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Risk factors for small bowel bacterial overgrowth and diagnostic yield of duodenal aspirates in children with intestinal failure: a retrospective review

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Abstract

Background—Children with intestinal failure (IF) are at risk of small bowel bacterial overgrowth (SBBO) due to anatomic and other factors. We sought to identify risk factors for SBBO confirmed by quantitative duodenal culture.

Methods—A single center retrospective record review of children who had undergone endoscopic evaluation for SBBO (defined as bacterial growth in duodenal fluid of $>10^5$ CFU/mL) was performed.

Results—We reviewed fifty-seven children with median (25–75th%) age 5.0 (2.0–9.2) years. Diagnoses included motility disorders (28%), necrotizing enterocolitis (16%), atresias (16%), gastroschisis (14%), and Hirschprung's disease (10.5%). Forty patients (70%) had confirmed SBBO. Univariate analysis showed no significant differences between patients with and without SBBO for the following variables: age, sex, diagnosis, presence of ileocecal valve, and antacid use. Patients receiving parenteral nutrition (PN) were more likely to have SBBO (70% vs. 35%, P = .02). Multiple logistic regression analysis confirmed that PN administration was independently associated with SBBO (adjusted OR= 5.1; adjusted 95% CI 1.4–18.3, P = .01). SBBO was not related to subsequent risk of catheter-related blood stream infection.

Conclusion—SBBO is strongly and independently associated with PN use. Larger, prospective cohorts and more systematic sampling techniques are needed to better determine the relationship between SBBO and gastrointestinal function.

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Keywords

Intestinal failure; Short bowel syndrome; Small bowel bacterial overgrowth; Catheter related bloodstream infection; Intestinal adaptation

Introduction

Intestinal failure (IF) is a consequence of either intrinsic intestinal enteropathies, massive small bowel resection resulting from disease processes such as necrotizing enterocolitis (NEC), congenital anomalies, or dysmotility syndromes. Medical management of children with IF is challenging because of the various associated medical and surgical complications. Small bowel bacterial overgrowth (SBBO) and catheter related blood stream infections (CRBSI) are two of the most common complications with a direct impact on morbidity and mortality [1, 2].

A component of intestinal adaptation after gastrointestional resection is bowel dilatation. SBBO is thought to be a direct result of intestinal dilation and subsequent stasis, which in turn promote excess bacterial proliferation and inflammation [3]. In children with SBBO, enteral nutrition (EN) tolerance is often limited because of symptoms associated with intestinal malabsorption, which renders them dependent on parenteral nutrition (PN). The administration of PN requires a central venous catheter and hence increases the risk for CRBSI in these children.

There are some data to suggest that children with IF have increased intestinal permeability, and it has been hypothesized that SBBO can be a potential source of bacteria contributing to CRBSI [2, 4, 5]. Bacterial translocation has been noted in animal models but data supporting its occurrence in humans is limited [6–8]. In addition, the medical literature describing the clinical and microbiologic features of SBBO in children is limited. In a cohort of children with IF, we therefore sought to determine possible predictors of SBBO confirmed by quantitative duodenal cultures, and to study the relationship between SBBO and CRBSI.

Methods

After obtaining institutional review board approval (M08-04-0163), we conducted a retrospective chart review of children with IF who were followed at the Center for Advanced Intestinal Rehabilitation (CAIR) at Children's Hospital Boston between April 2006 and November 2010. The CAIR program is composed of a group of gastroenterologists, general and transplant surgeons, nurses, dietitians, pharmacists, and social workers dedicated to the care of IF patients. All patients who underwent upper endoscopy for refractory gastrointestinal symptoms (i.e. abdominal bloating, emesis, and diarrhea or increased stoma output) were included. All patients had endoscopically-obtained duodenal aspirates sent for quantitative aerobic and anaerobic culture. All cultures were prepared and analyzed according to the microbiology guidelines of the Children's Hospital Boston Microbiology Laboratory [9]. Growth of 10^5 CFU/mL or more of any bacterial or fungal species was defined as a positive result for SBBO. Aspirates without any growth or less than 10^5 CFU/mL were considered negative for SBBO.

