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How Broad Should Gram-Negative Coverage be for Febrile Parenteral Nutrition Dependent Short Bowel Syndrome Patients?

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Abstract

Broader spectrum gram-negative antibiotics are commonly utilized empirically for central line-associated bloodstream infections (CLABSI) in febrile short bowel syndrome (SBS) patients receiving home parenteral nutrition compared to those used empirically for inpatient-acquired CLABSI. This analysis reports 57 CLABSI in 22 patients with SBS admitted from the community and 78 inpatient-acquired CLABSI in 76 patients over a 5-year period. Proportional gram-negative CLABSI was similar between the SBS and inpatient-acquired cohorts (43.8% versus 42.3%, respectively, p=0.78). 1.8% and 10.3% (p=0.125) of gram-negative CLABSI were non-susceptible to ceftriaxone and 0% and 3.8% (p=0.52) were non-susceptible to ceftazidime in the SBS and inpatient-acquired cohorts, respectively. In the SBS cohort, home ethanol lock therapy and prior culture results impacted gram-negative pathogen distribution. Broader empiric gram-negative coverage for CLABSI among SBS patients compared to inpatients is unnecessary. Third-generation cephalosporins represent appropriate empiric gram-negative agents for febrile SBS patients presenting from the community to our institution.

Keywords

pediatric; gram negative; central line-associated bloodstream infections; microbial drug resistance; antimicrobial stewardship; short bowel syndrome; parenteral nutrition

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Introduction:

Many short bowel syndrome (SBS) patients rely on parenteral nutrition (PN) administered through a central venous line (CVL) for long-term nutritional support.[1,2] Central line-associated blood stream infections (CLABSI) occur in up to 47.5% of febrile SBS patients admitted from the community and receiving PN.[3]

Empiric antibiotic administration (before a pathogen is identified with susceptibilities) for CLABSI management in SBS patients admitted from the community commonly includes broad-spectrum gram-negative coverage (e.g., cefepime, or meropenem) in addition to vancomycin.[4] Our institution historically used meropenem for empiric gram-negative coverage, which provided broader spectrum empiric gram-negative coverage compared to our inpatient-acquired CLABSI standard antibiotic regimen utilizing third-generation cephalosporins.[5] Unnecessarily broad-spectrum antimicrobial receipt can result in microbiota changes possibly leading to infections caused by multi-drug resistant pathogens.[6] Appropriate empiric antimicrobial coverage for suspected CLABSI in febrile SBS patients with a CVL is imperative for short-term management of potential infections, prevention of acute side effects, and prevention of development of resistance to antibiotics with future infections.

Prior analyses have identified potential risk factors for all cause CLABSI in community SBS patients,[3,7] but risk factors for occurrence of gram-negatives or resistant gram-negatives versus infections lacking these pathogens have not been well defined. Additional analyses of risk factors for gram-negative and resistant gram-negative infections could help guide empiric antimicrobial selection.

The present study aimed to identify the most narrow-spectrum empiric gram-negative agent for pediatric SBS patients receiving PN and presenting from the community with fever. We hypothesized that the agent would be similar in spectrum to that used for inpatient-acquired CLABSI at our institution. We also sought to determine factors impacting acquisition of gram-negative CLABSI among SBS patients receiving home PN and admitted from the community.

Methods:

This was an institutional review board (IRB) approved retrospective chart review performed at Le Bonheur Children’s Hospital, a tertiary referral center in Memphis, TN. The timeframe for the study was from March 1, 2013 through February 28, 2018. Our institution maintains internal databases of all patients with inpatient-acquired CLABSI and those with SBS that received antibiotics for a possible or confirmed CLABSI. These two databases were used for this study. Two cohorts were created to assess our aims, a “community SBS” cohort and an “inpatient-acquired” CLABSI cohort with intact gastrointestinal tracts.

