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ORIGINAL ARTICLE

Small intestinal bacterial overgrowth in children with intestinal failure on home parenteral nutrition

Kathleen H McGrath,*,† James Pitt‡,§ and Julie E Bines*,†,‡

*Department of Gastroenterology and Clinical Nutrition, The Royal Children's Hospital, †Intestinal Failure and Clinical Nutrition Group, Murdoch Children's Research Institute, §Victorian Clinical Genetics Services, Murdoch Children's Research Institute and ‡Department of Paediatrics, The University of Melbourne, Melbourne, Victoria, Australia

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Correspondence
Dr Kathleen H McGrath, Department of Gastroenterology and Clinical Nutrition, The Royal Children's Hospital, Parkville, Vic. 3052, Australia.
Email: mcgrath.kathleen@gmail.com

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Abstract

Background and Aim: Children with intestinal failure (IF) have abnormal intestinal anatomy, secretion, or motility, which impairs homeostatic mechanisms and can lead to small intestinal bacterial overgrowth (SIBO). We sought to describe clinical features at the time of clinically suspected SIBO by experienced clinicians in children with IF on home parenteral nutrition (PN), review specific challenges of diagnostic testing in this population, and describe potential new diagnostic surrogate markers.
Methods: A descriptive single-center retrospective chart review was performed during all episodes of clinically suspected SIBO over 33 months. Information was recorded on clinical symptoms, and diagnostic tests performed.
Results: Of all patients on home PN, 71% (12/17) had at least one episode of clinically suspected SIBO (mean 1 episode/year, range 1–7); 50% of patients had short bowel syndrome (SBS), and 50% had non-SBS IF. The average reported symptoms per episode were 1.9 (range 1–5). Children with SBS reported fewer symptoms per episode (1.5) than children with non-SBS IF (2.3). Diarrhea was the most commonly reported symptom, particularly in children with SBS.
Conclusions: Children with IF on home PN are a high-risk group for SIBO. Clinical features of SIBO vary depending on the cause of IF and may mimic symptoms of the underlying condition. Diagnostic tests have innate challenges in this group, and a strong index of clinical suspicion is paramount. Further research is recommended into potential new surrogate markers (urinary metabolite screen, gastric aspirate) for this diagnostically challenging population.

Introduction

Colonic bacteria are abundant and play an important role in normal metabolic pathways of digestion and absorption. In contrast, bacterial counts in the upper gastrointestinal tract and small intestine are tightly regulated to less than 10^3 colony-forming units (CFU) per milliliter (mL) of a specific species.[1] Small intestinal bacterial overgrowth (SIBO) is a pathological phenomenon where excessive bacteria are present in the small intestine because regulatory systems are impaired. These protective mechanisms include gastric acid secretion, small intestinal motility, ileocecal valve function, pancreatic and biliary secretion, and mucosal immunity. SIBO is traditionally defined as the overgrowth (>10^5 CFU/mL) of bacteria in a small intestinal aspirate, and some definitions include reference to the presence of colonic bacterial species.[2,3] A recent systematic review suggested that these diagnostic criteria are too high and also require consideration of the presence of specific bacterial species.[4]

SIBO is associated with a range of nonspecific symptoms that tend to be chronic, lasting for years in some and fluctuating in intensity.[1] Symptoms may overlap with those of the primary gastrointestinal disorder, delaying suspicion of SIBO, and include diarrhea, vomiting, abdominal pain, bloating, cramping, weight loss, and feed intolerance. Less common clinical manifestations include megaloblastic anemia, osteomalacia, neuropathy, weight loss, and peripheral edema.[5]

Beyond the challenges of its definition, accurate diagnostic testing of SIBO has difficulties in both research and clinical settings. There are three common practices used for the diagnosis of SIBO: quantitative microbiological culturing from a small intestinal aspirate, breath testing techniques using carbohydrates, or the symptomatic clinical response to a trial of antibiotics in the context of clinical suspicion. A combination of techniques has been suggested to strengthen the diagnostic approach; however, all tests have limitations.[6]

The quantitative culture of a small intestinal aspirate has been the traditional gold standard for diagnosing SIBO, although its validity has been questioned.[4] It is an invasive, costly test with limitations including the need for endoscopy, appropriate equipment, and laboratory services. Sampling can be problematic, with

the risk of contamination by oropharyngeal flora, and usually only reflects one portion of the small bowel.[5]

