Epidemiologic Associations Between Short-Bowel Syndrome and Bloodstream Infection Among Hospitalized Children

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Background. Children with short bowel syndrome (SBS) suffer from strikingly high rates of morbidity and mortality, due in part to their susceptibility to life-threatening infectious diseases. Few large, multisite studies have evaluated patient-specific factors associated with bacteremia in hospitalized children with and without SBS.

Methods. We conducted a case-control study to examine the epidemiological associations between SBS and bloodstream infections (BSI) in hospitalized children. Pediatric BSI cases and controls were selected from a prospective cohort study conducted at 3 New York City hospitals.

Results. Among 40 723 hospital admissions of 30 179 children, 1047 diagnoses of BSI were identified. A total of 64 children had a diagnosis of SBS. BSI was identified frequently among hospitalizations for children admitted with SBS ($n = 207/450$, 46%) compared to hospitalizations for children without the condition ($n = 840/40\ 273$, 2.1%, $P < .001$). While this population represented only 0.2% of our overall cohort, it accounted for nearly 20% of all hospital admissions with BSI. Multivariable analysis identified 8 factors significantly associated with pediatric hospitalizations with BSI. These included a diagnosis of SBS (odds ratio [OR] 19.0), ages 1–5 years (OR 1.33), presence of a non-Broviac-Hickman central venous catheter (OR 6.36), immunosuppression (OR 0.53), kidney injury (OR 6.67), organ transplantation (OR 4.44), admission from a skilled nursing facility (OR 2.66), and cirrhosis (OR 7.23).

Conclusions. While several clinical characteristics are contributory to the risk of BSI in children, SBS remains the single strongest predictor. Further research into the mediators of this risk will be essential for the development of prevention strategies for this vulnerable population.

Key words. bacteriology; bloodstream infections; health care-associated infections.

Short bowel syndrome (SBS) is associated with devastatingly high rates of morbidity and mortality among children [1]. Diarrhea and malabsorption are the hallmarks of SBS, which itself is caused by a spectrum of conditions that reduce the small intestine to an insufficient length [2]. In children, the most common etiology of SBS is extensive intestinal resection performed for the treatment of congenital gastrointestinal malformations or necrotizing enterocolitis [3]. Infants and children affected by SBS carry a high

burden of complications related to their initial surgical management, the resulting malabsorptive state, and their need for parenteral nutrition [1–8]. These include watery diarrhea, bloodstream infections (BSIs), electrolyte disturbances, catheter-related complications, liver and biliary diseases, complications of bacterial overgrowth (arthritis, colitis, D-lactic acidosis), nutritional deficiencies, and enteric hyperoxaluria [9]. Taken together, these conditions produce a strikingly high mortality rate (often estimated

between 20% and 40%) and contribute to the growing cost of health care in this population [9–11].

Recurrent BSI is a well-established complication of SBS and has been linked with increased childhood morbidity and mortality [3, 12, 13]. Despite a growing literature on this condition, the epidemiology of BSI among children with SBS remains incompletely characterized. The processes underlying BSI in this population are likely multifactorial in nature. Because the majority of children with SBS receive parenteral nutrition, they frequently require chronic indwelling intravenous catheters, which increase the risk of bloodstream contamination from endogenous skin flora [3]. In addition, the use of parenteral nutrition has been found to alter systemic inflammatory responses and contribute to small bowel bacterial overgrowth, which itself has been associated with villous atrophy and inflammation of gut mucosa, contributing further to impairments of the immunological and physical barriers provided by the intestinal wall [11–13]. Recent studies in both animals and humans have supported the hypothesis that systemic inflammation and altered intestinal permeability contribute to translocation of enteric bacteria across the bowel wall in SBS [14, 15]. Despite this insight into BSI pathogenesis, few large studies have evaluated patient-specific associations with bacteremia in children with and without SBS. Identification of those children at greatest risk of BSI would facilitate the targeted deployment of evidence-based infection-prevention measures (gut decontamination, ethanol locks, etc.), thereby reducing morbidity, mortality, and medical costs in this vulnerable population.