Our community SBS cohort included patients with infancy acquired SBS who remained dependent on PN and were admitted from the community for a possible CLABSI. Admissions were excluded if blood cultures were performed at an outside hospital or were negative, the patient did not receive treatment for a CLABSI, or the admission occurred after

undergoing bowel transplantation. The inpatient-acquired cohort consisted of patients with intact gastrointestinal tracts treated for a CLABSI acquired at least 72 hours after admission. Treatment was defined in both groups as durations of 7 days or more of antibiotics. More than one CLABSI episode per patient could be included in either group. As with prior pediatric CLABSI studies,[8] the CLABSI definition used was a modified version of the CDC definition and included any treated positive bloodstream culture in a patient with a central catheter that is not secondary to an infection at another body site.[9]

Patient demographics and data on infecting organisms and susceptibilities were collected for all CLABSI for descriptive purposes. Broth microdilution via the VITEK-2 system (bioMerieux Inc., Marcy-l'Etoile, France) was used to determine minimum inhibitory concentrations for gram-negative organisms except *Acinetobacter* species, where the Etest was utilized. Susceptibility determination was done using the Center for Laboratory Science Standards Institute breakpoints.[10] Polymicrobial infections containing a gram-negative organism were categorized as a "gram-negative" containing infection. Gram-negative pathogens were further subdivided based on the potential for AmpC mediated inducible third-generation cephalosporin resistance during therapy, despite an initial interpretation of susceptible.[11] Organisms considered pathogens capable of AmpC mediated induction included *Enterobacter, Citrobacter*, and *Serratia* species.

To identify factors associated with gram-negative or AmpC CLABSI in the SBS cohort, we used similar risk factors previously described as possibly associated with any CLABSI in SBS patients receiving PN.[3,7] The factors chosen focused on information available before admission and before starting empiric antibiotics. Central venous line dysfunction was defined as cracks, exit site drainage, inability to flush or inadvertent dislodgment/removal of the CVL within thirty days prior to the suspected CLABSI. Ethanol lock therapy receipt was defined as dwells of at least three times per week for 4 hours or more prior to the index admission as previously described.[12] Patients discharged from our institution on home PN are typically started on ethanol lock after they have one admission for a CLABSI, similar to a previously described process from a different institution.[13]

Statistical Analysis:

Generalized linear mixed models (GLMM) with a logit link (i.e., multilevel logistic regression models) were created. Individual patients were entered as a random effect to control for multiple infections occurring during the study period in the same patients. This modeling method was used to compare infection occurrence between the community SBS cohort and inpatient-acquired cohort. Two additional GLMM models with logit links were created to identify predictors of gram-negative infections and infections containing pathogens with the potential for AmpC mediated resistance induction in the community SBS cohort. Possible factors were screened for correlations with univariable analyses and any variables with a $p<0.2$ were included in a multivariable model to determine independent predictors of the outcomes. All p-values were two sided and significance was set at $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp, 2020, Armonk, NY).

Results:

There were 57 CLABSIs among 22 patients included in the community SBS cohort after excluding 75 admissions meeting exclusion criteria. This represents CLABSI in 43% of febrile admissions among the community SBS patients. Additional demographics not in Table 1 regarding the 22 unique community SBS patients include: 7 (32%) patients had an intact ileocecal value, 21 (95%) had a gastric tube, and the most common underlying causes for SBS were necrotizing enterocolitis (n=12, 55%) and gastroschisis (n=5, 23%). For the inpatient-acquired CLABSI cohort, 76 patients accounted for 78 CLABSI after excluding 13 hospital-acquired CLABSI occurrences in children lacking an intact gastrointestinal tract. The hospital-acquired CLABSI cohort was primarily an immunocompetent intensive care unit population, many being young infants (Table 1).

