standard quantity of 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 cutoff of increased breath hydrogen by 12 ppm over patient baseline within the 2–3 hour 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 breath hydrogen 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 comparison of breath tests to other populations made[5]. Dos Reis and colleagues expanded on these findings in a study where fifty asymptomatic children aged 5 to 11 years old living in an urban slum in Brazil were compared to a matched control group of fifty children who lived in the same city but had the financial resources to seek healthcare at a private clinic[4]. 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 to 10 year old children[3]. 85 children living in an urban slum were compared with 43 private school children. The slum children had an SIBO prevalence of 30.9%, while the controls had 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 three-fold reduction in hydrogen production tested one month after treatment[13]. Only results of breath tests were assessed and thus, the effect on clinical features of SIBO was not investigated. Despite the small sample size and non-controlled 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 would develop SIBO has been offered. Furthermore, with two of the studies in similar populations (Brazilian children) and varying 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 analogue 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 intestines 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 model of germ-free mice, *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 bacillary 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 as compared to controls, creating the set up for development of SIBO. Bangladeshi infants living in an urban slum had a high enteropathogen burden (i.e. 3–5 enteropathogens identified in non-diarrheal stool at any one time) that was evident as early as the first month of life[22]. In contrast, children from mid to high socioeconomic status in the U.S. 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, an infant's hands, toys, utensils, mother's hands, mother's breasts, sibling's hands, and soil, demonstrating that sources of fecal oral transmission are not limited to dietary exposure and even exclusively breast fed infants are at risk[23]. Changes in systemic endotoxin levels indicating altered GI tract permeability have been documented in children under one year of age, despite breastfeeding, emphasizing the point that even breastfed children are exposed to pathogens via the fecal-oral route[24]. With repeated and persistent exposure to LPS, the gastrointestinal tract may develop a functional motility disorder leading to intestinal stasis and overgrowth of commensal flora.

SIBO and childhood growth and development

The classic nutritional phenotype of SIBO and the mechanisms of its development are well described. SIBO causes vitamin B12 deficiency, steatorrhea due to fat malabsorption with resultant deficiencies in fat soluble vitamins (except vitamin K), hypoproteinemia, and poor carbohydrate absorption. B12 is utilized by commensals in both free and bound forms, depriving the host of B12 for absorption in the ileum[25–27]. Steatorrhea and fat malabsorption is primarily due to deconjugation of bile acids by luminal bacteria[28, 29] and symptomatic deficiencies in the fat soluble vitamins A[30], D[31, 32], and E[33] have been reported. SIBO is not associated with vitamin K deficiency as commensal production offsets fecal loss[34, 35]. Deficiencies of vitamins B2, B6, folate, thiamine, and nicotinamide have also been documented in the setting of SIBO, mostly in adult studies and case reports[36–38]. Deficiencies in thiamine and nicotinamide are particularly concerning in the context of developing world children as both can be associated with loss of cognitive function. Hypoproteinemia due to loss of absorptive surface along the intestine and destruction of brush boarder enzymes is common and can mimic the severe protein malnutrition of kwashiorkor[39–43]. Similarly, a diminished absorptive surface and destruction of brush boarder enzymes leads to decreased carbohydrate degradation and absorption in patients with SIBO[44–47].

While the effect of SIBO on nutrition when overgrowth is due to anatomic abnormality or slow gastrointestinal motility has been well studied, less work has been done on children living in unsanitary conditions. Only two studies link the presence of SIBO in the

developing world to nutrition and only one of these attempted to define causality. In a study of Nigerian children from a low income setting, Omoike *et al.* demonstrated that children with clinical malnutrition had higher rates of SIBO, as diagnosed by quantitative culture of duodenal aspirate, when compared to well-nourished controls[48]. This study confirmed previous reports that SIBO is associated with malnutrition but failed to delineate which was the etiologic factor, SIBO or malnutrition[48]. Khin-Maung *et al.* attempted to answer this question in Burmese children aged between one and 59 months, where they demonstrated children with SIBO had a relative risk of 10.7 to malabsorb rice (as defined by hydrogen breath testing after a standardized rice meal) [6]. Children in their study who were designated as rice malabsorbers had a relative risk of 59.7 of having linear growth delay. This group went on to perform a longitudinal study of rice malabsorbers showing they were deficit in linear growth of 2.7 cm/year for children aged 36 to 47 months old, and 1.9 cm/year for children aged 48 to 59 months[7]. This data suggested that the effect of SIBO on carbohydrate absorption is etiologic in malnutrition[6, 7]. No longitudinal studies showing higher rates of malnutrition in children with preexisting SIBO compared to children without overgrowth have been published.