MATERIALS AND METHODS

Study Design

We conducted a case–control study to examine the epidemiological associations between SBS and BSI in hospitalized children. BSI cases and controls were selected from a larger, National Institutes of Health–funded prospective cohort study examining the causes and consequences of infectious complications of hospital admissions (“Distribution of Costs of Antimicrobial Resistant Infections,” 5R01NR10822). This case–control study and the larger cohort were approved by the Institutional Review Board (IRB) of Columbia University Medical Center. Because of the retrospective, observational nature of the study, written informed consent was waived by the IRB.

Study Population

Demographic and clinical data was collected on all pediatric admissions to three hospitals between July 2006 and December 2008. The hospitals included were part of the larger New York–Presbyterian Healthcare System in

New York City and comprised a 220-bed community hospital serving adults and children in northern Manhattan, a 283-bed pediatric acute care hospital serving children from the northern Manhattan community and specialty referrals from surrounding areas in the New York metropolitan area, and a 914-bed tertiary referral medical center serving adults and children in the New York metropolitan area. All patients less than 18 years of age were eligible for inclusion in this study.

Study Variables

To eliminate cases of bacteremia secondary to another infectious process (eg, pneumonia, urinary tract infection), our study defined BSI as 1 or more positive blood cultures with no other positive culture with the same organism over the previous 14 days. Matching culture results from other body sites were permitted as long as they were obtained after the index positive blood culture. Of note, results from outside hospital microbiological specimens were not available in our database. A blood culture positive for common skin flora was considered a BSI if the organism was found in at least two blood cultures drawn on separate occasions within 2 days of each other. Organisms defined as common skin flora included *Staphylococcus epidermidis*, viridans group streptococci, *Corynebacterium*, *Bacillus* spp. (not *anthracis*), *Aerococcus*, *Micrococcus*, and *Propionibacterium*. Admissions selected as controls had no positive blood cultures for any organism or only 1 positive culture with a common skin contaminant as listed above. The International Classification of Disease, Ninth Revision (ICD-9) diagnosis code for “short bowel syndrome/other and unspecified postsurgical non-absorption” (579.3) was used for identification of children with SBS. Malignancy, history of solid organ transplant, diabetes, extremely low birth weight, and cirrhosis were also defined by the assignment of the corresponding ICD-9 codes.

The day incident of BSI was defined as the date on which the first positive blood culture was drawn. The relationship between inpatient interventions and the development of BSI was also assessed. To establish temporality and improve causal identification, we considered only candidate interventions that occurred at least 1 day prior to development of BSI. Associations with BSI considered in our analysis included the use of total and partial parenteral nutrition, presence of a central venous catheter (CVC), admission to an intensive care unit (ICU), development of acute kidney injury, and administration of immunosuppressive medications such as steroids and chemotherapeutic agents. “Inpatient time at risk for BSI” was defined as the number of hospital days prior to development of BSI for case subjects; the total number of hospital days was considered

“time at risk” for control subjects. Admission from a skilled nursing facility (SNF) was identified by matching the patient’s address with local SNF addresses. Of note, the same patient could be included in this study more than once but only through separate admissions. If multiple BSIs occurred in 1 admission, only the first infection was included in the analysis.

Data Sources

Electronically available data were extracted from multiple sources including New York–Presbyterian’s Clinical Data Warehouse, the electronic medical record, and the admission-discharge-transfer (ADT) system. The Clinical Data Warehouse acts as a repository of laboratory and clinical data for research and administrative purposes at each study hospital. Microbiology results, patient addresses, and medication administration records were obtained from this source. Administrative data extracted from the ADT system included dates of hospital admission and discharge, ICD-9 coding, and patient demographics. The electronic medical record was utilized for any data not found in the Clinical Data Warehouse or ADT systems.

Statistical Analysis

All identifying information was removed from our database and replaced by randomly generated unique study identification numbers for each admission. The unit of analysis was at the level of hospital admission, and multiple admissions were considered in some patients. We employed generalized estimating equation regression modeling to account for correlations with recurrent hospital admissions of the same patient. Descriptive analyses were initially performed, followed by univariate correlational analyses using Fisher’s exact, χ^2 , or Mann–Whitney *U* tests as appropriate. Independent variables tested for association with BSI included presence of SBS, presence of a CVC, use of partial or total parenteral nutrition, admission to an ICU, acute kidney injury, very low birth weight, administration of immunosuppressive medications, malignancy, history of organ transplantation, admission from a SNF, cirrhosis, and medical/surgical interventions performed over the hospital stay. We employed multilevel logistic regressions to estimate the strength of association with BSI. Variables that were significant in univariate analyses ($P < .1$) as well as those known to be clinically relevant were included in regression models. SAS version 9.1.3 (SAS Institute, Cary, NC) and SPSS (PASW Statistics version 18) were used for data extraction and analysis.