Table 1 also depicts details regarding cultured pathogens in the community SBS cohort and the inpatient-acquired CLABSI cohort. The proportion of CLABSI containing a gram-negative organism was similar between the community SBS and inpatient-acquired cohort (43.8% versus 42.3%, respectively, p=0.78). 1.8% and 10.3% of gram-negative CLABSI were non-susceptible to ceftriaxone in the community SBS and inpatient-acquired cohorts, respectively (p=0.125). The one gram-negative with intermediate susceptibility to ceftriaxone in the community SBS cohort was an *Acinetobacter* species. The eight organisms in the inpatient-acquired cohort with ceftriaxone non-susceptibility were 6 *Pseudomonas aeruginosa*, one *E. coli*, and one *Enterobacter* species. There were 0% and 3.8% (p=0.52) of organisms non-susceptible to ceftazidime in the community SBS and inpatient-acquired cohorts. The ceftazidime non-susceptible isolates among the inpatient-acquired CLABSI were two *E. coli* and one *Enterobacter* species.

Table 2 illustrates factors associated with a CLABSI containing a gram-negative organism and separately an AmpC organism in the community SBS cohort. Ethanol lock therapy receipt prior to the admission was the only factor independently associated with a lower odds of a CLABSI containing a gram-negative pathogen. Six admissions in the community SBS cohort had cultures obtained within the prior year containing a gram-negative that was intermediate or resistant to ceftazidime, but the gram-negative causing the CLABSI was susceptible. Having a culture with an AmpC organism in the past year increased the odds of a CLABSI containing an AmpC pathogen in the community SBS cohort. These prior cultures included three urine cultures, two wound cultures, one blood culture, and one respiratory tract culture, with two patients having an organism isolated from multiple sites.

Discussion:

These data suggest SBS patients with CLABSI admitted from the community do not have more gram-negative or resistant gram-negative pathogens compared to an inpatient, primarily intensive care unit-acquired CLABSI cohort. Third-generation cephalosporins were appropriate empiric gram-negative agents for CLABSI among the community SBS cohort admitted with fever at our institution. These data also identified factors that may impact CLABSI pathogen distribution in SBS patients.

Some institutions have used broader-spectrum agents like piperacillin/tazobactam, cefepime, or meropenem empirically in febrile SBS patients due to a concern for increased gram-negative pathogen resistance.[4,6] No isolate from the community SBS cohort in our study was resistant to ceftazidime therapy. As a result of our findings, we switched our institutional empiric gram-negative agent for febrile SBS patients from meropenem to ceftazidime. This is the same gram-negative antibiotic used for empiric coverage for inpatient-acquired CLABSI at our institution.[5] Cefotaxime would be the ideal empiric option if available, although it is not currently manufactured in the United States. Ceftriaxone was not considered the ideal option for most of the SBS population due to the risk of precipitation with co-administration of intravenous calcium, a common component of PN.[14] Our study suggests that institutions may be able to use the same or potentially more narrow-spectrum antibiotics empirically for community-acquired CLABSI in SBS patients compared to that used for hospital-acquired CLABSI.

In the present study, 14% of the SBS CLABSI were caused by organisms that can harbor inducible AmpC beta-lactamases, and other institutions may consider these organisms resistant to third-generation cephalosporins despite susceptibility.[4] However, a recent pediatric analysis suggests that third-generation cephalosporins can be used for bacteremia caused by AmpC pathogens with third-generation cephalosporin susceptibility.[15] Additionally, the present study suggests that patients at higher risk for a CLABSI due to an AmpC pathogen may be stratified based on prior cultures with AmpC organisms. Conversely, this same approach may not be applicable for predicting CLABSI with resistance to third-generation cephalosporins as multiple patients with CLABSI caused by gram-negative pathogens susceptible to third-generation cephalosporins had prior cultures with resistant gram-negative organisms isolated.