Statistical Analysis

Associations between possible risk factors and occurrence of SBBO were assessed by Fisher's exact test for binary proportions and the Mann-Whitney *U*-test for medians. Multiple logistic regression was applied to identify independent predictors of SBBO, adjusting for covariate imbalances, with the likelihood ratio test used to assess significance

[10]. A subgroup analysis was performed to examine the association between SBBO and CRBSI using Fisher's exact test for the 2 × 2 table. Statistical analysis was performed using the SPSS statistical package (version 19.0, SPSS Inc./IBM, Chicago, IL). Two-tailed $P < 0.05$ were considered statistically significant.

Results

Fifty-seven patients were identified who underwent upper endoscopy and duodenal aspirate culture during the study period. The underlying IF diagnoses included 16 (28%) patients with primary motility disorders, 9 (16%) with necrotizing enterocolitis, 9 (16%) with intestinal atresias, 8 (14%) with complicated gastroschisis, 6 (10.5%) with Hirschsprung's disease, 3 (5%) with cloacal exstrophy, and 6 (10.5%) with other conditions requiring surgical resection. The median age of the children was 5.0 years (range 2.0–9.2) and 27 (47%) were male. Thirty-four patients (60%) were receiving either full or partial PN at the time of upper endoscopy. The remaining patients received all of their nutrition through the oral route and/or via an enteral feeding tube.

Forty (70%) patients were found to have SBBO and 17 (30%) were not. Table 1 lists details of the spectrum of bacterial species found on duodenal aspirate cultures. The most common gram-positive organisms included *Streptococcus viridans* and *Enterococcus* species. Gram-negative organisms most often found included *Escherichia coli* and *Klebsiella pneumoniae. Candida* was found in two aspirates in association with other bacterial organisms.

Table 2 summarizes factors tested by univariate analysis and multivariable analysis. Univariate analysis did not show significant differences between patients with and without SBBO for the following variables: age, gender, and whether the primary diagnosis was a primary motility disorder. Therapeutic and anatomical differences such as the presence of an ileocecal valve, surgical management with a lengthening procedure, treatment with gastric acid-blocking medicines and ethanol lock therapy for prevention of CRBSI were also not significantly associated with the presence of SBBO. In addition, liver function (as assessed by hepatic transaminase level and bilirubin) and nutritional status (serum albumin) were not found to be associated with SBBO.

Patients receiving PN were significantly more likely to have SBBO (70% vs. 35%, $P = .02$). The length of time that PN was administered before endoscopy was not significantly associated with SBBO. A subset analysis comparing patients based on mode of nutrition (fully enterally fed vs. at least partial PN) demonstrated that those on PN were more likely to be younger ($P < .001$), male ($P = .014$), and have higher ALT ($P = .013$) (Table 3). Multiple logistic regression analysis, controlling for age, gender and ALT as covariates, confirmed that PN administration was independently associated with a higher risk of SBBO (adjusted OR= 5.1; adjusted 95% CI 1.4–18.3, likelihood ratio test 6.68, $P = .01$). Clearly, even after adjustment for age, gender, and ALT differences between patients on PN and those fully enterally fed, PN use was a significant predictor of SBBO with an estimated odds five times higher among patients on PN.

To evaluate the association between SBBO and risk for CRBSI, we determined the occurrence of CRBSI within the 12 months following endoscopy among the 34 children studied who had central venous catheters in place. Of 28 children with SBBO, 10 (36%) developed a CRBSI within one year after endoscopy, compared to 2 (33%) of 6 children without SBBO ($P = .99$). The most common organisms associated with a CRBSI were *Staphylococcus* (non aureus), *Escherichia coli*, and *Klebsiella pneumoniae*.

Discussion

In this retrospective review of 57 IF patients who underwent endoscopic evaluation for SBBO, we found an overall incidence of laboratory-confirmed bacterial overgrowth of 70%. *Escherichia coli* and *Klebsiella pneumoniae* were the most common gram-negative organisms cultured, and *Streptococcus viridans* and *Enterococcus* were the most common gram-positive organisms (Table 1). The spectrum of organisms found in this cohort supports previous findings by our group of the utility and high diagnostic yield of upper endoscopy in children with IF [11]. It also contributes additional data concerning commonly found organisms when considering the empiric treatment of children with symptoms of SBBO.