Recently, an increase in gut permeability leading to systemic endotoxemia and a resultant systemic inflammatory process has been implicated in growth stunting. Studies of infants in Gambia and Bangladesh have shown a positive correlation between high lactulose:mannitol ratios, a commonly used test of intestinal permeability, with both high anti-endotoxin antibody levels and lower weight-for-age Z score (WAZ) and height-for-age Z score (HAZ) [49–51]. Such changes have been documented in children as young as one year of age despite exclusive breastfeeding[24]. While the cause of increased intestinal permeability in developing world children is likely multifactorial, involving repeated enteric infections[52] and environmental enteropathy[53], SIBO may also be a contributing factor. SIBO has been shown to lead to tight junction dysfunction via decreased zonula occludens (ZO-1) expression, resulting in increased intestinal permeability as measured by lactulose:mannitol ratio[9, 10] and an increase in systemic endotoxemia[54].

The growing evidence suggests that SIBO may stunt childhood growth via two mechanisms. The first mechanism, decreased absorption and availability of nutrients, has been well established. The second, tight junction dysfunction leading to increased GI permeability and systemic inflammation, has yet to be fully explained. Currently studies are associative and lack investigation into the molecular mechanisms of how SIBO may affect tight junction and gut barrier function, or cause systemic inflammation that ultimately retards childhood growth.

Of great concern is a growing body of evidence demonstrating systemic inflammation, as evidenced by high levels of serum inflammatory cytokines, and linear growth delay are linked to poor neurodevelopmental scores in children as young as two years of age[55–57]. These studies do not elaborate a mechanism for this association but the implications suggest that phenotypes associated with SIBO may contribute to overall loss of cognitive function and productivity throughout the developing world. However, given the immense number of confounding variables involved in childhood undernutrition in the developing world,

longitudinal studies are needed to further assess the impact of SIBO on childhood growth and development in low income settings.

Commensal regulation of GI immune and barrier function

Our understanding of commensal interactions with the gut immune system has expanded immensely over the last decade. This new information has important implications for understanding the pathogenesis of SIBO (Figure 1). Commensal flora regulate both the intestinal barrier as well as intestinal immune function to maintain gut homeostasis via complex interactions that allow for a basal level of immune signaling while dampening inflammatory immune responses. These mechanisms have been excellently reviewed elsewhere[58–60]. It has become clear that dysbiosis, as well as dysfunctional localization of commensals, contributes to various gut pathology and systemic disease.

Although relatively unstudied, immune system deregulation in association with SIBO is logical. In SIBO, histology is often normal but villous atrophy and distortion, mitochondrial swelling, and vacuolization of microvillus membranes have been described[44, 46, 61] (Figure 2). SIBO has been shown to result in increased concentrations of interleukin 6 (IL-6), but not interferon γ (IFN- γ) and tumor necrosis factor α (TNF- α) in the small intestine, especially when SIBO involves colonic-type flora[62]. Total IgA has been shown to be significantly increased in the presence of SIBO with a shift toward increased IgA2 production, while IgG concentrations remain similar to controls[63, 64]. In one study, IgM plasma cells in the intestinal mucosa were decreased compared to controls[64], however other investigations have found increased luminal IgM concentrations in SIBO patients[64, 65]. SIBO has also been associated with both local and systemic derangements in complement and decreased levels of serum IgG subclass 3, the downstream effects of which are less well understood[66].

Commensal bacteria also regulate gut barrier function. Certain commensals, including *lactobacillus* species, are able to increase Paneth cell mucin production, which can be both protective against pathogenic bacteria and serve as nutritional substrate for species with the ability to utilize mucins for energy[67–71]. However, in SIBO, abnormal quantities of luminal mucous can lead to chronic diarrhea[40, 72]. Commensal control of barrier function also includes regulation of intestinal epithelial tight junction integrity[73]. As discussed previously, SIBO is associated with tight junction dysfunction and increased bacterial translocation across the gut mucosa[10, 54].