Receipt of ethanol lock therapy at home in patients with SBS admitted from the community with CLABSI independently decreased the odds of having a gram-negative containing CLABSI (Table 2). Prior studies have reported likely associations with ethanol lock prophylaxis and decreased CLABSI due to gram-negative pathogens.[16–18] Some studies have reported concerns with ethanol lock due primarily to catheter integrity issues,[8,19] but numerous studies in children with SBS have found significant decreases in CLABSI and catheter exchange rates.[13,20] Our institution continues to use home ethanol lock in our SBS patients receiving PN. Future studies could aim to assess the cost effectiveness of this intervention due to recent increases in ethanol drug cost.

The present analysis has some limitations. Our sample size overall was relatively small and thus associations not identified as significant could still arise with larger sample sizes. This was a single-center study and geographic differences in susceptibility could impact generalizability of some of our findings to other institutions. These data may not apply to CLABSI in SBS patients before they leave the hospital or other populations requiring a CVL as an outpatient. We did not look at all possible characteristics of the inpatient-acquired cohort that could have impacted resistance as this group only served as a basic comparator to the community SBS cohort. These data likely do not apply to the hematology/oncology population and empiric coverage for SBS may be less broad compared to an inpatient-acquired CLABSI cohort with more hematology/oncology patients. Our

comparative analysis for the community SBS cohort contained multiple infections per patient, but this possible bias was controlled for in our multilevel model. Since the study was retrospective in nature and not randomized, there also could be confounders unaccounted for, which is a common limitation of retrospective studies.

Conclusions:

Third-generation cephalosporins provide appropriate empiric gram-negative coverage for CLABSI in SBS patients admitted to our institution from the community. Broader empiric gram-negative antibiotic coverage in community SBS patients compared to that used for inpatient-acquired infections is likely unnecessary. Prior year cultures from any site containing AmpC organisms may help identify patients at higher risk for infections due to AmpC organisms. Ethanol lock may impact the proportion of CLABSI cause by gram-negatives in febrile SBS patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known:

- Patients with short bowel syndrome (SBS) requiring outpatient parenteral nutrition can have gram-negative containing central line-associated bloodstream infections (CLABSI)
- Utilization of appropriate spectrum empiric antibiotics is imperative to optimizing outcomes and preventing resistance development

What is new:

- Empiric gram-negative antibiotic therapy in febrile SBS patients admitted from the community should not be broader spectrum than empiric therapy utilized for inpatient-acquired CLABSI
- Third-generation cephalosporins likely provide appropriate empiric gram-negative coverage in community SBS patients admitted with a fever
- Ethanol lock therapy and prior culture data may be associated with pathogen distribution among community SBS patients admitted for CLABSI

Table 1:

Cohort Descriptive Characteristics (172 pathogens from 135 CLABSI[a])

Demographics	**Community SBS cohort (57 CLABSI[a])**	**Inpatient Cohort (n=78 CLABSI[a])**
Gender (F)	29 (51%)	40 (51%)
Transplant or hematologic/oncologic diagnosis	0	3 (4%)
Age at the time of infection		
<6 months	0	40 (51%)
6– <12 months	12 (21%)	12 (15%)
1–<5 years	35 (61%)	14 (18%)
5–18 years	5 (9%)	12 (15%)
CVL days since placement, median (range)	130 (2–1812)	17 (2–954)[b]
Location of CLABSI acquisition		
Outpatient	57 (100%)	0
Inpatient ICU	0	65 (83%)
Inpatient non-ICU	0	13 (17%)
Pathogens[c,d]	**Community SBS Cohort (n=87 pathogens[c,d])**	**Inpatient Cohort (n=85 pathogens[c,d])**
Coagulase-negative *Staphylococcus*	20 (23%)	25 (29%)
Methicillin-susceptible *S. aureus*	13 (15%)	8 (9%)
Klebsiella spp.	12 (14%)	7 (8%)
Enterococcus spp.	11 (13%)	5 (6%)
Organisms capable of AmpC mediated induction[e]	8 (9.2%)	14 (16.5%)
Methicillin-resistant *S. aureus*	6 (7%)	2 (2%)
E. coli spp.	6 (7%)	7 (8%)
Candida albicans	1 (1%)	3 (4%)
Pseudomonas spp.	0 (0%)	5 (6%)
Other gram-positives	4 (4%)	2 (2%)
Other gram-negatives	3 (3%)	2 (2%)
Other *Candida* spp.	3 (3%)	5 (6%)