Among candidate clinical and anatomic factors that were evaluated as potential risk factors for SBBO, the only variable identified in multivariable analysis was use of parenteral nutrition (PN). SBBO and enteritis in children with IF have been shown to strongly influence the duration of PN. In a study by Kaufman et al., children with SBBO required PN for twice as long as those without SBBO. For patients with SBBO and documented enteritis, PN was administered three times longer than for those without SBBO, independent of other factors, such as intestinal length [3]. Although the duration of PN prior to endoscopy was not different in our patients with and without SBBO, our findings show a strong, independent association between PN administration and SBBO and confirm these data.

The association between SBBO and PN dependence is most likely multifactorial. SBBO can cause various degrees of intestinal villus atrophy and mucosal damage, likely related to the effects of endotoxins and proteases produced by anaerobic and aerobic bacteria [12, 13]. Excess bacteria in the intestinal lumen can also cause deconjugation of bile acids, which in turn leads to steatorrhea. In one study, the degree of unconjugated bile acids in the duodenum positively correlated with the degree of SBBO and steatorrhea in children with malabsorption syndrome [14]. In addition, direct damage to the intestinal villi by bile acids and bacterial metabolites can lead to carbohydrate malabsorption. Therefore, it is not surprising that children with SBBO are at risk for increased gastrointestinal malabsorption and the resultant need for parenteral nutrition support.

The use of empiric antibiotics for SBBO has been found in some studies to improve enteral feeding tolerance, as well as to be associated with decreased episodes of sepsis [15, 16]. In 10 children under age 2 with IF due to necrotizing enterocolitis, Cole et al. defined SBBO by abnormal glucose hydrogen breath testing [2]. They noted a high rate of CRBSI's; all five children with SBBO had 2 or more episodes of CRBSI in a four-month time period. The odds of having CRBSI were 7.07 times greater in children with SBBO than among children without SBBO (p=0.009). In our series, however, children with SBBO were equally likely to have subsequent CRBSI than those without SBBO (36 vs. 33%). All children in our series had been initially treated with empiric antibiotics, and this treatment may have obscured the relationship between SBBO and risk of sepsis. Alternatively, the lower rate of CRBSI in our series may have hindered our ability to detect a relationship between bacteria found in the small bowel and blood stream infections. Interestingly, the spectrum of bacteria Cole et al. noted in blood culture results closely mirrored our SBBO results, with a predominance of *Enterococcus* and *Klebsiella pneumoniae* species (Table 1).

In this study we sought to evaluate clinical characteristics that had been previously suggested as predisposing factors for SBBO. For example, gastric hypochlorhydria in a population with prevalent use of proton pump inhibitors and H2 blockers is thought to contribute to the development of excess bacterial burden [17]. Also, patients with altered intestinal peristalsis or with abnormal intestinal anatomy (i.e. surgical blind loops, resected ileocecal valves) are thought to be at risk for altered intestinal motility, which can lead to

SBBO [12]. Although we had hypothesized that a lengthening procedure, primary motility disorders, and/or gastric acid suppression might contribute to the development of SBBO, we were not able to confirm these findings in our dataset (Table 2). Measurements of nutritional status (serum albumin) and liver function (alanine transaminase and total bilirubin) were also not found to be significant risk factors for the development of SBBO.

In addition to our small sample size and the retrospective nature of this study, our data are limited by the fact that children generally underwent endoscopy after empiric antibiotic therapy for SBBO. Thus the data are more likely to represent sicker, more symptomatic patients, which represents an important selection bias. However, empiric therapy for SBBO is often undertaken in these patients, so these results are representative of common clinical practice and are therefore likely generalizable to patients with refractory symptoms.

Our findings confirm a strong association between SBBO and dependence on PN (adjusted OR= 5.1; adjusted 95% CI 1.4–18.3, likelihood ratio test 6.68, $P = .01$). We did not, however, find any significant relationship between positive duodenal aspirates and subsequent risk for CRBSI. Combined with the high diagnostic yield of endoscopy (70%) and the findings of multiple species of gram negative and gram-positive organisms, these data support the use of endoscopy and evaluation of duodenal aspirates for patients with IF. A larger prospective study is needed to independently validate our findings, as well as to better determine any possible relationship between bacterial colonization of the small bowel and gastrointestinal function and adaption after resection. Newer, molecular diagnostic techniques may also help evaluate the possible relationships between SBBO and blood stream infections [18].