The most common noninvasive test for SIBO is the hydrogen (lactulose or glucose) breath test. Glucose is recommended in preference to the lactulose breath test for the diagnosis of SIBO.[7] The test protocol generally requires periods of dietary modification and fasting followed by ingestion of a concentrated glucose or lactulose solution and collection of repeated end alveolar breath samples using a mask. Protocols and result interpretation may differ between institutions, and SIBO may be missed as a consequence of overgrowth with nonhydrogen-producing bacteria.[8] Despite these limitations, there is evidence supporting this test for the diagnosis of SIBO in adults and older children.[2]

Carbon-labeled breath tests (C-labeled xylose BT) are another tool rarely used because of limited access to equipment and cost.[1] The use of a polymerase chain reaction denaturing gradient gel electrophoresis and bacterial 16S ribosomal DNA sequencing are emerging diagnostic tests not commonly used in clinical practice.

Different urinary tests have been used as indirect or surrogate markers for SIBO by detecting bacterial metabolites, indicating abnormal bacterial colonization in the small intestine (e.g. urinary phenol, indican, Cholyl-PABA, and 4-hydroxyphenylacetic acid).[2,4,9–12] Acetate, lactate, and formate have been shown to be significantly higher in upper gut aspirates of people with malabsorption syndrome and SIBO compared with malabsorption syndrome alone or a control group.[13] These bacterial metabolites can be measured in urine. A study of piglet short bowel syndrome (SBS) models identified specific panels of urinary metabolites associated with the presence of specific small intestinal bacterial species. Thus, urinary metabolite measurements may have a role in assisting the diagnosis of SIBO.[14] Although data are limited, and these tests have not been validated, it is recommended that urinary tests not be excluded from potential lists of diagnostic tests for SIBO.[4]

There is limited literature on the role of gastric aspirate culture in the diagnosis of SIBO. One study showed that it was a less sensitive diagnostic method than small bowel aspirate.[15] To our knowledge, there are no studies specifically assessing gastric bacterial overgrowth (GBO) in children with intestinal failure (IF). Other markers of malabsorption, studied in research and clinical settings for their utility as surrogate indicators of SIBO, include hemoglobin, folate, and vitamin B 12.[5]

Literature from adult studies does not support clinical suspicion as being a sensitive diagnostic modality.[16] In cases where SIBO is recurrent or multiple predisposing factors exist, empirical treatment may be chosen (intermittently or cycling) and monitored by clinical symptoms; however, concerns include potential misuse of antibiotics, development of drug resistance, and risk of *Clostridium difficile* colitis.[16]

Children with IF have abnormalities of intestinal anatomy, secretion, and/or motility, and physiological protective mechanisms regulating small intestinal bacterial counts are impaired, which can lead to SIBO. Children with IF receiving parenteral nutrition (PN) are much more likely to have SIBO than those not on PN, and PN administration has been independently associated with SIBO.[17] Furthermore, SIBO has been linked to a higher incidence of central line-associated bloodstream infections (CLABSI) via bacterial translocation and may impact the establishment of enteral feeding and weaning patients from PN.[18–21] This study aimed to evaluate clinical features present during episodes of clinically suspected SIBO in children with IF on home PN in a specialist tertiary unit with experience managing SIBO and to assess for differences in presentation between SBS and non-SBS patients. We hypothesized that current diagnostic tests for SIBO have additional limitations in children with IF on home PN and sought to review the specific benefits and limitations of these tests in this population using available literature. Furthermore, we describe potential new surrogate markers for SIBO that require further research but may have a future role in this diagnostically challenging population.

Methods

This is a descriptive single-center retrospective chart review. Children with a diagnosis of IF on home PN during the period July 2014 to January 2017 were identified using home PN service records. All patients with clinically suspected SIBO, based on new or unexplained clinical symptoms, had a urinary metabolite screen performed. Episodes were excluded from further analysis if an alternative explanation was identified for the clinical presentation, such as infection or surgical cause. Medical records were retrospectively reviewed for each episode of clinically suspected SIBO, including 2 weeks before and after each episode. Clinical symptoms were identified from medical records and recorded. Diarrhea was defined as increased frequency/volume of stool or decreased consistency of stool from baseline for the individual child for more than 24 h.

The presence and results of diagnostic tests (small intestinal aspirate, hydrogen breath test) including potential new surrogate markers (urinary metabolite screen, gastric aspirate) were recorded. Duplicate tests performed within the same episode of SIBO were only counted once. GBO was defined as bacterial counts greater than 10^5 CFU/mL. Where "bacterial overgrowth" was not specified as the test indication, quantitative organism counts had not been performed by the laboratory and so were only given as qualitative count (profuse, moderate, or scanty growth), and these tests were excluded from further analysis.