RESULTS

Among 40 723 hospital admissions of 30 179 children, 1047 diagnoses of BSI were identified. The median age at

admission was <1 year old, with an interquartile range (IQR) of <1 to 5 years old. A total of 4074 children were admitted more than once (median: 2 admissions; IQR: 2–4 admissions), with 1 patient having 38 admissions over our study period. Although a large proportion of identified BSI cases ($n = 498$, 48%) had positive blood cultures present upon admission, only 6% ($n = 59$) had an indwelling CVC at that time. Excluding patients who had BSI present on admission, the “inpatient time at risk” prior to BSI diagnosis was 56 days (IQR: 27–106 days). Among controls, the median “inpatient time at risk” was 3 days (IQR: 2–4 days; range: 1–274 days). For patients admitted more than once over our study period, the median time between hospitalizations was 42 days (IQR: 14–135 days).

A total of 64 children in our underlying cohort of 30,179 (0.2%) had a diagnosis of SBS. Over our study period, these patients were admitted a total of 450 times, accounting for 1.1% of our cohort’s 40,723 overall hospital stays. BSI was identified frequently among hospitalizations for

Table 1. Comparison of Characteristics Between Case and Control Hospital Admissions

Variable	Cases (With BSI) ($n = 1047$)	Controls (Without BSI) ($n = 39\,676$)	<i>P</i>
Gender (female)	474 (45)	18 908 (48)	.13
Age, categorical			<.001
≤1 y	545 (52)	26 654 (67)	
1–5 y	216 (21)	3776 (9.5)	
>5 y	286 (27)	9246 (23)	
Short bowel syndrome	207 (20)	243 (0.6)	<.001
Peripherally inserted central catheter ^a	150 (14)	1033 (2.6)	<.001
Broviac–Hickman catheter ^a	72 (7)	511 (1.3)	<.001
Subcutaneous catheter ^a	11 (1.1)	275 (0.7)	.17
Other central venous line, unspecified ^a	174 (17)	1376 (3.5)	<.001
ICU admission	357 (34)	6626 (17)	<.001
Immunosuppression	170 (16)	4274 (11)	<.001
Parenteral nutrition	278 (26.5)	2800 (7.1)	<.001
Very low birthweight	80 (7.6)	211 (0.5)	<.001
Renal failure	104 (10)	378 (1)	<.001
Malignancy	171 (16)	1495 (4)	<.001
History of solid organ transplant	85 (8)	422 (1.1)	<.001
Transfer from skilled nursing facility	13 (1.2)	96 (0.2)	<.001
Cirrhosis	12 (1.2)	42 (0.1)	<.001
Death	79 (7.6)	308 (0.8)	<.001
Inpatient time at risk prior to development of BSI (days), median (IQR)	16 (7, 51)	3 (2, 4)	<.001

All data are number (percent) unless otherwise stated; unit of case and control is hospital admission (rather than individual patient).

Abbreviations: BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range.

^aFor BSI cases, administration of these time-varying interventions was considered only if they occurred prior to culture collection for infection.

children admitted with SBS ($n = 207/450$, 46%) compared to hospitalizations for children without the condition ($n = 840/40,273$, 2.1%, $P < .001$). Enteric organisms (*Escherichia coli* or enterococci) were the causative agents for 22.7% ($n = 47/207$) of BSI in admissions for children with SBS; these were less common causes of BSI in children without SBS (11.9%, $n = 100/840$, $P < .001$). Demographic and medical characteristics of hospital admissions with BSI and those without are shown in Table 1. Most notably, mortality was significantly more common in children with BSI compared to those without BSI ($n = 79/1047$, 7.6% versus $n = 308/39,676$, 0.8%, respectively, $P < .001$). Table 2 compares similar variables between children with and without SBS. Sixty-five percent of admissions with SBS using a CVC developed BSI compared to only 16% of admissions without SBS using a CVC. Furthermore, our data showed a high rate of BSI among SBS patients with no indwelling CVC (43%). Multivariable analyses using generalized estimating equation identified 8 factors significantly associated with hospitalization with BSI. These included a diagnosis of SBS (odds ratio [OR] 19.0, 95% confidence interval [CI] 13.0–27.7), ages 1–5 years (OR 1.33, CI 1.04–1.69), presence of a non-Broviac-Hickman CVC (OR 6.36, CI 5.17–7.82), immunosuppression (OR 0.53, CI 0.42–0.67), kidney injury (OR 6.67, CI 4.9–9.08), solid