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Table 1

Spectrum of bacterial and fungal species found in patients with SBBO (n=40)*

Gram positive	(n)	Gram negative	(n)	Yeast	(n)
S. viridans (alpha)	15	*E. coli*	23	*Candida* species	2
Enterococcus not specified	8	*Klebsiella pneumoniae*	11		
Lactobacillus not specified	4	*Pseudomonas aeruginosa*	6		
Rothia mucilaginosa, S. aureus	4	*Enterobacter cloacae*	5		
Enterococcus faecium, Enterococcus faecalis, Corynebacterium, Stomatococcus	4	*Klebsiella oxytoca*	4		
		Non pathogenic *neisseria, Haemophilus influenzae, Haemophilus* (other types)	5		
		Klebsiella ozonae, Proteus mirabilis, Citrobacter diversus, Citrobacter freundii, Stenotrophomonas maltophilia, Morganella morganii	6		

*Patients had more than one organism present.

n= number of positive duodenal cultures for SBBO.

Table 2

Factors associated with SBBO in 57 children with intestinal failure.

Characteristic	Bacterial Overgrowth		Univariate *P* Value	Multivariable Logistic Regression *P* Value
	Yes (n=40)	No (n=17)		
Age, years, median (IQR)	5 (1.8–8.0)	7.5 (2.2–12.7)	.30	.62
Gender (% Male)	48	47	1.00	.44
Ethanol locks (%)	13	6	.66	
Primary Motility Disorder (%)	30	24	.75	
Lengthening Procedure (%)	18	6	.41	
Presence of ICV (%)	29	25	.75	
PPI/H2 blocker treatment (%)	83	65	.18	
Patients on PN (%)	70	35	.02	.01
Length of PN, months, median (IQR)	27 (11–74)	18 (8–36)	.44	
ALT, unit/L, median (IQR)	39 (20–71)	33 (22–69)	.88	.61
Total Bilirubin, mg/dL, median (IQR)	0.40 (0.20–0.70)	0.35 (0.20–0.60)	.31	
Direct Bilirubin, mg/dL, median (IQR)	0.10 (0.10–0.20)	0.10 (0.10–0.20)	.48	
Albumin, g/dL, median (IQR)	3.70 (3.30–4.20)	4.10 (3.70–4.40)	.12	

P values are factors significant at n=0.05

PN= parenteral nutrition, ICV= ileocecal valve, PPI = proton pump inhibitor, H2= histamine 2, ALT= alanine transaminase.

Table 3

Characteristics of 57 children with IF based on mode of nutrition.

	Mode of Nutrition		
Characteristic	**Parenteral (n=34)**	**Enteral (n=23)**	**Univariate *P* Value**
Age, years, median (IQR)	3.1 (1.6–6.6)	8.9 (3.7–14.6)	**.001**
Gender (% Male)	61.8	26.1	**.014**
Primary Motility Disorder (%)	29.4	26.1	.99
Ethanol locks (%)	17.6	0	.07
Lengthening Procedure (%)	20.6	4.3	.13
Presence of ICV (%)	17.6	39.1	.12
PPI/H2 Blocker Treatment (%)	79.4	73.9	.75
ALT, unit/L, median (IQR)	46.0 (23.5 – 110.5)	28.0 (18.5 – 45.5)	**.013**
Total Bilirubin, mg/dL, median (IQR)	0.30 (0.20 – 0.80)	0.35 (0.20–0.58)	.64
Direct Bilirubin, mg/dL, median (IQR)	0.10 (0.10 – 0.20)	0.10 (0.10 – 0.25)	.15
Albumin, g/dL, median (IQR)	3.70 (3.13 – 4.00)	4.10 (3.60 – 4.50)	.06

P values are significant at n=0.05

PN= parenteral nutrition, ICV= ileocecal valve, PPI = proton pump inhibitor, H2= histamine 2, ALT= alanine transaminase