The urinary metabolite screen is used for the diagnosis of children with a range of metabolic conditions by a state-wide genetics laboratory. Urinary metabolite screens were performed using gas chromatography–mass spectrometry. A urinary metabolite screen result suggestive of SIBO was defined as the excretion of metabolites previously reported to be associated with SIBO (e.g. indole lactic acid, phenyl lactic acid, fumaric acid, 4-hydroxyphenylacetic acid) of greater than the 99th centile for a control group of children. A specific profile of bacterial metabolites for the diagnosis of SIBO has been developed by our laboratory, informed by research using a preclinical model of SBS in children using a piglet model. [14]

Other markers of malabsorption (folate level, vitamin B12 level) during this period were recorded as possible surrogate indicators of SIBO. The study received ethics approval from the hospital's human research ethics committee (HREC 37374A).

Results

Twelve patients on our home PN program (12/17; 71%) had at least one episode of clinically suspected SIBO between July

Table 1 Frequency of reported symptoms for episodes of clinically suspected SIBO in children with intestinal failure on home parenteral nutrition

Number of reported symptoms per episode	Any intestinal failure (*n* [%])	Short bowel syndrome IF (*n* [%])	Nonshort bowel syndrome IF (*n* [%])
1	14 (41)	9 (56)	5 (28)
2	12 (35)	6 (38)	6 (33)
3	5 (15)	1 (6)	4 (22)
>3	3 (9)	0 (0)	3 (17)
Total	34 (100)	16 (100)	18 (100)

IF, intestinal failure; SIBO, small intestinal bacterial overgrowth.

2014 and January 2017. Five patients were female. Patient age at study commencement ranged from 5 months old to 16 years old. There were three patients (25%) on total PN and nine (75%) on partial PN and enteral nutrition.

The underlying reason for IF was SBS (50%) or non-SBS (enteropathy or dysmotility) (50%). Specific causes of SBS included necrotizing enterocolitis (two), malrotation and volvulus (two), ileal atresia and volvulus (one), and Hirschprungs (one). Causes of non-SBS IF included tufting enteropathy (two), chronic intestinal pseudo obstruction (one), gastroschisis (one), megacystis microcolon intestinal hypoperistalsis syndrome (one), and nonspecified dysmotility (one).

There were 34 episodes of clinically suspected SIBO in total (16 episodes in children with SBS; 18 episodes in non-SBS IF). The mean number of episodes of clinically suspected SIBO was 1.1 episodes/patient/year, with a range of 1–7 episodes per patient during the study period. The average number of reported symptoms per episode was 1.9 (range 1–5). Children with SBS reported fewer symptoms per episode (1.5) than children with non-SBS IF (2.3). Of episodes in all children with IF, 76% had two or fewer reported symptoms (Table 1). The most commonly reported symptom was diarrhea. A trend was noted, with diarrhea as the predominant presenting symptom in SBS (67% of reported symptoms) compared with non-SBS IF (29% of reported symptoms); however, this was not statistically analyzed due to small sample size. Of the patients who reported only one symptom at the time of clinically suspected SIBO, diarrhea accounted for 71% of symptoms. The frequency and pattern of reported clinical features at the time of clinically suspected SIBO are outlined in Figure 1.

Diagnostic testing using the small intestinal aspirate or hydrogen breath test was only performed in three episodes of clinically suspected SIBO (Table 2). All small intestinal aspirates (n = 2) had a positive result for SIBO. Of the episodes, 62% (n = 21) were associated with at least one positive result from the tests performed. Urinary metabolite screens showed a profile suggestive of SIBO in 13 episodes (38%). GBO was detected by the quantitative count of culture in seven of eight gastric aspirate samples, with all episodes occurring in children receiving gastric acid suppression therapy.

Results were available for serum folate assessment in 14 of 34 episodes and serum vitamin B12 assessment in 18 of 34 episodes. A total of 50% of patients had a serum folate level above the normal range (n = 7), and 28% (n = 5) of patients had a vitamin B12 level above the normal range.