The clinical effects of dysregulated immunity in the gut due to SIBO remain an outstanding question. Preliminary research has associated SIBO with oral vaccine underperformance and with celiac disease in the developing world setting, both of which may result from changes in local gut immune function.

SIBO and oral vaccine failure

In 1999, Lagos and colleagues demonstrated that Chilean children aged 5 to 9 years with SIBO had significantly lower geometric mean titers after administration of the oral cholera vaccine CVD 103-HgR as compared to children who tested negative for SIBO[8]. Despite

this being the only investigation of the effects of SIBO on oral vaccination, the implications of this work are extensive. Oral vaccinations in general are less effective in the developing world. In order to elicit protective immunity in Indonesian children living in poverty, 10^9 CFU of the oral cholera vaccine CVD 103-HgR was needed, compared to only 10^8 CFU in Americans and Europeans[74]. The same 10-fold higher dosage of CVD 103-HgR was needed to elicit protective immunity in Peruvian adults from lower socioeconomic status whereas the 10^8 CFU dose was effective in Peruvians of higher socioeconomic status, making an environmental predisposition to lower titers likely[75]. A similar result was seen in a comparison of investigational oral cholera vaccines OCV-023, OCV-024, and OCV-028 in children from Nicaragua and Sweden, with *Vibrio cholerae* titers being significantly lower in the Nicaraguan cohort after identical dosing[76].

The discordance in oral vaccine effectiveness between socioeconomic classes is not limited to oral cholera vaccines. Greater than 95% of children in India who developed paralytic polio received at least three doses of the oral polio vaccine and greater than 77% received more than 7 doses[77, 78]. This led some to recommend 5 or 7 doses of oral polio vaccine in lower socioeconomic settings, compared to the three doses recommended for the developed world[79, 80]. Similarly, the pentavalent oral rotavirus vaccine RotaTeq was only 46% effective at preventing severe rotavirus infection in Nicaragua, whereas it was more than 98% effective in Finland[81]. The vaccine had an 89% ability to prevent severe rotavirus diarrhea in the U.S. [82] but was only 64% effective in Vietnam [83], 63.9% effective in Kenya [84], 56% effective in Ghana [84], 43% effective in Bangladesh [83], and 18% effective in Mali [84].

Several hypotheses have been proposed for the discrepancy in oral vaccination efficacy between the developed and developing worlds. Previously excluded hypotheses include lack of a cold chain resulting in damage to the live virus vaccine and interference of co-administered oral vaccinations [85, 86]. Interestingly, increased IgA has been postulated as a cause of oral polio vaccine underperformance in the developing world due to non-specific interference. Given the upregulation of luminal IgA in SIBO, this would suggest a mechanism for the effect seen in Lagos' study[8, 73, 87]. Currently, however, this mechanism remains purely hypothetical. No other published work has studied the effect of SIBO on oral vaccination efficiency and thus studies are needed to establish whether what Lagos observed is unique to CVD 103-HgR. Oral polio and oral rotavirus vaccines are logical choices for future investigation, being the most relevant oral vaccines to children in resource-limited countries.

SIBO and Celiac Disease

Further evidence of a dysregulated microbiota leading to disease is mounting in the description of the link between SIBO and celiac disease. Celiac disease has recently been recognized as under-diagnosed in the developing world. Shared ancestry, and thus shared human leukocyte antigen (HLA) haplotypes which predispose to celiac disease, have been implicated suggesting that the problem is not new but newly recognized[88]. Although the rise in celiac disease diagnosis in the developing world may be due to more widely available diagnostics, the low-income environment may also be etiologic. SIBO has been shown to be

present in celiac patients living in low-income countries who are non-responsive to gluten-free diets, with resolution of symptoms after antimicrobial therapy directed at SIBO[89, 90]. Interestingly, while 9% of celiac disease patients in Minnesota, U.S. had SIBO, 20% of celiac disease patients in northern India were SIBO positive[11, 91].