organ transplantation (OR 4.44, CI 3.11–6.35), admission from SNF (OR 2.66, CI 1.24–5.71), and cirrhosis (OR 7.23, CI 3.11–16.8). Although presence of a Broviac-Hickman catheter was not found to be statistically associated with BSI ($P = 0.72$), it was kept in the model given its clinical significance. The final model is shown in Table 3.

DISCUSSION

This study contributes to a growing literature on the strikingly high burden of infectious diseases among children with SBS. While this population represented only 0.2% of our overall cohort, it accounted for nearly 20% of all hospital admissions with BSI. This marked association between SBS and BSI has been previously documented in smaller observational studies but not in a sample of this size. Apart from SBS, our study identified several other associations with BSI in the pediatric population (Table 1), and mortality was nearly 10 times higher in patients with BSI compared to those without.

Although the increased risk of BSI among children with SBS is attributed in part to their high prevalence of indwelling CVCs, it is clear that other host factors influence the risk of infection. In 2010, Cole et al reported high rates of BSI in infants with SBS dependent on parenteral nutrition [3]. Children with small-intestinal bacterial overgrowth had 7 times the odds of development of BSI compared to those without bacterial overgrowth as diagnosed by the breath hydrogen test. In addition, children with SBS and small-intestinal bacterial overgrowth were found to have elevated levels of stool calprotectin, a marker of mucosal inflammation. Several circulating cytokines, including tumor necrosis factor- α and interleukins-1 β , -6, and -8, were also found to be elevated in children with SBS; these diminished with the initiation of enteral feeding. Dysregulated mucosal inflammation with increased gut

Table 2. Comparison of Characteristics of All Hospital Admissions Based on Short Bowel Syndrome Status

Variable	SBS present (n = 450)	SBS absent (n = 40 273)	P
Female	274 (61)	19 182 (48)	<.001
Age on admission, categorical			<.001
≤ 1 y	240 (53)	26 959 (67)	
1–5 y	169 (38)	3823 (9.5)	
> 5 y	41 (9.1)	9491 (24)	
BSI	207 (46)	840 (2.1)	<.001
Peripherally inserted central catheter	18 (4.0)	1174 (2.9)	.17
Broviac-Hickman catheter	84 (19)	499 (1.2)	<.001
Subcutaneous catheter	0 (0)	286 (0.7)	.07
Other central venous line, unspecified	27 (6.0)	1523 (3.8)	.01
ICU admission	76 (17)	6907 (17)	.88
Immunosuppression	82 (18)	4362 (11)	<.001
Renal failure	19 (4.2)	463 (1.2)	<.001
Malignancy	0 (0)	1666 (4.1)	<.001
History of solid organ transplant	33 (7.3)	474 (1.2)	<.001
Transfer from skilled nursing facility	7 (1.6)	101 (0.3)	<.001
Cirrhosis	5 (1.1)	49 (0.1)	<.001
Death	6 (1.3)	381 (1)	.40
Inpatient time at risk prior to development of BSI (days, median (IQR))	6.5 (3, 14)	3 (2, 4)	<.001

All data are number (percent) unless otherwise stated; unit of case and control is hospital admission (rather than individual patient).

Abbreviations: BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range; SBS, short bowel syndrome.