Discussion

Clinically suspected SIBO was common in children with IF on home PN. The 12 patients included represented 71% of children on our home PN service during this period, which is similar to previously reported prevalence of SIBO in children with IF undergoing upper endoscopy for refractory gastrointestinal symptoms.[17] We found a similar prevalence of clinically suspected SIBO in children with SBS and non-SBS IF, which again reflects previous data showing no significant difference for the presence of SIBO in children with IF, where the cause was an underlying primary motility disorder.[17] This is in contrast to adult studies where dysmotility has been shown to be a strong influence on

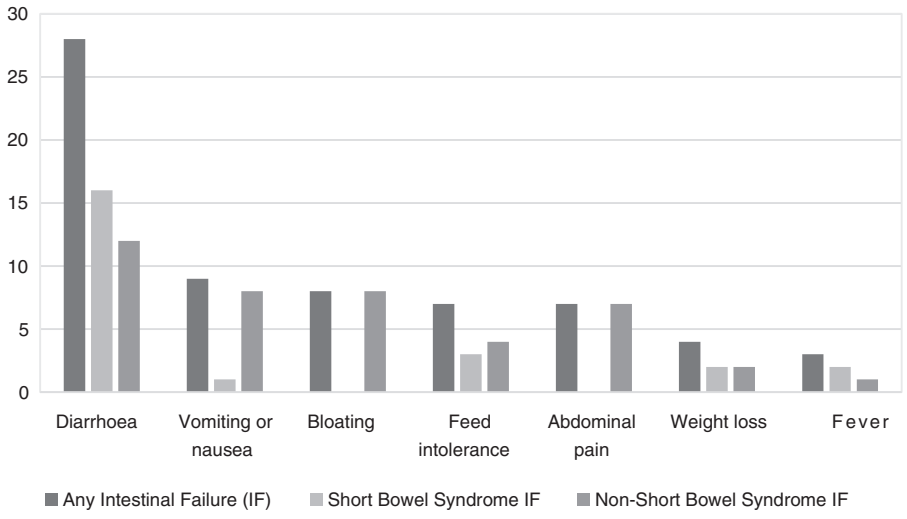

Figure 1 Frequency of reported clinical features at the time of clinically suspected SIBO in children with intestinal failure on home parenteral nutrition.

Table 2 Diagnostic tests and results of diagnostic tests performed during episodes of clinically suspected SIBO in children with intestinal failure on home parenteral nutrition

	Short bowel syndrome intestinal failure (*n* [%])	Nonshort bowel syndrome intestinal failure (*n* [%])	All intestinal failure (*n* [%])
Number of episodes	16	18	34
Urinary metabolite screen			
(i) Number performed	16	18	34
(ii) Number positive (%)	6 (37)	7 (39)	13 (38)
Gastric aspirate culture			
(i) Number performed	4	4	8
(ii) Number positive (%)	4 (100)	3 (75)	7 (88)
Hydrogen breath test			
(i) Number performed	0	1	1
(ii) Number positive (%)	0	0	0
Small Intestinal aspirate culture			
(i) Number performed	1	1	2
(ii) Number positive (%)	1 (100)	1 (100)	2 (100)

SIBO, small intestinal bacterial overgrowth.

the prevalence of SIBO and an independent significant risk factor.[22,23]

There are limited studies assessing the predominant symptoms of SIBO and few in children, especially children with IF.[5] The symptom prevalence rate reported in our study (59% of patients having greater than one symptom reported at the time of clinically suspected SIBO) is lower than rates reported in adults.[24] Eliciting symptoms in children and infants can be difficult and relies on accurate parental reporting and appropriate questioning. Symptoms of SIBO may also be difficult to distinguish from those of underlying IF. The use of a validated symptoms questionnaire would have improved our study and was a limitation of our retrospective chart review, where symptoms may have been underreported or documented.

A recently published review noted a high incidence of diarrhea reported in children with SIBO, with abdominal pain, bloating, and flatulence also commonly reported.[2] Diarrhea and bloating have been found to be the most common symptoms in adults with duodenal culture-proven SIBO.[24] We identified a similar trend, with diarrhea being the most commonly reported symptom, followed by vomiting/nausea, bloating, abdominal pain, and feed intolerance. Diarrhea was found to be predominant during episodes where patients reported only one symptom. We hypothesize that diarrhea may be an early clinical manifestation of SIBO in children with IF on home PN (when infective and surgical causes have been excluded), prompting clinical suspicion and/or early diagnostic testing.

Different symptom profiles may reflect the degree of bacterial overgrowth, extent of mucosal inflammation, bacterial type present, underlying cause of SIBO, or complications of SIBO.[25] We noted different patterns of symptoms in SBS and non-SBS patients at the time of clinical suspicion of SIBO. Diarrhea was predominant in children with SBS, accounting for 67% of reported symptoms compared with 29% of reported symptoms in non-SBS IF. There was more variation and a greater average number of symptoms noted in non-SBS.