CLABSI, central line associated bloodstream infection; CVL, central venous line; ICU, intensive care unit

[a]Infections were among 22 patients in the community SBS cohort and 76 patients in the inpatient cohort

[b]Three infections were not included due to unknown date of CVL placement outside our hospital

[c]All gram-negative pathogens in the community SBS cohort were ceftazidime susceptible and one was ceftriaxone intermediate. Three gram-negative pathogens in the inpatient cohort were not ceftazidime susceptibility and 8 were not ceftriaxone susceptible

[d]Twenty-one (36.8%) infections in the community SBS cohort and 7 (9%) in the inpatient cohort were polymicrobial

[e]Organisms capable of AmpC mediated induction included *Citrobacter, Enterobacter*, and *Serratia* species

Table 2:

Risk Factors for Infections Containing a Gram-Negative and AmpC[a] Organism among SBS Patients Receiving Home Parenteral Nutrition

Factor	Risk factors for gram-negative infections			Risk factors for AmpC harboring organism infections		
	Not Gram-negative (n=32)	**Gram- negative (n=25)**	**Multivariable[a] OR, 95% CI**	**Not AmpC Organism (n=49)**	**AmpC[b] Organism (n=8)**	**Multivariable[a] OR, 95% CI**
Months of age, median (range)	35.6 (6.8–252)	19.6 (7–122)	N/A	37.1 (6.8–122)	21.7 (7–252)	0.96 (0.9–1)
Leaking gastric tube in previous thirty days	9 (28%)	3 (12%)	0.2 (0.04–1.4)	11(22%)	1(12.5%)	N/A
CVL dysfunction in prior 30 days	17(53%)	11 (44%)	N/A	23(47%)	5(62.5%)	N/A
Presence of a salvaged line	8 (25%)	12 (48%)	3.1 (0.8–11.7)	17(35%)	3 (38%)	N/A
Home ethanol lock therapy	**29 (91%)**	**14 (56%)**	**0.1 (0.01–0.5)**	38(78%)	5 (63%)	N/A
Home erythromycin therapy	9 (28%)	7 (28%)	N/A	15(31%)	1(13%)	N/A
Absent ileocecal valve	11 (34%)	11 (44%)	N/A	19 (39%)	3 (38%)	N/A
Present gastric-tube	31 (97%)	23 (92%)	N/A	46 (94%)	8 (100%)	N/A
Blood culture with gram-negative bacteria in previous year	17 (53%)	11 (44%)	N/A	23 (47%)	5 (62%)	N/A
Any culture with gram-negative bacteria in previous year	23 (72%)	15 (60%)	N/A	32(65%)	6 (75%)	N/A
Blood culture with inducible AmpC[b] harboring organism in prior year	4 (13%)	1 (4%)	N/A	4 (8%)	1 (12%)	N/A
Any culture with inducible AmpC[b] harboring organism in prior year	7 (22%)	6 (24%)	N/A	**8 (16%)**	**5 (62%)**	**9.4 (1.3–68.1)**
CVL days since placement at the time of infection, median (range)	125.5 (2–1812)	158 (11–783)	N/A	130 (2–1812)	136 (13–531)	N/A

SBS, short bowel syndrome; OR, odds ratio, CI, confidence interval; CVL, central venous line

[a]AmpC harboring organisms consisted of *Enterobacter, Citrobacter, Serratia*, and *Morganella* species

[b]The multivariable generalized linear mixed models with logit links only included variables with $p<0.2$ on univariable analysis, and the outcome of the models were an infection that contained a gram-negative pathogen and an infection that contain an AmpC harboring organism

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