Table 3. Multivariable Association Between Short Bowel Syndrome and Bloodstream Infection, Adjusting for Factors Associated With Both Diagnoses at $P < .10$

Variable	Odds Ratio (CI)	P
Short bowel syndrome	19.0 (13.0, 27.7)	<.001
Age category		
> 5 y vs. < 1 y	0.82 (0.68, 0.98)	.03
1–5 y	1.33 (1.04, 1.69)	.02
Broviac-Hickman catheter	0.94 (0.66, 1.33)	.72
Other central venous catheter	6.36 (5.17, 7.82)	<.001
Immunosuppressive medication	0.53 (0.42, 0.67)	<.001
Renal failure	6.67 (4.9, 9.08)	<.001
History of solid organ transplantation	4.44 (3.11, 6.35)	<.001
Admission from SNF	2.66 (1.24, 5.71)	.01
Cirrhosis	7.23 (3.11, 16.8)	<.001

Abbreviations: CI, 95% confidence interval; SNF, skilled nursing facility.

permeability has been proposed as an etiology of BSI in the SBS population. Our cohort's high proportion of BSI caused by enteric pathogens (*E coli* and enterococci) in children with SBS compared to those without (23% versus 12%, respectively) supports this hypothesis.

This finding has important clinical implications, because prevention strategies targeting cutaneous bacterial reservoirs alone (ie, skin surrounding CVC sites) are likely to have incomplete efficacy if gastrointestinal bacteria cause a significant proportion of infections [16, 17]. As such, continued efforts to transition SBS patients from parenteral to enteral feeding—thereby decreasing small-intestinal bacterial overgrowth, intestinal inflammation, and gut permeability—remain an essential therapeutic goal for these children.

While the relationship between SBS and BSI has been characterized in previous investigations, there are several strengths that are unique to this study. Most notably, our sample size of over 40 000 hospital admissions provides additional statistical power for evaluating specific associations and outcomes that are comparatively rare in the pediatric population. The large and comprehensive nature of our cohort also contributes to high external validity with other populations. Indeed, our inclusion of a community children's hospital, a referral children's hospital, and a tertiary care hospital is likely to ensure that our study results are highly generalizable across diverse clinical settings. In addition, our use of overlapping clinical databases provides a comprehensive library of target variables for inclusion in our analysis. Each structured hospital dataset allowed for standardization between members of the research team, often a source of bias in smaller chart reviews. As noted above, our use of three discrete computer systems allowed investigators to establish data accuracy by assessing concordance between individual sources. Taken together, our large and diverse sample size contributes significantly to our characterization of epidemiological associations between BSI and SBS in the pediatric population.

Despite these strengths, our study is not without limitations. All data included were restricted to those parameters included in hospital databases. This employment of discrete sources of data, while useful in establishing internal validity, reflects diverse authors (physicians, nurses, medical assistants, billers, and hospital administrators), which may result in variable data quality. For example, admission from SNF was not directly coded for in our hospital databases. As such, we relied upon matching patient home addresses with locations of known SNFs in our hospital's catchment area. Although our team established a comprehensive list of New York and New Jersey facilities, this indirect method of SNF determination may have resulted in

misclassification. Similar limitations may be applicable to our ascertainment of BSI cases. While efforts were made to discriminate between true BSI and contamination (as defined in Materials and Methods), our definition of true infection may have differed from that of the treating physician. Similarly, it is possible that BSIs secondary to other sites of infection may have been missed if cultures from the primary site (ie, urine or sputum) were not obtained or returned with negative results. In addition, our use of ICD-9 classifications, while standardized, relies heavily on correct coding. Prior to study initiation, our team reviewed a subset of New York-Presbyterian admissions and found that ICD-9 579.3 was the conventional code applied for SBS at our study sites. Despite this, we acknowledge that ICD-9 definitions may produce misclassification. Unfortunately, our sample size of 40 723 hospital admissions required electronic identification of SBS and BSI cases because manual review was not feasible.

In conclusion, children with SBS suffer from strikingly high rates of morbidity and mortality, due in part to their susceptibility to life-threatening infectious diseases. This study is among the first large-scale investigations to characterize the epidemiology of SBS and BSI among children across diverse hospital settings. As hypothesized, children with SBS have astonishingly high rates of BSI. The mediators of this increased incidence are likely multifactorial but remain incompletely explained at present. While indwelling CVCs and health care exposure are contributory, SBS remains the strongest predictor of BSI. Indeed, after adjustment for multiple factors, our final model demonstrates that children with SBS have nearly 20 times the odds of having BSI compared to those without. Further research into the basic and clinical mediators of this risk will be essential for the development of evidence-based prevention strategies for this small but important population.

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