Recent work has shown the etiology of celiac disease may be multifactorial, with intestinal flora playing a role. While *Bifidobacterium bifidum* was protective against gliadin-induced changes in intestinal mucosa, the presence of enterobacteriaceae lead to increased gliadin-induced mucosal damage. Furthermore, the enterobacteriaceae led to increased gliadin translocation via changes in ZO-1 expression, decreasing tight junction integrity[92]. An increase in overall bacterial colonization of the GI tract was shown to affect the GI tract response to gliadin, with an increase in luminal anti-gliadin antibody production in the setting of SIBO[93]. It is plausible that the tight junction dysfunction and subsequent gliadin translocation associated with SIBO is, in part, responsible for celiac disease in the developing world. Again, the paucity of data to elucidate causality in the relationship between celiac and SIBO necessitates further study.

Concluding remarks and future perspectives

Currently, the effects of SIBO due to unsanitary living conditions are unclear. There are many unanswered questions regarding its pathogenesis, natural history, and deleterious effects (Box 1). However, the current body of evidence suggests significant morbidity for children in the developing world. It is our hypothesis that SIBO contributes to malnutrition, oral vaccine failure, and celiac disease in developing world children (Figure 3).

As malnutrition is estimated to contribute to as much as a third of all childhood deaths and as many as 25% of the world's children are stunted, defining predisposition to malnutrition and its downstream effects, both physical and cognitive, is a global imperative[94, 95]. SIBO is a known cause of nutrient malabsorption and may partially explain findings that antibiotics improve weight gain during treatment of severe acute malnutrition[96]. A focus on treatable factors predisposing to malnutrition should be a priority, especially when therapy is safe, widely available, and cost effective. Thus, clarifying the effect of SIBO on nutrition and development in impoverished children should be a research priority.

Furthermore, the oral polio and rotavirus vaccines have demonstrated a need to improve oral immunizations for the impoverished gut. Globally, the oral polio vaccine is being phased out and replaced with inactivated polio vaccine to decrease vaccine derived cases in a final push of the eradication campaign. However, over 400,000 children under the age of five die each year due to rotavirus infection, making improving oral vaccination urgent[97]. Again, preventable causes of oral vaccine failure should be specifically targeted. Although the evidence of the contribution of SIBO to oral vaccine failure is limited to a single study, the biologic plausibility of commensals causing immune dysregulation is growing with our increasing knowledge of how gastrointestinal flora interact with the human host. Further research is needed to clarify the association between SIBO and oral vaccine failure and to further elucidate the molecular mechanisms involved. Increased understanding will justify

pre-treatment of children or lead to development of more effective oral vaccines designed for use in the developing world.

Improved sanitation is clearly a global priority. Until this can be achieved efforts must be directed to identify and combat the effects of unclean drinking water and fecal contamination of the human environment. SIBO is a condition with available and affordable treatment that may have far reaching detrimental effects on the human condition. Minimal literature exists on SIBO and its effects in the developing world and thus future study is needed of this potentially significant cause of worldwide pediatric morbidity.

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Glossary

Aboral flow	Movement of gastrointestinal contents toward the rectum.
Celiac disease	An autoimmune disorder occurring in genetically predisposed persons which is precipitated by 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 commensal fashion to the host.
Dysbiosis	Alterations in the microbiota, usually associated with disease or clinical symptoms.
Hydrogen breath test	A means of detecting small intestinal bowel overgrowth by detecting increased fermentation of a carbohydrate substrate (glucose or lactulose) by luminal bacteria, as measured by hydrogen exhaled in breath.
Lactulose:Mannitol ratio test (L:M ratio)	A means of detecting increased intestinal permeability by comparing urinary excretion of two carbohydrates, one which does not permeate a healthy gut (lactulose) and one which 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 intestinal bacterial overgrowth (SIBO)	Defined greater than 10^5 CFU/ml of bacterial growth from small intestine luminal contents, usually representing an increase in small bowel flora over physiologic levels.
Zonula occludens	Tight junctions formed by the fusion of integral proteins of the lateral cell membranes of adjacent epithelial cells, limiting transepithelial permeability.

Box 1. Outstanding Questions

- What is the optimal protocol for hydrogen breath testing in children?
- Is SIBO caused by fecal contamination of soil and drinking water? If so, by what mechanism does fecal-oral contamination lead to SIBO?
- What are the long-term effects of SIBO on children in the developing world?
- Does SIBO predispose children to malnutrition, growth stunting, or poor cognitive outcomes?
- Does SIBO cause oral vaccine underperformance?
- Is SIBO a contributing factor to the development of celiac disease?
- How can SIBO be best treated and what will be the outcomes on child health?