The yield and limitations of existing diagnostic tests have been studied extensively in adults but less so in children, including those with IF. This may reflect the inherent challenges of current diagnostic tests in this high-risk patient group but also potential differences between institutions regarding access to endoscopy, specialized laboratories and breath testing facilities, and experience in performing these tests.

Small intestinal aspirate and culture are not an appropriate test for children with mild nonspecific symptoms or for those who may need repeated testing due to associated risks (anesthetic/sedation and endoscopy) and is too invasive for most research purposes.[2]

Protocol compliance and accuracy of results of hydrogen breath testing in children with IF may be affected by procedural anxiety, oral aversion, carbohydrate malabsorption, rapid intestinal transit, delayed gastric emptying, and commonly used medications affecting intestinal transit (prokinetics, antidiarrheals). It is recommended that special pediatric populations, including children with IF and SBS, may require different standards for hydrogen breath testing and interpretation, but these have not yet been defined.[2] Given the high prevalence and typically recurrent nature of SIBO in children with IF on home PN, specific consideration of limitations for the clinical setting is warranted.

Gastric aspirate culture has been shown to be less sensitive than the culture of small intestinal aspirate for the diagnosis of SIBO.[15] There is limited knowledge about gastric bacterial counts in healthy children and children with IF. We found a high rate of GBO at the time of clinically suspected SIBO in samples where a qualitative count was available (seven of eight; 88%). However, there is the potential for contamination through the skin in children with IF who have a gastrostomy tube. The significance of the high rate of GBO at the time of clinical suspicion of SIBO is unclear, but it is possible that gastric dysbiosis may have downstream effects on small intestinal bacteria. In all episodes with a positive gastric aspirate, the patient was receiving acid suppression therapy. Adult studies looking at the association between proton pump inhibitor (PPI) use and SIBO show variable results; however, pediatric data suggest that children may be prone to develop GBO and, potentially, SIBO even after short-term PPI therapy.[2,22,25–28]

The urinary metabolite screen may support the assessment of SIBO by the measurement of coliform metabolites that indicate abnormal bacterial colonization in the small intestine. In this study, 13 (38%) episodes of clinically suspected SIBO had a positive screen. The accessibility of urine collection makes this an attractive option in children. The current study focused on metabolites previously reported to be associated with abnormal bacterial colonization that were significantly increased (>99th percentile of healthy control children). There is scope to refine this test using nontargeted metabolomics methods to identify

additional markers in this cohort and for the use of statistical and multivariate analysis to identify more subtle patterns of metabolites indicative of SIBO. Further research and prospective cross-validation against small intestinal aspirates would help to validate and confirm the role of the urinary metabolite screen in diagnosis of SIBO in clinical practice.

This study had a number of limitations, including retrospective and descriptive methodology. The prospective use of a validated questionnaire would have provided more reliable data than the chart review undertaken. The small sample size affected the ability to perform statistical analysis. There was variability in the diagnostic tests performed and documentation of clinical response after treatment in patients with a negative urinary metabolite screen, which is a limitation of this retrospective study. The challenges inherent to the diagnosis of SIBO affect the ability to perform quality research in this area as there is no undisputed gold-standard test with which to compare other potential diagnostic tests. We explored novel diagnostic tests that may have a future role in assisting with the diagnosis of SIBO in this high-risk group. However, it was not our intention to validate these tests, and we acknowledge their limitations precluding common usage without further research.

SIBO should be considered with a high index of suspicion in children with IF on home PN. This group has a large number of predisposing risk factors, including rapid intestinal transit, ileocecal resection, stoma formation, reduced enteral intake, altered enterohepatic circulation, mucosal inflammation, and medication use (acid suppression therapy, prokinetics, antidiarrheal agents). Clinical predictors include persistent diarrhea from baseline, vomiting/nausea, bloating, abdominal pain, or evidence of malabsorption without an alternative explanation. Small intestinal aspirate and culture is impractical in this patient group and carries inherent risks. Noninvasive hydrogen breath testing is appropriate but may have practical challenges and risk of inaccurate results. Empirical treatment on clinical grounds may be considered where tests cannot be used to make a firm diagnosis. Well-designed, prospective, controlled studies are needed in this complex patient population to evaluate the potential role of noninvasive diagnostic markers such as the urinary metabolite screen and assessment of the gastric aspirate.

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