Figure 1. Proposed immune response to overgrowth of commensal flora in the small intestine

The left panel shows a normal upper intestinal environment representing bacterial colonization of 10^2 , while the right panel shows an increase in commensal colonization to $>10^5$, indicative of small intestine bacterial overgrowth (SIBO). Commensals have the ability to downregulate NF- κ B via inhibition of I κ B- α ubiquitination, just one of the ways in which they dampen the local immune response. It is possible that this dampened immune system allows enhanced virulence of pathogenic species. Furthermore, commensals increase Paneth cell mucin production which, in SIBO, can lead to diarrhea. SIBO stimulates an increase of IgA which may contribute to oral vaccination failure. SIBO has also been associated with presence of luminal anti-gliadin antibodies which are considered a precursor of celiac disease. Overgrowth has been shown to disrupt epithelial tight junctions leading to translocation of both gliadin and commensal flora. Increased GI permeability has been associated with systemic inflammation and growth stunting both of which have been shown to be independent risk factors for loss of cognitive function.

Figure 2. Biopsies of normal mucosa and mucosa in a subject with SIBO

(A) Biopsies from normal jejunal control (left panel) and test subject with blind loop anatomy (right panel). Villi in small intestine bacterial overgrowth syndrome become forked at the luminal edge. The muscular layer is thickened. Anaerobic stimulation leads to increased goblet cells and increased mucus production. (B) Electron micrograph of a columnar cell in the mid-villus of a blind loop. The lower cell on the left demonstrates unaltered villi while the right cell, closer to the lumen, demonstrates swollen mitochondria and microvilli that are blunted, swollen, and budding. Figure reproduced with permission from [46].

Figure 3. Hypothesis of small intestine bacterial overgrowth and possible deleterious outcomes relevant to children in the developing world

In the absence of anatomical defects or other gastrointestinal (GI) pathology leading to delayed GI transit, repeated ingestion of enteric fecal-oral pathogens leads to aberrant intestinal motor function which in turn leads to SIBO. SIBO causes altered GI immune function, increased intestinal permeability, and nutrient malabsorption. These outcomes, in turn, may lead to oral vaccine failure, celiac disease, and malnutrition which are major causes of morbidity and mortality in children living in impoverished conditions.

Table 1**Key Studies of Small Intestine Bacterial Overgrowth in Humans^a**

Authors	n	Location	Methodology	Results
<u>SIBO Prevalence in low income settings</u>				
Periera, et al. (Ref 5)	340	Burma (Myanmar)	Prevalence study conducted with lactulose breath testing of rural village infants aged 1–59 months.	SIBO prevalence of 27.2%.
Dos Ries, et al. (Ref 4)	100	Brazil	Prevalence study conducted using both glucose and lactulose breath testing on urban slum children and matched controls aged 5–11 years.	SIBO prevalence of 37.5% in the slum children compared to 2.1% of controls.
Mello, et al. (Ref 3)	128	Brazil	Prevalence study conducted using lactulose breath testing in urban slum children aged 6–11 yrs.	SIBO prevalence of 30.9% in the slum children compared to 2.4% in controls.
Tahan, et al. (Ref 13)	20	Brazil	Subgroup of [6], where SIBO positive children were treated with 14 days of trimethoprim/sulfamethoxazole and metronidazole prior to repeating breath testing.	19 of 20 children had cure of SIBO by breath test criteria 1 month after treatment, with an average 3 fold decrease in breath hydrogen. Relapse was not assessed.
<u>SIBO and Growth and Development</u>				
Omoike, et al. (Ref 48)	52	Nigeria	Duodenal aspirate was collected on 2mo–5yr old children.	Intestinal bacterial counts were significantly higher in malnourished children when compared to children with normal anthropometric indices.
Khing-Maung, et al. (Ref 6)	256	Burma (Myanmar)	Lactulose hydrogen breath testing on children was compared to hydrogen breath testing after a rice meal in 1–59 month old village children.	33% of rice malabsorbers had SIBO. Rice malabsorption conveyed a relative risk of 59.7 for being malnourished.
Riordan, et al. (Ref 9)	68	Australia	Intestinal aspirate was collected on adult subjects and the presence of SIBO was correlated to L:M ratios.	L:M ratios were significantly higher in patients with SIBO.
Miele, et al. (Ref 10)	35	Italy/United Kingdom	In adult patients with nonalcoholic fatty liver disease glucose breath testing was compared to the 51Cr-EDTA test of intestinal permeability. Subjects also had intestinal biopsy with immunohistochemical staining for ZO-1.	SIBO was significantly associated with increased intestinal permeability and decreased ZO-1 expression.
Bauer, et al. (Ref 53)	53	Switzerland	Adults with cirrhosis had jejunal culture compared to a Limulus amoebocyte assay (a measure of endotoxemia).	SIBO was significantly associated with increased systemic endotoxemia.
<u>Intestinal Immunity in SIBO</u>				
Riordan, et al. (Ref 62)	52	Australia	Endoscopy was performed in adult patients with known GI disorders. Villus height, crypt depth, counts of intraepithelial lymphocytes, lamina propria total mononuclear cells, IgA, IgM, and IgG plasma cells, mast cells, and B and T lymphocytes populations were determined in relation to the presence or absence of SIBO.	Lamina propria IgA plasma cell counts were significantly increased in subjects with SIBO.
Fagundes-Neto, et al. (Ref 61)	16	Brazil	Infants with persistent diarrhea had endoscopy performed and electron microscopy performed of biopsy specimens.	SIBO was associated with a mucus-fibrinoid pseudomembrane partially coating the enterocytes.
Riordan, et al. (Ref 64)	18	Australia	Adult subjects had endoscopy performed with culture of proximal small-intestinal luminal secretions and measurement of luminal INF- γ , IL-6, and TNF- α concentrations.	Patients with SIBO had increased concentrations of IL-6 but not INF- γ and TNF- α in the small intestine, especially when SIBO involved colonic-type flora.
Riordan, et al. (Ref 64)	33	Australia	Elderly adults had endoscopy performed with culture of proximal small-intestinal luminal secretion and luminal measurement of IgA, IgM, total IgG, IgG subclass, and IgD concentrations.	Luminal concentrations of IgA2 and IgM were significantly increased in patients with SIBO.

Authors	n	Location	Methodology	Results
<u>SIBO in Oral Vaccine Underperformance</u>				
Lagos, et al. (Ref 8)	202	Chile	Children aged 5–9 years had lactulose breath tests 1 day before ingesting the oral cholera vaccine CVD 103-HgR. Titers were measured 10 days after vaccine administration.	Presence of SIBO was associated with lower geometric mean titers of antibody to the CVD 103-HgR vaccine.
<u>SIBO in Celiac Disease</u>				
Tursi, et al (Ref 88)	15	Italy	Adult patients with known celiac disease who had symptoms unresponsive to a gluten-free diet had lactulose breath testing performed. Those with SIBO were treated with a 7 days of Rifaximin.	10 of 15 patients had SIBO. Symptoms in all 10 patients with SIBO responded to Rifaximin treatment.
Rana, et al. (Ref 90)	174	India	87 patients with confirmed celiac disease had glucose hydrogen breath testing conducted and were compared to age-sex matched controls.	The prevalence of SIBO among celiac patients was 20.7%. No SIBO patients were identified in the control group.
Riordan, et al. (Ref 92)	26	Australia	Adults had endoscopy with culture of proximal small-intestinal luminal secretion and luminal measurement of total IgA, IgA-antigliadin antibody, and local mucosal IgA-plasma cells. Corresponding serum anti gliadin antibody concentrations were also measured.	Presence of SIBO was significantly associated with increases in luminal total IgA concentrations, mucosal IgA-plasma cell counts, and intraepithelial lymphocyte counts. Luminal IgA-antigliadin antibodies were detected in 35.3% subjects with SIBO in none of the subjects without SIBO.
Rubio-Tapia, et al. (Ref 11)	149	U.S.	Adults with celiac disease had endoscopy performed with culture of proximal small-intestinal luminal secretion. No control group was assessed.	Prevalence of SIBO in the study cohort was 9.3%.

^a Abbreviations: IFN- γ , interferon γ ; IL-6, interleukin 6; SIBO, small intestinal bacterial overgrowth; TNF- α , tumor necrosis factor α ; ZO, zonula occludens.